Portal biliopathy

Report on three cases and review of literature

Paula Sopirjaková[1], Antonín Krajina[2], Jolana Bártová[1], Petr Hůlek[1], Tomáš Vaňásek[1], Rudolf Repák[1], Tomáš Fejfar[1], Ondřej Renc[2], Pavel Eliáš[2], Stanislav Rejchrt[1], Jan Bureš[1]

[1]2nd Department of Internal Medicine, Charles University in Praha, Faculty of Medicine at Hradec Králové, University Teaching Hospital, Hradec Králové, Czech Republic
[2]Department of Radiology, Charles University in Praha, Faculty of Medicine at Hradec Králové, University Teaching Hospital, Hradec Králové, Czech Republic

Summary

Portal biliopathy is defined as biliary abnormalities associated most commonly with extrahepatic portal vein obstruction. We report on three cases of portal biliopathy collected within the past 15 years. All three cases were presented with variceal bleeding due to portal hypertension. Clinical signs of subsequent portal biliopathy appeared as biliary obstruction with jaundice. All patients were treated endoscopically with dilation and duodeno-biliary stenting with a long-term favourable effect. Review of literature on clinical features, diagnostic and therapeutic options and possible complications of portal biliopathy is provided. Portal biliopathy should always be considered in the event of biliary obstruction in patients with extrahepatic portal vein obstruction. Portal biliopathy might be complicated with bile duct stones and/or cholangitis. ERCP is the method of choice both for diagnosis and treatment.

Key words: *portal biliopathy, extrahepatic portal vein obstruction, portal hypertension, transjugular intrahepatic portosystemic shunt, TIPS*

Souhrn

Portální biliopatie. Popis tří případů a přehled literatury

Portální biliopatie jsou definovány jako abnormality žlučovodů spojené s obstrukcí extrahepatálního portálního řečiště. Prezentujeme tři případy portální biliopatie, které byly na našem pracovišti diagnostikovány v uplynulých 15 letech. U všech nemocných bylo prvním příznakem variceální krvácení v důsledku portální hypertenze. Následná portální biliopatie se klinicky projevila známkami biliární obstrukce s ikterem. Všichni nemocní byli léčeni endoskopicky (s dilatací a zavedením duodeno-biliárních stentů) s dlouhodobým příznivým efektem. Přehled literatury rekapituluje klinické projevy, diagnostické a léčebné možnosti a případné komplikace portální biliopatie. Tato diagnóza by měla být zvažována ve všech případech, kdy je extrahepatální portální obstrukce komplikována obstrukčním ikterem a/nebo cholangoitidou. ERCP je metodou volby jak pro diagnózu, tak pro léčbu.

Klíčová slova: *portální biliopatie, obstrukce extrahepatického portálního řečiště, portální hypertenze, transjugulární, intrahepatická, portosystémová spojka, TIPS*

Portal biliopathy is defined as biliary abnormalities associated most commonly with extrahepatic portal vein obstruction (EHVPO) [2–4,8,12]. This is a rare cause of biliary obstruction in Central Europe. We report on three cases of patients who suffered from portal biliopathy recorded within past 15 years at our Department where more than 7,000 GI endoscopies are accomplished per year. Literature on clinical features, diagnostic and therapeutic management with possible complications is reviewed.

CASE REPORTS

Case 1

A 50-year-old man investigated for suspected myeloproliferative disease (presented as splenomegaly with thrombocytosis) was admitted elsewhere because of haematemesis and melaena. Gastro-oesophageal varices were found by means of upper GI endoscopy as the source of bleeding (Fig. 1). Vasoactive treatment with terlipressin controlled the bleeding. Thereafter, the patient was referred to our Department to consider transjugular intrahepatic portosystemic shunt (TIPS). Computerised tomography (CT) and abdominal ultrasonography (US) revealed signs of prehepatic portal hypertension due to chronic thrombosis of the portal vein with portal cavernoma: thrombosis of the lienal vein with a marked splenomegaly (22 cm), subacute thrombosis of the superior mesenteric vein, multiple portosystemic collaterals in subhepatic space, peripancreatic and perisplenic region, and mild ascites. Both intra- and extrahepatic bile ducts were undilated, the

gallbladder contained some sludge. Moderate enlargement of the liver was accompanied by a mild increase in laboratory liver tests (total serum bilirubin 48 μmol/L, ALT 0.96 μkat/L, AST 0.83 μmol/L, GMT 1.8 μkat/L, INR 1.52, albumin 36.2 g/L). The blood count found borderline haemoglobin (117 g/L), normal leukocytes count and borderline platelets (392×10^9/L, followed by a maximum of $1{,}448\times10^9$/L during subsequent course). A hypercoaguble state due to factor V Leiden mutation or lupus anticoagulans was ruled out. Bone marrow biopsy confirmed myeloproliferative disease – primary myelofibrosis (heterozygote for JAK2 gene mutation). TIPS and local thrombolysis of portal thrombosis were accomplished, followed by therapy with low molecular weight heparin and cytostatic treatment (hydroxyurea). However, the TIPS was soon re-thrombosed (Fig. 2,3). Because of the persisting high risk of variceal re-bleeding, splenectomy was indicated. The postoperative course was uncomplicated and the patient was discharged seven days after surgery. Histologic examination of the spleen confirmed extramedullary haematopoiesis in line with myeloproliferation.

Three weeks after surgery, the patient was re-admitted because of painless obstructive jaundice (total serum bilirubin 126 μmol/L, GMT 9.17 μkat/L, C-reactive protein 6 mg/L, leukocytes 9.7×10^9/L). US showed mild dilatation of intrahepatic bile ducts. ERCP revealed stenosis of the middle and proximal third of extrahepatic bile ducts and irregularities of the common bile duct (Fig. 4). Papillotomy was performed and a biliary stent was inserted. Cytology taken from the stenosis was benign, CA 19-9 was normal. All these findings were considered as changes in the biliary ducts due to initial portal biliopathy. The patient has been scheduled for regular stent exchange, continually treated with beta blockers, anticoagulants (warfarin) and hydroxyurea (with stable platelet count). Variceal bleeding was not repeated.

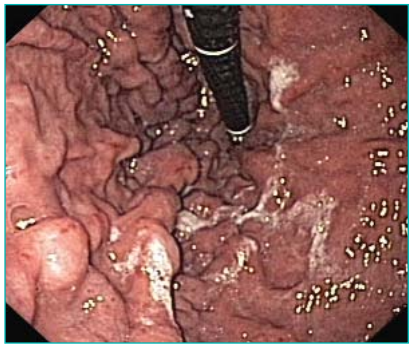

Fig. 1./Obr. 1.
Gastroscopy. Gastric varices of the fundus (GOV1) in the retroflexion endoscopic view.
Gastroskopie. Žaludeční varixy ve fundu (GOV1), endoskopický obraz v retroflexi.

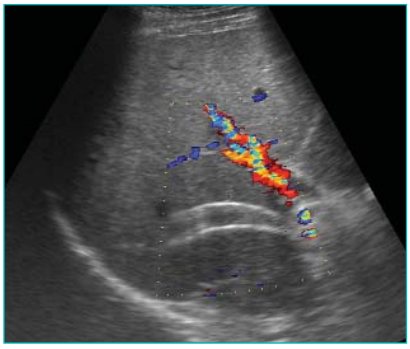

Fig. 3./Obr. 3.
Doppler ultrasonography of the liver. Obstructed thrombosed TIPS.
Dopplerovská ultrasonografie jater. Neprůchodný trombozovaný TIPS.

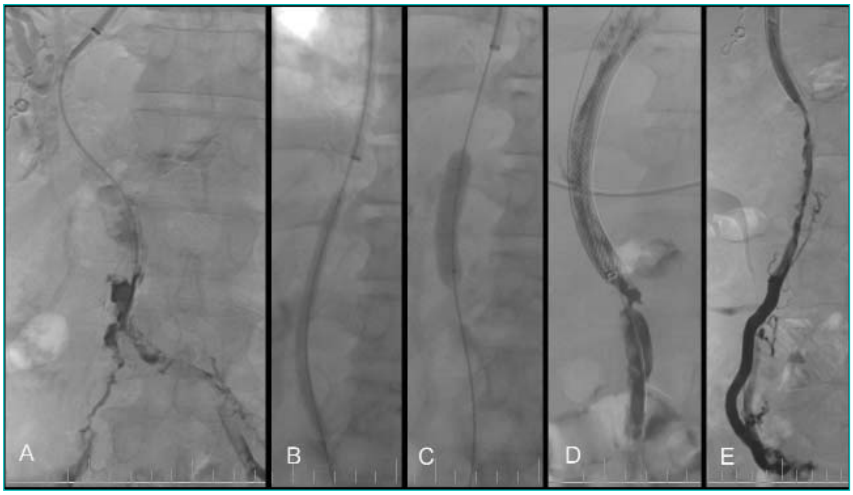

Fig. 2./Obr. 2.
Vasographic interventions in a patient with portal vein thrombosis.
A: chronic thrombosis of the portal and splenic veins. Thrombosis of main branches of the superior mesenteric vein;
B and C: balloon dilation of the portal vein;
D and E: situation after dilation, thrombus fragmentation and local thrombolysis in the portal vein; patent unobstructed TIPS (Transjugular Intrahepatic Porto-systemic Shunt).
Vazografické intervence u pacienta s trombózou portální žíly.
A: chronická trombóza portální a lienální žíly, trombóza hlavních kmenů horní mezenterické žíly;
B a C: dilatace portální žíly balonem;
D a E: stav po dilataci a fragmentaci trombu a lokální trombolýze portální žíly; volně průchodný TIPS (Transjugulární Intrahepatická Portosystémová Spojka).

Case 2

A 47-year-old man with known portal cavernoma diagnosed in childhood at the age of six (1968) presented as haematemesis. After splenectomy (1968), bleeding disappeared for years. A couple of operations were performed later, in 1993 an azygo-portal shunt was accomplished. Despite eradication of oesophageal varices by sclerotherapy, varices in the duodenum remained and re-bleeding occurred. On that account, a mesenterico-caval shunt was performed during surgery in 2000. Four years later, gastrointestinal re-bleeding occurred, the source was not identified by upper GI endoscopy. Angiography found an obstructed mesenterico-caval shunt. Wireless capsule endoscopy found multiple varices in the small bowel which were assumed to be the source of the bleeding. Another porto-systemic shunt was not feasible. To date, bleeding has not reoccurred under

the treatment with beta blockers. In September 2008, the patient was re-admitted for painless obstructive jaundice (total serum bilirubin 103 μmol/L, GMT 15.6 μkat/L) with no systemic inflammatory response (C-reactive protein 5.0 mg/L, leukocytes 5.5×10⁹/L). US showed dilated intrahepatic bile ducts, lithiasis and sludge in the gallbladder. ERCP was accomplished, several varices were around the major papilla (Fig. 5). The intra- and extra-hepatic biliary tree was irregular with several stenoses and lithiasis in the distal common bile duct (Fig. 6). With knowledge of the patient's history of changes in the biliary system, these findings were classified as portal biliopathy. Small papillotomy was performed and a duodenobiliary stent was inserted. One month later, new ERCP was scheduled, the stent was removed, choledocholithiasis was extracted and papillotomy was extended. During the subsequent 6-month follow-up period, the patient has been symptom-free, with no signs of bleeding, jaundice and/or cholangitis.

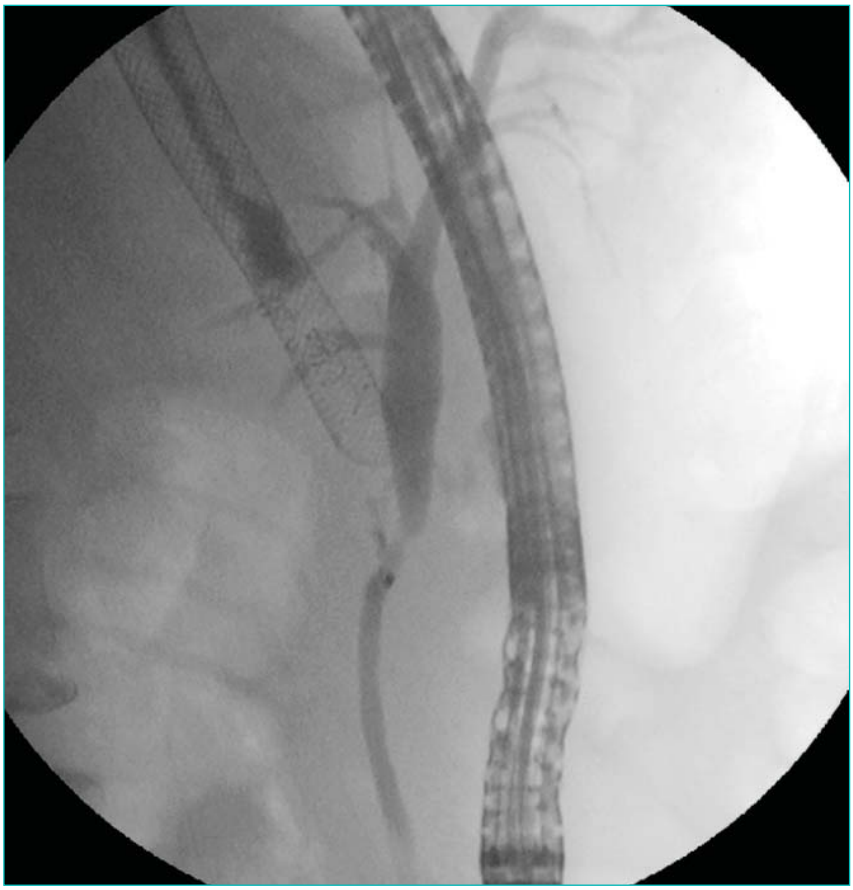

Fig. 4./Obr. 4.
ERCP. Stenosis at the middle third of the extrahepatic biliary duct in a patient with TIPS.
ERCP. Stenóza střední třetiny extrahepatálních žlučových cest u pacienta s TIPS.

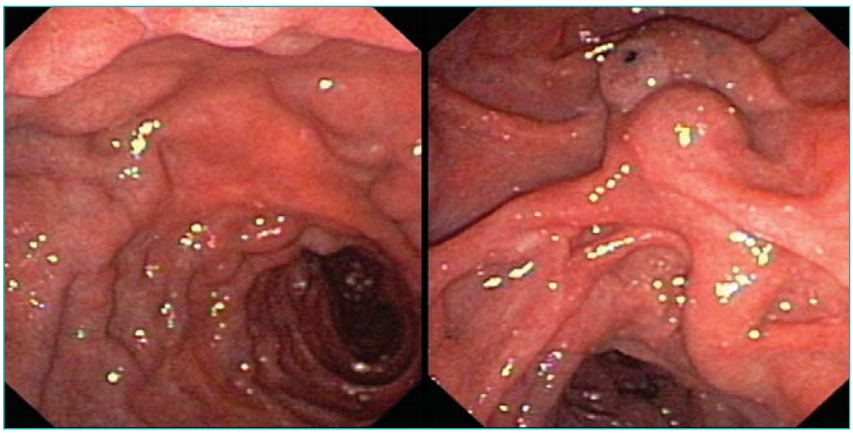

Fig. 5./Obr. 5.
Duodenoscopy. Varices in the duodenum above and around the major papilla.
Duodenoskopie. Varixy v duodenu nad a kolem Vaterovy papily.

Case 3

A 46-year-old woman registered a neonatal sepsis in her history. Since childhood she suffered from repeated variceal bleeding (despite endoscopic therapy). In 1969, the patient underwent splenectomy but its effect was only temporary. In 1972, endoscopic treatment followed, sclerotherapy of the oesophageal varices was accomplished. A surgical porto-systemic shunt (mesentero-iliac anastomosis) was performed two years later having had a beneficial effect to prevent variceal re-bleeding. In her adulthood, she delivered two healthy babies, (she also had a miscarriage and one abortion). Afterwards the patient underwent cholecystectomy (1997). In 1997, the patient was referred to our Department for the first time because of hepatic bile duct stones. Imaging methods, US and CT, confirmed portal cavernoma with numerous portosystemic collaterals most marked around the uterus, and found portal biliopathy. Since that time she has been treated endoscopically, ERCP was performed repeatedly (Fig. 7A) with papillotomy, stenting and/or temporary nasobiliary drainage and multiple techniques of stone extraction including extracorporal shockwave lithotripsy (during 1997–1998). For the next ten years, the patient remained asymptomatic (treated with ursodeoxycholic acid). By the end of 2008, a control US revealed asymptomatic hepaticolithiasis. ERCP was performed (Fig. 7B) and extraction of bile duct stones was completed on the third attempt. During the subsequent

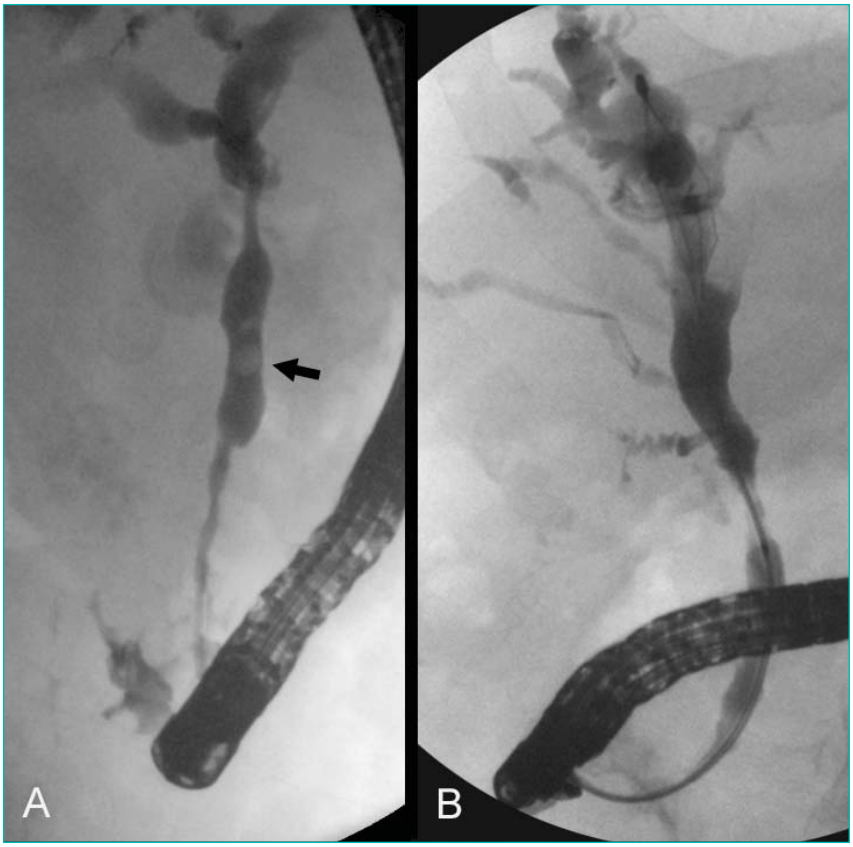

Fig. 6./Obr. 6.
ERCP. Multiple stenoses and dilation of the biliary tree, lithiasis in the common bile duct (arrow).
A: left lateral position;
B: supine position of the patient.
ERCP. Vícečetné stenózy a dilatace žlučových cest, choledocholitiáza (šipka).
A: pozice pacienta na levém boku;
B: pozice na zádech.

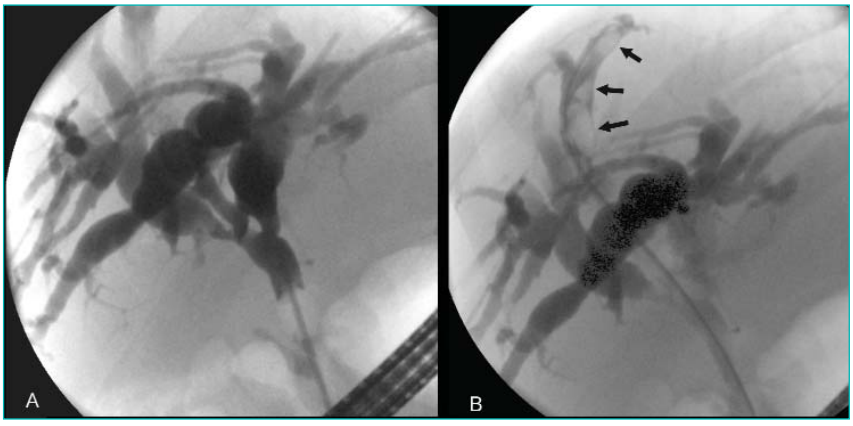

Fig. 7./Obr. 7.
ERCP. Dilation of intrahepatic ducts, lithiasis in the eighth liver segment (arrows).
ERCP. Dilatace nitrojaterních žlučovodů a intrahepatická litiáza v VIII. segmentu (šipky).

4-month follow-up period, the patient remained symptom-free (on maintenance therapy with ursodeoxycholic acid).

DISCUSSION

We present three cases of portal biliopathy collected at our Department within the past 15 years. All three cases were presented previously with variceal bleeding due to portal hypertension. Clinical signs of subsequent portal biliopathy appeared as biliary obstruction with jaundice.

Portal biliopathy is defined as biliary abnormalities associated most commonly with **extrahepatic portal vein obstruction** (thrombosis of the portal vein), which is an important cause of portal hypertension in developing countries (up to 40% of all patients with portal hypertension), with less frequent other causes of portal hypertension such as liver cirrhosis, idiopathic portal hypertension or non cirrhotic portal fibrosis. Causes for subsequent development of EHPVO are omphalitis, umbilical vein catheterisation and intra-abdominal sepsis. In adults, secondary EHVPO is associated with hypercoaguble states, chronic myeloproliferative disorders, chronic pancreatitis or local tumour invasion [2,13]. As a general rule, the clinical consequences of portal hypertension are similar regardless of the cause or site of obstruction. However, several pathophysiological changes are related to specific types and causes of portal hypertension which may influence their clinical presentation and therapy [8]. The portal vein in EHVPO is transformed into a cavernoma which is a network of multiple collateral veins developed to bypass the thrombosed portal vein. In the biliary tract, venous drainage passes through two venous plexus: *the epicholedochal venous plexus of Saint* which is a fine reticular network on the outer surface of common bile duct and hepatic ducts and *the paracholedochal venous plexus of Petren* that runs parallel to the wall of the common bile duct. Their conversion into vein collaterals causes pressure and protrusion over thin and pliable biliary and hepatic ducts and results in changes called portal biliopathy [2,3,5,10–12]. Besides hypothesis of variceal compression of bile ducts, there is an ischemic hypothesis that in case of portal vein thrombosis the vascular supply of bile ducts is compromised and it leads to scarring of ductal walls, which results in biliary strictures and cholangiectasias [2,3,12]. Biliary compressions by periportal collaterals are reversible, how-

ever, ischaemic changes persist despite decompression of collaterals [3].

Clinical presentation of EHPVO can be acute and chronic. Symptoms of acute EHPVO are abdominal pain, ascites, fever and absence of portal cavernoma and porto-systemic collaterals. Chronic EHPVO may be presented initially with variceal bleeding and splenomegaly [4]. Long term portal hypertension leads to other disorders presented in adulthood, including portal biliopathy. The mean time from portal cavernoma diagnosis to biliary symptoms was eight years [10]. Despite the fact that 80–100% of patients with EHPVO develop biliary changes seen on ERCP, the majority of them are asymptomatic. Clinical signs of portal biliopathy are related to biliary obstruction [2,3,6,8,9]: persistent jaundice, pruritus, cholecystolithiasis and choledocholithiasis (as a result of biliary stasis) or cholangoitis. Biliary obstruction can result in secondary biliary cirrhosis. Probably the first reported case was a female patient with omphalitis after birth and consequent portal cavernoma, who finally developed biliary cirrhosis at the age of 23 [7].

Abnormal biochemical test can include increased serum bilirubin and alkaline phosphatase, gama-glutamyl transferase as markers of cholestasis. Endoscopic retrograde cholangiography is the most important diagnostic method revealing typical changes of the common bile duct and hepatic ducts, such as strictures, luminal irregularity, segmental dilatation, ectasias, duct displacements and angulations [2,3,11]. These changes are similar to those in primary sclerosing cholangitis or cholangiogenic cancer ("pseudo-cholangiocarcinoma sign"). Biliary abnormalities in EHPVO are commonly involved in the common bile duct and left hepatic duct, less in the right hepatic duct. Defects of filling of contrast media in cirrhosis are located intrahepatically [2,3,11]. The advantage of ERCP and superior position of this method over others is given by possible therapeutic intervention during the same session.

Among non-invasive diagnostic methods, CT scan is useful in making a diagnosis. Magnetic resonance imaging (MRI) cholangiography and portography is another sensitive and non-invasive imaging modality. Portal cavernoma is vascular soft tissue surrounding the portal vein on MRI. Shin et al described findings on MRI scans in patients with EHPVO and classified biliary abnormalities as varicoid, fibrotic, or mixed type on the basis of pathogenesis [10]. In the varicoid "reversible" type, irregularities of bile ducts were caused by multiple smooth extrinsic compressions of the cavernoma. In the fibrotic type there were localised strictures with proximal duct dilatation, caused by fibrous scarring related to ischaemic injury or chronic inflammation [10]. This method can also differentiate choledochal varices from bile duct stones. MRI portography delineates spleno-porto-venous axis and collaterals, which helps to assess the possibility of shunt surgery [2]. Abdominal US is the most available and basic imaging. It can reveal splenomegaly, dilated portal vein, and collaterals in portal cavernoma, which conceal the common bile duct, dilated intrahepatic ducts, gallbladder varices and lithiasis. Endoscopic ultrasonography is useful to differentiate other causes of biliary obstruction (varices, stones, malignancy) especially if other modalities are unrevealing [11].

Consensually, asymptomatic patients do not require any treatment. Therapy should be reserved for symptomatic patients alone. There are endoscopic, surgical and radiological options for treatment. The chosen approach should be determined by the individual patient's characteristics. The first recommended one is endoscopic treatment [1] performing ERCP with papillotomy of the sphincter of Oddi, biliary stricture dilation and biliary stent or nasobiliary drain placement. Sphincterotomy should be performed with caution because dilated collaterals around the major papilla represent an increased risk of bleeding during the procedure. Haemobilia may also occur during biliary dilatation [2,11]. In the event of failure endoscopic treatment, surgery may be considered. Bilio-digestive anastomosis in the setting of portal cavernoma is associated with a high risk of bleeding. Thus, surgical porto-systemic anastomosis should be provided first to collapse collaterals of portal cavernoma. If the patient remains symptomatic, bilio-digestive anastomosis should be considered. Pharmacological agents such as somatostatin, octreotid, terlipressin can be helpful during surgery to decrease blood loss [2,12]. Liver transplantation may be required in secondary biliary cirrhosis [2]. Transjugular intrahepatic porto-systemic shunt (TIPS) can relieve the compression caused by portal cavernoma [9]. In our first case, TIPS was introduced to reduce the risk of re-bleeding and to influence portal biliopathy. However, the TIPS was soon re-thrombosed case due to the hypercoaguable state in this particular case. Use of ursodeoxycholic acid seems to be a beneficial supportive therapy [2,5]. This treatment was helpful in one of our cases too.

In conclusion, portal biliopathy should always be considered in the event of biliary obstruction in patients with EHPVO. Portal biliopathy might be complicated with bile duct stones and/or cholangitis. ERCP is the method of choice both for diagnosis and treatment.

Acknowledgement

The study was supported by research project MZO 00179906 from the Ministry of Health, Czech Republic.

References/Literatura

1. Bhatia V, Jain AK, Sarin SK. Choledocholithiasis associated with portal biliopathy in patients with extrahepatic portal vein obstruction: management with endoscopic sphincterotomy. Gastrointest Endosc 1995; 42(2): 178–181.
2. Dhiman RK, Behera A, Chawla YK et al. Portal hypertensive biliopathy. Gut 2007; 56(7): 1001–1008.
3. Dhiman RK, Puri P, Chawla Y et al. Biliary changes in extrahepatic portal venous obstruction: compression by collaterals or ischemic? Gastrointest Endosc 1999; 50(5): 646–652.
4. de Franchis R. Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2005; 43(1): 167–176.
5. He ZP, Fan LJ. Diagnosis and treatment of portal biliopathy. Hepatobiliary Pancreat Dis Int 2002; 1(4): 581–586.
6. Kochhar R, Nagi B, Singh K. Portal biliopathy in extrahepatic and intrahepatic portal hypertension. Gastrointest Endosc 2001; 53(5): AB96.
7. Perlemuter G, Béjanin H, Fritsch J et al. Biliary obstruction caused by portal cavernoma: a study of 8 cases. J Hepatol 1996; 25(1): 58–63.
8. Sanyal AJ. Extrahepatic portal vein obstruction (portal vein thrombosis). UpToDate [online], vol 17.1. Welleysley, 2009. Available from: <http://www.uptodate.com>.
9. Senzolo M, Cholongitas E, Tibballs J et al. Relief of biliary obstruction due to portal vein cavernoma using a transjugular intrahepatic portosystemic shunt (TIPS) without the need for long-term stenting. Endoscopy 2006; 38(7): 760.
10. Shin SM, Kim S, Lee JW et al. Biliary abnormalities associated with portal biliopathy: Evaluation on MR cholangiography. AJR Am J Roentgenol 2007; 188(4): W341–W347.
11. Umphress JL, Pecha RE, Urayama S. Biliary stricture caused by portal biliopathy: diagnosis by EUS with Doppler US. Gastrointest Endosc 2004; 60(6): 1021–1024.
12. Vibert E, Azoulay D, Aloia T et al. Therapeutic strategies in symptomatic portal biliopathy. Ann Surg 2007; 246(1): 97–104.
13. Zargar SA, Javid G, Khan BA et al. Endoscopic ligation vs. sclerotherapy in adults with extrahepatic portal venous obstruction: a prospective randomized study. Gastrointest Endosc 2005; 61(1): 58–66.

Correspondence to/
Adresa pro korespondenci:
Paula Sopirjaková, MD
2nd Department of Internal Medicine
Charles University Teaching Hospital
Sokolská 581
500 05 Hradec Králové
Czech Republic
e-mail: sopirjakova@fnhk.cz