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A clinico-etiological profile of adult extrahepatic portal venous obstruction in patients from Northern India. Is it a novel subset of occult extrahepatic portal vein obstruction?

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ABSTRACT

Background: Extrahepatic portal vein obstruction (EHPVO) is caused by occlusion and cavernomatous transformation of the portal vein. The EHPVO is well characterized in children. However, the same is not valid for adults. We aimed to evaluate the clinico-etiological profile along with the management of adult patients. **Aims and Objectives:** We evaluated the clinico-etiological profile along with the management and outcomes of adult patients presenting with EHPVO. **Materials and Methods:** In a descriptive, observational study, patients between ages 15 and 75 years diagnosed with EHPVO on ultrasonography abdomen were included in the study. Liver cirrhosis and malignancy were considered as an exclusion criterion. There was evaluation of clinical and imaging findings along with biochemical analysis, workup for thrombophilia, treatment given to the patients, and follow-up. **Results:** Out of total 109 patients enrolled in the study, the median age of patients was ±40.25. Main clinical features were dyspepsia, abdominal discomfort, and splenomegaly. Out of 109, 27.5% patients showed fatty liver and 5.5% had both splanchnic vein thrombosis and fatty liver. Idiopathic EHPVO in majority of patients (80%), adult EHPVO with polycythemia rubra vera in 7.33% patients, adult EHPVO with heterozygous MTHFR mutation in 7.33% patients, and adult EHPVO with antiphospholipid antibody in 3.66%. No mortality was seen in this 5-year observational study and majority of the patients, i.e., 96 (88.1%) did not require any treatment. **Conclusion:** Relatively benign nature of adult EHPVO was found in the selected group of patients. Majority of the cases in our study were idiopathic and few had positive thrombophilia profile.

Key words: Extrahepatic portal venous obstruction; Splanchnic venous thrombosis; Fatty liver; Splenomegaly; Thrombophilia

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INTRODUCTION

Vascular condition of the liver known as extrahepatic portal vein obstruction (EHPVO) causes occlusion and cavernomatous transformation of the portal vein with or without involvement of the intrahepatic portal vein, splenic vein, or superior mesenteric vein.[1] The occurrence of EHPVO takes place when there is blockade in portal vein preventing the entry of blood into liver. This results in the development of portal cavernoma (a collection of collateral vessels and bypasses) around the obstruction leading to extrahepatic portal hypertension.[2,3] EHPVO accounts for one-third of cases in adults and more than half of the cases in children of portal hypertension in

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India.[1] EHPVO is categorized based on the location of the portal vein thrombosis, the acute or chronic presentation, complete or incomplete occlusion of the portal vein, and the degree of extrahepatic portal venous system involvement. It is a heterogeneous disease in terms of demography, etiology, pathogenesis, and outcome.[4,5] Various etiological variables may contribute to its development, but they are unidentified or idiopathic in most of the cases of adult EHPVO.[6] EHPVO does not include portal vein obstruction linked to chronic liver disease or neoplasia since it is a distinct condition.[4] EHPVO is more prevalent in children or lower age groups and rarely encountered in adults.[7] Umbilical sepsis, neonatal systemic sepsis, umbilical catheterization, and developmental defects are the most common causes in children. Other reasons include dehydration, frequent exchange transfusions, and sepsis.[8] Adults, however, often experience blockade due to cirrhosis, surgery, pancreatitis, and malignancies.[9-11] Variceal bleeding (70–80%), abdominal pain (36%), splenomegaly (20%), and altered metabolic features are the most prevalent clinical presentations in these patients.[10-15] The EHPVO is well characterized in children in terms of clinical features, etiology, natural course, and management. However, the same is not valid for adults.

There is very limited data available regarding adult EHPVO in India. We aimed to evaluate the clinico-etiological profile along with the management and outcomes of adult patients presenting with EHPVO in the tertiary care centers of Kashmir, India.

Aims and objectives

To evaluate the clinico-etiological profile along with management of adult patients presenting with EHPVO.

MATERIALS AND METHODS

This was a descriptive, observational study conducted in the multicenter tertiary care hospitals in Kashmir, Northern India. All the patients between age 15 and 75 years diagnosed with EHPVO on ultrasonography (USG) abdomen were included in the study. All the cases of EHPVO associated with liver cirrhosis and malignancy were excluded from the study. The patients were reported to outpatient department with diagnostic USG abdomen, done either for some abdominal complaints or for mere screening.

In patients with documented adult EHPVO, the data were collected through a proforma which included features such as demographic profile, clinical profile, laboratory workup, upper gastrointestinal endoscopy, liver function test, viral markers and risk factors for any vascular occlusion such as obesity, hypertension, diabetes, impaired fasting glycemia, dyslipidemia, JAKV617F mutation, other prothrombotic states, and antiphospholipid antibody (APLA) (Table 1). These patients had a variable follow-up time period at the time of enrollment. It included repeated endoscopies and ultrasounds to look for the development of any portal hypertension complications such as esophageal varices and splenomegaly. Some patients had already been started on treatment if indicated.

Patient's etiological factors, clinical parameters, and outcomes were statistically analyzed using Chi-square test. All the variables were categorized by frequencies and percentages (Table 1). Institute ethical clearance was obtained.

RESULTS

A total of 109 adult patients were included in this study out of which 56 (51.4%) were males and 53 (48.6%) were females. Median age of patients was ±40.25 years with majority of the patients belonging to 25–35 age group. All the patients underwent or had already undergone abdominal USG for the primary diagnosis of EHPVO. The clinical features included dyspepsia in 35 (32.1%) patients followed by abdominal discomfort in 27 (24.8%) patients, while majority of patients, i.e., 39 (35.8%) were picked up incidentally.

Out of 109 patients on whom abdominal USG was conducted, 30 (27.5%) patients were found to have fatty liver, 6 (5.5%) had both splanchnic vein thrombosis (SVT) and fatty liver, 4 (3.7%) had splenomegaly, and 2 (1.8%) presented with combination of SVT, fatty liver, and splenomegaly. Only 1 patient (0.9%) had nephrolithiasis.

Complete blood counts showed hemoglobin (g/dl) of 12.870±2.6377 (mean±SD), total leukocyte count of 6.897±1.8636 (mean±SD), and platelet count (PLT) per mm^3 of 179.21±96.029 (mean±SD).

All the patients underwent upper GI endoscopy or esophagogastroduodenoscopy. 3 (2.8%) patients had prominent lower esophageal veins while esophageal varices of grade 1 and 2 were seen in only 1 (0.9%) patient.

Etiologic workup for those adult non-cirrhotic, non-malignant EHPVO patients was included, thrombophilia panel and screening for myeloproliferative neoplasms (overt or latent) with JAKV617F mutation PCR. 4 (3.7%) patients had positive APLA profile, 8 (7.2%) patients were found positive for heterozygous MTHFR, and 10 (9.2%) patients had JAKV617F mutation positive. Majority of patients, i.e., 97 (89%) had normal thrombophilia profile (Table 1).

Table 1: Clinical and etiological characteristics of the patient with extrahepatic portal vein obstruction

Parameters	Adult EHPVO with APLA (%)	Adult EHPVO with heterozygous MTHFR (%)	Adult EHPVO with latent PRV (%)	Adult EHPVO with PRV (%)	Idiopathic adult EHPVO (%)	Total
Age group						
15–25	0	0	0	0	6 (100%)	6
25–35	3 (9.09)	5 (15.5)	0	0	25 (75.75)	33
35–45	1 (3.22)	1 (3.22)	0	0	29 (93.54)	31
45–55	0	2 (8.6)	1 (4.3)	2 (8.6)	18 (78.2)	23
55–65	0	0	1 (50)	5 (62.5)	7 (8)	13
65–75	0	0	0	1 (33.3)	2 (66.67)	3
Sex						
Female	2 (3.7)	0	0	1 (1.88)	50 (94.33)	53
Male	2 (3.5)	8 (14.2)	2 (3.5)	7 (12.5)	37 (66.07)	56
BMI						
Normal	4 (4.5)	6 (6.97)	2 (2.32)	5 (5.81)	69 (80.23)	86
Obese	0	0	0	1 (16.6)	5 (83.4)	6
Overweight	0	2 (14.2)	0	2 (14.2)	10 (71.6)	14
Underweight	0	0	0	0	3 (100)	3
Hypertension						
Yes	0	4 (12.1)	1 (3)	5 (15.15)	23 (69.69)	33
Diabetes						
Yes	0	0	0	1 (6.3)	15 (93.8)	16
Dyslipidemia						
Yes	0	0	0	2 (6.7)	28 (93.3)	30
Hyperuricemia						
Yes	0	0	0	2 (16.7)	10 (83.3)	12
JAKV617F mutation						
Positive	0	0	2 (20)	8 (80)	0	10
Thrombophilia						
APLA	4 (100)	0	0	0	0	4
Heterozygous MTHFR	0	2 (100)	0	0	0	2
MTHFR heterozygous	0	4 (100)	0	0	0	4

APLA: Antiphospholipid antibodies, HCV: Hepatitis C virus, MTHFR: Methylenetetrahydrofolate reductase, BMI: Body mass index, LFT: Liver function test, PRV: Polycythemia rubra vera

To generate a comprehensive etiological profile, especially in patients with no thrombophilia or negative JAK2 mutation, the patients were screened for metabolic syndrome elements such as obesity (body mass index [BMI]), hyperuricemia, dyslipidemia, hypertension, and diabetes or pre-diabetes. 86 (78.9%) patients had normal BMI, 6 (5.5%) patients were obese, 14 (12.8%) overweight, and 3 (2.8%) underweight. Dyslipidemia was seen in 30 (27.5%) patients, hyperuricemia in 12 (11%) patients, pre-diabetes in 16 (14.7%) patients, and hypertension in 33 (30.3%) patients (Table 1).

On the basis of the etiological profile of patients, the final diagnosis was divided into various etiological groups: Adult EHPVO with APLA – 4 (3.66%) patients; adult EHPVO with heterozygous MTHFR mutation – 8 (7.33%) patients, adult EHPVO with latent polycythemia rubra vera (PRV) – 2 (1.83%) patients, adult EHPVO with PRV – 8 (7.33%) patients, and idiopathic EHPVO – 87 (80%) patients.

All the patients included in the study had a variable follow-up period, maximum up to 5 years. 100% patients had 6-month follow-up, 94.5% patients had 1-year follow-up, 61.5% patients had 2-year follow-up, 25.7% patients had 3-year follow-up, and 4.6% patients had 5-year follow-up. Majority of the patients, i.e., 96 (88.1%) did not require any treatment. 7 (6.4%) patients of PRV and latent PRV were prescribed aspirin alone. 6 (5.5%) patients were treated with low-molecular-weight heparin and warfarin with 3 patients in PRV group and 3 patients in idiopathic group. 8 (7.3%) patients who were diagnosed as EHPVO with PRV were prescribed hydroxyurea for cytoreduction. No mortality was witnessed in this 5-year observational study.

DISCUSSION

Ultrasound Doppler (US Doppler) is considered the initial radiological test to confirm the diagnosis of EHPVO having a sensitivity of 70–90% and a specificity of 99%.[11] All our adult EHPVO patients were picked up on USG abdomen, done for some abdominal symptoms, or as a routine screening. This is in contrast to childhood EHPVO which presents with complications such as variceal bleed and symptomatic massive splenomegaly and USG is done later for evaluation.

Non-cirrhotic and non-malignant EHPVO is one of the common causes of portal hypertension in India.[9] The etiological profile of EHPVO includes various hypercoagulable states, trauma, congenital abnormality of the portal vein, liver cirrhosis, malignancies, catheterization of umbilical cord, and myeloproliferative disorders. However, in adults, the most common predisposing factors linked with venous thrombosis is found to be gene mutations.[6]

Previous studies revealed that majority of the cases of adult EHPVO are idiopathic which is in concurrence with our study where 79.8% (87/109) patients were idiopathic cases.[9] In our study, the thrombophilia conditions that were detected included heterozygous MTHFR gene mutation along with PVR. Overall, JAKV617F mutation was found in only 9.2% (10/109) patients. This is in contrast with the data available in the published literature where JAK mutation was one of the major etiological factors of non-cirrhotic, non-malignant EHPVO.[16-18] However, a previous study conducted in a north Indian tertiary care hospital by Mishra et al., provided the similar result where JAK mutation was seen in only 10% (13/122) adult patients.[9] We found that in idiopathic EHPVO group, the features of metabolic syndrome such as diabetes, obesity, dyslipidemia, and hypertension were common, depicting some endothelial dysfunction as the initiating factor for adult EHPVO.

The clinical presentation of EHPVO seen in majority of the patients is gastrointestinal disturbances including variceal bleeding, splenomegaly, abdominal pain, and jaundice.[16-18] In contrast to the existing studies conducted in both West and India where majority of the patients suffered from features of portal hypertension such as variceal bleeding and splenomegaly, only 0.9% (1/109) patient experienced variceal bleeding in our study.[17] Dyspepsia and abdominal discomfort were the major gastrointestinal symptoms seen in the patients involved in our study. Gastritis, hiatus and hiatal hernia, pan gastritis, partially healed duodenal ulcer, prominent veins, and folds in the fundus were some other rare clinical presentations seen in the patients. These features suggest that adult EHPVO is predominantly a silent disease as compared to childhood EHPVO patients.

During follow-up, majority of the patients did not experience any complication nor was any mortality witnessed. 7.2% (8/109) patients who developed PRV were prescribed hydroxyurea for cytoreduction while 11.9% (13/109) patients were treated with anticoagulants.

Limitations of the study

The current study included a limited number of patients and lacked uniform follow-up protocol in all study subjects.

CONCLUSION

In comparison to the existing available literature on adult EHPVO, the clinico-etiological parameters were found to be different in our study. While majority of the cases in our study were revealed to be idiopathic, few had positive thrombophilia profile, rare number of patients were found to be positive for JAKV617F mutation. Majority of the patients in the idiopathic group had features of metabolic syndrome. No major complication or mortality was seen in this study, signifying the relatively benign nature of adult EHPVO patients in this part of the world.

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ZAW- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation, and submission of article; **ZAW, MMM-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **AAK, MMM-** Design of study, statistical analysis, and interpretation; **ZAW, SNL-** Review manuscript; **AAK, SNL-** Review manuscript; **ZAW, MMM-** Literature survey and preparation of table; **ZAK, AAK-** Coordination and manuscript revision.

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