

CASE REPORTS

Hepatic venous outflow obstruction in patients with polycystic liver disease: pathogenesis and treatment

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Abstract

Polycystic liver disease is commonly asymptomatic but may present with hepatomegaly, abdominal distension, and dull abdominal pain. Transudative ascites is a rare manifestation in these patients but may occur when portal hypertension is present resulting from associated hepatic fibrosis or after deroofting procedure of a cyst. Exudative ascites might suggest hepatic venous outflow obstruction. Four cases are described where hepatic venous outflow obstruction occurred in patients with polycystic liver disease. Three patients had orthotopic liver transplantation and one had a mesocaval shunt. Of the two patients that survived orthotopic liver transplantation both have shown considerable improvement in their symptoms. None of the patients had any confirmed procoagulant disorder. The mechanism of hepatic venous outflow obstruction in these patients seems to be mechanical compression of hepatic veins by the cysts and associated formation of thrombi in small hepatic vein tributaries. Patients with severe polycystic kidney/liver disease are at risk of hepatic venous outflow obstruction and the onset of this complication is heralded by tender hepatomegaly and presence of exudative ascites.

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Autosomal dominant polycystic kidney/liver disease is the second most common inherited monogenic disease after familial hypercholesterolaemia.¹ It has a prevalence that

ranges from 1 in 200 to 1 in 1000 in different populations. Liver cysts represent the most frequent extra renal manifestation of autosomal dominant polycystic kidney disease. The incidence of liver polycystosis in these patients ranges from 15-40%.² This incidence increases with age, reaching a frequency of 65% in patients above 60 years of age.³⁻⁴ Symptoms caused by the polycystic liver become manifest in only 10-15% of patients, but the percentage is rising with the prolonged survival of patients receiving renal replacement treatment.

Most patients with liver polycystic disease present with a dull aching abdominal pain, but jaundice (which may be caused by an associated cholangiocarcinoma) and severe abdominal pain are also important presenting symptoms.⁵ Ascites is uncommon and is usually seen late in the disease.⁶ When present, it is usually transudative and is caused by portal hypertension related to associated hepatic fibrosis. Occasionally a ruptured cyst may also present as ascites, which again has characteristics of a transudate.

Finding exudative ascites in patients with polycystic liver/kidney disease has to date implied a second disorder. We describe four cases of autosomal dominant polycystic kidney/liver disease who presented with exudative ascites, in whom the mechanism was shown to be hepatic venous outflow obstruction caused by compression of the hepatic veins leading to thrombotic occlusion of small hepatic vein branches.

Case histories

CASE 1

A 51 year old woman, was referred with massive ascites and gross pedal oedema. She had been diagnosed as having polycystic kidney/liver disease 25 years ago and needed β blockers for control of hypertension. Four years previously she had developed ascites, which had become progressively worse. For the past six months she had been greatly incapacitated by massive ascites and oedema of the feet. She was confined to a wheel chair, was breathless on minimum exertion, could not lie flat in bed, and could only manage a few steps

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Liver function tests and original ascitic protein and cell content

	Serum					Ascites	
	Bilirubin ($\mu\text{mol/l}$)	TP (g/l)	Albumin (g/l)	AST (IU/l)	ALP (IU/l)	Protein (g/l)	Cells (/mm ³)
Case 1	8	67	35	16	131	36	75
Case 2	11	68	44	19	123	58	36
Case 3	12	69	39	14	64	42	89
Case 4	10	65	35	12	113	40	105

TP=total protein; AST=aspartate aminotransferase; ALP=alkaline phosphatase.

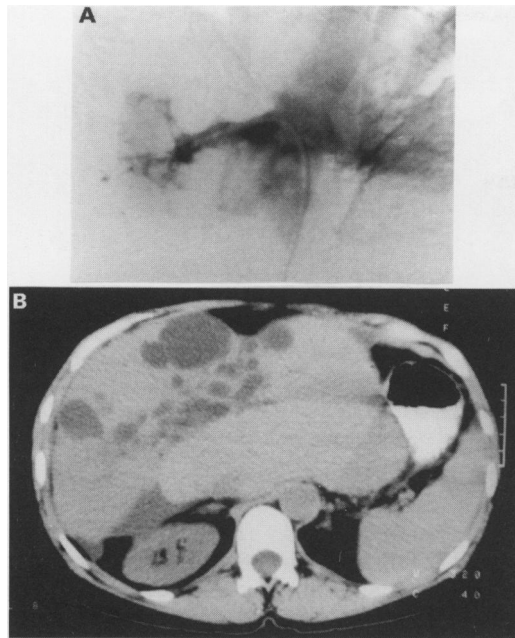


Figure 1: (A) Case 3, hepatic venography. Digital subtraction image with catheter in the right hepatic vein showing distortion of the right main hepatic vein and collateralisation of more peripheral branches; (B) computed tomography showing paucity of liver cysts (case 4) and enormous caudate hyperplasia.

on her own. Investigations showed: haemoglobin 9.9 g/dl, white cell count $9.1 \times 10^9/l$, platelets $310 \times 10^9/l$. The Table shows the results of the liver function tests. Serum electrolytes were normal but creatinine was raised to 199 $\mu\text{mol/l}$. Twenty four hour urinary protein was normal. The ascitic protein content was 36 g/l; cytology and microbiological investigations were negative. Ultrasound and computed tomography of the abdomen showed a very large liver with multiple cysts varying in size from a few millimetres to 6 cm. Aortoportography showed a normal portal vein. Hepatic venography showed that the hepatic veins were grossly distorted with multiple collaterals, changes consistent with hepatic venous outflow obstruction.

She had an orthotopic liver transplantation in January 1993 and at operation 17 litres of ascitic fluid was drained and the liver weighed 8.9 kg. The patient has done well after her transplant. She is ambulatory with considerable improvement in her quality of life. Although there has been some reaccumulation of transudative ascites (protein 21 g/l), this is easily controlled with diuretics.

CASE 2

A 47 year old woman with a seven year history of asymptomatic polycystic disease of the liver and kidney was referred to the gynaecology department because of ascites and a uterine mass. Investigations showed haemoglobin 10.1 g/dl, white cell count $5.6 \times 10^9/l$, platelets $289 \times 10^9/l$. The urea, liver functions tests, and electrolytes were normal and plasma albumin was 44 g/l. Ascitic protein content was 58 g/l and microbiological and cytology investiga-

tions were negative. Ultrasound and computed tomography confirmed a uterine mass with inconclusive fibroid like features. After hysterectomy she was well for one month before ascites recurred.

On examination a cystic liver was easily palpable below the umbilicus. Ascitic protein content was again high at 56 g/l. Ultrasound and Doppler studies showed a patent portal vein but the left hepatic vein was occluded. Hepatic venography confirmed occlusion of the left hepatic vein. Evaluation for a hypercoagulable state showed that the antithrombin III, cardiolipin antibody, protein C and S, Ham's test, and clot lysis test were all normal. Marrow aspirate was normal and culture showed no excess of megakaryocyte colonies. Reaccumulation of ascites required repeated paracenteses and she therefore had an orthotopic liver transplantation. During the reperfusion phase of the operation she developed severe hypotension from which she could not be resuscitated. The removed polycystic liver weighed 5.9 kg.

CASE 3

A 42 year old woman diagnosed as having polycystic kidney/liver disease 12 years previously was referred for transplant assessment because of resistant ascites. She had been well except for occasional mild pain in the right upper quadrant until September 1992, when she rapidly developed ascites and gross pedal oedema, which was resistant to high dose diuretics.

On physical examination the liver was enlarged to 10 cm below the costal margin, but the kidneys were not palpable because of very tense ascites. Ultrasound confirmed the findings of an enlarged liver with multiple cysts varying in size from a few millimetres to 5 cm. The kidneys were also enlarged with multiple cysts. Investigations showed haemoglobin 11.5 g/dl, white cell count $6.7 \times 10^9/l$, platelets $185 \times 10^9/l$. Creatinine was 168 $\mu\text{mol/l}$, but 24 hour urinary protein excretion was normal. Ascitic fluid protein content was 42 g/l with a negative microbiology and cytology examination.

A hepatic venogram showed grossly distorted hepatic veins with multiple collaterals consistent with hepatic venous outflow obstruction (Figure 1A). The patient had an orthotopic liver transplantation. The removed liver weighed 7.7 kg and macroscopic examination showed multiple cysts varying from a few millimetres to 8 cm in size.

The patient had an uneventful post transplant course and although she continues to have some ascites it requires only low dose diuretic treatment for control. The ascites is now transudative with protein content of 16 g/l.

CASE 4

A 52 year old woman was referred to the local hospital by her general practitioner in April 1991 when she suddenly developed severe pain



Figure 2: Posterior view of the polycystic liver in patient 1 showing the caudate lobe (CL) and the major hepatic vein branches whose lumens (arrowed) are patent, though considerably distorted, seemingly squeezed between cysts.

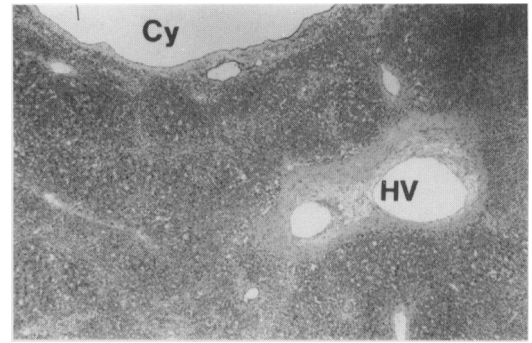


Figure 3: Liver histological examination. There is extensive congestion and parenchymal loss nearby a cyst (Cy). Note a hepatic vein branch (HV) whose lumen is narrowed by an organised thrombus. Haematoxylin and eosin, original magnification $\times 60$.

in her right abdomen. Ultrasound showed multiple cysts in the liver and a few cysts in both kidneys. Between April 1991 and July 1992 she required three liver cyst aspirations, necessitated by pain. In July 1992 one of the large hepatic cysts was deroofed. Within two weeks of surgery she was admitted again with acute onset of abdominal distension and transient confusion. On examination she was found to have ascites for the first time. Investigations showed haemoglobin 12 g/dl, white cell count $9.2 \times 10^9/l$, platelets $213 \times 10^9/l$. The urea, electrolytes, and liver function tests were normal with a plasma albumin of 40 g/l. Ascitic fluid protein content was 40 g/l, with negative microbiology and cytology. The patient improved during her hospital stay and remained well until December 1992 when the ascites reappeared. Her diuretic dose was increased resulting in some improvement. She was admitted again in February 1993 with painful and tender hepatomegaly. Ultrasound and computed tomography showed an enlarged left lobe and a considerably enlarged caudate, the right lobe showing a few small cysts (Fig 1B). Doppler ultrasound showed that the portal vein was patent with normal flow. The right and middle hepatic veins were occluded and left hepatic vein, although distorted, was patent on hepatic venography. All haematological and biochemical investigations were normal. Investigations for procoagulant states showed a normal antithrombin III, and protein C and S. Plasminogen values were also normal. Autologous erythroid cultures in erythropoietin poor media were negative. The patient successfully had a mesocaval shunt, with lowering of portal venous pressure and relief of symptoms of the grossly enlarged caudate lobe, and is at present asymptomatic while receiving a small dose of diuretics.

Pathological examination

The livers removed at transplantation in cases 1 to 3 weighed respectively 8.9 kg, 5.9 kg, and 7.7 kg and were similar on gross examination. Their surface was considerably distorted by numerous protruding cysts, which on the cut section were diffusely distributed and extensively replaced the liver parenchyma.

Their sizes ranged from a few millimetres to 8 cm in maximum diameter. They variably contained serous fluid, yellow or lightly bile stained jelly like material, or altered blood. The amount of intervening parenchyma ranged from inconspicuous to sleeves of tissues up to 5 cm in thickness. There were broad areas showing red haemorrhagic mottling, some as large as a liver segment, though a precise distribution could not be identified because of the complete obliteration of the liver anatomy by the cysts. Appearances were those of localised Budd-Chiari. The less affected parenchyma exhibited a slight nodularity suggesting regenerative hyperplasia. The main branches of the hepatic veins were free from thrombosis, though they were considerably distorted, seemingly compressed in between or stretched at the periphery of major cysts (Fig 2).

Histologically, most of the cysts were lined by flattened biliary epithelium. Scattered biliary hamartomas (von Meyenburg complexes) were present in the intervening parenchyma, their lumens being filled with inspissated bile. There were extensive areas of sinusoidal dilatation and congestion associated with hepatocyte loss affecting the whole of acinar zones 2 and 3, and to a lesser extent and focally zone 1. Appearances were typical of venous outflow block (Fig 3). In these areas, small supralobular branches of the hepatic vein had their lumens narrowed or occluded by loose fibrous tissue containing entrapped red cells and neolumens in keeping with organised thrombi.

Discussion

Polycystic liver disease is thought to be caused by a failure of excess intralobular bile ducts to involute during embryonic development.⁷⁻⁸ The disease is genetically determined with an autosomal dominant mode of inheritance. Associated polycystic kidney disease is often present. Most patients with liver polycystic disease remain asymptomatic. Abdominal pain and distension are common presenting complaints in symptomatic patients and are caused by the enlarging liver. Ascites is the most common clinical manifestation of hepatic venous outflow block, being present in

90–96%⁹ of patients. Abdominal pain and tender hepatomegaly are also common. Ascitic fluid has a high protein content, which most probably results from the high permeability to proteins of the sinusoidal walls. Increased sinusoidal pressure enhances the filtration of interstitial fluid and when drainage capacity of hepatic lymphatics is exceeded, filtration of fluid through the liver capsules occurs.

Most patients with polycystic liver disease do not require any treatment. Active treatment should be considered only when patients become symptomatic or develop complications secondary to cysts. Uncomplicated but symptomatic polycystic liver disease requires treatment that varies from simple aspiration of the cyst to deroofing of the cyst, partial hepatic resection or orthotopic liver transplantation. The choice of procedure depends on the number and size of the cysts, severity of symptoms, degree of portal hypertension, and underlying hepatic function.¹⁰ Patients who develop complications secondary to cysts more commonly require active treatment. Hepatic venous outflow obstruction secondary to liver polycystosis can be treated initially with diuretics and oral anticoagulants. Anticoagulation should be used very cautiously because of the association of this condition with intracranial berry aneurysms. Porto-systemic shunting remains a good option assuming that hepatic venous outflow obstruction is not long standing, and that patients have reasonable synthetic liver function. When patients have severe symptoms from huge liver cysts and resistant ascites, or have longstanding venous outflow block with poor liver function, orthotopic liver transplantation is the only logical choice.

It is unlikely that all patients with multiple large liver cysts need longterm anticoagulation treatment to prevent the uncommon complication of hepatic venous outflow obstruction, especially as there is an association of intracranial berry aneurysms with polycystic disease.

Orthotopic liver transplantation seems to be a successful treatment option in patients with polycystic liver disease and hepatic venous outflow obstruction and the role of the mesocaval shunt remains unproved. We describe here four cases of hepatic venous outflow obstruction in polycystic liver disease (one of which, case 2, has been reported before¹¹). Three of the cases had an orthotopic liver transplant and in these cases the hepatic veins were clearly distorted by the large cysts. In case 4 the cysts were smaller and mainly confined to the right lobe. As the liver has not been removed, it cannot be proved that the cysts caused hepatic vein compression in this case. No procoagulant state was identified, however, and the vein occlusion was of the right vein (in the area where cysts were present) and it is probable that the cystic disease and venous occlusion were related. These cases show the different ways in which the condition can present and give a clearer picture of the pathogenesis and treatment of this unusual syndrome.

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