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RISK FACTORS REGARDING PORTAL VEIN THROMBOSIS IN CHRONIC LIVER DISEASE

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Abstract: *The portal vein thrombosis (PVT) is one of the most frequent vascular diseases of the liver, with a high rate of morbidity and mortality. The most common causes of the PVT are hepatic cirrhosis, hepatobiliary neoplasms, inflammatory and infectious abdominal diseases, and myeloproliferative syndromes.(1,2) The natural progress of the PVT has as a result portal hypertension which leads to splenomegaly and the formation of portosystemic collateral vessels, as well as gastroesophageal, duodenal and jejunal varices. Ultrasonography, especially Doppler ultrasound, is the most widely used imaging method to asses, supervise and diagnose PVT in patients with hepatopathies. The purpose of acute PVT treatment is to re-permeabilize the obstructed vessels; the endoscopic ligature of the varices in the eventuality of their rupture is safe and extremely efficient in chronic PVT. To conclude, PVT is the most common hepatic vascular disorder, and its prevalence has increased particularly among the patients with chronic hepatopathies.(3)*

INTRODUCTION

Portal vein thrombosis is the most frequent complication of the chronic liver disease and its prevalence increases with disease severity.(1) The natural progress of the PVT has as a result portal hypertension which leads to splenomegaly and the formation of portosystemic collateral vessels, as well as gastroesophageal, duodenal and jejunal varices.(3) Ultrasonography, especially Doppler ultrasound, is the most widely used imaging method to asses, supervise and diagnose PVT in patients with hepatopathies.(3) The purpose of acute PVT treatment is to re-permeabilize the obstructed vessels; the endoscopic ligature of the varices in the eventuality of their rupture is safe and extremely efficient in chronic PVT.

AIM

Identification of risk factors for the development of portal vein thrombosis.

MATERIALS AND METHODS

We conducted a retrospective observational study in which we included all the patients with chronic hepatopathies disorders (decompensated hepatic cirrhosis of different etiologies and hepatocellular carcinoma) who had portal vein thrombosis and a witness group consisting of 38 consecutive patients with compensated cirrhosis, without portal vein thrombosis, hospitalized in Gastroenterology, Oncology and Medical I and II Sections of the County Clinical Emergency Hospital of Sibiu, during January 2016 until December 2019, and who had given their consent to participate in the study.

Fifty-seven patients with decompensated hepatic cirrhosis and hepatocellular carcinoma agreed to be included in the study which was approved by the Ethics Committee of the County Clinical Emergency Hospital of Sibiu. The diagnosis of chronic hepatopathy was established based on the clinical evidences (laboratory analyses and imagistic investigations), whilst the portal vein thrombosis was revealed through abdominal ultrasound and CT.

The exclusion criteria were the following: patients with vascular and parenchymal decompensated hepatic cirrhosis with no portal vein thrombosis.

We studied the observation sheets from which the clinical data of the patients were extracted: hemoglobin (Hgb), hematocrit (Hct), White blood cells (Leuc), platelet count (PLT), activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR), fibrinogen, total bilirubin (Bt), direct bilirubin (Bd), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (SAP), albumin, gamma globulin, albumin/gamma globulin ratio (A/G), proteinemia (total prot.), creatinine, urea, cholesterol (Col), triglyceride, glycemia, erythrocyte sedimentation rate (ESR) C reactive protein (CRP), sodium (Na), potassium (K). The ultrasound examination revealed the diameter of portal vein and spleen, and the presence of thrombosis. The diagnosis and the degree of esophageal varices were highlighted through upper digestive endoscopy. The patients' data were processed by the SPSS program, version 23. The demographic features were analysed by using descriptive statistics, while the frequency and the percentage were generated using tables.

RESULTS

Fifty seven patients with chronic hepatopathies were included in the study, as follows: 24 patients with decompensated hepatic cirrhosis and PVT, representing 42% (group 1), 33 patients with decompensated hepatic cirrhosis, hepatocellular carcinoma and PVT, representing 58% (group 2) and 38 patients with compensated hepatic cirrhosis (group 3 – the witness group). The first group included 10 men (42%) and

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14 women (58%); the second group consisted of 27 men (63%) and 6 women (37%), and in the witness group there were 32 men (61%) and 15 women (39%).

Hepatic cirrhosis has been classified according to etiology and Child-Pugh stage; 4 patients had B-virus cirrhosis (representing 70%), 26 patients had C-virus etiology (representing 46%), other 18 patients had ethanolic etiology (representing 32%), 7 patients cryptogenic cirrhosis (representing 12%), 2 patients with combined etiology (hepatitis B virus + ethanolic hepatitis) representing 3%. In Child-Pugh A stage there were 3 patients (representing 5%), in Child-Pugh B – 8 patients (14%) and in Child-Pugh C – 46 patients (81%).

Ascites was revealed on ultrasound in 50 patients, representing 88%; 25% of the studied patients showed signs of encephalopathy. The presence and the degree of the esophageal varices were assessed by superior digestive endoscopy; thus, 4 patients (representing 7%) had first degree esophageal varices, 4 patients (7%) had second degree esophageal varices, 14 patients (25%) were discovered with third degree varices, 2 patients (3%) with fourth degree varices; in 33 of the patients there were no esophageal varices. 19%, that is 11 patients, experienced at least one episode of superior digestive hemorrhage, externalized by hematemesis and melena.

With patients within the witness group, the average diameter of portal vein is significantly smaller than that of the patients from groups 1 and 2 (p=0,004), who have portal vein thrombosis. The spleen diameter is larger in patients from group 1, as compared to witness group (p=0,001). The average platelet count in patients with portal vein thrombosis is higher than the witness group, but the difference is statistically significant only between group 2 and the witness group (p=0,02). The average leucocyte count is significantly higher in groups 1 and 2 as compared to the witness group (p =0,0028); consequently, patients with portal vein thrombosis have a higher number of leucocytes as compared to the witness group. The average value of serum alkaline phosphatase in group 2 is obviously greater than that in the witness group (p=0,044); therefore, it has a higher value in patients with hepatocellular carcinoma and PVT as compared to the witness group.

In group 1, there is a direct correlation between the ultrasound diameter of portal vein and leucocyte count; the larger the diameter of the portal vein, the higher the leucocyte count. A reverse correlation (-0,540) exists between the albumin value and the leucocyte count in group 1; the higher the leucocyte count, the lower the albumin value. There is also negative correlation between albumin value from group 1 and platelet count -0,669; the higher the platelet count, the lower the albumin value. The spleen diameter in the first group negatively correlates to the hemoglobin value in the same group (p=0,023); the larger the diameter of the spleen, the lower the value of hemoglobin.

Table no. 1. Descriptive statistics

	Group 1 (N=24)	**Group 2 (N=33)**	**Group 3 (N= 38)**	**P value**
Age (Years)	62.00 ± 8.891	66.19±8.581	62.29±	0,133
Sex men (n, %)	10 (42%)	27 (63)	23(61%)	
women (n, %)	14 (58%)	6 (37%)	15(39%)	
Portal vein (mm)	14.105 ± 3.035	14.421 ± 1.774	12.886 ± 2.538	0.041
Spleen (cm)	16.3909±3.37482	14.0474±2.13265	13.94865±20.89208	0,001
PT (s)	17.7833±9.44649	15.6903±3.05912		-
Prothrombin activity (%)	61.0833±19.75854	64.2806±18.80887		0,543
INR	1.4417±.71531	1.5510±1.36114	1.4212±.33264	0,417
APTT (sec)	37.2167±7.43655	38.0677±10.98130	39.4212±10.95091	0,439
Plasma fibrinogen (mg/dL)	258.3063±70.50522	311.8125±183.56797	235.5290±80.55163	0,101
Hemoglobin (g/dL)	10.2818±2.56638	11.5000±2.25306	10.9921±2.69337	0,245
Hematocrit (%)	31.2864±6.70055	33.7630±6.09301	32.7158±7.45536	0,458
White blood cells (10^6/ul)	11.0112±18.27931	9.5452±5.72686	5.9676±2.56597	0,028
Platelets (10^6/ul)	138.0000±101.01202	163.4286±82.10762	121.4211±76.54380	0,077
Total bilirubin (mg/dL)	2.3610±1.67240	3.4607±3.53946	3.5594±4.45165	0,771
Direct bilirubin (mg/dL)	1.5906±1.10356	3.0244±3.20596	3.6886±4.46759	0,14
Plasma total cholesterol (mg/dL)	151.1538±96.75471	144.2353±53.98904	130.0000±45.57071	0,522
Blood glucose (mg/dL)	122.19±40.531	116.89±44.533	145.50±155.671	0,69
Serum creatinine (mg/dL)	1.5568±1.59870	1.3343±1.15286	1.1186±.59319	0,335
Serum urea (mg/dL)	51.5000±41.41974	87.7241±81.25792	55.3333±41.22066	
AST (IU/L	107.0500±139.95882	113.8276±101.73392	72.2000±59.29627	0,146
ALT (IU/L)	44.9000±46.36117	66.1034±59.01716	46.9429±38.50588	0,203
GGT (U/L)	156.2778±236.37503	182.1250±164.92721	141.6471±248.92580	0,101
SAP (U/L)	131.5909±66.92189	162.9565±93.71013	111.8148±60.17349	0,044
Serum albumin (%)	41.3250±7.51279	43.8000±6.82766	45.3000±9.14564	0,433
Serum gamma-globulins (%)	32.4500±10.56164	27.1429±7.89008	30.2312±9.94845	0,366
Albumins/Gglobulins	.7067±.22346	.8036±.20376		
Serum proteins (g/dL)	6.6438±.97432	6.8172±.97747	7.0367±1.10062	0,458
ESR (mm/h)	28.83±17.140	40.06±31.938	29.60±22.385	
CRP (mg/dL)	29.5767±44.08333	48.6240±33.03221		
Plasma trigycerides (mg/dL)	88.0909±46.61213	105.0000±67.45939	84.8788±33.38952	
Na (mEq/l)	126.5000±24.27328	135.9565±5.74835		
K (mEq/l)	4.6243±.83232	4.8726±1.23918		

Note: the data presented in the table are an average ± standard deviation

DISCUSSIONS

Cirrhotic patients present a dysfunction of the hemostatic system due to the low plasma levels of pro and anticoagulant factors that are synthetized at hepatic level; these are associated with the risk of thrombotic and hemorrhagic complications.(4)

The study of Chen et al. analysed whether the Hb level can be an independent risk factor for PVT occurrence. In fact, splenomegaly drops the Hb level and the hypersplenism is even more severe in patients with PVT. Although Hb has been associated with PVT, it has not been considered a risk factor in PVT development.(5)

Other studies have displayed extremely different conclusions as regarding the association of thrombocytes with PVT. A low platelet count can also be caused by splenomegaly, because the latter is more obvious in patients with PVT than in patients with no thrombosis. Moreover, it has been speculated that the observed qualitative changes in platelets count may have contributed to the development of PVT, and these were considered even more important than the quantitative changes during the evolution of PVT, although platelets count may not be a real risk factor in PVT.(5,6)

The multilevel analysis in our study has revealed that the leucocytes could be an independent predictor for PVT. Leucocytes play a vital role in phagocytosis, immunity and body defence against infection. The leukocytosis in our study could be the result of the endotoxin that reaches the portal system and is capable to activate coagulation process and lead to thrombus.(7) Endotoxemia has long been discovered in patients with hepatic disorders at higher levels than in healthy individuals which increase progressively with the hepatic disease, depending on the Child-Pugh stage.(8)

Acute infections are associated with an increased transient risk in the development of venous thromboembolic events.(9) Some viral infections almost invariably lead to hemostatic abnormalities ranging from insignificant laboratory changes to severe disseminated intravascular coagulation. Direct infection of endothelial cells and systemic inflammation leads to activation of coagulation due to tissue factor-mediated thrombin generation, decreased regulation of the anticoagulant physiological mechanism, and inhibition of fibrinolysis. Moreover, similar to other viral infections, systemic inflammatory response syndrome and inflammatory changes in surrounding tissues may be associated with acute viral hepatitis; the spread of acute liver inflammation to the endothelium of the venous system by contiguity could activate the coagulation system and increase the risk of PVT.(10)

Another study showed that preoperative splenic vein diameter was a risk factor for the development of portal or splenic vein thrombosis post splenectomy. An increased diameter of the portal vein could be involved in the development of PVT. Nevertheless, the multivariate analyses failed to detect a correlation between the diameter of the portal vein and PVT. The results showed that the size of the spleen was associated with the occurrence of PVT. Splenomegaly was associated to portal hypertension; the more important the growth of the spleen, the more severe the portal hypertension. Moreover, the risk of developing DVT increases due to the aggravation of portal hypertension. Thus, increasing the diameter of the splenic vein can contribute to the occurrence of PVT.(5)

In the PRO-LIVER study conducted by Basili et al, predictive factors in the occurrence of portal vein thrombosis were investigated in patients with liver cirrhosis; they found that serum albumin was lower in patients with PVT compared with those without PVT and it was independently associated with thrombosis occurrence after adjusting several factors, including the degree of liver failure, assessed with the Child-Pugh score. Accordingly, serum albumin has been associated with PVT not only in patients considered to be in B and C Child-Pugh classes, but also in those in class A, reinforcing the hypothesis that albumin may be a major determinant of thrombosis.(11)

Kim et al conducted a study showing that elevated SAF levels correlate with increased liver tumour size; high levels of serum alkaline phosphatase, the maximum tumour enlargement and intrahepatic metastases were independent predictive factors of malign invasion of portal vein in HCC. Therefore, these factors may be helpful in predicting portal vein malignancy prior to surgery for HCC.(12)

In 1954, Hunt et al. stated that “blood stasis in the portal vein is probably the only constant etiological factor of real importance” for the development of PVT in cirrhosis.(13) However, many years passed before this issue came to light. Amitrano et al concluded that portal blood flow stasis is the most important risk factor for PVT.(14) Only recently have Zocco et al found a significant correlation between the decrease in the portal blood flow <15 cm/sec and PVT; the decrease in portal blood flow below the mentioned limit was the only factor that independently predicted the development of PVT in a prospective study in which 73 patients were enrolled, a study conducted over a period of one year.(15) In addition to the portal hemodynamic implication, the hypothesis has been proposed that portal blood flow stagnation could lead to higher thrombin levels in the portal circulation due to a deficient washout system.(15) This theory is yet to be confirmed. However, despite specialized guidelines to reduce interpretation variables between radiologists, there is a considerable difference between Doppler assessment of blood flow in the same patient during longitudinal measurement as well as between radiologists' interpretations, which makes it difficult to use blood flow velocity as a reliable predictive factor in estimating the development of PVT. Chen et al. found no differences between groups in a study involving 162 patients; 40 of them had documented PVT; however, this was a cross-sectional study that did not allow a rigorous assessment of risk factors for the development of portal vein thrombosis.(5)

CONCLUSIONS

Splenomegaly, increased portal vein size, leukocytosis and increased serum alkaline phosphatase correlate with portal vein thrombosis in patients with cirrhosis of the liver examined by us.

The identification of risk factors for the occurrence of portal vein thrombosis would allow the option of a prophylactic anticoagulant treatment in selected patients with chronic hepatopathies, who have no contraindications and in whom the thrombotic risk is imminent.

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