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Etiological Distribution of Chronic Portal Vein Thrombosis in Adult Patients Without Cirrhosis

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ABSTRACT

Objective: Portal vein thrombosis (PVT) is one of the rare causes of portal hypertension unrelated to chronic liver disease (CLD), which differs in its clinical course and treatment. Knowing the age, gender and etiological distribution of the disease is very important in follow-up and treatment. This study aims to review the etiological distribution of the disease.

Material and Methods: This study was designed to be descriptive and retrospective. Patients who were followed up on with the diagnosis of PVT in the Hacettepe University Faculty of Medicine Gastroenterology Department over the last 40 years were screened retrospectively. A total of 119 patients were selected after excluding CLD, cirrhosis, and portal vein obstruction due to any tumoral formations compressing the portal vein. Sociodemographic characteristics, laboratory, endoscopy, and imaging results of the patients were analyzed.

Results: Mean age of the patients was 45.5 ± 15.3, and the mean age at diagnosis was 36.0 ± 16.4. The number of female patients was slightly higher (female/male= 62/57). In patients who presented with nonspecific complaints such as abdominal pain, distension, and fatigue, the most common physical examination finding was splenomegaly. The majority of the patients had one or more thrombophilic factors in their etiology, according to our findings (10.0%/12 patients, 31.9%/38 patients, respectively). Myeloproliferative disease was detected in 25 patients (21.0%), and 14 patients (12.0%) were considered idiopathic. Protein C and S deficiency were the most common thrombophilia factors (27.7%/33 patients and 19.3%/23 patients, respectively).

Conclusion: In conclusion, non-cirrhotic PVT should be considered in every patient presenting with massive splenomegaly, variceal bleeding, abdominal pain, and pancytopenia, and these patients should be investigated for thrombophilia and myeloproliferative disease.

Keywords: Portal vein thrombosis, thrombophilia, myeloproliferative, cirrhosis, splenomegaly

ÖZ

Sirozu Olmayan Erişkin Hastalarda Oluşan Kronik Portal Ven Trombozunun Etyolojik Dağılımı

Giriş: Portal ven trombozu (PVT), portal hipertansiyonun kronik karaciğer hastalığı yokluğunda farklı klinik seyir ve tedavisi olan nadir sebeplerinden birisidir. Hastalığın yaş, cins ve etyolojik dağılımının iyi bilinmesi izlem ve tedavide çok önemlidir. Çalışmanın amacı sirozu olmayan kronik portal ven trombozlu hastaların etyolojilerine göre dağılımını belirlemektir.

Gereç ve Yöntemler: Bu çalışma tanımlayıcı, retrospektif olarak tasarlandı. Hacettepe Tıp Fakültesi Gastroentereloji bölümünde 40 yıl boyunca portal ven trombozu tanısıyla izlenen hastalar geriye dönük olarak tarandı. Kronik karaciğer hastalığı, siroz ve portal vene bası yapan herhangi tümoral oluşumlara bağlı portal ven obstruksiyonu dışlandıktan sonra toplam 119 hasta etyolojik dağılım açısından incelendi. Hastaların sosyodemografik özellikleri, hemogram, biyokimya, trombofili testleri, endoskopi ve görüntüleme sonuçları toplandı.

Bulgular: Hastaların ortalama yaşı 45.5 ± 15.3, ortalama tanı yaşları ise 36.0 ± 16.4 idi. Kadın hasta sayısı daha fazlaydı (kadın/erkek= 62/57). En sık karın ağrısı, karında şişlik, çabuk yorulma gibi nonspesifik şikayetlerle başvuran hastalarda başlıca fizik muayene bulgusu splenomegali idi. Hastaların büyük çoğunluğunun etyolojisinde bir ve birden fazla trombofilik faktör bozukluğu olduğu (sırasıyla, %10.0/12 hasta, %31.9/38 hasta), 25 hastada (%21.0) ise myeloproliferatif hastalık olduğu görüldü. On dört hasta (%12.0) ise idiyopatik olarak kabul edildi. Trombofili faktörleri arasında en sık görülen protein C ve S eksikliği idi (sırasıyla, %27.7/33 hasta, %19.3/23 hasta).

Sonuç: Sonuç olarak masif splenomegali, varis kanaması, karın ağrısı, pansitopeni ile gelen herbir hastada siroz dışı PVT düşünülmeli ve bu hastalar trombofilik durumlar, miyeloproliferatif hastalık açısından araştırılmalıdır.

Anahtar Kelimeler: Portal ven trombozu, trombofili, myeloproliferatif, siroz, splenomegali

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INTRODUCTION

The portal venous system formed by the venous vessels draining the intraperitoneal organs is characterized by low pressure. An increase in this pressure for any reason is defined as portal hypertension. The increased portal pressure gradient is determined by the pressure difference between the portal vein and the inferior vena cava or hepatic vein. This pressure gradient is normally less than or equal to 5 mmHg. A gradient of 6 mmHg or more suggests the presence of portal hypertension in most cases. If the gradient rises above 10 mm Hg, portal hypertension becomes clinically significant (1). This pressure is caused by obstruction or resistance to flow in the vascular bed. The most common causes of portal hypertension are cirrhosis and chronic parenchymal liver disease, but it also occurs when the liver parenchyma is normal. The most important cause of prehepatic non-cirrhotic portal hypertension is portal vein thrombosis (PVT) (2). PVT occurs because of the occlusion of the main, right, or left portal vein. According to autopsy reports, its incidence in the general population is 1% (3). It can be acute or chronic. There are many local, hereditary, and acquired causes. If the vessel wall occurs because of injury from the inside of the lumen, it is called primary, and if it is caused by external pressure (tumor, cyst, etc.), it is called secondary. It is generally multifactorial (3). There are focal inflammatory causes such as diverticulitis, appendicitis, inflammatory bowel diseases, and cholecystitis, as well as causes that may cause local damage to the portal vein such as colectomy and appendectomy (3,4). With the advances in thrombophilia testing and diagnosis of myeloproliferative diseases, the rate of diagnoses labeled as "idiopathic" decreased. For example, with the identification of the Janus kinase 2 (JAK 2) V617F gene mutation, the diagnosis of myeloproliferative disorders (such as polycythemia vera, essential thrombocythemia) known as the cause of PVT has increased by 20% (5). The most important etiological causes of PVT are myeloproliferative diseases and systemic causes including prothrombic events (5). Systemic inherited causes include factor 5 Leiden mutation, prothrombin mutation, MTHFR gene mutation, protein C and S deficiency, and acquired causes include myeloproliferative diseases, antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria, and hyperhomocysteinemia (6). Thrombophilic factors may vary depending on the functional state of the liver. Therefore, it is important to exclude cirrhosis or liver failure in causality assessments (6). Much rarer microbial causes of PVT such as cytomegalovirus, Bacteroides fragilis, and novel coronavirus (COVID19) have also been reported (7).

Knowing the etiology of non-cirrhotic portal vein thrombosis is important in terms of treatment and follow-up. In this study, we determined the etiological distribution of noncirrhotic portal vein thrombosis.

MATERIALS and METHODS

Data Source and Study Population

This study is based on my Internal Medicine Specialization Thesis (2011, Yöksis Thesis no: 282140). The study was conducted in accordance with the Declaration of Helsinki. The study population consists of patients who were followed up with the diagnosis of portal vein thrombosis at Hacettepe University Faculty of Medicine, Department of Gastroenterology between 1970 and 2011. Patient complaints, examination findings, risk factors, age, age at diagnosis, radiological imaging (Abdominal USG, Doppler USG, CT or MR-angiography), endoscopy results, thrombophilia factors, prothrombin levels, liver function test results were collected. After excluding patients with cirrhosis and/or tumor compressing the portal vein, the remaining 119 patients were included in the study.

Statistical Analysis

IBM SPSS Statistics 24 program was used in the analysis of the data. Categorical variables were expressed in crosstabs and numerical variables were expressed as mean, median, standard deviation, minimum and maximum.

RESULTS

The number of female patients (62 women/52.1%) was slightly higher than males (57 men/47.9%). The mean age of the patients was 45.5 ± 15.3, and the mean age at diagnosis was 36.0 ± 16.4. The mean follow-up period was 106.1 ± 93.4 months (Table 1).

Based on the complaints at the time of admission, it was discovered that 12 patients were diagnosed incidentally (without any active finding). It was observed that most of

Table 1. Sociodemographic characteristics of the patients

Variables	n	Mean ± sd	Min	Max
Age (years)	119	45.5 ± 15.3	15	82
Age of diagnosis (years)	119	36.0 ± 16.4	1	75
Follow-up time (months)	119	106.1 ± 93.4	2	495

n: Number of patients, sd: Standard deviation.

Table 2. The patients' complaints at admission, physical examination findings, comorbidities, and associated vein involvement in the main portal vein

	n= 119 (%100)					
Complaints	Nonspecific 46 (38.7)	Signs of anemia 6 (5.0)	GI bleeding findings 5 (4.2)	Asymptomatic 12 (10)	Ns + Sa 35 (29.4)	Ns + GI bf 15 (12.6)
*Physical examination	Splenomegaly 72 (60.5)	Dullness over Traube's space 66 (55.4)	Hepatosplenomegaly 16 (13.4)	No finding 11 (9.2)	Splenectomy 7 (5.9)	-
Additional illness	No 73 (61.3)	Diabetes mellitus 12 (10.1)	Hypertension 8 (6.7)	Heart disease 5 (4.2)	Thyroid disease 3 (2.5)	-
*Affected additional vein	No 60 (50.4)	Splenic vein 40 (33.6)	Superior mesenteric vein 34 (28.5)	Hepatic vein 6 (5.0)	-	-
*Endoscopy	Esophageal varices 73 (61.3)	Portal gastropathy 29 (24.4)	Normal 24 (20.2)	No data 20 (16.8)	-	-
Hepatic imaging	Mild chronic changes 63 (53)	Normal 56 (47)	-	-	-	-

N: Number of patients. *It may be accompanied by more than one in the same patient.
Ns (Nonspecific): Abdominal pain, distension.
Sa (Signs of anemia): Weakness, fatigue, tiredness.
GI bf (GI bleeding findings): Melena, hematochezia, hematemesis.

the patients applied with nonspecific complaints (abdominal pain, distension, and fatigue). Twenty of 119 patients (5 + 15 patients/16.8%) presented with gastrointestinal bleeding. When we investigated the physical examination findings at the time of admission, we found splenomegaly in 60.5% of the patients and dullness to percussion over Traube's space in 55.4%. It was observed that 9.2% of the patients had no significant physical examination findings (Table 2).

The most common comorbid systemic diseases were diabetes mellitus and hypertension (12 patients/10.1% and 8 patients/6.7%, respectively). The most common vessels accompanying the main portal vein involvement were the splenic vein and superior mesenteric vein (SMV) (40 patients/33.6% and 34 patients/28.5%, respectively). Esophageal varices were found to be prominent in the endoscopic evaluations of the patients when they were diagnosed (73 patients/61.3%). The upper endoscopy of 24 (20.2%) patients was normal. Endoscopy was performed in 99 of the patients at the time of diagnosis, and portal gastropathy was observed in approximately 1/3 of them (29 patients/24.4%). The patients were examined with various imaging methods (such as ultrasound, and magnetic resonance). It was reported that 63 (53%) patients had mild chronic changes in the liver parenchyma, and the liver parenchyma images were normal in 56 (47%) patients (Table 2).

Table 3. Etiological distribution of the patients

Disease	n (%)
Multiple thrombophilia factor disorders	38 (31.9)
Myeloproliferative disease	25 (21.0)
Idiopathic	14 (12.0)
Single thrombophilia factor disorder	12 (10.0)
Antiphospholipid syndrome	4 (3.4)
Behçet's disease	3 (2.5)
Others	12 (10)
No diagnostic evaluation	11 (9.2)
Total	**119 (100)**

It was concluded that no diagnostic research was conducted on 11 patients. Twenty-five patients had myeloproliferative disease [Polycytemia Vera (16 patients), Essential Thrombocytosis (six patients), Myelofibrosis (three patients)]. Three patients had Behçet's disease, and four patients had antiphospholipid syndrome. Thrombophilia factor disorder was observed in most patients (41.9%). Many had more than one factor deficiency (31.9%) (Table 3). The most common thrombophilia factor deficiency was protein C and S deficiency (27.7% and 19.3%) (Table 4).

Table 4. Thrombophilia factor distribution

Thrombophilia factors	n (%)
Protein C deficiency	33 (27.7)
Protein S deficiency	23 (19.3)
MTHFR gene mutation	14 (11.7)
Hyperhomocysteinemia	12 (10.0)
Factor Leiden 5 mutation or activated protein C resistance	7 (5.9)
Antithrombin 3 deficiency	6 (5.0)
Factor 8 or 9 elevation	6 (5.0)
PT 20210 mutation	2 (1.7)
Lipoprotein elevation	1 (0.8)
Total	**119 (100)**

DISCUSSION

In our study, the mean age of the patients was 45.5 ± 15.3, the number of women was slightly higher, and thrombophilic factor abnormalities and myeloproliferative diseases were prominent in their etiology.

The most important factor in determining the etiology of chronic PVT is the exclusion of local causes such as cirrhosis, primary or metastatic cancers of the liver, liver cysts, and other vascular anomalies (web, aneurysm). At this stage, imaging methods are very helpful in diagnosis. After excluding these causes, possible thrombophilic status and some special investigations would provide guidance (eg JAK2 mutation, bone marrow analysis) (8).

To determine the etiology of PVT, it is necessary to properly understand its pathophysiology. The pathophysiology is defined by the Virchow triad, which includes decreased portal blood flow, hypercoagulability, and vascular endothelial damage. Highly regulated proteins take an active part in the coagulation cascade. These proteins circulate in their inactive form (9,10). Coagulation is initiated when factor VII a binds to the tissue factor on the surface of endothelial cells or monocytes at the site of vascular injury. Factor VII is the only factor that circulates in significant amounts in its active form and constitutes factors Xa and IXa. These activated coagulation components bind to specific platelet receptors to activate prothrombin to form a prothrombinase complex and produce small amounts of thrombin. Antithrombin III and protein C and protein S systems oppose thrombin formation (9,10). Prothrombin is brought into close contact with the prothrombinase complex on the platelet surface. Thus, significant amounts of thrombin can be produced, which can convert soluble fibrinogen to insoluble fibrin (9,10).

Based on the studies conducted between 1979-1997, the etiology of chronic PVT was trauma (5%-17%), intra-abdominal sepsis (5%-36%), umbilical sepsis (5%-12%) (an important cause in children), pancreatitis (4%-5%) and prothrombotic diseases (2%-28%), yet the etiology could not be determined in approximately 50% of the patients (11). However, advances in medical care, potent antibiotic therapy, improved medical technology, research, and discovery of genetic thrombophilia factors, and the notion that myeloproliferative diseases are among the underlying causes have changed the etiology profile (11). In the study conducted by Rajani et al. on the etiology of PVT, thrombophilic status was found to be 22%, and myeloproliferative disease was found to be 11%. They found that more than one risk factor affected the etiology of 37% of patients with noncirrhotic PVT (12).

Denninger et al. suggested that 72% of patients with chronic PVT had an underlying prothrombic state. In a study of 36 patients, it was determined that 26 cases had one or more prothrombic conditions, and 30% of the patients had a myeloproliferative disease (13). In a study by Janssen et al. on the etiology of 92 patients with chronic PVT, factor 5 Leiden mutation was found in 7 patients (7.6%) and protein C deficiency was found in 6 patients (6.5%) (14). In a recent study in Türkiye, Factor 5 Leiden mutation was found in 6% of the patients, and MTHFR C677T homozygous gene mutation was found in 16% (15).

One of the interesting discoveries of medicine, JAK2 mutation (V617F activating tyrosine kinase mutation, JAK2) is held responsible for the development of Philadelphia chromosome-negative myeloproliferative diseases (MPD). This finding can be considered a milestone in the early detection of overt or latent MPD (16,17). In a study of the prevalence of JAK2 in patients with chronic PVT, the mutation was found in 17.2%-35.6% of the patients (11). In another study, the JAK2 V617F mutation was identified in six (21.4%) of 28 patients with idiopathic PVT or Budd-Chiari Syndrome (18).

It would be more accurate to think that there is more than one disease and factor in the etiology of chronic PVT. For example, someone with a myeloproliferative disease may have decreased liver function and decreased synthesis of prothrombotic factors. From this perspective, most chronic PVTs are multifactorial.

CONCLUSION

In this study, we discussed the etiological distribution of 119 patients with PVT who were not cirrhotic and had no compressive malignancy. One or more thrombophilic factor deficiencies and myeloproliferative diseases were the most common causes. A point to be considered is that most of these patients present with nonspecific complaints, such as abdominal pain, distension, weakness, and fatigue. These patients may not have thrombocytopenia or anemia in the lab-

oratory evaluation at presentation. This is because most of the patients have a myeloproliferative disease, and the complete blood count may be masked due to hypersplenism. On abdominal imaging, we observed that the basic structure of the liver was preserved. Finding esophageal varices and portal gastropathy on endoscopy in most of the patients may suggest chronic liver disease or cirrhosis in the differential diagnosis. To summarize, chronic non-cirrhotic PVT should be considered in the differential diagnosis of patients in their fourth and fifth decades who present with abdominal pain, abdominal distension, weakness, gastrointestinal bleeding, anemia findings, massive splenomegaly, or hypersplenism. Such patients should be evaluated for thrombophilic factors, myeloproliferative disease, and Behçet's disease. It should be noted that in some patients it may occur without any symptoms.

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