

## Etiology of Portal Hypertension in Children: A Single Center's Experiences

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### ABSTRACT

#### BACKGROUND

All conditions that interfere with blood flow at any level within the portal system can lead to portal hypertension. For better management of this disorder, it is important to determine the underlying cause. In previous studies, extra-hepatic disorders have been reported as the main cause of portal hypertension in children. In this study, we investigate the underlying causes of portal hypertension in children.

#### METHODS

This prospective, descriptive study investigated the etiology of 45 children with portal hypertension who referred to Nemazee Hospital Pediatric Gastroenterology Ward from 2005 to 2007. The underlying causes of portal hypertension were determined by liver biopsy, abdominal sonography, abdominal computed tomography scan, and liver Doppler sonography.

#### RESULTS

In this study, 42 of 45 patients (93.3%) developed portal hypertension due to intrahepatic diseases. Extra-hepatic portal hypertension was detected in 3 (6.7%) patients with portal vein thrombosis.

#### CONCLUSION

Intrahepatic diseases were the most common etiology of portal hypertension among children who referred to our center.

#### KEYWORDS

Portal hypertension; Children; Etiology; Extra-hepatic; Intrahepatic

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### INTRODUCTION

Portal hypertension is hemodynamically defined as the pathological increase of the portal pressure gradient or the pressure difference between the portal vein and inferior vena cava. Clinically significant portal hypertension is diagnosed when clinical manifestations of the disease appear or the portal pressure gradient exceeds 10 mmHg.<sup>1</sup> It has been estimated that esophageal varices are present in 30%-40% of the compensated cases and 60% of the decompensated patients at the time of diagnosis.<sup>2,3</sup> In cirrhotic patients with no varices noted on endoscopy, the annual incidence of new varices is reported as 5%-

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10% according to published studies.<sup>4,5</sup> A careful investigation of the cause of the portal hypertension is essential for choosing the best treatment. For patients with extra-hepatic portal vein thrombosis, supportive treatments should be performed prior to surgical treatment with a Meso-Rex bypass.

Patients with well-compensated cirrhosis should be offered selective surgical shunting, and those with advanced disease should have liver transplantation. In this study the causes of portal hypertension have been investigated in children who referred to Nemazee Hospital with esophageal varices.

## MATERIALS AND METHODS

### Patients

In this prospective, descriptive study, 45 children younger than 18 years of age who were diagnosed with portal hypertension and referred to Nemazee Hospital Pediatric Gastroenterology Ward affiliated with Shiraz University of Medical Sciences from March 2005 to March 2007 were investigated. Portal hypertension in the patients was clinically defined based on the presence of splenomegaly and esophageal and/or gastric varices.

### Liver biopsy

All biopsies were performed using 18- to 20-gauge needles (Chiba). Two passes were performed in order to reduce the sampling error. The aspirated tissue was immediately placed in a preservative solution of 10% formalin buffer and sent for histopathology examination.

### Abdominal sonography

Duplex-Doppler ultrasonography (DDUS) was performed by means of a combined ultrasonic system that consisted of a 3.5-MHz mechanical sector scanner (ALOKA SSD-650) and a pulsed Doppler device that had an insonating frequency of 3.5 MHz, a pulse-repetition frequency of 2.1 KHz, and a filter of 100 Hz (ALOKAUGR-650). All DDUS data were collected by the same examiner who followed a strictly standardized method

in order to minimize systematic and random errors.<sup>6</sup>

### Abdominal CT scan

All patients underwent CT portography (CTP) on a sub-second helical CT scanner (Somatom Plus 4, Siemens, Erlangen, Germany) according to the method used by Gulati et al.<sup>7</sup> Briefly, prior to the beginning of the study, one liter of water was given as a negative oral contrast agent in the bowel loops, for stomach distension. Then, the patient was positioned on a couch with arms fully abducted. A dose of 3 ml/kg body weight of iodinated contrast medium [Urografin (76%), diatrizoatemeglumine (597.3 mg/ml), and diatrizoate sodium (100 mg/ml), Schering AG, Berlin) was administered intravenously at a rate of 3 ml/s using a power injector (Medrad, Medrad Inc., Pennsylvania, USA). Helical scanning began 60 s after the beginning of the injection, in a cranial to caudal direction. The considered volume coverage was from just above the dome of the diaphragm to the iliac crest. On occasion the lower limit was relaxed depending on the inability of a given patient to hold their breath for the scan volume. Usually the scan acquisition time did not exceed 40–45 s. In addition, scanning characteristics were 2 mm collimation, 3 mm/s table speed at 240 mAs, and 120 kVp.

### Liver Doppler sonography

A Toshiba Sonolayer SSA-270 (Toshiba, Tokyo, Japan) with color Doppler and a 3.75 MHz sector electronic probe was used. The portal vein was scanned longitudinally and the sample volume was positioned in the middle of the portal trunk with an angle of 55.75 degrees or less and a width of approximately half the volume, as near as possible to the crossing of the hepatic artery. The underlying cause of portal hypertension was determined by abdominal sonography, abdominal CT scan, liver Doppler sonography, and liver biopsy.

### Statistical analysis

Analysis of agreement was performed by calculating the bias, estimated by the mean difference between the two measurements and the standard

deviation of the differences.<sup>8</sup> The differences among the study groups were evaluated by the student's t- test.

## RESULTS

A total of 45 patients participated in this prospective, descriptive study. Subjects' mean age was  $7.6 \pm 4.7$  years. There were 23 (51.1%) males and 22 (48.8%) females. The mean age at onset of the first variceal bleeding was at  $4.3 \pm 4.5$  years of age.

The results of the liver biopsies and Doppler sonography studies revealed that 42 of 45 patients (93.3%) developed portal hypertension due to intrahepatic diseases and 3 (6.7%) developed prehepatic portal hypertension as a result of portal vein thrombosis.

The main causes of intrahepatic portal hypertension in our patients were as follows: cryptogenic cirrhosis in 12 (26.6%), biliary atresia in 11 (24.4%), and Wilson's disease in 8 (17.7%). Other intrahepatic causes were congenital hepatic fibrosis in 3 (6.6%), autoimmune hepatitis in 3 (6.6%), hepatocellular carcinoma in 2 (4.4%), familial cholestasis in 1 (2.2%), glycogen storage disease in 1 (2.2%), and idiopathic neonatal hepatitis in 1 (2.2%) patient (Table 1).

**Table 1:** Frequency of underlying causes of portal hypertension and mean age for first variceal bleeding in children with portal hypertension.

Underlying causes of portal hypertension	Frequency (%)	Mean age for first variceal bleeding (year)
Cryptogenic cirrhosis	12 (26.7%)	10.1
Biliary atresia	11 (24.4%)	3.3
Wilson's disease	8 (17.8%)	7.5
Congenital hepatic fibrosis	3 (6.7%)	3
Portal vein thrombosis	2 (4.4%)	10.3

## DISCUSSION

Portal hypertension occurs by the formation of portal-systemic collaterals which shunt a portion of the portal blood flow to the systemic circulation, bypassing the liver. Portal hypertension can arise from disorders with blood flow at any level within the portal system.<sup>9</sup>

Chronic portal vein thrombosis is characterized by the formation of collateral vessels that bridge the obstruction and cause the appearance of the so-called portal cavernoma. Patients with chronic portal vein thrombosis show the same hemodynamic abnormalities as with other causes of portal hypertension and are frequently diagnosed after the first episode of variceal bleeding. Gastric varices are frequently found in portal vein thrombosis.<sup>9</sup> All underlying causes of portal hypertension can be classified into three groups, prehepatic, hepatic and post-hepatic (Table 2).

The more frequent cause of post-hepatic portal hypertension is Budd-Chiari syndrome (hepatic vein thrombosis). Obstruction can occur in the suprahepatic inferior vena cava or at the main hepatic veins. In portal vein thrombosis one or several underlying prothrombotic disorders are usually present, the most common of which is an occult primary myelo-proliferative disorder. The major complications of the disease are gastrointestinal bleeding and ascites which are associated with liver failure. The disease can present as an acute, subacute, or chronic disease and diagnosis is usually by imaging techniques.<sup>10,11</sup>

Hepatopulmonary syndrome and intrapulmonary vascular dilation are relatively frequent in patients with portal hypertension.<sup>12</sup> Portal hypertension in children can lead to significant morbidity and is a leading indication for liver transplantation.<sup>13</sup>

Several studies have reported the pattern of portal hypertension to be different in children and adults. In adults the pattern of portal hypertension is mostly intrahepatic, whereas the pattern is extra-hepatic in children.<sup>14-17</sup> In one study from South India the most common causes of pediatric portal hypertension were extra-hepatic portal venous obstruction and cirrhosis, with Wilson's disease the most common cause for liver cirrhosis.<sup>18</sup>

In another study, extra-hepatic portal venous obstruction was also the major cause of portal hypertension in children.<sup>19</sup> Grimaldi et al. have reported that the main causes of portal hypertension in children are cirrhosis and congenital hepatic fibrosis.<sup>20</sup>

Bernard et al. have also reported that cirrhosis was responsible for 51% of portal hypertension cases and extra-hepatic portal venous obstruction was found in 34% of cases.<sup>21</sup>

However, controversy exists regarding the suggested patterns of portal hypertension in children and adults, and

**Table 2: Classification of portal hypertension in children.<sup>10</sup>**

Prehepatic	Intrahepatic	Post-hepatic
Splenic vein thrombosis	Autoimmune hepatitis	Budd-Chiari syndrome
Portal vein thrombosis	Hepatitis B and C	Congestive heart failure
Congenital stenosis of the portal vein	Alfa1 anti-trypsin deficiency	Inferior vena cava obstruction
Arteriovenous fistula	Wilson's disease	
Splenomegaly	Steatohepatitis	
	Glycogen storage disease type IV	
	Toxins	
	Biliary atresia	
	Primary sclerosing cholangitis	
	Cystic fibrosis	
	Congenital hepatic fibrosis	
	Caroll's disease	
	Choledochal cyst	
	Familial cholestasis	
	Veno-occlusive disease	
	Schistosomiasis	
	Gaucher's disease	
	Idiopathic portal hypertension	
	Peliosishepatis	
	Primary biliary cirrhosis	

it appears that this pattern is regionally variable. In some studies performed in the West, intrahepatic portal hypertension was more frequent in children,<sup>22,23</sup> whereas studies performed in India observed that extra-hepatic portal hypertension was more frequent in children.<sup>24</sup>

The results of this study differ from previous studies. In this study, intrahepatic disorders were considered to be the main cause for portal hypertension in 93.3% of children. Cryptogenic cirrhosis (26.7%) and biliary atresia (24.4%) were two major diseases that accounted for 50% of portal hypertensions. Intrahepatic causes of portal hypertension have been classified according to the results of hepatic vein catheterization.<sup>25</sup> This classification includes: (a) pre-sinusoidal portal hypertension with normal wedged and free hepatic venous pressures; (b) sinusoidal portal hypertension with increased wedged and normal free hepatic venous pressures; and (c) post-sinusoidal portal hypertension with increased wedged and free hepatic venous pressures. Portal hypertension is

typically associated with an increased cardiac index, hyperkinetic syndrome, characterized by hypervolemia, hypotension, and decreased systemic vascular resistance.<sup>9</sup>

In extra-hepatic portal hypertension patients tolerate variceal bleeding relatively well because of an intact liver function and coagulation system.<sup>26,27</sup> Unlike children with intrahepatic portal hypertension, those diagnosed with extra-hepatic portal hypertension seem healthy prior to the sudden onset of symptoms.<sup>28</sup>

Limitations for this study include the small numbers of cases as this data has been derived from one center.

We concluded that intrahepatic diseases are the most common causes of portal hypertension in children in this center.

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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