International Journal of Biomedical and Advance Research
ISSN: 2229-3809 (Online); 2455-0558 (Print)
Journal DOI: https://doi.org/10.7439/ijbar
CODEN: IJBABN

Original Research Article

Clinicopathological Correlation of Portal Hypertension in Children and Management Strategies

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***Article History:**
Received: 20/02/2018
Revised: 28/02/2018
Accepted: 28/02/2018
DOI: https://doi.org/10.7439/ijbar.v9i2.4667

Abstract

We studied 51 children with clinical setting of portal hypertension over a period of one and half years. Out of these, 27 (52.94%) were males and 24 (47.05%) were females. All the cases were subjected to biochemical, diagnostic, radiological investigations and liver biopsy. Portal hypertension was diagnosed by demonstrating on USG abdomen/ Doppler, the presence of collaterals of portal vein and esophageal varices on endoscopy. Treatment was initiated depending upon clinical presentation. The most common presenting complaints were hematemesis and malena (35.3%) followed by their combination with abdominal distension (19.6%). 86.3% patients had anemia mostly due to upper GI bleed. 35.3% patients had leucopenia while 47.1% had thrombocytopenia. Only 18 (i.e. 35.3%) had Hypersplenism. Maximum patients who bled more than twice had a mild (41.2%) or severe (29.4%) derangement of prothrombin time. The etiology of portal hypertension turned out to be extra- hepatic portal vein obstruction in 86.3% cases. There were 2 cases each (3.9% each) of Wilson's disease and Budd-Chiari syndrome. One (2%) was secondary to chronic liver disease due to hepatitis C infection, one was extra- hepatic biliary atresia and one was autoimmune hepatitis. 9.8% cases required drugs in the form of somatostatin drip and all these required a packed cell transfusion as well. 23 patients (45.1%) required only blood transfusion without a somatostatin infusion. Those with severe acute bleeding usually were given somatostatin infusion. The variceal size at presentation was a very important predictor of the morbidity and outcome.

Keywords: Portal hypertension, USG abdomen/ Doppler, Endoscopy, Thrombocytopenia, Hypersplenism, Extra- hepatic portal vein obstruction, Wilson's disease.

1. Introduction

A portal system is one which is by definition begins and ends with capillaries. The major portal system in humans is the one in which the capillaries originate in the mesentery of the intestines and the spleen and end in the hepatic sinusoids [1]. Normal portal venous pressure is about 7 mm of Hg. Portal hypertension (PHT) is defined as portal pressure above 10-12 mm of Hg [2,3]. It is generally a result of a combination of increased portal blood flow or increased portal resistance [1]. The latter may be due to prehepatic, intrahepatic or posthepatic obstruction to the flow of portal blood. Thus, chronic liver disease is a major cause of portal hypertension.

In Indian children, extrahepatic portal vein obstruction (EHPVO) is the cause of Portal hypertension in 68-76% cases. The other common causes are cirrhosis (24-28%), non-cirrhotic portal fibrosis (4%) and Budd- Chiari syndrome (3%) [2]. Portal hypertension leads to portosystemic communicating venous channels at various sites giving rise to oesophageal, gastric and colonic varices. Upper GI varices are important as upper GI bleed contributes majorly to the morbidity and mortality of Portal hypertension [2]. Children with EHPVO commonly present with variceal bleeding and splenomegaly whereas patients with cirrhosis present with splenomegaly, ascites, engorged

abdominal veins and signs of chronic liver disease [2]. In Indian children variceal bleeding has been found to be the most important cause of upper GI bleed as against peptic ulcer disease in Western studies.

Hence the present study was carried out with objectives to identify the various etiologies of portal hypertension in children, to analyze the clinical, pathological and biochemical profile of the cases, to assess the various management strategies of portal hypertension in a tertiary care set-up and to study the prognosis and outcome of portal hypertension.

2. Material and Methods

This prospective study was carried out in a tertiary care centre mainly in the department of Pediatrics and department of Gastroenterology over a period of one and half year. The study included patients with bleeding from oesophageal varices, with or without jaundice or presenting with ascites or abdominal lump or features of chronic liver disease and those having age between 1 month – 12 years. Total 51 children presenting with the clinical setting of portal hypertension (PHT) formed the study group. Before enrolling the patients, parents' written informed consent was taken after explaining the purpose of the study. The exclusion criteria included patients who were lost to follow-up during diagnostic work-up, Non-availability of consent, other documented causes of GI bleed or splenomegaly or ascites and children < 1 month or > 12 yrs of age.

A detailed history of all the cases was taken and child was examined for vital parameters and anthropometry. Then all the patients were subjected to biochemical and hematological, diagnostic, radiological investigations and liver biopsy. Only in few selected cases percutaneous biopsy was done with spring loaded trucut liver biopsy gun. It is useful in patients with suspected chronic liver disease. Portal hypertension was diagnosed by demonstrating on USG abdomen/ Doppler, the presence of collaterals of portal vein and esophageal varices on endoscopy. EHPVO was proved by showing on USG abdomen portal vein thrombosis with multiple collaterals at porta hepatis suggestive of cavernoma or splenic vein thrombosis (with) normal liver size and echotexture. Chronic liver disease was diagnosed if – deranged LFT's > 3 months, hepatomegaly/ shrunken liver size, Jaundice, ascites with distended veins, Signs of liver cell failure e.g. spider nevi, palmar erythema, gynecomastia, testicular atrophy, parotid gland enlargement, paper money skin, jaundice, ascites, flapping tremors, etc, Encephalopathy. Cirrhosis was diagnosed mainly on the basis of liver biopsy or clinically palpable liver nodules with deranged productive function (e.g. low serum albumin and prolonged PT) supported by USG findings.

The gastroenterologists were consulted for most of the patients as they all required endoscopy for management. The pediatric surgeons' opinion was sought in cases of suspected biliary atresia. The pathologists examined the liver biopsy slides for liver histopathology. The ophthalmologists conducted a fundus examination and a slit lamp examination to look for K-F rings. Treatment was initiated depending upon clinical presentation. Follow up of patients included clinical and biochemical monitoring as well as upper GI endoscopies.

2.1 Statistical Analysis

All the presenting clinical symptoms, examination abnormalities and laboratory findings were compared for all the cases. The statistical significance was evaluated by student's t test, unpaired t test, Chi square test and correlation tests.

3. Results and Discussion

We studied 51 children with the clinical setting of portal hypertension. Out of these, 27 (52.94%) were males and 24 (47.05%) were females, (p value > 0.05) which was similar to other studies of Sharma *et al* [4] and Fonkalsrud *et al* [5]. Thus there was male preponderance in our study; the reason may be that male children are generally brought to hospitals earlier for treatment than female children. Also the sex ratio in the general population is always favorable to boys and this was depicted in our study group as well. Total 88.88% males were from the age group of 3-12 years and 79.16% females were from the same age group. Thus, portal hypertension rarely manifests before the age of three years. The age at presentation was slightly earlier for girls than for boys as 45.83% girls presented with the first symptom of portal hypertension within 3-6 years of life while it was 6-12 years for 55.6% boys (Figure 1). The mean age at presentation of portal hypertension in our study group was 80±36 months for males and 66±34 months for females, this was compared with other studies by Sharma *et al* [4] and Prasad *et al* [6].

Figure 1: Age Wise Distribution of Portal Hypertension (n=51)

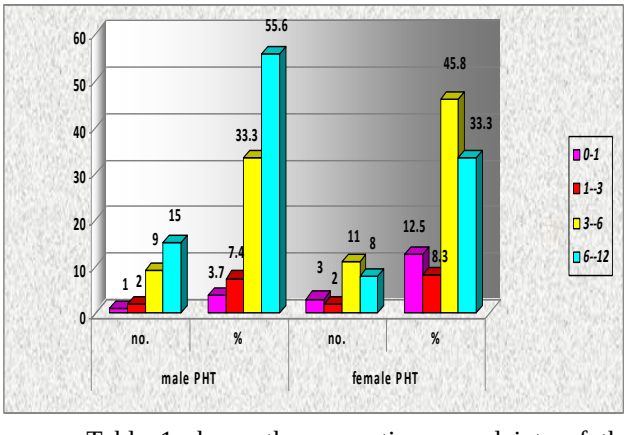

Table 1 shows the presenting complaints of the children and was comparable to previous studies [5, 7-9]. Upper gastrointestinal bleeds thus form a major chunk of the presenting complaints. In fact, portal hypertension

forms the most common cause of upper GI bleed in children. Malena never usually presents alone, it is almost always associated with hematemesis as seen in our study. Generally the cause of portal hypertension is extrahepatic portal venous obstruction, hence the liver parameters are usually not deranged and patients don't present with signs of hepatic involvement. Splenomegaly also is very common and many times an asymptomatic splenomegaly or an abdominal lump may lead to the diagnosis of portal hypertension if USG is done on the basis of high degree of suspicion. Whenever there is associated liver disease, the course of portal hypertension per se becomes more complicated due to signs of liver failure like jaundice, ascites, encephalopathy, etc. along with the usual GI bleed. At times, the patient may present like a liver disease only without evidence of portal hypertension. Hence, such patients should undergo diagnostic endoscopies to look for varices.

Table 1: Presenting complaints (n= 51)

Complaints	Cases		Mortality	
	No.	%	No.	%
Abdominal Lump	6	11.8	0	0
Malena (only)	1	2	0	0
Hematemesis and malena	18	35.3	0	0
Hematemesis , malena , CCF	6	11.8	0	0
Abdominal distension	2	3.9	0	0
Jaundice and distension	2	3.9	1	50
Jaundice, malena/hematemesis and Abdominal distension	4	7.8	1	25
Malena/hematemesis and distension	10	19.6	1	10
Incidental diagnosis	2	3.9	0	0

Only 39.21% patients had some form of signs of liver cell failure and remaining (60.79%) had no hepatic involvement. All three deaths were from group that had signs of liver cell failure. Thus, there was a significant statistical association between presence of liver cell failure and poor prognosis and mortality (p value < 0.001). From the Lorance *et al* [10] study, we can easily see that all clinical and metabolic complications were more in liver disease rather than EHPVO. There was 5.9% mortality found by Mowat *et al* in EHPVO group [11]. In our study, there was no mortality in EHPVO group; this difference depends on the time lag between onset of symptoms and admission to a tertiary care set up for further management of varices.

Though there were 43.13% home deliveries with an equal percentage of institutional deliveries, the statistical association between home deliveries and the incidence of portal hypertension was found to be strong by Pearson's Chi square test (p < 0.001). There has been no other study that explored this variable and hence, we would like to postulate that home deliveries may be associated with portal hypertension as a causative factor because when home deliveries were conducted by untrained *Dais*, as was usually the case in our country, the umbilical cord was either cut by an unsterile blade or tied with an unsterile thread. This gives rise to the possibility of further infection and periumbilical sepsis. Thus, the septic processes associated with a home delivery may herald umbilical and portal vein thrombosis leading to portal hypertension later in life. A history of umbilical vein catheterization was elicited only in 3 patients, one during NICU stay due to being born through thick meconium stained amniotic fluid and two were catheterised for the purpose of exchange transfusion, one for neonatal jaundice and the other one for Rh isoimmunisation set-up. Only one patient had documented umbilical sepsis with the pus culture having grown coagulase negative *S. aureus*. 3 patients (i.e. 5.88%) had been low birth weight deliveries. Thus we should restrict the use of intravascular catheters in a neonate only when absolutely indicated. If catheters have to be placed, then they should be of the smallest possible caliber and should be made from very flexible material in order to avoid fibrogenesis. Their introduction must be done with full aseptic precautions and the placement must ideally be fluoroscopy guided. Infusion fluids that irritate the vascular walls have to be avoided as much as possible. It should always be borne in mind that, by introduction of an intravascular catheter, we place a time bomb inside the child [12].

Organomegaly was found in 100% of our patients, but maximum patients presented either with splenomegaly alone (19 cases, 37.25%) or splenohepatomegaly (20 cases, 39.21%). This underlines the fact that splenomegaly was the predominant presenting feature of portal hypertension, (p < 0.001). Only 3 patients had hepatomegaly alone.

Table 2 shows the hematological abnormalities of children. Anemia, as defined by age specific criteria, was present in 44 cases (i.e. 86.27%). Thus, anemia was found to be very significantly (p value < 0.001) common in our study group. In the setting of portal hypertension, this may either be due to acute bleeding manifestations or due to hypersplenism. Majority of our patients thus had clinical pallor. Maximum patients (i.e.22 patients, 43.1%) had normal WBC count. That means these children had no documented leucopenia or leucocytosis. Another 18 patients (35.29%) had leucopenia, while the rest i.e. 11 patients (21.55%) had leucocytosis. Majority of the patients had normal platelet counts i.e. 27 out of 51 cases (52.94%) had no evidence of thrombocytopenia. Anemia was present in a statistically significant majority (p value < 0.001) while thrombocytopenia was not (p value > 0.05). Our results were correlated with other studies [13,14].

Table 2: Hematological Abnormalities (N=51)

	Anemia		WBC Count			Platelet Count	
	Present	Absent	N	Decreased	Increased	N	Decreased
No.	44	7	22	18	11	27	24
%	86.3	13.7	43.1	35.3	21.6	52.9	47.1
p value	<.001		<0.05			>0.05	

18 (35.29%) cases in our study group had evidence of Hypersplenism with Splenomegaly and more than one cell line being depressed. Of these, 13 patients (72.22%) manifested with Hypersplenism between 6-12 years of age. This gives us a clue that Hypersplenism develops gradually as the spleen size increases and with age, becomes more clinically evident in older children. In the study by Bhandarkar *et al* [8], Hypersplenism was found in 16.7% cases which were matching the results of our study. 15 patients (29.41%) showed involvement of other systems as well but 70.6% patients did not show any associated systemic features (Table 3).

Table 3: Incidence of other systemic features (n=51)

Other systemic features	Cases	
	No.	%
Convulsion	3	20
Murmur	3	20
Pneumonia	2	13.3
Hydrocele / Hernia	2	13.3
Congenital Lymphedema	1	6.7
PUJ obstruction	1	6.7
Cardiomyopathy	1	6.7
Delayed milestones	2	13.3
Total	15	29.41

Maximum patients in our study group who bled more than twice had a mild (41.2%) or severe (29.4%) derangement of prothrombin time. There were statistically significant more patients in the given groups but no statistical significance seems to be attached to association of prothrombin time values and recurrence of variceal bleeding. In case of a normal prothrombin time or moderate derangements, one patient (8.33%) each developed recurrent bleeds. Certain special tests done where indicated to pinpoint the diagnoses were shown in table 4.

Three cases were proven to be Wilson's disease by documenting low serum ceruloplasmin levels. 2 had Anti-Nuclear Antibodies positive, suggestive of autoimmune etiology. One patient had a low protein C, protein S level while one had anti-cardiolipin antibodies positive. One had positive CMV titers. All these findings suggest that the etiology of portal hypertension is usually cryptogenic in majority of the cases.

Table 4: Specific Tests (N=32)

Test	Test done	Test positive	
	no.	no.	%
ANA/dsDNA	7	2	28.6
Sr Ceruloplasmin	12	3	25
Sickling Test	3	0	0
Protein C/S/Antithrombin III	3	1	33.3
ACLA	1	1	100
HbEPP	5	1	20
CMV titers	1	1	100

On ultrasonography, 4 patients (i.e. 7.84%) had Periportal fibrosis while in 6 patients (11.76%) portal vein was not visualized at all. In a significant 21 patients (41.17%) there was cavernoma formation due to collaterals, and this was a statistically more significant data ($p< 0.01$) and ascites was present in 10 (19.6%) patients of total. This reflects the fact that extra hepatic portal venous obstruction remains the single most important cause of portal hypertension. Liver echo texture was normal in 30 patients (58.82%), ($p< 0.001$). The liver echo texture was coarse in remaining 21 patients (41.17%). Although on USG Doppler, 45 patients (i.e. 92.15%) had hepatopetal flow of these, 10 patients had more than 2 bleeds (22.22%) and 3 patients expired. Of the 6 patients who had a hepatofugal direction of blood flow, 2 patients bled more than twice (33.33%) and none of these patients succumbed to the disease, (p value < 0.001). But this was contrary to the established fact that reversal of flow indicates more severe disease and poor prognosis. Thus, though other studies [13,15] have proved that reversal of portal blood flow is seen in only severe cases of portal hypertension, our study incidentally had all three deaths from the group in which there was hepatopetal flow. This may be an incidental finding.

With respect to therapeutic interventions, 5 patients required both somatostatin drip and packed cell transfusion one or more times. Only one patient underwent surgery in the form of splenectomy for hypersplenism. 23 patients (45.09%) required packed cell transfusions one or more times. This was statistically significant (p value < 0.001). Most of the patients who have had a severe acute bleeding episode, required somatostatin as well as packed cell transfusion.

Thus, we can conclude that in severe bleeding we have to follow a more aggressive treatment protocol for recovering the acute blood loss and preventing further bleeds. The incidence of bleed more than twice was equally divided (33.33%) in the groups having large, moderate and moderate with small varices on the first Endoscopic procedure. But, the group with only small or no varices on first scopy never bled more than once. If there was no varix or just a small varix at presentation, none of the patients had recurrent bleeds. Thus the variceal size at presentation is a very important predictor of the morbidity and outcome.

All 51 cases underwent either a diagnostic endoscopy or a therapeutic one. The scopies of 6 patients (11.76%) turned out to be normal. 3 patients out of the total 8 patients who underwent sclerotherapy more than 4 times, developed portal hypertensive gastropathy. All 8 patients (100%) developed a bleed more than 2 times. Our study group showed the requirement of more number of sessions of sclerotherapy required probably due to the irregular follow-up of these patients for repeat scopies, thus allowing the varices to develop again and again before complete eradication. Band ligation was done in 13 patients (25.49%) and was never needed more than thrice in any case of our study group indicating its better efficacy over endosclerotherapy. Also only 15.38% of these patients bled more than twice. None of them ever developed portal hypertensive gastropathy during our study period. This underlines the fact that band ligation is a better method of managing oesophageal varices in portal hypertension due to its higher efficacy and favorable side effect profile.

Liver biopsies help in making a diagnosis in cases on chronic liver disease only. It is generally not indicated when the clinical scenario is one of extrahepatic portal venous obstruction. But still if the liver function tests are deranged, a biopsy can be done to rule out hepatic involvement. Of the total 7 liver biopsies that were done in our study, where indicated and when possible, 2 (28.6%) were suggestive of Wilson's disease. Of the rest, 1 each was suggestive of cirrhosis, non-cirrhotic portal fibrosis, neonatal hepatitis, infantile cholangiopathy and one biopsy was normal.

The major cause of portal hypertension in our study group was found out to be extra hepatic portal venous obstruction (86.27%) and this result was correlated with previous studies [16-19]. Other etiologies of portal hypertension were shown in table 5.

Table 5: Etiologies of Portal Hypertension (N=51)

Etiology	Cases	
	No	%
EHPVO	44	86.3
Chronic liver diseases due to Hepatitis C	1	2
Extrahepatic biliary atresia	1	2
Wilson's disease	2	3.9
Autoimmune hepatitis	1	2
Budd-Chiari syndrome	2	3.9

The mortality was highest in infancy; 2 out of 4 having succumbed to complications related to chronic liver disease or portal hypertension. Of the 3 deaths, one patient was a case of neonatal hepatitis, one was an operated case of biliary atresia and one was a thalassemia major with iron overload and cardiomyopathy. There was only one death in the age group from 6-12 years of age i.e. 4.34% of all patients presenting with in this group. Thus, this indicates that an earlier presentation in life means a grave prognosis and that older children may sustain the clinical complications better; we found that there was significant statistical association in the mortality data (p value < 0.01).

4. Conclusion

The present case study reveals extrahepatic portal venous obstruction as the major etiology of portal hypertension in children. All other etiologies form a statistically insignificant minority. The study was able to meet its objectives of defining the etiology of portal hypertension in childhood, analyzing the clinical, biochemical and pathological profile of the cases, assessing the management protocols and studying the general prognosis and outcome with respect to the therapeutic interventions and the etiological diagnoses.

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