Long Term Outcomes of Patients with Significant Biliary Obstruction Due to Portal Cavernoma Cholangiopathy and Extra-Hepatic Portal Vein Obstruction (EHPVO) With No Shuntable Veins

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Aims: The natural history of portal cavernoma cholangiopathy (PCC) in patients with significant biliary obstruction (SBO) who cannot undergo shunt surgery, is not known. We therefore, analyzed data of patients of extra-hepatic portal venous obstruction (EHPVO) with PCC. **Methods:** Prospectively recorded details of 620 (age 21.2 [11.4] years; 400 [65%] males) patients with primary EHPVO were reviewed. Outcomes (hepatic decompensation/mortality) of patients with PCC and SBO without shuntable veins were noted at follow up of 7 [4–11] years. **Results:** Ninety-seven of 620 (15.6% [60 men]) EHPVO patients had PCC-SBO. Of these 57 did not have shuntable veins. The median duration from any index symptom to symptomatic PCC was 7 (0–24) years and from index bleed to symptomatic PCC was 12 (5–24) years, respectively. Thirteen patients underwent endoscopic retrograde cholangiography; nine repeatedly over 7 (4–10) years. Decompensation was seen in 5 patients. Presentation other than variceal bleed was associated with hepatic decompensation (5/19 versus 0/38, $P = 0.003$). **Conclusions:** Majority of patients with PCC-SBO do not have shuntable veins, and may have good long-term outcomes. Patients presenting with variceal bleed have low chance of decompensation. Symptomatic PCC appears to be a late event in EHPVO. (J CLIN EXP HEPATOL 2017;7:328–333)

Core Tip: Our study demonstrates that most patients with significant portal cavernoma cholangiopathy (PCC) do not have shuntable veins, making them ineligible for shunt surgery, which is the standard of care. Our study shows that these patients have good long-term outcome with medical and endoscopic management. Patients of extra-hepatic portal venous obstruction (EHPVO) and PCC who present with symptoms other than variceal bleed are more likely to develop hepatic decompensation. Symptomatic PCC appears to be a late event in natural history of EHPVO and endoscopic therapy is a safe and effective option in patient who cannot undergo shunt surgery.

Primary EHPVO is defined as obstruction of the extra hepatic portal vein with or without involvement of the

intra hepatic portal veins and does not include isolated thrombosis of splenic vein or superior mesenteric vein (SMV).¹ Patients with liver cirrhosis and consequent chronic portal vein thrombosis are not included in EHPVO. Portal vein cavernoma is a cluster of collateral veins which occurs as a sequelae to portal vein thrombosis and the native portal vein can often not be identified. PCC is defined as abnormalities in the extrahepatic biliary system including the cystic duct and gallbladder with or without abnormalities in the 1st and 2nd generation biliary ducts in a patient with portal cavernoma, due to para-choledochal and epicholedochal venous plexuses compressing the common bile duct (CBD) and/or vascular injury leading to ischemia and fibrous stricture.^{2,3} Fourteen per cent patients of EHPVO with PCC develop symptoms of biliary obstruction.^{4,5} The treatment of symptomatic PCC is portosystemic shunt surgery (PSSS), and followed by biliary bypass if required. Endotherapy is indicated in patients with cholangitis or in those who cannot undergo PSSS. In patients with EHPVO, the portal vein is replaced by collaterals; therefore PSSS is possible if there is a patent splenic vein (SV) or SMV. However, PSSS cannot be done in patients who have SV and SMV thrombosis. The management of patients who cannot undergo PSSS thus becomes challenging.

There is a paucity of data about long-term outcomes of patients with PCC who cannot undergo shunt surgery. We therefore, analyzed our data of patients with EHPVO, who

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Abbreviations: CT: computed tomography; EHPVO: extra-hepatic portal venous obstruction; PCC: portal cavernoma cholangiopathy; PSSS: portosystemic shunt surgery; MRCP: magnetic resonance cholangiopancreatography; SBO: significant biliary obstruction; SMV: superior mesenteric vein; SV: splenic vein; US: ultrasound

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had dilated CBD or intra hepatic biliary radicals (IHBR) due to PCC, but could not undergo surgery due to lack of shuntable veins.

METHODS

Approval from Institutional Review Board was obtained. Prospectively maintained data of 620 consecutive patients of chronic EHPVO from August 2003 with at least 4 years of follow-up were analyzed retrospectively. EHPVO was diagnosed by presence of portal vein cavernoma on ultrasound (US) of abdomen or computed tomography (CT) of abdomen. PCC with significant biliary obstruction (PCC-SBO) was defined by presence of dilated CBD or IHBR on US, CT or magnetic resonance cholangiopancreatography (MRCP); corresponding to grade III of classification given by Llop et al.⁶

Patients with PCC-SBO who were unsuitable for shunt surgery because of thrombosis of SMV and SV were included in this study. Patients with no or insignificant cholangiopathy (Llop et al.⁶ grade I/II) were excluded. For patients of PCC-SBO, who were either symptomatic or had CBD stones, our management protocol was endoscopic retrograde cholangiography (ERC). ERC was done carefully in these patients with Terlipressin 1 mg given intravenously just before starting the procedure. We did a small sphincterotomy if there were no stones to be retrieved. We used biliary balloon for stone retrieval, and avoided the use of biliary baskets. Regular biliary stent exchanges were done at 3-monthly intervals, or as required for patients with refractory CBD strictures and/or persistent stones. Asymptomatic patients with PCC-SBO were monitored at 6-monthly intervals. Serial investigations of all patients with PCC-SBO were noted and analyzed, including complete blood count, liver function tests, renal function tests, US, CT, MRCP, ERC and upper gastrointestinal endoscopy. Patients with liver disease and portal hypertension due to other causes like viral hepatitis, autoimmune hepatitis, alcoholic liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, α -antitrypsin deficiency, haemochromatosis and non-alcoholic fatty liver disease were excluded. The clinical course of patients was recorded from onset of symptoms to the last follow-up or by phone call interview in October 2014. The duration of symptoms from the index symptom was noted. The duration from index symptom to first symptom of PCC was also recorded. Hepatic decompensation was defined as persistent ascites and/or hepatic encephalopathy. Transient ascites after variceal bleed was not considered as hepatic decompensation. The time to decompensation from onset of symptoms was recorded.

Statistical Analysis

Baseline characteristics of patients with PCC were studied using descriptive statistics. Characteristics of patients with

PCC who developed decompensated liver disease were compared to those who did not. Dichotomous variables were compared using Chi-square test or Fischer exact test, and continuous variables were compared using non parametric tests. Kaplan-Meier curve was plotted for hepatic decompensation. All statistical analysis was done using SPSS software 16.0.

RESULTS

Overall 620 (400 [65%] men) patients of chronic EHPVO were screened. The mean age, at presentation to our hospital, was 21.2 (11.4) years. Ninety-seven (15.64%; 60 [61.8%] men) patients had PCC-SBO. Elevated aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) were seen in 45 (46.4%), 24 (24.7%), and 55 (56.7%) patients respectively. Forty patients had shuntable veins.

Of the 40 patients with PCC-SBO with shuntable veins, 8 were symptomatic. These eight patients were referred for shunt surgery. The 8/40 patients who were referred for shunt surgery had symptomatic obstructive jaundice. The details of post operative follow up of these patients are not available. Of the 32 remaining patients, 31 remained asymptomatic at follow-up of 7 (3–17) years. Elevated AST, ALT and ALP were seen in 19 (47.5%), 10 (25%), and 21 (52.5%) patients, respectively. One patient developed jaundice at 5 years of follow up after which he was referred for shunt surgery.

Fifty-seven (9.2%; 33 [56.9%] men) patients with PCC-SBO could not be considered for shunt surgery due to lack of shuntable veins. These patients were further analyzed (Figure 1). Their median duration of symptoms of EHPVO was 11 (4–39) years. The median follow-up for this study was 7 (4–11) years. Baseline characteristics of patients of PCC-SBO with and without hepatic decompensation are shown in Table 1. Eleven of 57 (19.3%) patients with PCC-SBO had jaundice, 38 (66.7%) had variceal bleed, and 9 developed transient ascites after variceal bleed. None of the patients developed encephalopathy. Elevated AST, ALT and ALP were present in 26 (45.6%), 14 (24.6%) and 34 (59.6%) patients, respectively. In these 57 patients, without shuntable veins, the age of detection of PCC on US was higher as compared to age of onset of index symptom (23.7 [12.9] years versus 19.12 [13.7] years; $P = 0.000$; 95% CI for difference 2.91–6.24). The median duration from any index symptom to onset of symptomatic cholangiopathy was 7 (0–24) years. In patients presenting with variceal bleed, the median duration to symptomatic cholangiopathy was 12 (5–24) years. Age at onset of index symptoms among patients with ($n = 13$) and without ($n = 44$) symptomatic cholangiopathy was similar (18.72 [4.4] years versus 20.8 [10.8] years; $P = 0.65$).

ERC was done in 13 patients with CBD stones and/or jaundice. Seven patients had CBD stones. CBD stones

Figure 1 Outline of result.

Table 1 Baseline Characteristics of Patients of PCC-SBO, Managed Medically/Endoscopically, With and Without Hepatic Decompensation (*P = 0.003, AST: Aspartate Transaminase; ALT: Alanine Transaminase).

			No hepatic decompensation (n = 52)	Hepatic decompensation (n = 5)	OR [95% CI]	95% CI for difference of in means
Age	Years	Mean (SD)	26.6 (13.4)	29 (4.8)	–	–9.9 to 14.55
Gender	M	n (%)	30 (57.6)	3 (60)	1.1 [0.17–7.15]	–
	F	n (%)	22 (42.3)	2 (40)		
Patients with jaundice		n (%)	10 (19.2)	1 (20)	0.95 [0.096–9.47]	–
Patients with gastrointestinal bleed		n (%)	38 (73.1)	0	3.71 [2.3–5.8]*	–
Serum bilirubin	mg/dl	Median (range)	1.00 (0–32)	0.8 (0.3–14)	–	–6.7 to 7.6
Serum AST	U/l	Median (range)	37.5 (7–248)	45 (14–76)	–	–39.6 to 25.14
Serum ALT	U/l	Median (range)	24 (5–195)	27 (18–78)	–	–33.9 to 24.48
Serum alkaline phosphatase	U/l	Median (range)	144 (31–1450)	290 (115–1015)	–	–295.79 to 610.91
Patients with elevated AST		n (%)	23 (44.2)	3 (60)	0.529 [0.08–3.43]	–
Patients with elevated ALT		n (%)	13 (25)	1 (20)	1.33 [0.196–13.02]	–
Patients with elevated alkaline phosphatase		n (%)	30 (57.7)	4 (80)	0.341 [0.04–3.27]	–

could be cleared in 4 patients. Nine patients underwent ERC with biliary stent exchanges every 3 months for a median of 7 years (range: 4–10 years; 2 for stones, 5 for strictures). There was no major bleeding complication during ERCs. One patient of PCC-SBO with mid-CBD stricture was treated with fully covered biliary stent. After 2 weeks of stent placement, she presented with gall bladder empyema, due to cystic duct blockage by the stent and was managed with antibiotics and stent removal. Subsequent cholangiogram revealed complete resolution of stricture. Two patients, who presented with symptomatic PCC and developed decompensation, had variceal bleed subsequently.

Decompensation due to secondary biliary cirrhosis (SBC) was seen in five patients; three at the time of presentation whereas two developed hepatic decompensation after 23 and 24 years of index symptom (Figure 2). One of these patients died due to liver cell failure, two years after decompensation. SBC was confirmed by trans-jugular liver biopsy in patients who presented with/developed hepatic decompensation.

Proportion of patients with jaundice, elevated AST, ALT and elevated ALP at presentation was similar in patients who developed hepatic decompensation and patients with PCC who did not. None of the patients with PCC-SBO who had variceal bleed at presentation ($n = 38$) developed hepatic decompensation, (Table 1), as against 5 of 19 (26.38%) patients who did not have variceal bleed at presentation ($P = 0.003$; Relative risk: 3.71[95% CI 2.3–5.8]). The clinical details of these patients are mentioned in Table 1.

Figure 2 Kaplan Maier curve for hepatic decompensation in patient with PB with significant obstruction without surgical management [time from index symptoms].

DISCUSSION

Our study found that 15.64% of patients with EHPVO have significant biliary obstruction (PCC-SBO). MRCP or ERC, are sensitive for subtle biliary changes (grade I/II, Llop et al.⁶), which may not be of clinical significance. Therefore, we studied only patients of PCC-SBO who could not be considered for PSSS due to lack of shuntable vein. These patients were managed medically/endoscopically with 6 monthly monitoring of liver biochemistry and ultrasonography of the abdomen. Thirteen patients of PCC-SBO with symptoms attributable to cholangiopathy were subjected to endotherapy. Nine patients had persistent biliary obstruction despite initial endoscopic therapy and were put on a regular schedule of CBD stenting. At a median follow-up of 7 years decompensation due to SBC was seen only in five patients; three at presentation whereas two developed decompensation after 23 and 24 years after onset of symptoms. Our data showed 57/97 patients did not have shuntable veins. Amongst patients with shuntable veins 9/40 had symptomatic cholangiopathy. The 8/40 patients who were referred for shunt surgery had symptomatic obstructive jaundice. The details of post operative follow up of these patients are unfortunately not available with us. It would have indeed been interesting to analyze their post operative course and outcomes.

Cholangiographic abnormalities are present in 78–100% patients of EHPVO, liver biochemical abnormalities have been reported in 10–80% of patients, but only 14% are symptomatic.^{4,5} Most of the cholangiographic abnormalities are not considered significant as they do not cause significant obstruction to flow of bile. Lesions are classified according to severity as grade I (irregularities or angulations of the biliary tree), grade II (indentations or strictures without upstream biliary dilation) and grade III (strictures with upstream biliary dilation).⁶ In a study of 67 patients with non tumoral, non cirrhotic portal vein thrombosis, Llop et al.,⁶ found 34 patients with grade III lesions. All of the 14 patients with symptomatic PCC had grade III lesions and there was no progression of lesions from grade I/II to grade III on follow-up MRCP over a period of 12 years.⁶ For analysis of our data, we defined PCC-SBO as dilated CBD and IHBR on USG, CT or MRCP; corresponding to grade III of above classification since these patients would be at higher risk for liver failure due to secondary biliary cirrhosis.

The first line of treatment for symptomatic PCC is PSSS thereby decompressing the varices and relieving the CBD obstruction due to protruding varices. Persistent biliary obstruction after shunt surgery is managed by biliary bypass surgery for adequate biliary drainage.^{2,3} In a series from India, 37 patients with PCC were subjected to PSSS. Biliary bypass surgery was required in 13 patients for persistent biliary stricture. After a mean follow-up of 32 months, 35 of these 37 patients remained asymptomatic.⁷

In another series, 2 out of 29 patients who were subjected to PSSS required bilioenteric bypass, 16 and 48 months after shunt surgery.⁸ However this treatment algorithm cannot be offered to patients with extensive portovenous thrombosis, in whom PSSS is not possible. In a series of patients reported from France, 47% patients needing PSSS did not have veins amenable to PSSS.⁹ In another series from UK, extent of vascular thrombosis precluded PSSS in most cases of symptomatic PCC.¹⁰ In these patients, endoscopic therapy was successful in 6 out of 13 and portal decompression in three, while one was subjected to combined liver and small bowel transplantation.¹⁰

Surgical treatments described for symptomatic cholangiopathy, in absence of shuntable veins are direct bilioenteric bypass without prior PSSS,^{9,11} splenectomy and devascularisation⁸ and combined liver and small bowel transplantation.¹⁰ Direct bilioenteric bypass without PSSS is technically difficult and hazardous due to presence of multiple collaterals in the surgical field which can cause torrential bleeding during surgery. Chaudhary et al.¹¹ described two patients who underwent direct biliary surgery without PSSS, both of whom had excessive bleeding during the surgery; one died after surgery and the other developed anastomotic stricture. Vibert et al.⁹ described intrahepatic bilioenteric anastomosis for 4 patients of PCC who did not have shuntable veins. No postoperative mortality was reported and all patients had reduction in symptoms initially, but required repeated percutaneous biliary cholangioscopies via the afferent bowel loop to remove symptomatic intrahepatic calculi in all of them. Biliary obstructive symptoms reappeared at 7–40 months after surgery. Direct bilioenteric anastomosis without PSSS is hazardous and may be associated with reappearance of obstructive symptoms as the portal system is not decompressed. Hence, one stage surgical biliary drainage is not an advocated treatment option. Another study showed some reversal of cholangiopathy with splenectomy and devascularisation in 8 patients of EHPVO postulating that this may alter the natural history of PCC, probably by decreasing the portal flow, and thus may be considered an option in patients without shuntable veins.⁸ However, the specific outcomes, especially long-term results in this subgroup have not been mentioned in the study. Subgroup analysis showed that the serum alkaline phosphatase level did not fall after surgery and fall in serum bilirubin may have been due splenectomy thereby decreasing unconjugated bilirubin.¹² Although devascularisation with splenectomy can lead to a decrease in portal pressure, its effect on the natural history of PCC is uncertain. This surgery may also lead to development of ectopic varices over a period of time which would be difficult to manage. In the above series, one patient died due to massive bleeding from jejunal varices, 10 years after splenectomy and devascularisation.⁸

The most common presentation of EHPVO is variceal bleed.¹ It is likely that patients who develop adequate natural shunts that effectively decompress the portal system do not bleed. These patients may remain asymptomatic for a long time and present with either splenomegaly or symptomatic PCC. On the contrary, patients without effective decompression of portal hypertension may present early with gastrointestinal bleed. This may explain the finding in our study that none of the patients who presented with variceal bleed developed decompensated liver disease as against 5 of the 19 who did not have variceal bleed at presentation. It would be interesting to compare outcome of these patients to those who underwent PSSS but unfortunately, these data are not available.

To the best of our knowledge, ours is the only study that describes long-term outcomes of a large cohort of patients of EHPVO with PCC-SBO who could not be managed surgically due to lack of shuntable veins. Intuitively, this cohort of patients is expected to have poor long-term outcomes. However, in our study, these patients had a good long-term outcome with supportive/endoscopic therapy. The findings of our study also indicate that symptomatic PCC appears to be a late event in patients of EHPVO. Long-term prospective studies are required to confirm our observations.

ETHICAL

Institutional review board statement: This study was approved by Institutional Ethics Committee of Institution (Seth G.S. Medical College and KEM Hospital).

Biostatistical statement: Statistical Analysis was done using SPSS 16.

CONFLICTS OF INTEREST

The authors have none to declare.

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REFERENCES

1. Sarin SK, Sollano JD, Chawla YK, et al. Consensus on extra-hepatic portal vein obstruction. *Liver Int.* 2006;26:512–519.
2. Dhiman RK, Saraswat VA, Valla DC, et al. Portal cavernoma cholangiopathy: consensus statement of a working party of the Indian National Association for study of the liver. *J Clin Exp Hepatol.* 2014;4(suppl 1):S2–S14.
3. Khanna R, Sarin SK. Non-cirrhotic portal hypertension – diagnosis and management. *J Hepatol.* 2014;60:421–441.
4. Khuroo MS, Yattoo GN, Zargar SA, et al. Biliary abnormalities associated with extrahepatic portal venous obstruction. *Hepatol.* 1993;17:807–813.

5. Malkan GH, Bhatia SJ, Bashir K, et al. Cholangiopathy associated with portal hypertension: diagnostic evaluation and clinical implications. *Gastrointest Endosc*. 1999;49:344–348.
6. Llop E, de Juan C, Seijo S, et al. Portal cavernoma cholangiopathy: radiological classification and natural history. *Gut*. 2011;60:853–860.
7. Agarwal AK, Sharma D, Singh S, Agarwal S, Girish SP. Portal biliopathy: a study of 39 surgically treated patients. *HPB (Oxford)*. 2011;13:33–39.
8. Chattopadhyay S, Govindasamy M, Singla P, et al. Portal biliopathy in patients with non-cirrhotic portal hypertension: does the type of surgery affect outcome? *HPB (Oxford)*. 2012;14:441–447.
9. Vibert E, Azoulay D, Aloia T, et al. Therapeutic strategies in symptomatic portal biliopathy. *Ann Surg*. 2007;246:97–104.
10. Oo YH, Olliff S, Haydon G, Thorburn D. Symptomatic portal biliopathy: a single centre experience from the UK. *Eur J Gastroenterol Hepatol*. 2009;21:206–213.
11. Chaudhary A, Dhar P, Sarin SK, et al. Bile duct obstruction due to portal biliopathy in extrahepatic portal hypertension: surgical management. *Br J Surg*. 1998;85:326–329.
12. Gupta V, Chandra A. Portal biliopathy: is splenectomy with devascularization really effective? *HPB (Oxford)*. 2013;15:559.