Original Article

A Study on Antithromin III Deficiency in Children with Extrahepatic Portal Hypertension Attending a Tertiary Care Hospital in Bangladesh

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Abstract:

Background: Extrahepatic portal venous obstruction accounts for 80% of cases of portal hypertension. Of all cases of portal hypertension (PHT) in developing countries, 40% are due to portal vein thrombosis. No risk factors were found in most of the cases of extrahepatic portal hypertension. To date, numerous observational studies have reported the prevalence of antithrombin III deficiency in patients with portal vein thrombosis. In Bangladesh, a largely populated country, we see a good number of patients with EHPVO every year. But there is a lack of such studies in our country about the frequency of antithrombin III deficiency. **Objective:** To find out the frequency of antithrombin III deficiency in children with extrahepatic portal hypertension. **Methods:** Over a period of 18 months, this cross-sectional descriptive study was carried out at the Department of Paediatric Gastroenterology and Nutrition of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Children of either gender diagnosed with cases of extrahepatic portal hypertension were included in this study. Informed written consent was obtained from the parent/caregiver of each child. Data were analyzed by using SPSS 22.0 for Windows 10 (SPSS, Inc, Chicago, IL). In all cases, the significance level of p value was <0.05. **Results:** A total of 18 patients diagnosed with extrahepatic portal hypertension were enrolled in this study, out of which 14 (78%) were males. The mean age at presentation was 8.6 ± 4.7 years. The most common (83%) presenting symptom was upper gastrointestinal bleeding manifested as hematemesis and melena. On physical findings, the majority (89%) of patients were pale, splenomegaly was present in 83% of patients. On full blood count, anemia was present in all (100%) patients, leucopenia in 4 (22.2%), and thrombocytopenia in 14 (78%) patients. Cavernous transformation was found in 9 (50%) patients, portal vein thrombosis (PVT) was identified in one (5.6%) patient. All (100%) patients had esophageal varices. Nine (50%) patients had Antithrombin III deficiency. **Conclusion:** Antithrombin III deficiency was seen in half (50%) of the studied patients. No significant difference or association was identified between the antithrombin III deficient with the normal group in terms of clinical profile, biochemical parameters, and endoscopic findings.

Key words: EHPVO, Portal Hypertension, Antithrombin III, Thrombophilia.

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Introduction:

Portal hypertension (PHT) may be defined as a direct measurement (usually not performed) of blood pressure in the portal system of over 11 mm Hg or by the presence of a pressure gradient of over 10 mm Hg between the portal system and the right atrium.[1] A combination of two concurrently occurring hemodynamic processes, including 1) increased intrahepatic resistance to blood flow through the liver caused by cirrhosis and 2) increased splanchnic blood flow as a result of vasodilatation within the splanchnic vascular bed, results in portal hypertension. Portal hypertension can be due to many different causes at prehepatic, intrahepatic, and posthepatic sites. It can be hepatic or extrahepatic. [2]

Three points are common in patients with extrahepatic portal hypertension. First, they have no underlying liver disease, and their liver functions are expected to remain normal throughout life. Second, they have a more or less extended obstruction or occlusion of the extra-hepatic portal venous system. Third, they have developed the so-called "cavernous transformation of the portal vein". [1]

Extra-hepatic portal venous obstruction (EHPVO), a paediatric illness with well-retained liver function, is characterised by a chronic blockage of the portal venous blood flow, which causes PHT and accompanying complications. In children from the developing world, extrahepaticportal venous blockage is a significant (54%) contributor to PHT and upper gastrointestinal haemorrhage (68–84%).[3]

The etiologies of EHPVO in children have not been well documented. There are many etiologies for EHPVO, namely infections, surgical procedures, vascular interventions, abdominal trauma, dehydration, congenital anomalies, etc. Extrahepatic portal venous obstruction is considered heterogeneous concerning etiology and pathogenesis and varies for age and geographical location. The causes can broadly be of five types; infection and inflammation, portal vein injury, developmental anomaly, prothrombotic causes, and idiopathic.[4]

Patients presenting with portal venous thrombosis should be investigated for an underlying thrombophilic condition such as a myeloproliferative disorder or a hereditary thrombophilic state. Certain mutations in the prothrombin or factor V genes, as well as a deficit in one of the natural anticoagulant proteins C, S, or antithrombin III are examples of hereditary thrombophilias that are known to predispose to PVT. Reduction in circulating concentrations of natural anticoagulant proteins has been reported in patients with PVT, even in the presence of biochemically normal liver function.[5]

Deficiency of antithrombin III may predispose an individual to a higher thrombotic tendency. It was reported that it is a risk factor for causing portal venous thrombosis. So this study has been undertaken to observe the frequency of antithrombin III deficiency in extrahepatic portal hypertension. Thus the etiologies of portal vein thrombosis and the clinical and laboratory profile of such cases in Bangladesh who are attending a tertiary hospital in Dhaka can be explored as well as the etiological management can be provided to them.

Methods:

This was a Cross-sectional descriptive study conducted in the Department of Pediatric Gastroenterology and Nutrition, BSMMU, Dhaka, Bangladesh from December 2019 through July 2021. Children of either gender aged less than 18 years with upper gastrointestinal bleeding diagnosed as extrahepatic portal hypertension attending the pediatric Gastroenterology & Nutrition department of BSMMU were included in the study. Children with upper GIT bleeding due to liver disease, having any life-threatening complications of extrahepatic portal hypertension and who didn't give consent were excluded from the study. Finally, 18 patients were included in the study. Informed written consent was taken from the parents or legal guardians after giving the information about the objectives of the study and assurance was given about the safety of the patient. A semi-structured questionnaire was used for taking the detailed case history, physical examination, and laboratory reports.

Blood samples were collected at the Department of Pediatric Gastroenterology and Nutrition by the senior staff nurses in the supplied vials. Serum ALT, serum albumin, complete blood count, serum prothrombin time, and INR of patients were estimated at the Department of Biochemistry and Hematology, BSMMU. Doppler Ultrasonography was done at the nuclear medicine department, BSMMU by Afiniti 70G apparatus equipped with a 3.5 MHz transducer having both grayscale and Doppler facility. Using the grayscale diameter of the portal vein, thrombus in the portal vein, liver size & echogenicity, cavernous transformation, and splenic size were recorded. Doppler study detected portal vein flow velocity and direction of blood flow in

the portal vein. Then endoscopy of upper GIT was done to see the presence or absence of esophageal varices with associated findings using an Olympus video endoscope GIF Q 150 endoscopy machine. Gastroenterologists of the Pediatric Gastroenterology & Nutrition department did all endoscopies. Finally, blood (2-3 ml) was collected for Antithrombin III assay. First, the collected blood was centrifuged for 15 minutes, and then it was kept in the coagulation analyzer (STA-Compact Max2, STAGO, France). Within the analyzer, the test kits (STACHROM AT III) were placed. Each kit contains 4 vials of reagent and each vial contains 3 types of reagents (thrombin, substrate, and thrombin solvent). The remaining processes were automated and the test result was expressed in percentage (%). The result was obtained after 6 hours. These investigations were done at the Armed Forces Institute of Pathology (AFIP), Dhaka.

Portal hypertension was defined as an increase in portal pressure above the normal limit that clinically manifests as splenomegaly and/or variceal bleeding.[6] Chronic liver disease (CLD): A patient having any one or more of the following criteria was considered as CLD. (1) Jaundice or raised ALT with any stigmata of CLD (Palmer erythema, clubbing, leukonychia, thenar and hypothenar wasting, spider angioma, gynaecomastia, Dupuytren's contracture, etc.) (2) presence of jaundice for a long period (>6 months) with elevated ALT (3) those diseases which are chronic like Wilson's disease, autoimmune hepatitis, Alfa 1 antitrypsin deficiency, etc. (4) histologically diagnosed as a case of chronic hepatitis or cirrhosis.[7]

Extra Hepatic Portal Hypertension (EHPHTN): Patients with portal hypertension without any clinical or biochemical features of chronic liver disease were diagnosed as extrahepatic portal hypertension.[8] Portal hypertension is not due to the chronic liver disease having the following criteria: (History of gastrointestinal bleeding, splenomegaly, normal liver function, and esophageal varices on endoscopy). Any patient having serum antithrombin III level less than normal (80-120%) level was identified as deficient antithrombin III level.[9]

Results:

In this study, 41.2% of the children were between 6-10 years of age, 35.3% were between 11-15 years, 17.5% were between 16-18 years and the rest were between 1-5 years. The mean age at presentation was 8.67 ± 4.59 years [Figure-1]. Among them 78% of them were male and only 22% of the studied participants were female. Male female ratio was 3.5:1.

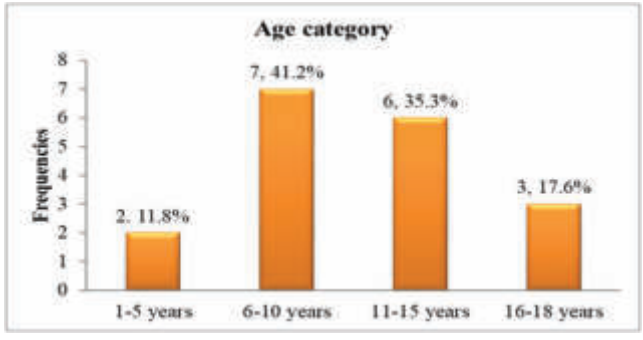

Figure-1: Age distribution of the patients (n=18)

A common presenting symptom was upper gastrointestinal bleeding manifested as hematemesis and/or melena (15, 83%). Other presenting features were abdominal distention (5, 27.8%) and abdominal mass (9, 50%). H/O consanguinity was identified in one patient and no other risk factor was seen.[Table-I]

Table-I: Presenting features of the studied patient (n=18)

Symptoms	Number (%)
Hematemesis	15 (83.3)
Melena	15 (83.3)
Abdominal distension	5 (27.8)
Abdominal mass	9 (50)
Consanguinity	1 (5.6)

On physical findings, the majority of patients were pale (16, 89%) and had splenomegaly (15, 83%). Other physical findings included hepatosplenomegaly (2, 11.1%), and ascites (1, 5.6%). No one had jaundice or any stigmata of chronic liver disease. Of 18 patients, 2 (11.1%) were below the 3rd percentile of weight for age, while 4 (22.2%) were below the 3rd percentile of height for age.

On full blood count, anemia was present in all patients (18,100%), leucopenia in 4 (22.2%), and thrombocytopenia in 15 (83.3%) patients. None had raised ALT but one (5.6%) patient had raised INR and low albumin. [Table-II]

Table-II: Laboratory findings of the studied patient. (n=18)

Findings	n (%)
Anemia (Hb< 12g/dl)	18 (100)
Leucopenia (<4000/cmm)	4 (22.2)
Thrombocytopenia (<150000/cmm)	15 (83.3)
Raised alanine aminotransferase (ALT) (>40U/L)	0 (0)
Raised INR (> 1.1)	1 (5.6)
Low Albumin (<35gm/L)	1 (5.6)

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All patients had undergone ultrasound (US) of the abdomen (conventional and Doppler). The cavernous transformation was found in 9 (50%) patients, portal vein thrombosis was identified in one patient (5.6%), while in remaining portal vein obstruction was not visualized. Blood flow in portal vein were hepatopetal in 14 (77.8%) and hepatofugal in 4 (22.2%) patients. [Table III]

Table-III: Doppler USG findings of studied patient (n=18)

Doppler USG	**n (%)**
Doppler USG findings of portal vein	
Cavernous formation	9 (50)
Thrombosis	1(5.6)
Direction of blood flow	
Hepatopetal	14 (77.8)
Hepatofugal	4 (22.2)

All patients had undergone upper gastrointestinal endoscopy. All patients (100%) had esophageal varices. Grade-I varices in 4 (22.2%), grade II varices in 1 (5.6%), grade III varices in 2 (11.1%) and grade IV varices was observed in 11 (61.1%) patients. None had fundic varices or portal hypertensive gastropathy.

Figure-2 showing that frequency of Antithrombin III deficiency and that was 9 (50%).

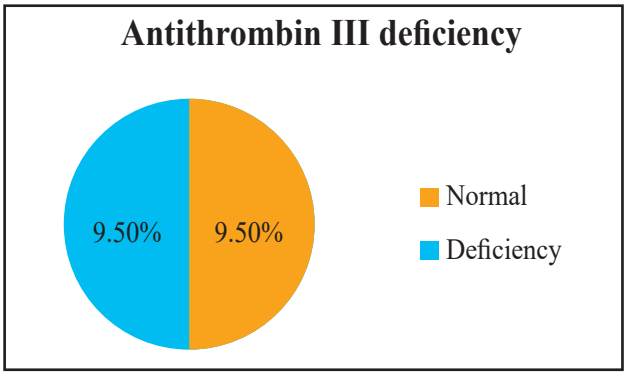

Figure 2: Antithrombin III deficiency among the studied patients. (n=18)

Table IV represents the comparison of clinical presentations between of antithrombin III deficient group and antithrombin III normal group. No feature was found significant between two groups.

Table-IV: Comparison of clinical presentations of antithrombin III normal and deficient patients (n=18)

	Antithrombin III normal (n=9)n (%)	Antithrombin III deficiency (n=9)n (%)	p
Hematemesis	6 (66.7)	9 (100)	0.082 [f]
Melena	8 (88.9)	7 (77.8)	1.000[f]

f = Fisher exact test

Table V showed the comparison of doppler USG findings of Portal vein between theantithrombin III deficiency and antithrombin III normal group. None features were found significant between two groups.

Table-V: Comparison of doppler USG findings of Portal vein between antithrombin III deficient and antithrombin IIInormal group (n=18)

	Antithrombin III normal (9)n (%)	**Antithrombin III deficiency (9)n (%)**	**p**
Cavernous formation	4 (44.4)	5 (55.6)	1.000 [f]
Thrombosis	1 (11.1)	0 (0)	1.000 [f]

f=Fisher exact test

Table VI shows the comparison of common endoscopic findings between of antithrombin III deficient group and antithrombin III normal group. None feature was found significant between two groups.

Table-VI: Endoscopic findings of Antithrombin III deficient and Antithrombin III normal group (n=18)

	Antithrombin III normal (9)n (%)	**Antithrombin III deficiency (9)n (%)**	**p**
Esophagus			
Gr-1	2 (22.2)	2 (22.2)	0.688[a]
Gr-2	1 (11.1)	0 (0)	
Gr-3	1 (11.1)	1(11.1)	
Gr-4	5 (55.6)	6 (66.7)	
Stomach			
Fundicvarices	0 (0)	0 (0)	N/A
Gastropathy	0 (0)	0 (0)	N/A

a=Likelihood ratio

Extrahepatic portal venous obstruction was defined by either presence of thrombus or cavernous transformation within the portal vein. Table X showed that no significant association was observed between EHPVO and non EHPVO for antithrombin III deficiency. However, the odds for EHPVO due to low antithrombin III level were 12.25 (95% CI: 1.33 – 113.06).

Table-VII: Association of antithrombin III deficiency between EHPVO and non EHPVO group (n=18)

		EHPVO		OR	95% CI	p
		Yes (n=9)	No (n=9)			
Antithrombin III	Low	7 (77.8)	2 (22.2)	12.25	1.33 – 113.06	0.057[f]
	Normal	2 (22.2)	7 (77.8)			
Total		9 (100)	9 (100)			

Discussion:

Portal hypertension is one of the most common problems in children attending pediatric gastroente rology clinics. EHPVO constitutes 70–80% of all types of portal hypertension in children. Although it is a rare condition, the number of cases continues to grow.[10] A total of 18 patients were included in the study, among whom there was a male predominance and a male-female ratio of 3.5:1. Poddar et al. (2008) also found male predominance and a male-female ratio of 2:1.6 Grama et al. (2021) found male predominance, but Karakurt et al. (2019) found female predominance, and M: F was 1:3.[11, 12]

The mean age at presentation in this study was 8.67 ± 4.59 years (range: 2-16 years), but Di Giorgio et al. (2019) found 4 ± 3.7 years and similarly in a study by Grama et al. (2021) &Karakurt et al. (2019) found mean age 5.14 ± 4.90 and 4.6 ± 3 years respectively.[11,12, 13]

On full blood count, anemia was present in all patients, 22.2% had leucopenia and 83.3% had thrombo cytopenia. Regarding liver function tests none had raised ALT but 5.6% of patients had prolonged PT and low albumin. Karthikeyan et al. (2015) found, anemia in 91.6% of patients & Di Giorgio et al. (2019) found thrombocytopenia in 69% of patients.[10,13] Karakurt et al. (2019) found, 83% had cytopenia(s) at diagnosis; 67% had anemia, 42% had leukopenia, 75% thrombocytopenia, and pancytopenia was detected in 25% patients.[12]

Conventional and Doppler ultrasound (US) of the abdomen was done for the confirmation of the diagnosis of EHPVO and cavernous transformation was found in 50% of patients, 5.6% had portal vein thrombosis (PVT), while in the remaining portal vein, obstruction was not visualized. 77.8% of cases were hepatomegaly blood flow in the portal vein and 22.2% cases were hepatofugal. Karakurt et al. (2019) found thrombus in 83%, and portal cavernoma in 83% of patients.[12]

Upper gastrointestinal endoscopy was done in all the patients. All patients (100%) had esophageal varices. Grade-I varices in 22.2%, grade II varices in 5.6%, grade III varices in 11.1%, and grade IV varices in 61.1% of patients. None had fundic varices, gastric ulcer, or portal hypertensive gastropathy. Karakurt et al. (2019) also found varices in 100% of patients.[12] In a study by Hanif et al. (2015), varices were found 90% of cases where, grade-I varices in 6.7%, grade II varices in 20%, grade III varices in 33.3%, grade IV varices in 30% and also gastric varices in 33.3% patients.[14]

The main inhibitor of blood coagulation, antithrombin (AT), is a powerful inactivator of thrombin and factor Xa. The prevalence of inherited AT deficits in the general population ranges from 1 in 500 to 1 in 5000. They might be either qualitative or quantitative (type I or type II). They are either quantitative (type I) or qualitative (type II). Acquired antithrombin III deficiencies are caused by liver cirrhosis, nephrotic syndrome, protein-losing enteropathy, sepsis, burn, DIC, etc.[15] Before determining whether a patient has inherited antithrombin deficiency, acquired sources of the illness must be ruled out, and testing should be performed once those symptoms have improved. Liver function tests, urinalysis to detect proteinuria, and a DIC screen (D-dimer, PT, PTT, fibrinogen, platelet count, and if available, PTT waveform) are among laboratory tests that can identify some acquired reasons of reduced antithrombin. Moreover, antithrombin assay of parents should also be undertaken to define it as a hereditary deficiency.[16]

In the present study, a total of 50% of patients had antithrombin III deficiency, out of which 89% were males while females were 11% patients. The mean age of presentation was 11.67 ± 3.78 years was more in comparison to the normal group aged 5.67 ± 3.20 years. Grama et al. (2021) found decreased serum levels of Protein S, Protein C, or Antitrhombin III in 91.67% of patients.[11] However, Dubuisson et al. (1997), and Jena et al. (2017) found AT III deficiency of 50%, and 12.7% respectively.[17,18] The wide variation in the frequencies of antithrombin III deficiency implies the impact of geographic and ethnic variations among patients as the mentioned studies were done in different parts of the world like Denmark and India respectively.

This study did not find any significant association in the context of baseline parameters, clinical presentations as well as in the laboratory parameters between the antithrombin III deficient and normal groups probably

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due to the small sample size. Pietrobattista et al. (2010) also did not find any association between the initial presentation and the inherited prothrombotic disorder.[19] Further large-scale studies can be undertaken to gather deep knowledge regarding such associations.

Conclusion:
Antithrombin III deficiency was seen in half (50%) of the studied patients. No significant difference or association was identified between the antithrombin III deficient with the normal group in terms of clinical profile, biochemical parameters, and endoscopic findings.

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Conflict of interest: The authors declare no conflict of interest.

Ethical approval: The study was approved by the Institutional review board, BSMMU, Dhaka, Bangladesh.

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