Long-term Outcome of Budd-Chiari Syndrome: A Single Center Experience

Neda Nozari[1], Hassan Vossoghinia[1,2*], Fatemeh Malekzadeh[1], Lila Kafami[3], Mahyar Mirheidari[2,3], Reza Malekzadeh[1]

1. Digestive Diseases Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran Iran
2. Gastroenterology Section, Department of Internal Medicine, Mashhad University of Medical Sciences, Mashhad Iran
3. Researcher, Mashhad University of Medical Sciences, Mashhad, Iran

* **Corresponding Author:**
Hassan Vossoghinia, MD
Gastroenterology Section, Department of Internal Medicine, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
Tel: +98 511 840001
Fax:+98 511 8409612
Email: vosoghiniah@mums.ac.ir
Received: 18 Apr. 2013
Accepted: 24 Jun. 2013

ABSTRACT

BACKGROUND

Budd-Chiari syndrome (BCS) is defined as hepatic venous outflow obstruction (HVOO). BCS is an uncommon, life-threatening liver disorder. This study describes the clinical and etiological characteristics in addition to the long-term outcome of BCS in a single referral center in Tehran, Iran.

METHODS

We reviewed long-term outcome of patients who were diagnosed with BCS between 1989 and 2012 at Shariati Hospital, a tertiary hospital affiliated with Tehran University of Medical Sciences, Tehran, Iran. The diagnosis was confirmed by at least two imaging techniques. A comprehensive analysis of the clinical and paraclinical manifestations, etiology and long-term outcome of the disease was conducted.

RESULTS

Seventy one patients (43 female) with a diagnosis of Budd-Chiari syndrome were identified during the 22 year period of study. The age were ranged from 17 to 64 years (median: 29 years). We excluded 16 patients because of incomplete information or follow up. The remaining 55 cases were the subjects of this study. Underlying etiologies consisted of congenital thrombophilia factors in 50% (28 cases) which was defined as protein C deficiency (12 cases), protein S deficiency (3 cases), antithrombin deficiency (3 cases) and factor V Leiden mutation (10 cases). Etiology was unknown in 18% (10 cases). Acquired causes of thrombophilia were observed in 25% (14 cases) that consisted of 9 cases of myeloproliferative disease and 5 cases of autoimmune diseases. In 3 cases pregnancy was the only etiology. The main clinical presentations were abdominal pain in 33 (60%), abdominal distention in 21 (38.2%), and jaundice in 10 (18%) cases. The main clinical signs were ascites (76.4%), splenomegaly (34%), hepatomegaly (25.5%) and deep vein thrombosis (1.8%). All 55 patients were treated with anticoagulants (heparin followed by warfarin) and supportive care. Two cases underwent mesocaval shunt surgery, 2 patients required transjugular portosystemic shunt (TIPS) and 5 were referred for liver transplantation. A total of 17 (30%) patients died during 22 years of follow up.

CONCLUSION

BCS, although uncommon in Iran, is a challenging liver disease with an important burden. Medical therapy that includes anticoagulation seems to be effective in most cases although the prognosis is guarded. In long-term follow up, 40% of cases will need liver transplant or die from end stage liver disease.

KEYWORDS
Budd-Chiari syndrome; Hepatic vein thrombosis; Survival; Iran; Etiology

Please cite this paper as:
Nozari N, Vossoghinia H, Malekzadeh F, Kafami L,Mirheidari M, Malekzadeh R. Long-term Outcome of Budd-Chiari Syndrome: A Single Center Experience. *Middle East J Dig Dis* 2013;5:146-50.

INTRODUCTION

Budd-Chiari syndrome (BCS) is an uncommon liver disease defined as hepatic venous obstruction (HVOO) at the level of the hepatic venules, hepatic veins (HV), or the inferior vena cava (IVC).[1] According to published studies 80% of cases are caused by either acquired or hereditary hypercoagulable states, whereas 20% are idiopathic.[2,3] The etiology of BCS varies among reported studies from different countries. Most Western cases of BCS have a known etiology,[2-4] however the etiology in numerous patients from India[5,6] and Japan[7] is unknown. In China and Japan the most common etiology is membranous obstruction (MO) and in the majority of cases treatment with percutaneous transluminal angioplasty results in an excellent clinical outcome.[7,8] Pregnancy and infections are commonly reported from developing countries such as South Africa and India.[5,9,10] In Western countries the most common etiology is a hypercoagulable state secondary to myeloproliferative disorders as well as other thrombophilic hereditary or acquired hypercoagulable states.[2,4,11] Recently due to clinical and diagnostic advances in thrombophic studies such as the discovery of the Janus tyrosine kinase 2 (JAK2) mutations and fibrinolysis pathways and the role of factor V Leiden and tetrahydrofolate reductase mutations, the etiologies of primary BCS have been clarified and much improved.[12] In addition, chronic intake of contraceptives and the presence of malignant tumors have more frequently been reported worldwide.[11,12]

The clinical presentations of BCS depend on the extent and rapidity of HV occlusion. Abdominal discomfort and pain, Enlarged liver and abdominal protrusion secondary to ascites are the main clinical presentation.[2] Gastrointestinal bleeding, dilated venous collaterals in the trunk of the body, pedal edema, and jaundice are less common.[3,11] There is no consensus on the definition of disease severity or duration (acute or chronic). Even in subjects who present with a short period from the onset of disease significant liver fibrosis, suggestive of a protracted preclinical course is evident.

Initially, BCS was thought to be an uncommon disease with a progressive course. Most patients died within several months to three years following diagnosis.[1,2] Recent studies, however, have shown that BCS is not as rare as previously believed and there are subgroups of patients that have good prognoses and long-term survival.[4,6,8]

In Iran, previous studies of BCS enrolled small numbers of cases with short follow up periods.[13-15] Thus, the current study include a large series of cases with a longer follow up period in one of the main hepatology referral centers of Tehran, Iran.

MATERIALS AND METHODS

This was a retrospective long-term follow up study of all consecutive patients diagnosed with BCS who were seen between 1989 and 2012 at Shariati Hospital, Tehran University of Medical Sciences. Patients were considered eligible for the study when the diagnosis of BCS was made by using, in addition to sonography (including color Doppler), conventional venography (Figure 1) or magnetic resonance (MR) venography and the exclusion of all other etiologies for liver disease.[16,17] Laboratory tests included a liver and kidney function test biochemistry profile, complete blood count, and a detail blood coagulation tests. The coagulation profile include Protein C, Protein S ‘lupus anticoagulant ,anti-cardiolipin antibodies,antinuclear antibodies, antithrombin level and factor V Leiden mutation. Patints were invited to do the test when these gradually became available in our center during follow up period.

Radiological assessment by abdominal duplex ultrasonography (US) was performed to assess the patency of all HVs, the portal vein, and the IVC. Either abdominal MR imaging, MR venography, or multislice computed tomography (Figure 2) were performed to confirm the BCS diagnoses and to assess vascular anatomy. Bone marrow examinations and upper gastrointestinal endoscopy reports were available for all cases. The onset of disease was estimated to be from the beginning of clinical symptoms suggestive of BCS and included leg edema, abdominal pain or

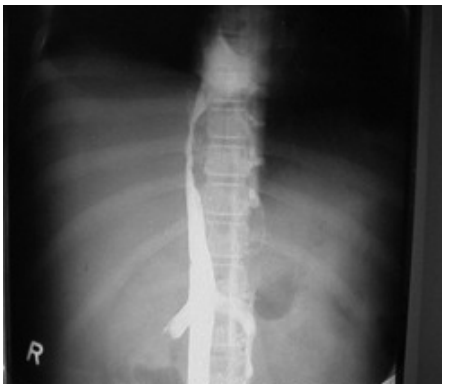

Fig. 1: Venography. Inferior vena cava (IVC) obstruction by thombosis that extended to the hepatic vein (HV) orifice.

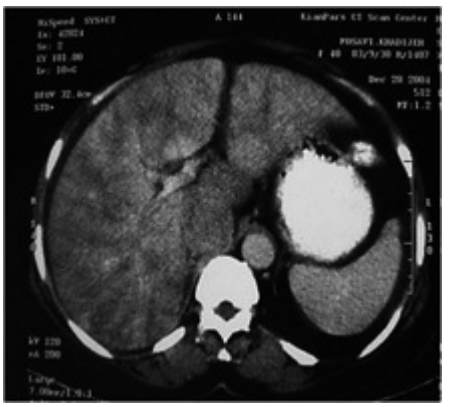

Fig. 2: Delayed or absent filling of the three major hepatic veins. Peculiar, patchy flea-bitten appearance of the liver is noted. Rapid clearance of dye from the caudate lobe. Narrowing and/or lack of opacification of the inferior vena cava (IVC) is observed.

subcutaneous venous dilatation over the trunk. The presence of esophageal varices and bleeding from the varices were confirmed by endoscopy. Viral hepatitis was excluded in all cases. Medical treatments that consisted of anticoagulation and diuretic therapy were the mainstay of therapy. Patients with deteriorating liver function or refractory ascites were considered for radiological intervention or surgery. Those who responded to medical therapy as evidenced by the disappearance of ascites and improved liver function tests remained on medical therapy with variceal band ligation as treatment for esophageal varices. Coagulopathy and encephalopathy were indicative of an urgent relief of hepatic venous obstruction by using surgical shunts or transjugular portosystemic shunting (TIPS).

Statistical analyses were performed using the SPSS software program. This study was approved by the Ethics Committee of the Digestive Diseases Research Center at Tehran University of Medical Sciences.

RESULTS

From 71 patients with BCS admitted to the Digestive Diseases Department at Shariati Hospital, 55 fulfilled the inclusion criteria for enrollment in this study. The remaining 16 patients were excluded because of incomplete information or follow up. Study patients comprised 33 females and 22 males with a female to male ratio of 1:0.7. The average age at the patient's first medical visit was 29 years (range: 17-64 years). The largest number of patients were seen in their 20's (n=18; 32.7%). The average period from suspected onset of disease to the first medical consultation was 5.9 months, which suggested a recent onset of disease in 34 (61.8%) cases. The underlying etiology (Table 1) was unknown in 10 (18%) cases, whereas congenital thrombophilia factors were observed in 28 (50%) cases, as protein C deficiency (12 cases), protein S deficiency (3 cases), antithrombin deficiency (3 cases) and factor V Leiden mutation (10 cases). Acquired causes of thrombophilia were noted in 14 (25%) cases, with myeloproliferative disease (9 cases) and autoimmune diseases (5 cases). In 3 cases pregnancy was the only etiology.

The main clinical features are listed in Table 2. The most frequent subjective symptoms were abdominal pain noted in 33 (60%) cases and distention in 21 (38.2%) cases. Jaundice was reported in 10 (18%) cases. Ascites was detected in 42 (76.4%) cases, splenomegaly in 19 (34%), hepatomegaly in 14 (25.4%), and deep vein thrombosis in 1 (1.8%) of the cases.

All cases underwent medical treatment that included salt restriction, diuretics, anticoagulants and in case of autoimmune disease, glucocorticoids. There were 2 patients treated with surgical mesocaval shunting and 2 with radiologic TIPS. Two

Table 1: Etiological factors for Budd-Chiari syndrome (BCS) in study patients (n=55).

Etiological factors	No. of patients (%)
Acquired causes of thrombophilia	14 (25)
Myeloproliferative disease	9 (16)
Autoimmune diseases	5 (9)
Congenital thrombophilia factors	28 (50)
Protein C deficiency	12 (20)
Factor V Leiden mutation	10 (18)
Protein S deficiency	3 (6)
Antithrombin deficiency	3 (6)
Pregnancy	3 (6)
Unknown (idiopathic)	10 (18)

Table 2: Clinical features of study patients with Budd-Chiari syndrome (BCS).

Clinical features	No. (%)
Abdominal pain	33 (60)
Abdominal distention	21 (38.2)
Jaundice	10 (18)
Ascites	42 (76.4)
Splenomegaly	19 (34)
Hepatomegaly	33 (60)
Deep vein thrombosis	1 (1.8%)

cases underwent venoplasty by an interventional cardiologist. A total of 5 patients were referred for liver transplantation, all of them are doing well post-transplant. During the follow up 17 patients died of complications from end stage liver disease. Survival ranged from 1 month to 22 years (mean survival time: 64.8 months).

DISCUSSION

This retrospective study focused on long-term follow up of BCS cases in Tehran. Hypercoagulable etiologies were observed in more than 80% of cases. The average age at presentation of BCS in Iran was 29 years, which was almost 10 years younger than reported series from other areas of the world. The majority were young females.[2,8-11] The etiologic pattern of disease in Iran was similar to Western countries.[11] Long-term prognosis was not as bad as previously thought. Long-term survival was observed in over 60% of cases and the mainstay of management was medical therapy.

Patients unresponsive to medical therapy who remain symptomatic, particularly with intractable ascites and evidence of liver failure, should undergo liver transplant as soon as possible. In the current study only 5 patients underwent liver transplant because of limitations on the availability of a liver transplant center in Iran during the first 10 years of this study. Invasive or minimally invasive procedures were effective in a minority of cases due to the lack of MO. This is in contrast to observations of Eastern cases where the predominant etiology is MO (IVC) and minimally invasive techniques are quite effective.[8,11]

There are few published BCS studies from Iran.[13-15] According to a report from the main liver transplant center in Iran, only 0.01% of liver transplants have been attributed to BCS.[16] In another study the median survival of 22 cases was only 14 months (range: 1-20 months). In the present study the mean survival time was 64.8 months (range: 1 month-22 years), which was mostly attributed to a more rapid onset, continued lifelong anticoagulation and better supportive care.[17-19]

Hereditary thrombophilia was the main etiology in 50% (28) of cases. Among these, protein C deficiency and factor V Leiden mutation were the most common predisposing factors. This finding suggest that approximately 50% of BCS cases in Iran should receive lifelong anticoagulation therapy.[18,19] In 18% of cases no etiology was noted for BCS. Most likely the diagnosis of inherited deficiencies in protein C, protein S and antithrombin in BCS was not possible due to the acquired deficiencies of these factors which developed during active thrombosis, liver failure and anticoagulation therapy. Most BCS subjects might have one, two or more likely three of the above conditions at the time of presentation to the hospital. Another reason might be the unavailability of tests for other newly confirmed thrombogenic factors such as factor XI, factor VIII e and homocysteine at the time of diagnosis and during follow up. A short course of oral contraceptive pills for one or two months, as a com-

mon practice among newly married females, has not been considered. Oral contraceptive use might have played a role by enhancing a pre-existing pro-thrombotic tendency and might be a reason for the excess number of younger female cases in the current study.

The main strength of this study is its long-term follow up and complete possible investigation of etiologies during the follow up period. The main weakness is the retrospective nature of this study.

The findings of this study, as the largest BCS study from Iran and one of the longest follow-up published studies to date, has shown that this disease in the majority of cases is an in situ thrombosis similar to Western countries that has a rapid onset and continued maintenance anti-coagulation therapy. The majority of BCS cases can have a good prognosis and long-term survival.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

REFERENCES

1. Ludwig J, Hashimoto E, Mc Gill DB, van Heerden JA. Classification of hepatic venous outflow obstruction: ambiguous terminology of the Budd-Chiari syndrome. *Mayo clin proc* 1990;**65**:51-5.
2. Mitchell MC, Boitnott JK, Kaufman S, Cameron JL, Maddrey WC. Budd-Chiari syndrome. Etiology, diagnosis and management. *Medicine (Baltimore)* 1982;**61**:199-218.
3. Dilawari JB, Bambery P, Chawla Y, Kaur U, Bhusnurmath SR, Malhotra HS,, et al. Hepatic outflow obstruction (Budd-Chiari syndrome). Experience with 177 patients and a review of the literature. *Medicine (Baltimore)* 1994;**73**:21-36.
4. Janssen HL, Garcia-Pagan JC, Elias E, Mentha G, Hadengue A, Valla DC, et al. Budd-Chiari syndrome: a review by an expert panel. *J Hepatol* 2003;**38**:364–371.
5. Datta DV, Saha S, Singh SA, Gupta BB, Aikat BK, Chhuttani PN. Clinical spectrum of Budd-Chiari syndrome in Chandigarh with particular reference to obstruction of intrahepatic portion of inferior vena cava. *Ind J Med Res* 1972;**60**:385-402.
6. Amarapurkar DN, Punamiya SJ, Patel ND. Changing spectrum of Budd-Chiari syndrome in India with special reference to non-surgical treatment. *World J Gastroenterol* 2008 14;**14**:278-85.
7. Okuda H, Yamagata H, Obata H, Iwata H, Sasaki R, Imai F, et al. Epidemiological and clinical features of Budd-Chiari syndrome in Japan. *J Hepatol* 1995;**22**:1-9.
8. Cheng D, Xu H, Lu ZJ, Hua R, Qiu H, Du H, et al. Clinical features and etiology of Budd-Chiari syndrome in Chinese patients: a single-center study. *J Gastroenterol Hepato*l 2013;**28**:1061-7.
9. Simson IW. Membranous obstruction of the inferior vena cava and hepatocellular carcinoma in South Africa. *Gastroenterology* 1982;**68**:171-8.
10. Khuroo MS, Datta DV. Budd-Chiari syndrome following pregnancy. Report of 16 cases, with roentgenologic, hemodynamic and histologic studies of the hepatic outflow tract. *Am J Med* 1980;**68**:113-21.
11. Menon KV, Shah V, Kamath PS. The Budd-Chiari syndrome. *N Engl J Med* 2004;**350**:578-585.
12. Shetty S, Ghosh K. Thrombophilic dimension of Budd Chiari syndrome and portal venous thrombosis-a concise review. *Thromb Res* 2010;**127**:505-12.
13. Malekzadeh R, Bidad K, Radmehr A, Kamalian N, Buddchiari syndrome in Iran:An experience with 22 patients. *Iranian J Med Sci* 1994;**19**:88-94.
14. Ebrahimi M, Modaghegh MH, Esmaeilzadeh A. Presentation of hospital outcomes and different treatment methods of patients with Budd-chiari syndrome: A report from two tertiary hospitals in Iran. *Med Princ Pract* 2011;**20**:287-90.
15. Ebrahimi M, Esmaeilzadeh A . Brief Review: Budd-Chiari Syndrome in Iran. *Govaresh* ;**16**:163-8.
16. Malek-Hosseini SA, Mehdizadeh AR, Salahi H, Saberi-Firouzi M, Bagheri-Lankarani K, Bahador A, et al. Results of liver transplantation: analysis of 140 cases at a single center. *Transplant Proc* 2005;**37**:3157-8.
17. Ferral H, Behrens G, Lopera J. Budd-Chiari syndrome. *AJR Am J Roentgenol* 2012;**199**:737-45.
18. MacNicholas R, Olliff S, Elias E, Tripathi D. An update on the diagnosis and management of Budd-Chiari syndrome. *Expert Rev Gastroenterol Hepatol* 2012;**6**:731-44.
19. Mancuso A. Budd-chiari syndrome management: Timing of treatment is an open issue. *Hepatology*. 2013 Jul 15. doi: 10.1002/hep.26619. [Epub ahead of print]