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A STUDY ON CLINICO-LABORATORY PROFILE IN CHILDREN WITH EXTRA HEPATIC PORTAL VENOUS OBSTRUCTION

Dr Chetna Periwal* — Post Graduate Resident, Department of Pediatrics, SMS Medical College, Jaipur, A-104, Jhulelal Society, Pitampura, New Delhi -110034 *Corresponding Author

Dr Raj Kumar Gupta — Senior Professor, Department of Pediatrics, SMS Medical College, Jaipur, D2, First Floor, Doctors Flats, Gangwal Park, Jaipur -302003

ABSTRACT **Context:** Extrahepatic portal vein obstruction (EHPVO) is a common cause of portal hypertension in children. It is characterized by cavernomatous transformation of the extrahepatic portal vein leading to portal hypertension and its sequelae. This article reviews the demographic, clinical, and laboratory profile of children with EHPVO. **Method:** This prospective analysis of 50 patients of EHPVO was conducted in the department of paediatrics at Sawai Man Singh Medical College & Hospital, Jaipur. The children with clinical profiles suggestive of EHPVO were enlisted and detailed history, clinical examination, anthropometric evaluation, and laboratory profile comprising of complete hemogram, anemia profile, liver function tests, and levels of thrombophilic factors of the cases were recorded. **Result:** A total of 50 participants, 27 (52.9%) males and 23 (47.1%) females with a mean age of 8.09 ± 3.09 years were studied. Hematemesis (92.20%) and splenomegaly (90.20%) were the most common clinical features and growth retardation was observed in 49% of cases. All the cases were anemic with leukopenia and thrombocytopenia seen in 45.1% & and 82.4% of cases respectively. The most common etiology was umbilical sepsis in 25.5% followed by umbilical vein catheterization and NICU admission for sepsis in 19.6% of cases. Amongst the thrombophilic factors studied protein S deficiency (15.69%) was found to be the most common cause followed by protein C deficiency and antithrombin III deficiency (13.73% each). **Conclusion:** EHPVO is a disorder of childhood with a higher incidence in males. Etiology in the majority of patients was umbilical sepsis and umbilical vein catheterization. Patients commonly presented with hematemesis, splenomegaly, and impaired somatic growth. Investigations depict abnormal anemia profile and liver function tests.

KEYWORDS : Extrahepatic Portal Venous Obstruction, Thrombophilia

INTRODUCTION-

Portal hypertension is defined as abnormally increased portal venous pressure in the portal vein and its branches[1] with hepatic venous pressure gradient ≥ 5 mmHg.[2,3] Portal hypertension causes are classified as: prehepatic- originating in the portal venous system before it reaches the liver, intrahepatic- within the liver and post-hepatic- between the liver and the heart.[4]

Extra Hepatic portal vein obstruction (EHPVO) is a vascular disorder of liver defined by obstruction of the extra hepatic portal vein with or without the involvement of the intrahepatic portal vein, splenic vein, or superior mesenteric vein. It is one of the most common causes of portal hypertension in children (70-80%)[5].

Clinical Presentation

ACUTELY patient presents with abdominal pain, low-grade fever and transient ascites (10- 20%) following surgery or bleed. CHRONIC cases present with upper gastro-intestinal bleed (UGI) in 60 – 70%[5,6], splenomegaly, growth retardation (51%), hypersplenism (5-10%), anaemia, biliopathy (90- 100%), hepatic dysfunction and psychomotor changes.[6,7,8] The usual age of presentation is 4-7 years with most of these children belonging to low and lower-middle socio-economic strata.

Etiologically, EHPVO is a heterogenous disease and the causes vary concerning age and geographic location with factors being Congenital anomalies: Portal vein atresia, associated cardiovascular, urinary, limb anomalies, cleft lip & palate, Genetic: MTHFR deficiency, prothrombin gene mutation, factor-V Leiden, protein-C, S, antithrombin-III deficiency,[5] Infections: Omphalitis, liver abscess, pyelephlebitis, pancreatitis, cholangitis, neonatal sepsis, necrotizing enterocolitis Acquired: Diarrhea, Nephrotic syndrome, APLA, Surgery: Billroth-II.[9]

Usually, the entire length of the portal vein is obstructed by the thrombus but the most common site is the portal vein formation [39%], followed by the entire length of portal vein [34%], splenic vein [16%] and the entire spleno-renal axis [11%].[9]

Portal cavernoma is the pathognomonic feature of chronic EHPVO where the portal vein is grossly replaced by a sheath of variably sized tortuous channels in a connective tissue matrix.

METHODS:

This was a hospital-based prospective observational study conducted in the Department of Paediatrics at Sawai Man Singh Medical College & Hospital, Jaipur from May 2021 to May 2022 over 50 subjects. The sample size was calculated at a 95% confidence level expecting 85.9% of children of EHPVO presenting with hemorrhage. Children with clinical profiles suggestive of EHPVO like UGI bleed and abdominal lump were enlisted and a detailed history was taken. Clinical examination and anthropometric evaluation were done and recorded. Complete hemogram and anemia profile, liver function tests and levels of thrombophilic factors like protein C and S, antithrombin III, and factor V were done. The data thus collected was recorded in a preformed proforma and used for further correlation and data analysis.

Inclusion Criteria: children < 18 years of age with USG and Triple-phase CT findings suggestive of EHPVO.

Exclusion Criteria: patients diagnosed with other causes of portal hypertension like NAFLD, hepatitis, budd-chiari syndrome and children with bleeding disorders not involving the liver.

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 22.0 for Windows) and MS - Excel (Microsoft Inc. version 2010). Sample data collected was described in terms of mean, standard deviation, frequencies, and percentages as appropriate. The means of two groups were compared using Student's t-test whereas the means of several groups were compared using one-way ANOVA. Categorical data was compared using the Chi-square test or Fisher exact test and tThe proportions were compared using the Z test. A probability value (p-value) less than 0.05 was considered statistically significant with a 95% confidence interval (two-sided).

RESULT:

Table1: Baseline demography of the patients

			SEX		Total
			Female	Male	
Age	0-5 years	Count	2	11	13
		% of Total	3.9%	21.6%	25.5%
	6-10 years	Count	9	15	24
		% of Total	17.6%	29.4%	47.1%
	11-18 years	Count	13	1	14
		% of Total	25.5%	2.0%	27.5%
Total		Count	24	27	51
		% of Total	47.1%	52.9%	100.0%

	Mean	sd	Median	Minimum	Maximum
AGE	8.09	3.60	8.00	1	14

As shown in table, majority of patients in our study belonged to 6-10 years (47.1%) followed by 27.5% in 11-18 years age group and the least (25.5%) in < 5 years.

Table 2: Etiology of EHPVO and their age and gender wise distribution

	AGE			SEX		Total
	0-5 years	6-10 years	11-18 years	Female	Male	
UMBILICAL SEPSIS	30.8%	33.3%	7.1%	16.7%	33.3%	25.5 %
UMBILICAL VEIN CATHETERIZATION	23.1%	25.0%	7.1%	8.3%	29.6%	19.6 %
NICU ADMISSION FOR SEPSIS	30.8%	20.8%	7.1%	8.3%	29.6%	19.6 %
INTRA ABDOMINAL INFECTION	23.1%	12.5%	0.0%	12.5%	11.1%	11.8 %
RECURRENT DIARRHOEA/VOMITING CAUSING DEHYDRATION	23.1%	12.5%	0.0%	4.2%	18.5%	11.8 %

Based on history, umbilical sepsis was found to be the most common factor responsible for EHPVO in 25.5% patients followed by umbilical vein catheterization in 19.6% and history of NICU admissions in 19.6%. History of repeated admission for recurrent diarrhea or vomiting leading to dehydration was observed in 11.6% of patients.

Table 3: Clinical profile of patients with EHPVO:

	Age			SEX		Total
	0-5 years	6-10 years	11-18 years	Female	Male	
PALLOR	76.9%	87.5%	92.9%	95.8%	77.8%	86.3%
HEMATEMESIS	84.60%	91.70%	100%	88.90%	95.80%	94%
MELENA	61.50%	75%	78.60%	77.80%	66.70%	74%
PAIN ABDOMEN	23.1%	37.5%	42.9%	45.8%	25.9%	35.3%
ABDOMINAL LUMP	84.6%	70.8%	64.3%	75.0%	70.4%	72.5%
RECURRENT INFECTIONS	30.8%	41.7%	50.0%	37.5%	44.4%	41.2%
GROWTH RETARDATION	53.8%	45.8%	50.0%	58.3%	40.7%	49.0%
PETECHIAE	38.5%	33.3%	64.3%	54.2%	33.3%	43.1%

As shown in table 3, hematemesis (94%) was the most common symptom reported by the patients, followed by pallor (86.3%), melena (74%), and abdominal lump (72.5%). Recurrent infections and petechiae were among the least reported symptoms. Amongst all the patients, females had more complaints of bleeding episodes, pallor, petechiae, short stature, and pain abdomen than males while history of recurrent infections and complaints of abdominal lump were more common amongst males. The adolescents (11-18 years) were the most symptomatic among all the three age groups. None of the presenting complaints in the patients were found to be statistically significant for age or sex.

Table 4: Signs observed in patients with EHPVO

Presentation								
Symptom	Age				SEX			Total
	0-5 years	6-10 years	11-18 years	Chi-Square/ Fisher's test	Female	Male	Chi-Square/ Fisher's test	
				P value			P value	
SPLEENOMEGALY	92.3%	87.5 %	92.9%	.022*	91.7%	88.9%	.896	90.2%
ASCITIS	23.1%	29.2 %	57.1%	.078	37.5%	33.3%	.771	35.3%
HEPATOMEGALY	23.1%	33.3 %	28.6%	.805	16.7%	40.7%	.073	29.4%

*significant at p-value <0.05

On clinical examination, splenomegaly was found in 90.20% of patients and was found to be statistically significant for different age groups (P value = 0.022). Ascites and hepatomegaly were seen in 35.3% and 29.4% cases respectively.

Table 5: Anemia profile in EHPVO patients

			AGE			SEX		Total
			0-5 years	6-10 years	11-18 years	Female	Male	
Anemia	Mild	N	3	3	1	1	6	7
		%	23.1 %	12.5%	7.1%	4.2%	22.2%	13.7%
	Moderate	N	4	7	4	9	6	15
		%	30.8 %	29.2%	28.6%	37.5%	22.2%	29.4%
	Severe	N	6	14	9	14	15	29
		%	46.2 %	58.3%	64.3%	58.3%	55.6%	56.9%
Leucopenia		N	1	11	11	15	8	23
		%	7.7%	45.8%	78.6%	62.5%	29.6%	45.1%
Thrombocytopenia		N	7	21	14	22	20	42
		%	53.8 %	87.5%	100.0 %	91.7%	74.1%	82.4%
B12 Deficiency		N	1	4	6	6	5	11
		%	7.7%	16.7%	42.9%	25.0%	18.5%	21.6%
Folate Deficiency		N	1	4	3	4	4	8
		%	7.7%	16.7%	21.4%	16.7%	14.8%	15.7%

According to our study anemia was found in 100% patients of which severe anemia (<7gm/dl) was found in 56.9% patients, moderate anemia (7-10gm/dl) in 29.4% and mild anemia (10-12gm/dl) in 13.7% patients. Leukopenia (<4000/mm3) was seen in 45.1% patients, thrombocytopenia (<1.5 ×103 /mm3) in 82.4% patients and B12 and folate deficiency in 21.6% and 15.7% respectively.

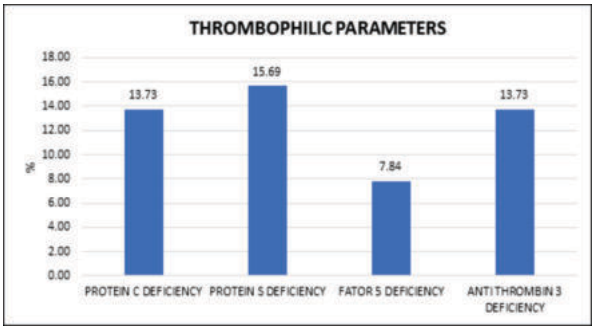

Figure 1: Thrombophilic Parameters

On investigating the patients for thrombophilic parameters protein S deficiency was found to be the most (15.69%), followed by protein C deficiency in 13.73% patients, and factor 5 deficiency in only 7.84% of patients.

DISCUSSION

Table 1 depicts the recruitment of 50 patients in the study of which 27 (52.94%) were males and 23 (47.06%) were females. A maximum of 15 (29.4%) males out of 27 belonged to 6–10 years age group and 13 (25.5%) females belonged to 11-18 years age group. The mean age of our study group was 8.09 ± 3.6 years with the youngest case of 9 months and the oldest being 14 years. In their study **Alina grama et al (2021)**[10] evaluated 63 EHPVO children in Romania of which 33 (52.38%) were reported to be males and the mean age was 5.14 ± 4.9 years. **Singh Swati et al (2021)**[11] in Wadia hospital, Mumbai studied 81 patients, 51 (62.29%) of which were males.

Our study identified history of umbilical sepsis in 13 (25.5%) patients as the most common risk factor, followed by a history of umbilical vein catheterization in 10 (19.6%) and NICU admission for sepsis in 10 (19.6%) patients. This was similar to the study by **Jena SK et al**

(2017)[12] where neonatal umbilical sepsis was identified as the commonest risk factor in 10 (16.1%) patients and umbilical vein catheterization contributed to 9.6% of the cases. In contrast to our study **Grama A. et al (2021)**[10] reported umbilical vein catheterization to be responsible for 72.02% cases followed by bacterial infections in (47.62%) and dehydration in 19.08% cases.

Among the clinical features of EHPVO hematemesis (94%) was the commonest presentation followed by pallor (86.3%) and abdominal lump (72.5%) and pain abdomen (35.3%). Amongst upper GI bleeds maximum number of cases 39 (76.5%) presented with ≥3 episodes. This was similar to the study by **Grama A. et al (2021)**[10] who also reported 35% of cases with ≥3 episodes of UGI bleeding. **Chawla Y. et al (2014)**[13] found abdominal pain in 91%cases, growth retardation in 50% and ascites in 38% patients which was similar to our study.

With reference to Table 4, splenomegaly was found in 46 (90.2%) cases of which massive splenomegaly was seen in 12 (21%) cases. This was similar to the study by **Goyal S. et al (2014)**[14] who reported splenomegaly in 49 out of 53 patients (92.5%), upper GI bleeding in 46 (86.8%) children and growth retardation in 30 (56.6%) EHPVO patients. **Weiss B et al (2010)**[1] depicted splenomegaly only in 13 (43.3%) patients.

Mean Hb levels in our study was 6.78 ± 2.46 gm/dL with severe anaemia found in all the age groups. Females were reported to be more severely anaemic 6.12 ± 2.41 gm/dl as compared to males. Anaemia could be possibly due to frequent variceal bleeds before presentation and poor nutritional status. Mean total leukocyte count (TLC) was 5,164.7 ± 3,060.83/mm3 and leukopenia was found in 45.1% patients (p value=0.002) with maximum number of patients in 11-18 years age group. Leukopenia and lymphopenia were found to be statistically significant for age. This finding may be due to progressive hyper splenic state. This was similar to the results reported by **Jean SK et al (2017)**[12] in their study where anaemia was found in 90.3% and leukopenia in 40.3% patients with EHPVO. **Singh I.K. et al (2011)**[15] reported mean haemoglobin of 9.48 ± 1.45 gm/dl and the mean haemoglobin ranged from 6.6 to 11.8 gm/dl and mean TLC count reported was 3,608.33 ± 1,528.83/mm3. Thrombocytopenia was found in 82.4% cases in our study with mean platelet count as 99,176.5 ± 58,212.27/mm3 (p value= 0.005) which is similar to that evaluated in the study by **Singh I.K. et al (2011)**[15] where mean platelet count was found to be 87,083.33 ± 44,626.87/mm3 in EHPVO patients. While In contrast **Jean S.K et al (2017)**[12] had reported thrombocytopenia only in 40.3% cases. Vitamin B12 and folate deficiency was found in 21.6% (p value=0.140) and 15.7% (p value= 0.035) cases respectively with maximum number of cases found in < 5 years age group. The deficiencies were predominantly seen in males as 18.5% and 14.8% respectively of Vitamin B12 and folate. With increasing age the folate deficiency was found to increase in the patients and was found to be statistically significant for age (p value= 0.035) in our study.

Amongst the thrombophilic factors studied protein S deficiency (15.69%) was found to be the most common cause followed by protein C deficiency and antithrombin III deficiency which were seen in 13.73% each, factor 5 deficiency was reported only in 7.84% of the cases in our study. **Jean S.K et al (2017)**[12] in their study found protein C deficiency in 19.1% patients followed by protein S deficiency in 17% cases and anti thrombin III deficiency in 12.7% cases.

Limitation

Our study was a single-center study with a small sample size. The patients presented with severe symptoms which could be due to referral bias as our center was a tertiary care referral center. Our study does not include follow-up and outcomes of patients, so long-term follow-up studies would be more fruitful in assessing the profile and risk factors of EHPVO in children. Genetic mutations could not be studied due to financial constraints.

CONCLUSION

EHPVO is a common cause of portal hypertension in children. Umbilical sepsis, umbilical vein catheterization, history of NICU admissions, dehydration due to recurrent diarrhea and vomiting, and abnormal thrombophilic parameters (Protein S deficiency (15.69%) followed by Protein C deficiency and antithrombin III deficiency (13.73%) each) are common etiological factors. Patients most commonly presented with hematemesis (94%) followed by pallor (86.3%) and melena (74%), growth retardation (49%) and abdominal pain (35.3%). Anemia was observed in all the patients of which 45% children had pancytopenia.

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