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Pattern of Vascular Involvement in Egyptian Patients with Budd-Chiari Syndrome: Relation to Etiology and Impact on Clinical Presentation

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ABSTRACT

Introduction and aim. Budd-Chiari syndrome (BCS) is caused by hepatic venous outflow obstruction. This work aims to analyze the pattern of vascular involvement in Egyptian patients with BCS, demonstrates its relation to etiology and shows its impact on clinical presentation. **Material and methods.** The current retrospective study was conducted at The Tropical Medicine Department, Ain Shams University on one hundred Egyptian patients with confirmed diagnosis of primary BCS who were presented to the Budd-Chiari Study Group (BCSG) from April 2014 to May 2016 by collecting clinical, laboratory and radiological data from their medical records. **Results.** Isolated hepatic vein occlusion (HVO) was the most common pattern of vascular involvement (43%), followed by combined HVO and inferior vena cava (IVC) compression by enlarged caudate lobe (32%), then combined HVO and IVC stenosis/webs (21%), and lastly isolated IVC occlusion (4%). Ascites was more significantly encountered in BCS patients with HVO than in those with isolated inferior vena cava (IVC) occlusion and patent HVs (P = 0.005). Abdominal pain was significantly encountered in patients with occluded three major HVs (P = 0.044). Behcet's disease was significantly detected in isolated IVC occlusion. Protein C deficiency was significantly detected in patients with combined HVO and IVC compression. **Conclusion.** Isolated HVs occlusion was the most common pattern of vascular involvement in Egyptian patients with primary BCS. Vascular pattern of involvement affected the clinical presentation and was related to the underlying thrombophilia in those patients.

Key words. Hepatic vein occlusion. Thrombophilia. Vena cava occlusion.

INTRODUCTION

Budd-Chiari syndrome (BCS) is a potentially life-threatening disorder that results from obstruction of the hepatic venous outflow at any level from the hepatic venules to the right atrium.[1] According to the etiology, BCS can be classified as primary (due to intraluminal thrombosis or webs) or secondary (due to intraluminal invasion by a parasite or a malignant tumor or extraluminal compression by an abscess, a cyst or a solid tumor).[2] Previous studies have shown that primary BCS should be regarded as a multifactorial disease due to the co-occurrence of several prothrombotic disorders. BCS patients from different geographic regions tend to show distinct disease etiologies. At least one hereditary or acquired pro-coagulative disorder is present in 74% of cases. It has been previously reported that intravascular thrombosis in patients with primary myeloproliferative disorders (MPD) was the most common etiological factor. As many as 30% of BCS patients carry a Factor V Leiden mutation (FVLM) and some showed the inherited deficiency of Protein C, S, and antithrombin III.[1,2]

The classic triad of abdominal pain, ascites, and hepatomegaly is considered non-specific.[3] According to the duration of liver disease, BCS can be classified as acute, subacute or chronic form; where the chronic form is the most common presentation.[4] Radiological imaging plays an important role in the evaluation of suspected cases of BCS. The relevant imaging modalities are Doppler ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) and hepatic venography.[5]

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BCS can be classified according to the site of obstruction into/small hepatic veins (HVs) occlusion which includes veins that cannot be shown clearly by hepatic venography or ultrasonography; large HVs occlusion which includes veins that are regularly demonstrable by hepatic venography and ultrasonography; inferior vena cava (IVC) occlusion, which includes a segment of the IVC extending from the entry level of the right, middle and left HVs to the junction between the IVC and the right atrium; and lastly combined obstruction of the large HVs and IVC.[6,7] Recently, BCS has been classified according to the site of obstruction into 3 types and 6 subtypes; Type I: "IVC lesions" including membranous lesions, short segmental occlusion (< 5 cm) and long segmental occlusion (> 5 cm), Type II: "lesions of HVs" including membranous lesions and diffuse occlusion, and Type III: mixed type (type I & II).[8]

The present study seeks analyzing the pattern of vascular involvement in Egyptian patients with BCS and demonstrating its relation to etiology and impact on clinical presentation in these patients.

MATERIAL AND METHODS

This retrospective cohort study enrolled one hundred Egyptian patients with confirmed diagnosis of primary BCS. They were referred to the Budd-Chiari Study Group (BCSG), Tropical Medicine Department of Ain Shams University Hospital (Cairo, Egypt) from April 2014 to May 2016. All patients provided an informed written consent for data collection and the study protocol was approved by the Research Ethical Committee of Faculty of Medicine, Ain Shams University according to the ethical guidelines of the 1975 Declaration of Helsinki.

Patients with other etiologies of liver disease unrelated to BCS (e.g. viral, autoimmune or metabolic), secondary BCS (due to intraluminal invasion by a parasite or a malignant tumor or extraluminal compression by an abscess, a cyst or a tumor) and those with hepatocellular carcinoma were excluded.

Documented diagnosis of primary BCS was done through a stepwise abdominal imaging assessment including Doppler ultrasonography, contrast-enhanced or multislice computed tomography (CT) and/or magnetic resonance imaging (MRI) in patients with clinically suspected BCS (after excluding cases with secondary BCS).

Data of the patients were retrieved from their medical records regarding the following points:

- Complete clinical data.
- Laboratory investigations included a complete blood count (CBC), a liver profile, and a coagulation profile. A thrombophilia workup was done to determine the underlying etiology of BCS. It included the assessment of anti-cardiolipin antibodies, lupus anticoagulant, antinuclear antibodies (ANAs), protein C, protein S, antithrombin III, factor V Leiden mutation (FVLM), prothrombin, and methylene tetrahydrofolate reductase (MTHFR) gene mutations. Additionally, flow cytometry quantitating CD55 and CD59 levels were performed to diagnose paroxysmal nocturnal hemoglobinuria (PNH). JAK2 mutational status was assessed, and/or a bone marrow biopsy for detecting the possible presence of a myeloproliferative disorder (MPD).
- Imaging techniques: included abdominal Doppler ultrasonography which was performed to assess the status of the major HVs whether patent or occluded and number of occluded veins; the status of IVC regarding its diameter, patency, occlusion or compression and description of the pattern of its occlusion whether isolated or associated with HVs occlusion; the status of the portal vein (PV) regarding its diameter, patency or occlusion, and description of the pattern of its occlusion; and lastly the status of extra and intrahepatic collaterals. Data of multi-slice computed tomography (CT) and/or magnetic resonance venography (MRV) were recorded in cases of non-conclusive Doppler ultrasound findings.

Statistical Analysis

The qualitative data were presented as number and percentages while the quantitative data were presented as mean, standard deviations (SD), and ranges. Analysis of variance (ANOVA) was used to test the difference between mean values. Multiple comparisons between pairs of groups were performed using LSD (Post hoc range test) where results were presented as mean and SD.

Chi-Square test χ^2 and Fisher's Exact Test were used to test the difference in proportions of variables among the presentations.

All data were analyzed using SPSS version 17. A P-value less than 0.05 was considered significant (S); a P-value less than 0.01 was considered highly significant (HS), and a P-value less than 0.001 was considered very highly significant (VHS).

RESULTS

The present study enrolled 100 Egyptian patients with primary BCS. There were 57 females (57%) and 43 males (43%). Their mean age was 27.24 ± 7.64 years (Range: 16-55 years). 18% of our patients had a fulminant form of presentation with marked jaundice and hepatic encephalopathy, while 16% had acute presenting form and 66% had

the chronic form (duration of disease > 6 months). Abdominal enlargement was the most common clinical presentation (90%) among the studied patients followed by abdominal pain (80%). Hepatomegaly (88%), ascites (80%), hepatic tenderness (53%) and splenomegaly (62%) were the most frequent clinical findings on examination. Other clinical findings were hepatic encephalopathy (23%), lower limb edema (59%), jaundice (43%), oral & genital ulcers (6%), and dilated veins over the trunk (30%).

As regards the etiologies of BCS in our enrolled cohort, the most common underlying thrombophilia was protein C deficiency (42%), followed by myeloproliferative disorder (MPD) (39%), protein S deficiency (39%), antiphospholipid antibody syndrome (APA) (38%), Methyl tetrahydrofolate reductase deficiency (MTHFR) (27%), and factor V Leiden mutation (FVLM) (23%). Multiple etiologies were present in 55% of patients.

Table 1 shows the findings of abdominal Doppler ultrasonography among the studied patients. 96% of patients showed occluded HVs with or without IVC involvement, while 4% had isolated IVC occlusion along with patent HVs.

Table 1 Patterns of vascular involvement among patients subject to study (n=100).

Findings		N	(%)
HVs: patency	Occluded	96	(96)
	Patent	4	(4)
Occluded HVs: number	0	4	(4)
	Single HV	4	(4)
	2 HVs	18	(18)
	3 HVs	74	(74)
Portal vein: diameter (mm)	Mean ± SD	10.93 ± 1.94	
	Range	8 - 18	
Portal vein: patency	Occluded	7	(7)
	Patent	93	(93)
IVC: diameter	Mean ± SD	19.28 ± 4.71	
	Range	9 - 30	
IVC: pattern of occlusion	Occluded	4	(4)
	Stenosis	12	(12)
	Webs	9	(9)
	Compression	32	(32)
	Patent	43	(43)
Detailed pattern of vascular involvement			
Isolated HVO		43	(43)
Isolated IVC occlusion		4	(4)
Combined HVs and IVC occlusion		0	
Combined HVO and IVC stenosis		12	(12)
Combined HVO and IVC webs		9	(9)
Combined HVO and IVC compression		32	(32)

HV: hepatic vein. HVO: hepatic vein occlusion. IVC: Inferior vena cava.

Single HV occlusion was detected in 4%, two HVs occlusion in 18% and three HVs occlusion in 74% of studied cases.

Patients with occluded HVs were distributed as follows: isolated hepatic vein occlusion (HVO) (43%), combined HVO and IVC narrowing by stenosis (12%), HVO combined with narrowing of IVC lumen by venous webs (9%), and HVO combined with IVC compression by hypertrophied caudate lobe (32%).

Table 2 shows a comparison between patients with occluded HVs and those with patent HVs regarding demographic and clinical data. The Presence of arthralgia and ascites were significantly detected among the group of occluded HVs (P = 0.005).

We compared between patients with single HVO, those with two occluded HVs and those with three occluded HVs. We found that abdominal pain was statistically significant (P = 0.04) where it was the main presenting symptom in 86% of patients with the three occluded HVs, 75% in patients with single occluded HV, and 61% in patients with two occluded HVs.

As regards the relation between the clinical presentation and the detailed pattern of vascular involvement (HVO, IVC thrombosis, stenosis/webs or compression), we found that both lower limb edema and tender hepatomegaly were significantly detected among patients with isolated IVC thrombosis (P = 0.020 and 0.006, respectively) (Table 3).

The Impact of different patterns of vascular involvement of BCS on the severity of its clinical presentations (whether fulminant, acute or chronic); showed a non-significant statistical difference (Table 4).

The most common etiologies of isolated HV thrombosis were protein S deficiency (48.8%), protein C deficiency (41.9%), antiphospholipid antibody syndrome (APA) (32.6%), Methyl tetrahydrofolate reductase mutation (MTHFR) (30.2%) and factor V Leiden mutation (FVLM) (20.9%). JAK2V617F mutation (as a sensitive marker for diagnosis of myeloproliferative disorders) has been observed in only 9.3% of patients with isolated HVO. In patients with isolated IVC occlusion, the most common etiological factor was Behcet's disease (100%) (Table 5).

DISCUSSION

The currently accepted definition of primary BCS is hepatic venous outflow obstruction regardless of its cause or level.[7,9] The obstruction can range from the small HVs to the IVC orifice into the right atrium and its location is clinically and prognostically significant.[10] It has been previously reported that the clinical manifestations of BCS can be explained by the site of venous obstruction whether within the HVs or the IVC.[11-14] A recent systematic re-

Table 2 Comparison between patients with occluded HVs and those with patent HVs regarding demographic and clinical data.

		Occluded HVs (n = 96) N (%)	Patent HVs* (n = 4) N (%)	P-value
Age	Mean ± SD Range	27.20± 7.64 16-55	28.25 ±8.69 19-40	0.789
Sex	Female Male	55 (57.3) 41 (42.7)	2 (50.0) 2 (50.0)	0.773
Abdominal pain	Negative Positive	18 (18.8) 78 (81.2)	2 (50.0) 2 (50.0)	0.126
Photo sensitivity	Negative Positive	73 (76.0) 23 (24.0)	4 (100.0) 0 (0.0)	0.265
Arthralgia	Negative Positive	17 (17.7) 79 (82.3)	3 (75.0) 1 (25.0)	**0.005**
Oral and genital ulcers	Negative Positive	96 (100.0) 0 (0.0)	0 (0.0) 4 (100.0)	0.606
Jaundice	Negative Positive	55 (57.9) 40 (42.1)	1 (25.0) 3 (75.0)	0.194
Encephalopathy	Negative Positive	73 (76.0) 23 (24.0)	4 (100.0) 0 (0.0)	0.265
Dilated veins over the trunk	Negative Positive	68 (70.8) 28 (29.2)	2 (50.0) 2 (50.0)	0.373
Hepatomegaly	Negative Positive	11 (11.5) 85 (88.5)	1 (25.0) 3 (75.0)	0.568
Ascites	Negative Positive	17 (17.7) 79 (82.3)	3 (75.0) 1 (25.0)	**0.005**

** All have isolated IVC thrombosis. HV: hepatic vein.*

Table 3 Relation between the clinical presentation and the detailed pattern of vascular involvement (HVO, IVC thrombosis, stenosis/webs or compression) among patients subject to study.

	Isolated HVO (n = 43)		Combined HVO and IVC stenosis/webs (n = 21)		Combined HVO and IVC Compression (n = 32)		Isolated IVC thrombosis (n = 4)		P-value
	N	%	N	%	N	%	N	%	
Abdominal enlargement	40	93	18	85.7	28	87.5	4	100	0.675
Abdominal pain	37	86	17	81	23	71.9	3	75	0.498
Encephalopathy	10	23.2	6	28.6	5	15.6	2	50	0.392
Lower limb edema	20	46.5	17	81	18	56.3	4	100	0.020*
Jaundice	16	37.2	20	95.2	6	18.8	1	25	4.800
Oral & Genital Ulcers	1	2	2	9.5	2	6.25	1	25	0.255
Ascites	35	83.3	16	76.2	27	84.4	2	50	0.411
Hepatomegaly	38	88.4	19	90.4	27	84.4	4	100	0.784
Splenomegaly	31	72.1	11	52.4	17	53.1	3	75	0.257
Tender liver	26	60.4	15	71.4	9	28.1	3	75	0.006**
Dilated veins over the trunk	16	37.2	5	23.8	7	21.9	2	50	0.359

*HVO: hepatic vein occlusion. IVC: inferior vena cava. * Isolated IVC thrombosis* vs. *Isolated HVO. ** Isolated IVC thrombosis* vs. *Combined HVO and IVC Compression.*

Table 4 Impact of different patterns of vascular involvement of BCS on the severity of its clinical presentations; (whether fulminant, acute or chronic) among patients subject to study.

	Isolated HVO (n = 43)		Combined HVO and IVC stenosis/webs (n = 21)		Combined HVO and IVC Compression (n = 32)		Isolated IVC thrombosis (n = 4)		P-value
	N	%	N	%	N	%	N	%	
Fulminant	8	18.6	0	0	9	28.1	1	25	0.073
Acute	5	11.6	5	23.8	5	15.6	1	25	0.613
Chronic	30	69.8	16	76.2	18	56.3	2	50	0.383

HVO: hepatic vein occlusion, IVC: inferior vena cava.

Table 5 Relation between the etiology of BCS[1] and the pattern of vascular involvement in patients subject to study.

	Isolated HVO N = 43		HVO + IVC stenosis webs N = 21		HVO + IVC Compression N = 32		Isolated IVC thrombosis N = 4		P-value
	n	%	n	%	n	%	n	%	
APA	14	32.6*	10	47.6*	14	43.8	0	0	**< 0.05***
PC	18	41.9	17	80.9*	7	21.9	0	0	**< 0.0001***
PS	21	48.8*	11	52.4	7	21.9	0	0	**< 0.05***
AT3	9	20.9	7	33.3	10	31.3	3	75	> 0.05
PNH	4	9.3*	14	66.7*	6	18.9	0	0	**< 0.0001***
FVLM	9	20.9*	11	52.4*	2	6.3	1	25	**< 0.001***
MTHFR	13	30.2	6	28.6	8	25	1	25	> 0.05
MPD	4	9.3*	17	80.9*	15	46.9	3	75	**< 0.001***
Behcet	0	0*	0	0*	0	0*	4	100*	**< 0.0001***

*HVO: hepatic vein occlusion. PVT: portal vein thrombosis. IVC: inferior vena cava. APA: antiphospholipid antibody syndrome. PC: protein C deficiency. PS: protein S deficiency. AT3: antithrombin 3 deficiency. PNH: paroxysmal nocturnal haemoglobinuria. FVLM: factor V Leiden mutation. MTHFR: methyl tetrahydrofolate reductase mutation. MPD: myeloproliferative disorder. [1] Multiple etiologies were detected in 55% of patients. * Significance is detected among groups marked by (*) in each row.*

view proposed a clarification of the general BCS term into either the classical BCS (isolated hepatic vein thrombosis, HVT) or the hepatic vena cava-Budd Chiari syndrome (HVC-BCS).[12]

The current study was performed to evaluate the pattern of hepatic venous outflow tract involvement in Egyptian patients with BCS/ and to demonstrate its relation to the etiology and its impact on clinical presentation. In the current study, the patterns of vascular involvement were isolated HVO in 43% (the most common one), isolated IVC obstruction in 4%, combined HVO and IVC stenosis in 12%, combined HVO and IVC webs in 9%, and finally combined HVO and IVC compression in 32% of cases. Our results agreed with Darwish, *et al*.[15] who studied 163 incident BCS cases and found 80 (49%) patients were presented with isolated HVO, 4 (2%) had isolated IVC occlusion and 79 (48%) had combined HVO and IVC occlusion. Recently, Zhou, *et al*.[16] studied 338 cases with BCS; they concluded that there were 8 cases (2.4%) of isolated IVC membranous obstruction, 45 cases (13.3%) of isolated HVO, and 285 cases (84.3%) with both IVC membranous obstruction and HVO.

In our series, the chronic presentation of BCS was the most common one; this is consistent with a previous Egyptian study performed by Sakr, *et al*. in 2011.[17]

Regarding the impact of vascular involvement pattern on the clinical presentation of BCS in the current study, there was a statistically significant association between arthralgia and the HV involvement. Whenever the etiology of Budd-Chiari syndrome is related to an autoimmune disease like antiphospholipid antibody syndrome, arthralgia is a common symptom and this reflects the severity of presentation. In the current study, antiphospholipid antibody syndrome was detected in 32.6% of cases with isolated HV thrombosis and in nearly 50% of those with HV thrombosis + IVC compression or stenosis.

In our study, the main clinical data in the group of patients with isolated HVO were abdominal pain, abdominal enlargement due to ascites and hepatomegaly. In addition, lower limb edema and dilated veins over the abdomen and the trunk were more prevalent in patients with isolated IVC occlusion. This is in agreement with Darwish, *et al*.[15]

Eapen, *et al*.[18] postulated that the clinical features of different patterns of vascular involvement in BCS often over-

lap. In a patient with isolated HVO, extrinsic compression of the IVC by the engorged liver especially hypertrophied caudate lobe can lead to clinical features of combined type.

The disease severity depends on both the extent of obstruction (number of occluded vessels, complete or incomplete occlusion)/ and the chronicity of symptoms.[12] In the current study, we compared between patients with single HVO, those with two occluded HVs and those with three occluded HVs. We found that abdominal pain was statistically significant (P = 0.04) where it was the main presenting symptom in 86% of patients with the three occluded HVs, 75% in patients with single occluded HV, and 61% in patients with two occluded HVs.

Accurate determination of the number of occluded HVs and the pattern of their occlusion whether long or short segment stenosis has a prognostic and a decision-making important role. Eldorry, *et al.*[19] emphasized the importance of early intervention, especially by performing angioplasty and stenting in patients with two occluded HVs, to avoid the occurrence of complications as well as to relieve symptoms, and as a bridge to liver transplantation. In patients with three occluded HVs, it is urgent to perform transjugular intrahepatic portosystemic stent shunting (TIPSS) to avoid consequences of portal hypertension, and as a bridge for liver transplantation.[19] In the current study, we did not find any impact of different patterns of vascular involvement of BCS on the disease severity, the matter which may be attributed to variations in the collaterals that develop to overcome venous obstruction in such patients.

The etiology of BCS changes according to the geographical distribution, while thromboses are more common in the West, webs are more common in the East and in Japan.[20] Recent data from many centers have shown that primary BCS must be regarded as a multifactorial disease because several prothrombotic disorders may share for its development.[21]

In our series, the most common thrombophilic causes of isolated HV thrombosis among the enrolled cohort were protein S deficiency (48.8%), protein C deficiency (41.9%), antiphospholipid antibody syndrome (APA) (32.6%), Methyl tetrahydrofolate reductase mutation (MTHFR) (30.2%) and factor V Leiden mutation (FVLM) (20.9%). Myeloproliferative disorders (MPD) have been observed in only 9.3% of patients with isolated HVO.

Several studies continue to report MPD as the most common cause of classical BCS or isolated HVO, with an incidence ranging from 41% to 62% in a recent systematic review.[12] Out of these studies, the largest one was the study reported by Seijo, *et al.*[22] who studied 157 patients with BCS and stated that 33% of their series with classic BCS had MPD as the underlying etiology, while inherited thrombophilia was reported as follows: FVLM (12%), prothrombin gene mutation (3%), protein C deficiency (3%), antithrombin III deficiency (3%) and protein S deficiency (2%). In fact, BCS patients from different geographical regions tend to have different disease etiologies.

On the other hand, several large Chinese studies agree with our results and stated that MPD was only found in 4%-5% of primary BCS patients.[23,24]

In the current study, the most common etiological factor was Behçet's disease (100%) in patients with isolated IVC occlusion. Sakr, *et al.*[17] agreed with our results as they found a highly significant positive relationship between the presence of Behçet's disease and IVC occlusion, either alone or combined with HVO.[17]

In our study, membranous obstruction of the IVC was documented in 9% of cases. Membranous obstruction of the IVC was previously listed as one of the etiologies of BCS.[12] In classical BCS patients, membranous obstruction is rare (1%), except in one study of 23 consecutive patients diagnosed with BCS in Germany, where five patients (22%) were found to have a membranous obstruction of the IVC.[15]

To the best of our knowledge, this is the first and largest study of BCS in Africa and Middle East that shows the pattern of vascular involvement in BCS , demonstrates its relation to etiology and its impact on clinical presentation. The study has a limitation in fewer number of patients having isolated IVC obstruction.

CONCLUSION

Isolated HVs occlusion was the most common pattern of vascular involvement in Egyptian patients with primary BCS. The pattern of vascular involvement affected the clinical presentation and was related to the underlying thrombophilia in those patients.

ABBREVIATIONS

- **ANA:** antinuclear antibody.
- **BCS:** budd-Chiari syndrome.
- **BCSG:** budd-Chiari study group.
- **CBC:** complete blood picture.
- **CD:** cluster of differentiation.
- **CT:** computed tomography.
- **FVLM:** factor V Leiden mutation.
- **GIT:** gastrointestinal tract.
- **HCC:** hepatocellular carcinoma.
- **HS:** highly significant.
- **HVO:** hepatic vein occlusion.
- **HVs:** hepatic veins.
- **IVC:** inferior vena cava.
- **JAK II:** janus tyrosine kinase-2.
- **MELD:** model for end-stage liver disease.

- **MRI:** magnetic resonance imaging.
- **MRV:** magnetic resonance venography.
- **MTHFR:** methyl tetrahydrofolate reductase mutation.
- **PNH:** paroxysmal nocturnal haemoglobinuria.
- **US:** ultrasound.

COMMERCIAL RELATIONSHIP

None.

CONFLICTS OF INTEREST

None of the authors has any conflicts of interest and no financial support is provided.

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