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BRIEF ARTICLE

Etiology and long-term outcome of extrahepatic portal vein obstruction in children

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Abstract

AIM: To study the management and outcome of children with extrahepatic portal vein obstruction (EHPVO) in a whole country population.

METHODS: A nationwide multicenter retrospective case series of children with EHPVO was conducted. Data on demographics, radiographic studies, laboratory workup, endoscopic and surgical procedures, growth and development, were extracted from the patients' charts. Characteristics of clinical presentation, etiology of EHPVO, management and outcome were analyzed.

RESULTS: Thirty patients, 13 males and 17 females, 19 (63.3%) Israeli and 11 (36.7%) Palestinians, were included in the analysis. Age at presentation was 4.8 ± 4.6 years, and mean follow-up was 4.9 ± 4.3 years. Associated anomalies were found in 4 patients. The incidence of EHPVO in Israeli children aged 0-14 years was 0.72/million. Risk factors for EHPVO were detected in 13 (43.3%) patients, including 9 patients (30%) with perinatal risk factors, and 4 patients (13.3%) with prothrombotic states: two had low levels of protein S and C, one had lupus anticoagulant, and one was homozygous for methyltetrahydrofolate reductase mutations. In 56.6% of patients, no predisposing factors were found. The most common presenting symptoms were an incidental finding of splenomegaly (43.3%), and upper gastrointestinal bleeding (40%). No differences were found between Israeli and Palestinian children with regard to age at presentation, etiology and clinical symptoms. Bleeding occurred in 18 patients (60%), at a median age of 3 years. Sclerotherapy or esophageal banding was performed in 20 patients. No sclerotherapy complications were reported. Portosystemic shunts were performed in 11 patients (36.6%), at a median age of 11 (range 3-17) years: splenorenal in 9, mesocaval in 1, and a meso-Rex shunt in 1 patient. One patient underwent splenectomy due to severe pancytopenia. Patients were followed up for a median of 3 (range 0.5-15) years. One patient died aged 3 years due to mucopolysaccharidase deficiency type Ⅲ. None of the patients died due to gastrointestinal bleeding.

CONCLUSION: EHPVO is a rare disorder. The etiological factors are still mostly unknown, and the endoscopic and surgical treatment options ensure a good long-term prognosis.

Key words: Children; Extrahepatic; Obstruction; Outcome; Portal; Vein

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INTRODUCTION

Extrahepatic portal vein obstruction (EHPVO), although rare in children, is an important cause of portal hypertension and upper gastrointestinal (UGI) bleeding in the pediatric age group[1,2]. The etiology of EHPVO is diverse and risk factors are usually detected in less than half of patients, and include perinatal events such as umbilical catheterization and sepsis, and prothrombotic disorders[2-4].

We aimed to study the evaluation, management and outcome of children with EHPVO in a whole country population.

MATERIALS AND METHODS

This study is a multicenter retrospective case series of children with EHPOV diagnosed and followed in all pediatric gastroenterology and hepatology divisions in Israel during the period January 1, 1993 to December 31, 2008. All pediatric gastroenterologists and hepatologists registered in the country were approached by mail and telephone and asked to participate in the study. The patients were allocated *via* the hospital or outpatient clinic archive registrations, including searches for hospitalizations, outpatient visits, radiological, endoscopic and surgical procedures with one or more of the following diagnoses: portal vein, thrombosis, splenomegaly, hepatomegaly, gastrointestinal bleeding, varices, sclerotherapy, ligation, liver biopsy, elevated liver enzymes, and shunt. Patients with portal vein obstruction and portal hypertension due to chronic liver disease were excluded after chart reviews. The referral population included both Israeli and Palestinian children referred to a medical center in Israel from the Gaza Strip and West Bank.

Data on demographics, radiographic studies, laboratory workup, endoscopic and surgical procedures, growth and development, were extracted from the patients' charts.

Table 1 Demographic data, clinical presentation and risk factors for extrahepatic portal vein obstruction in the study group

	n (%)
Gender	
Male	13 (43.3)
Female	17 (56.7)
Ethnicity	
Jewish	15 (50)
Arab	14 (46.6)
Russian	1 (3.3)
Referral	
Israeli	19 (63.3)
Palestinian	11 (36.7)
Gestational age	
Term	23 (76.7)
Preterm	7 (23.3)
Clinical presentation	
Splenomegaly	13 (43.3)
UGI bleeding	12 (40.0)
Cytopenia	5 (16.6)
Elevated liver enzymes	2 (6.6)
Risk factor for EHPVO	
Perinatal events	
Umbilical catheterization	6 (20)
Omphalitis	2 (6.6)
Sepsis, NEC	1 (3.3)
Hypercoagulable state	
APLA syndrome	2 (6.6)
Protein S and C deficiency	1 (3.3)
MTHFR mutation homozygosity	1 (3.3)
Unknown	17 (56.6)

EHPVO: Extrahepatic portal vein obstruction; UGI: Upper gastrointestinal; MTHFR: Methyltetrahydrofolate reductase; APLA: Anti phospholipid antibodies.

Characteristics of clinical presentation, etiology of EHPVO, management and outcome were analyzed.

Statistical analysis

The data were analyzed using Bio-medical P-series[5]. Discrete variables were compared using Fisher's exact test. Continuous variables were compared using the Mann-Whitney *U*-test, since the sample sizes were relatively small. A P-value $\leqslant 0.05$ was considered significant.

RESULTS

Thirty-two children were identified. Two patients were excluded due to missing clinical data, and 30 patients, 13 males and 17 females, were included in the analysis. The demographic data of the patients are presented in Table 1. Fourteen patients (46.6%) were Jewish, 15 (50%) were Arab, and 1 (3.3%) was of Russian descent. Nineteen (63.3%) patients were Israeli and 11 (36.7%) were Palestinians. The age at presentation was 4.8 ± 4.6 years (median 3.5 years, range 1 mo-14 years), and the mean follow-up was 4.9 ± 4.3 years (median 3 years, range 1-15 years). Associated congenital anomalies were found in 4 patients, including: cardiac anomalies (3) and mucopolysaccharidase deficiency type Ⅲ (1).

The diagnosis of EHPVO was based on clinical signs and symptoms of portal hypertension, as well as ultrasonographic findings of portal vein cavernous transformation, in the absence of any chronic liver disease. Additional radiographic evaluations were performed in 8 patients at diagnosis and during follow-up, including computed tomography (CT) with angiography (5), magnetic resonance imaging (MRI) (4), and angiography + venography (2).

Liver biopsy was performed in 20 (66.6%) patients. The histology of 10 biopsies was within normal limits. In 6 biopsies, minor changes including hepatocyte ballooning with mild sinusoidal dilatation were reported, and in 4 biopsies regenerative nodular hyperplasia was found. In these 4 patients EHPVO obstruction was diagnosed by US and CT-angiography or MRI. The mechanism of regenerative nodular hyperplasia may be similar to other hepatic findings resulting from deprivation of portal flow to the liver[4].

Incidence of EHPVO

The calculated incidence in Israeli children aged 0-14 years was 0.72/million. This calculation was based on an average number of children at this age in Israel during the years 1993-2008 (1.85 million, range 1.7-2.0 million). However, it cannot be ruled out that children with no symptoms and no complications of EHPVO were not diagnosed, and that the incidence may be higher.

The incidence in Palestinian children could not be calculated, due to referral bias. Some children may have been referred to other countries for evaluation, or followed-up in local hospitals if no bleeding or other complications occurred.

Etiology of EHPVO

Risk factors for EHPVO were detected in 13 (43.3%) patients (Table 1). Nine patients (30%) had perinatal risk factors including umbilical catheterization (6), omphalitis (2), and neonatal sepsis with necrotizing enterocolitis (1). Detailed prothrombotic profiles were available in 28 patients, including: protein S, protein C, antithrombin Ⅲ, lupus anticoagulant, factor V Leiden and factor Ⅱ mutations and methyltetrahydrofolate reductase (MTHFR) mutations. Janus kinase 2 (JAK2) V617F mutation of the prothrombin gene was assessed in 5 patients. Prothrombotic states were found in 4 patients (13.3%): two had low levels of protein S and C, lupus anticoagulant was positive in one, and one was homozygous for MTHFR mutations. In addition, 2 patients had mildly reduced activity of protein C levels, however, such levels were thought to be secondary.

In the majority of patients, 17 (56.6%), no predisposing factors for EHPVO were found.

Clinical course

The most common presenting symptoms were an incidental finding of splenomegaly on physical examination (43.3%), and UGI bleeding manifested as hematemesis and/or melena (40%). In two patients, failure to thrive with a weight under the 3rd percentile was noted at presentation in addition to the presenting symptoms.

Table 2 Clinical characteristics and course of Israeli and Palestinian children with extrahepatic portal vein obstruction *n* (%)

	Israeli	Palestinian	*P*
Gender (M/F)	11/8	2/9	0.06
Age at diagnosis (yr)			
mean ± SD	6 ± 5.1	3.5 ± 3.8	
Median (range)	7 (0.1-16)	2 (0.75-12)	NS
Etiology			
Perinatal events	4 (21)	4 (36.3)	NS
Hypercoagulability	2 (10.5)	2 (18.2)	
Variceal bleeding	9 (47.3)	9 (81.8)	NS
Follow-up (yr, mean ± SD)	6.5 ± 5.3	3.0 ± 2.2	NS
Surgery	7 (36.8)	4 (36.3)	NS

NS: Not significant.

Table 3 Endoscopic and surgical treatment of children with extrahepatic portal vein obstruction

Procedure	*n* (%)
Sclerotherapy	13 (43.3)
Variceal banding	7 (23.3)
Surgery	
Splenorenal shunt	9 (30.0)
Mesocaval shunt	1 (3.3)
Meso-Rex shunt	1 (3.3)
Splenectomy	1 (3.3)

A comparison between Israeli and Palestinian children did not reveal any significant differences with regard to the age at presentation, etiology and clinical symptoms (Table 2).

Outcome

Overall, 18 patients (60%) had bleeding: 12 (40%) at presentation and an additional 6 patients (20%) during follow-up. The median age at the first bleeding episode was 3 (range 0.75-13) years. Twenty-two patients, who had esophageal varices on upper endoscopy, received propranolol for secondary or primary bleeding prevention. Sclerotherapy or esophageal banding was performed in 20 patients. In 18 of these patients, the procedures were performed during and after bleeding, and in 2 patients banding was performed as primary prevention (Table 3). No complications of sclerotherapy were reported.

Shunt operation was performed in 11 patients (36.6%), at a median age of 11 (range 3-17) years. The indication was uncontrolled bleeding despite variceal banding in 10 patients, and emergency shunt for failure of bleeding control in one. The types of shunt were splenorenal in 9, mesocaval in 1, and meso-Rex in 1 patient. One patient underwent splenectomy due to severe pancytopenia (Table 3).

Patients were followed up for a median of 3 (range 0.5-15) years. One patient died aged 3 years due to mucopolysaccharidase deficiency type Ⅲ. None of the patients died due to gastrointestinal bleeding.

DISCUSSION

The present study summarizes a national experience of EHPVO in children with over 15 years of follow-up. The average incidence of EHPVO in children age 0-14 years in the current study was very low at 0.72 per million. Although EHPVO is an important cause of portal hypertension and gastrointestinal bleeding in children, the exact incidence of the disorder is unknown[6]. The available case series are mostly retrospective, summarizing the experience of one or multiple referral centers[2,7]. The current study is the only nationwide study including all patients diagnosed over a 15-year period, enabling the calculation of EHPVO incidence.

The results are in agreement with previous studies reporting an unknown etiology for EHPVT in over 50% of children[2-4]. Neonatal events, including umbilical catheterization and sepsis, were possible causes of EHPVO in a small number of patients in the current study, as reported by others[2]. In a retrospective study of 133 infants diagnosed with portal vein thrombosis (PVT) within the first month of life, an umbilical catheter was inserted in 73%[8]. Of 29 infants with grade Ⅲ PVT, 62% progressed to portal hypertension. It is, therefore, surprising that umbilical catheterization accounts for a minority of cases of EHPVO in children in different studies[2,7]. Since the mean follow-up period of the infants in the study by Morag *et al*[8] was only 79 d, this may indicate that most of the PVT seen post-umbilical catheterization either resolve or remain without clinical significance.

Venous thrombosis has been associated with thrombophilia[3]. Factor V Leiden mutation, which is the most common inherited cause of thrombophilia, has been described in association with hepatic vein thrombosis, but its association with PVT is questionable[3,9]. A lack of association between factor V Leiden mutation and PVT was reported in 3 studies[7,10,11]. In contrast, a high prevalence of this mutation in children with PVT (6/23 and 12/40 patients) was found in 2 other studies[12,13]. In the current study, one child had factor V Leiden mutation and an umbilical catheter, thus, the exact cause of EHPVO cannot be determined. Inherited deficiencies in protein C, protein S, antithrombin Ⅲ and prothrombin, increase the risk of venous thrombosis and are associated with EHPVO in adults[10,14,15]. Gurakan reported 5 of 12 pediatric patients with EHPVO to have protein C, S, anti thrombin Ⅲ or combined deficiencies[7]. Higher rates were found in Egyptian children - 27.5% had protein C and 2.5% had antithrombin Ⅲ deficiency[13]. However, in a study of 14 patients and their parents, the frequency of protein C, S and antithrombin Ⅲ deficiency was 43% in the PVT patients but none were inherited[16]. Mack *et al*[17] showed, that coagulation defects are pathophysiologic consequences of EHPVO, the consequence of depriving the liver of portal venous flow, and that surgical restoration of intrahepatic portal venous flow corrects the abnormalities. In the current study, 2 patients (6.6%) had low protein C values, one of them combined with protein S deficiency. Antiphospholipid antibody syndrome, identified in one of our patients, may also manifest as arterial or venous thrombosis[18]. An acquired JAK2 mutation (JAK2V617F) was recently reported in the majority of patients with polycythemia vera and essential thrombocytosis[19], and in 36% of adults with EHPVO[20]. In children, JAK2V617F screening was negative in one study[2], and was negative in the 5 patients screened in the current study.

The outcome of children with EHPVO depends on the control of variceal bleeding. Sclerotherapy and banding are effective therapies for bleeding esophageal varices[2,21,22], and may achieve long-term variceal eradication in 50% of patients[2]. Similarly, in the current study, long-term bleeding control was achieved in 50% of bleeding children. Portosystemic shunts were performed in 36.6% of patients, a higher rate than that of 8%-17% reported by others in recent studies[2,6,7]. The rate of surgery was similar for Israeli and Palestinian patients, demonstrating that there was no selection of patients living in remote areas for shunt operation. Most of the patients were followed in large centers, in which all endoscopic techniques are available, and the high surgical rate may reflect patients with more severe disease. The prognosis of patients in the current study was good, with no bleeding or liver related mortality, in agreement with other studies reporting mortality in less than 10% of patients[2,7].

The current study has a few limitations. One is the possibility of under detection in children with no symptoms and no complications of EHPVO, resulting in a lower than actual incidence. Another limitation is the shorter patient follow-up compared with other studies. The median follow-up in the current study was 3 years with a mean of 4.9 years, compared to a median of 6 years in one study[2] and a mean of 7.4 years in another study[7]. As a result, the long-term outcome may be worse than that found in the current study.

In conclusion, although EHPVO is an important cause of portal hypertension in children, it is a rare disorder. The etiological factors are still mostly unknown, and the endoscopic and surgical treatment options ensure a good long-term prognosis.

COMMENTS

Background

Extraintestinal portal vein obstruction (EHPVO), although rare in children, is an important cause of portal hypertension and upper gastrointestinal bleeding from varices in the pediatric age group. It accounts for almost 70% of children with portal hypertension. The etiology of EHPVO is diverse and risk factors are usually detected in less than half of patients and include congenital abnormalities and perinatal events such as exchange transfusions, umbilical catheterization and sepsis, and hypercoagulable states.

Research frontiers

Improvements in the definitions and tests for hypercoagulable states allow more extensive studies on the etiology of EHPVO. Medical control of acute variceal bleeding and long-term endoscopic control of varices by sclerotherapy/ ligation may improve the long-term outcome of children with EHPVO. Surgical options for shunts in patients who fail endoscopic control of bleeding include the recent introduction of the meso-Rex bypass, which results in restoration of normal blood flow to the liver.

Innovations and breakthroughs

Calculation of the incidence of EHPVO in this first national study revealed a low incidence of 0.72/million.

Applications

The long-term outcome of EHPVO in children is good, with low mortality. Variceal bleeding can be controlled in most patients, and shunt surgery is needed in about a third of patients.

Terminology

Portal hypertension caused by extrahepatic portal vein obstruction occurs when the site of the blockage is the portal vein before the blood reaches the liver. A portal cavernoma is usually formed. This disease entity is distinct and not primarily associated with primary liver disease.

Peer review

The study, though it is a retrospective analysis, is informative, well written and gives a good overview on the incidence, underlying causes and treatment of EHPVO in children in Israel.

REFERENCES

1 **Gauthier F**. Recent concepts regarding extra-hepatic portal hypertension. *Semin Pediatr Surg* 2005; **14**: 216-225

2 **Abd El-Hamid N**, Taylor RM, Marinello D, Mufti GJ, Patel R, Mieli-Vergani G, Davenport M, Dhawan A. Aetiology and management of extrahepatic portal vein obstruction in children: King's College Hospital experience. *J Pediatr Gastroenterol Nutr* 2008; **47**: 630-634

3 **Yadav S**, Dutta AK, Sarin SK. Do umbilical vein catheterization and sepsis lead to portal vein thrombosis? A prospective, clinical, and sonographic evaluation. *J Pediatr Gastroenterol Nutr* 1993; **17**: 392-396

4 **Sarin SK**, Sollano JD, Chawla YK, Amarapurkar D, Hamid S, Hashizume M, Jafri W, Kumar A, Kudo M, Lesmana LA, Sharma BC, Shiha G, Janaka de Silva H. Consensus on extrahepatic portal vein obstruction. *Liver Int* 2006; **26**: 512-519

5 **Dixon WJ**. BMDP Statistical Software. Los Angeles: University of California Press, 1993

6 **Poddar U**, Thapa BR, Rao KL, Singh K. Etiological spectrum of esophageal varices due to portal hypertension in Indian children: is it different from the West? *J Gastroenterol Hepatol* 2008; **23**: 1354-1357

7 **Gürakan F**, Gürgey A, Bakkaloğlu A, Koçak N. Homozygous factor V Leiden mutation in a child with Budd-Chiari syndrome. *J Pediatr Gastroenterol Nutr* 1999; **28**: 516-517

8 **Morag I**, Epelman M, Daneman A, Moineddin R, Parvez B, Shechter T, Hellmann J. Portal vein thrombosis in the neonate: risk factors, course, and outcome. *J Pediatr* 2006; **148**: 735-739

9 **Heller C**, Schobess R, Kurnik K, Junker R, Günther G, Kreuz W, Nowak-Göttl U. Abdominal venous thrombosis in neonates and infants: role of prothrombotic risk factors - a multicentre case-control study. For the Childhood Thrombophilia Study Group. *Br J Haematol* 2000; **111**: 534-539

10 **Sharma S**, Kumar SI, Poddar U, Yachha SK, Aggarwal R. Factor V Leiden and prothrombin gene G20210A mutations are uncommon in portal vein thrombosis in India. *Indian J Gastroenterol* 2006; **25**: 236-239

11 **Seixas CA**, Hessel G, Ribeiro CC, Arruda VR, Annichino-Bizzacchi JM. Factor V Leiden is not common in children with portal vein thrombosis. *Thromb Haemost* 1997; **77**: 258-261

12 **Egesel T**, Büyükasik Y, Dündar SV, Gürgey A, Kirazli S, Bayraktar Y. The role of natural anticoagulant deficiencies and factor V Leiden in the development of idiopathic portal vein thrombosis. *J Clin Gastroenterol* 2000; **30**: 66-71

13 **El-Karaksy H**, El-Koofy N, El-Hawary M, Mostafa A, Aziz M, El-Shabrawi M, Mohsen NA, Kotb M, El-Raziky M, El-Sonoon MA, A-Kader H. Prevalence of factor V Leiden mutation and other hereditary thrombophilic factors in Egyptian children with portal vein thrombosis: results of a single-center case-control study. *Ann Hematol* 2004; **83**: 712-715

14 **Hackeng TM**, Seré KM, Tans G, Rosing J. Protein S stimulates inhibition of the tissue factor pathway by tissue factor pathway inhibitor. *Proc Natl Acad Sci USA* 2006; **103**: 3106-3111

15 **Primignani M**, Martinelli I, Bucciarelli P, Battaglioli T, Reati R, Fabris F, Dell'era A, Pappalardo E, Mannucci PM. Risk factors for thrombophilia in extrahepatic portal vein obstruction. *Hepatology* 2005; **41**: 603-608

16 **Pinto RB**, Silveira TR, Bandinelli E, Röhsig L. Portal vein thrombosis in children and adolescents: the low prevalence of hereditary thrombophilic disorders. *J Pediatr Surg* 2004; **39**: 1356-1361

17 **Mack CL**, Superina RA, Whitington PF. Surgical restoration of portal flow corrects procoagulant and anticoagulant deficiencies associated with extrahepatic portal vein thrombosis. *J Pediatr* 2003; **142**: 197-199

18 **Uthman I**, Khamashta M. The abdominal manifestations of the antiphospholipid syndrome. *Rheumatology* (Oxford) 2007; **46**: 1641-1647

19 **Baxter EJ**, Scott LM, Campbell PJ, East C, Fourouclas N, Swanton S, Vassiliou GS, Bench AJ, Boyd EM, Curtin N, Scott MA, Erber WN, Green AR. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. *Lancet* 2005; **365**: 1054-1061

20 **Primignani M**, Barosi G, Bergamaschi G, Gianelli U, Fabris F, Reati R, Dell'Era A, Bucciarelli P, Mannucci PM. Role of the JAK2 mutation in the diagnosis of chronic myeloproliferative disorders in splanchnic vein thrombosis. *Hepatology* 2006; **44**: 1528-1534

21 **McKiernan PJ**, Beath SV, Davison SM. A prospective study of endoscopic esophageal variceal ligation using a multiband ligator. *J Pediatr Gastroenterol Nutr* 2002; **34**: 207-211

22 **Baroncini D**, Milandri GL, Borioni D, Piemontese A, Cennamo V, Billi P, Dal Monte PP, D'Imperio N. A prospective randomized trial of sclerotherapy versus ligation in the elective treatment of bleeding esophageal varices. *Endoscopy* 1997; **29**: 235-240

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