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Clinical Characteristics and Outcome of Budd-Chiari Syndrome at a Tertiary Care Hospital in Pakistan.

Om Parkash
Aga Khan University, om.parkash@aku.edu

Aysha Khan
Aga Khan University

Saeed Hamid
Aga Khan University, saeed.hamid@aku.edu

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Om Parkash[1], Aysha Khan[2] and Saeed Hamid[1]

Abstract

Objective: To determine the clinical characteristics of Budd-Chiari syndrome (BCS), its causes and outcome at a tertiary care hospital.

Study Design: An observational study.

Place and Duration of Study: The Aga Khan University Hospital, Karachi, from 2004 to 2014.

Methodology: A retrospective analysis of data was conducted. A predesigned questionnaire was filled from medical records of patients with BCS. Clinical features, etiology, management and outcome was noted from 2004 to 2014. Descriptive statistics were determined.

Results: Forty-five patients' charts were reviewed; 26 (57.8%) were male patients. The median (IQR) age at diagnosis was 26.0 (20.5 to 34.5) years. Primary BCS was seen in 27 (60.0%) patients. The most frequent clinical features included ascites (82.2%), abdominal pain (55.6%), and hepatomegaly (31.1%). A combined hepatic vein/inferior vena cava block was found in 25 (55.6%) patients. Out of the 28 tested patients protein C and protein S deficiencies were detected in 22 (78.6%) and 17 (60.7%) patients, respectively. Antithrombin III deficiency was detected in 14 (58.3%) of those tested patients. Anticoagulants were used in 24 (53.3%) patients. TIPS was done in 11 (24.4%) patients. Mortality was 6.7% (n=3).

Conclusion: Congenital thrombophilia was a major causal factor. Age, clinical features, biochemistry and management are important factors in survival.

Key Words: *Budd-Chiari syndrome. Hepatic vein. Thrombophilia.*

INTRODUCTION

Budd-Chiari syndrome (BCS) is characterized by the obstruction of the hepatic venous outflow tract which can be at the level of the hepatic venules, hepatic veins (HV), inferior vena cava (IVC) or a simultaneous HV/IVC block.[1] Obstruction due to cardiac or pericardial diseases and sinusoidal obstruction syndrome (SOS) are not considered as BCS.[2]

Mostly patients with BCS have an underlying thrombophilic disorder, i.e. primary BCS. This can be inherited as protein C, protein S, antithrombin III deficiencies or factor V Leiden (FVL) mutation, or acquired as mostly myeloproliferative disorders (MPD).[3] Compression or invasion of venous structures due to an external source, such as a neoplasm, results in secondary BCS.[4] Clinical manifestations of BCS vary from asymptomatic to symptomatic; acute, subacute, chronic or fulminant. Classical signs include abdominal pain, ascites, and hepatomegaly.[3] Other manifestations include pedal edema, jaundice, splenomegaly, gastro-intestinal bleeding and hepatic encephalopathy.[5]

Department of Medicine[1] / Medical Student[2], The Aga Khan University, Karachi.

Correspondence: Dr. Om Parkash, Assistant Professor, Section of Gastroenterology, Department of Medicine, The Aga Khan University, Karachi.
E-mail: om.parkash@aku.edu

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There is a lack of evidence-based strategies regarding the management of BCS in South Asia like those mentioned in the EASL and AASLD practice guidelines. Anticoagulation and thrombolysis is the first-line treatment, followed by angioplasty/stenting for those patients with short-length stenosis.[6] Transjugular intrahepatic portosystemic shunt (TIPS) is the next step, while liver transplantation (LT) is the ultimate rescue option.[7] As there is a dearth of published literature from Pakistan reporting the trends, clinical features and outcome of this syndrome in our population, this study was focused on these clinical aspects of BCS which will enhance the understanding of the disease spectrum in local population.

The aim of this study was to determine the clinical characteristics of Budd-Chiari syndrome (BCS), its causes and outcome at a tertiary care hospital.

METHODOLOGY

A retrospective analysis of data was conducted at the Aga Khan University Hospital after permission was obtained from the Ethical Review Committee. A proforma was used for data collection which included demographics, history and examination findings, investigations, course and disease outcome. Medical records of patients with BCS diagnosed on the basis of imaging, admitted from 2004 to 2014, were obtained from the Health Information Management Services (HIMS).

Patients diagnosed with other comorbid conditions such as hypertension, diabetes mellitus and ischemic heart disease were excluded from the study. Forty-five patients' charts were reviewed for the study.

Continuous variables were described as mean ± standard deviation (SD) or median (IQR), and categorical variables were presented as a number (%). SPSS version 19 was used to develop the frequency tables.

RESULTS

There were 26 (57.8%) male patients. The median IQR (interquartile range) age at diagnosis was 26.0 (20.5 to 34.5) years.

Twenty-seven (60.0%) patients were classified as primary BCS, while 3 (6.7%) patients were classified as secondary BCS. The diagnosis of the type of BCS was not confirmed in the remaining 15 (33.3%) patients.

Thirty-six (80.0%) patients presented with abdominal distension, and 25 (55.6%) complained of abdominal pain. On physical examination, 37 (82.2%) patients had ascites and 20 (44.4%) had abdominal tenderness (Table I).

Table I: Clinical features of BCS.

Clinical features	n=45	Percentage of n (%)
Male patients	26	57.8
Female patients	19	42.2
Ascites	37	82.2
Abd. distension	36	80.0
Abd. pain	25	55.6
Jaundice	25	55.6
Abd. tenderness	20	44.4
Pedal edema	18	40.0
Hepatomegaly	14	31.1
Splenomegaly	10	22.2
GI bleeding	8	17.8
Spider nevi	6	13.3
Fever	5	11.1
Encephalopathy	2	4.4

Table II: Etiology of BCS.

Etiological factor	Patients tested/ accounted for	Patients w/positive etiology	Percentage (%)
Protein C deficiency	28	22	78.6
Protein S deficiency	28	17	60.7
Antithrombin III deficiency	24	14	58.3
Factor V Leiden mutation	17	5	29.4
Postpartum period	19	3	15.8
Myeloproliferative disorder	45	3	6.7
Hyperhomocysteinemia	45	3	6.7
MOVC	45	3	6.7
HCC	45	2	4.4
Antiphospholipid syndrome	31	1	3.2
Prothrombin gene mutation	45	1	2.2
PNH	45	1	2.2
Hydatid cyst disease	45	1	2.2

MOVC = Membravous obstruction of veva cava; HCC = Hepatocellular carcinona; PNH = Paroxysmal nocturnal hemoglobinuria.

Patients were classified as those with primary and secondary BCS on the basis of the etiological workup (Table II). Twenty-two (78.6%) and 17 (60.7%) out of the 28 tested patients had protein C and protein S deficiencies, respectively. Out of the 24 patients who were tested, 14 (58.3%) patients had antithrombin III deficiency. Three (6.7%) patients had myeloproliferative disorder. Three (6.7%) patients had webs in the IVC resulting in obstruction. Out of the 3 patients with secondary BCS, 2 had hepatocellular carcinoma (HCC).

Using imaging modalities including US Doppler and/or CT angiography, 25 (55.6%) patients were seen to have a combined HV/IVC block, 11 (24.4%) had an isolated HV block, and 3 (6.7%) had an isolated IVC block. Venous collaterals were present in 11 (24.4%) patients. Caudate lobe hypertrophy was reported in 18 (40%) patients, hepatomegaly was seen in 27 (60%) patients and splenomegaly in 20 (44.4%) patients. Esophagogastroduodenoscopy (EGD) was performed in 28 (62.2%) patients, while 22 (48.8%) patients were reported to have esophageal varices.

Out of 45 patients, 42 (93.3%) survived. Of these, 30 (66.7%) patients had a chronic course. The course and outcome of the disease has been summarized in Table III. Death was the outcome in 3 (6.7%) patients. Of these, 2 (4.4%) had an acute course and died as a result of septic shock, and 1 (2.2%) developed hepatic encephalopathy, followed by heart failure, after a chronic course.

Table III: Course and outcome of BCS.

Course of BCS	n=45	Percentage (%)
Inpatients who survived	42	93.3
Chronic	30	66.7
Subacute	8	17.8
Acute	2	4.4
Fulminant	2	4.4
Inpatients who died	3	6.7
Acute	2	4.4
Chronic	1	2.2

For management, antiplatelet agents (Aspirin 75 mg/ Clopidogrel 75mg) were given to 5 (11.1%) patients; anticoagulants were used in 24 (53.3%) patients and thrombolytic therapy in 1 (2.2%) patient. For symptomatic therapy, proton-pump inhibitors were used in 34 (75.6%) patients, diuretics in 27 (60.0%) patients and antiemetic agents in 28 (62.2%) patients. Angioplasty/stenting was done in 5 (11.1%) patients. Eleven (24.4%) patients underwent TIPS; mesocaval shunt was done in 1 (2.2%) patient after TIPS failure. No liver transplants were done in our setting, but patients were referred to other places for getting a liver transplant.

DISCUSSION

BCS has been seen to vary epidemiologically from one place to another. In a study from Western India, the highest prevalence was seen during the ages of 21-40

years, with women contributing towards most of the cases falling between ages 31-40 years.[8] Plessier and Valla have mentioned in their article, in 2008, that men show a higher prevalence in Asia; whereas in western countries, women have taken the lead.[2] In this study, there were more men than women. However, this could be due to the patriarchal society of Pakistan, where female health issues are underreported.

Most of the patients with BCS present with ascites, abdominal pain, and hepatomegaly.[9] Ascites has been seen as the most common symptom, being present in more than 80% of the patients in one study from India and in another from Pennsylvania.[10,11] Such was also the case in this study.

Chronic presentation is the most common among BCS patients.[5] In a study from Turkey, more than half of the patients had the chronic form, while the acute and subacute forms had much lower representation.[12] Similarly, in this study, the most common presentation was a chronic course.

BCS has been classified as primary or secondary. In a study including 115 patients, from Algeria, primary BCS was reported in 109 (94.7%) patients and secondary BCS was reported in 6 (5.3%) patients.[13] This is similar to the present study, which also showed a predominance of primary BCS.

Different prothrombotic conditions have been described as etiological factors for primary BCS. Congenital thrombophilia is more common etiology in western countries.[5] However, there have been studies from the East which showed hereditary deficiencies as the major cause of BCS. In a study from Western India, FVL mutation was seen as the most common state of hereditary thrombophilia and antithrombin III deficiency as the least common.[8] In another study, protein C deficiency has been seen as the most common cause among congenital hypercoaguable states, resulting in BCS.[14] In this study, protein C deficiency was the most common hereditary predisposing condition to thrombosis as well, followed by Protein S and antithrombin III deficiencies. However, some of these deficiencies could have been a result of chronic liver disease. PT value helps evaluate whether this is truly an inherited deficiency or not. The median value (IQR) of PT was 15.9 (13.4 to 21.0) seconds. Twenty-nine (14.5%) patients had a higher than normal value for PT. A positive family history for these deficiencies also helps confirm their hereditary nature,[15] but accounting for data from relatives was not quite economical in the study setting.

Membranous obstruction of the IVC (MOVC) has been described as the major cause of BCS in eastern countries.[5,12] In this study, only 3 (6.7%) patients had webs in the IVC causing obstruction.

Generally, MPD are known to be the most common cause of BCS, with polycythemia vera (PV) occurring with the highest frequency and accounting for 10-40% cases of BCS.[16] Previous studies have had results which described MPD as the predominant causal factor, being present in 70%, and 34% of the patients in two different studies.[13,17] However, among our patients, the prevalence of MPD was quite low, with only 3 (6.7%) patients representing cases secondary to PV. The detection of JAK2 V617F mutation helps make the diagnosis of MPD.[18] Two patients in this series with PV tested positive for this mutation.

Pregnancy is one of the precipitating factors of BCS, especially in eastern countries.[19] In this study, 3 (15.8%) female patients were seen to have pregnancy as one of the potential causal factors of BCS. FVL mutation has been observed to be present in most of the cases associated with pregnancy.[16,17] In this study, 1 of the 3 women having a history of recent pregnancy also tested positive for the FVL mutation. However, she was not classified as primary BCS, because on CT scan, she was seen to have a cyst in segment VIII of the right lobe of her liver which was resulting in direct compression of the IVC. She was confirmed as a case of hydatid cyst disease, and therefore, classified as a case of secondary BCS. In one study, from Turkey, hydatid cyst disease was the second highest cause of BCS among all the patients.[12]

Isolated hepatic vein obstruction has been described as the most common anatomy in BCS, followed by a combined HV and IVC obstruction. Isolated IVC obstruction is relatively low.[12] This study also described isolated IVC obstruction as the least common type of obstruction. However, a combined obstruction of HV and IVC was the most common type seen in this study, followed by isolated HV obstruction.

Most of these patients survived the disease with death being the outcome in 3 (6.7%) patients. This is a much lower number than that reported in other studies with death rates as high as 21.3% and 27.0%, respectively.[6,11]

This study is limited to its small sample size and retrospective nature. Also, because of financial constraints, not all patients were tested for all the etiological factors. Hence, further research is required to fully encompass the understanding of this disease and its management.

CONCLUSION

This study has elucidated features regarding the clinical aspects and course of BCS, which will be conducive to wise decision-making regarding the management of this condition.

REFERENCES

1. Riggio O, Marzano C, Papa A, Pasquale C, Gasperini M, Gigante A, *et al*. Small hepatic veins Budd-Chiari syndrome. *J Thromb Thrombolysis* 2013; **37**:536-9.

2. PlessierA, Valla D. Budd-Chiari syndrome. *Semin Liver Dis* 2008; **28**:259-69.
3. Menon K, Shah V, Kamath P. The Budd-Chiari Syndrome. *New Engl J Med* 2004; **350**:578-85.
4. Balaceanu L, Diaconu C, Aron G. Budd-Chiari syndrome as an initial presentation of hepatocellular carcinoma: a case report. *Med Ultrason* 2014; **16**:172-4.
5. Akamatsu N, Sugawara Y, Kokudo N. Budd-Chiari syndrome and liver transplantation. *Intractable Rare Dis Res* 2015; **4**:24-32.
6. Mancuso A. An update on management of Budd-Chiari syndrome. *Ann Hepatol* 2014; **13**:323-6.
7. Mancuso A. Budd-Chiari syndrome management: Lights and shadows. *World J Hepatol* 2011; **3**:262.
8. Mohanty D, Shetty S, Ghosh K, Pawar A, Abraham P. Hereditary thrombophilia as a cause of Budd-Chiari syndrome: A study from Western India. *Hepatology* 2001; **34**:666-70.
9. Hefaiedh R, Cheikh M, Marsaoui L, Ennaifer R, Romdhane H, Nejma H. *et al*. The Budd-Chiari syndrome. *La Tunisie Medicale* 2013; **91**:376-381.
10. Amarapurkar D, Punamiya S, Patel N. Changing spectrum of Budd-Chiari syndrome in India with special reference to non-surgical treatment. *World J Gastroenterol* 2008; **14**:278.
11. Pavri T, Herbst A, Reddy R, Forde K. Budd-Chiari syndrome: A single-center experience. *World J Gastroenterol* 2014; **20**: 16236-44.
12. Uskudar O, Akdogan M, Sasmaz N, Yilmaz S, Tola M, Sahin B. Etiology and portal vein thrombosis in Budd-Chiari syndrome. *World J Gastroenterol* 2008; **14**: 2858.
13. Afredj N, Guessab N, Nani A, Faraoun S, Cheikh I, Kerbouche R, *et al*. Aetiological factors of Budd-Chiari syndrome in Algeria. *WJH* 2015; **7**:903.
14. Tasneem A, Soomro G, Abbas Z, Luck N, Hassan S. Clinical presentation and predictors of survival in patients with Budd-Chiari syndrome: experience from a tertiary care hospital in Pakistan. *J Pak Med Assoc* 2015; **65**:120-4.
15. Bourliere M, Le Treut Y, Arnoux D, Castellani P, Bordigoni L, Maillot A, *et al*. Acute Budd-Chiari syndrome with hepatic failure and obstruction of the inferior vena cava as presenting manifestations of hereditary protein C deficiency. *Gut* 1990; **31**: 949-52.
16. Aydinli M, Bayraktar Y. Budd-Chiari syndrome: Etiology, pathogenesis and diagnosis. *World J Gastroenterol* 2007; **13**:2693-6.
17. Smira G, Gheorghe L, Iacob S, Coriu D, Gheorghe C. Budd-Chiari syndrome and V617F/JAK 2 mutation linked with the myeloproliferative disorders. *J Gastrointestin Liver Dis* 2010; **19**:105-110.
18. Akoum R, Mahfoud D, Ghaoui A, Haddad N, Mahfoud N, Farhat H, *et al.* Budd-Chiari syndrome and heparin-induced thrombocytopenia in polycythemia vera: Successful treatment with repeated TIPS and interferon alpha. *J Can Res Ther* 2009; **5**:305-8.
19. Pati H, Dayal S. Budd-Chiari syndrome: aetiology and geography. *Q J Med* 1996; **89**:719-21.