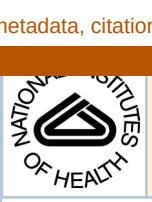

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Persistent portosystemic shunts after deceased donor liver transplant causing episodic hepatic encephalopathy despite good graft function

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Abstract

We describe two cases of post liver transplant encephalopathy caused by persistent portosystemic shunts despite good graft function. Such recurrence of encephalopathy due to persistent shunting has not been reported in the deceased donor liver transplant literature. Our patients had episodic hepatic encephalopathy concordant with elevated serum ammonia levels due to well documented persistent portosystemic shunts. In one of our cases, the shunt was obliterated via coil embolization. This patient's encephalopathy resolved completely and has not recurred over seven months of follow up. The second patient has declined an intervention, but has remained symptom free on maintenance lactulose and rifaximin.

Keywords

Liver Transplantation; Encephalopathy; Portosystemic shunt; Embolization; Interventional Radiology

Introduction

Many patients with cirrhosis suffer from hepatic encephalopathy due to decreased function of the diseased liver and shunting of portal blood around the liver into the systemic circulation. Accumulation of nitrogen containing compounds, including ammonia, in the systemic circulation is thought to be the etiology of the resulting encephalopathy(1). Portosystemic shunts may also arise in non cirrhotic patients as well. These shunts may be the result of congenital anomalies, trauma, or intentional/iatrogenic complications from surgery or other procedures(2). These portosystemic shunts can cause a similar type of encephalopathy even without overt liver disease.

The natural history of portosystemic shunts after liver transplant is not well documented, but prevailing thought is that most of these shunts close or quickly become clinically irrelevant soon after transplant. Clinical problems from ascites, encephalopathy and varices generally resolve.

Our patients had well documented hepatic encephalopathy due to persistent portosystemic shunts after liver transplant. To our knowledge, there is only one other case of this phenomenon reported in the literature and this involved a 23 year recipient of only a left

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Conflicts of Interest: None

lobe (3). We describe two patients who received whole livers from deceased donors. Both have been successfully treated, one by closing the shunt with intravascular embolization and the other with maintenance lactulose and rifaximin.

Case 1

A 45 year-old Caucasian female had an orthotopic liver transplant in late May 2007 for decompensated cirrhosis due to chronic hepatitis C. She had an uncomplicated immediate post operative course and was discharged from the hospital 13 days after transplant. Prior to transplant, she had difficulty with hepatic encephalopathy, ascites, gastroesophageal varices and peripheral edema. Her MELD score was 31 at transplant. Her post-transplant course was otherwise unremarkable without episodes of significant rejection or disease recurrence.

In September of 2007, four months post transplant, she was readmitted to the hospital for altered mental status. There was no clear precipitating reason for the altered mental status according to her family. During that admission, her evaluation included normal liver enzymes, bilirubin, complete blood count with normal platelet count, serum chemistries, and negative blood and viral cultures, negative urine toxicology screen. Her synthetic function was good with an INR of 1.2. Imaging consisted of a normal head CT and a normal liver transplant ultrasound that showed no evidence of nodularity or morphologic abnormalities. However, her venous ammonia level was 65 umol/L (normal 9 –33). She responded to lactulose and her mental status returned to her normal baseline.

For the next three months, she remained in her usual state of good health. She had an upper endoscopy that showed no varices and mild portal hypertensive gastropathy. She was seen in clinic in late December 2007 and she was doing quite well. Three days after her clinic visit, however, she became combative and irrational. Per her friends and family, there were no clear precipitating factors that lead to her decline. She was admitted to an outside hospital and then transferred to our institution. Again, other than an elevated venous ammonia level of 165 umol/L, her evaluation was unrevealing. Again, she had a rapid clinical response to lactulose with a corresponding drop in ammonia to 19 umol/L. A repeat liver transplant ultrasound showed diminished portal vein velocities, but was otherwise normal. At this point the diagnosis of a persistent porto-systemic shunt was entertained.

The patient underwent an abdominal CT scan (Figure 1) which was without any architectural changes in the liver but was notable for an inferior mesenteric vein to left renal vein shunt via a dilated left gonadal vein. Subsequently, the patient had a transhepatic portogram with embolization of the inferior mesenteric vein-gonadal vein collateral (Figures 2-4.) Afterwards, doppler ultrasound of the hepatic vasculature showed improved flow within the portal vein.

In seven months of follow up, the patient has done well and has not required any lactulose, nor has she had any further episodes of hepatic encephalopathy or altered mental status.

Case 2

A 55 year old male was transplanted in 1997 for cryptogenic cirrhosis. His post operative course was marked by chronic lower extremity edema, managed with diuretics.

Overall, he maintained his state of good health until January 2008 when he was admitted to his local hospital with altered mental status. There were no clear precipitating events that lead to his illness. Liver function tests, chemistries, complete blood count including platelet count, toxicology screen and cultures were all normal. His evaluation was unrevealing except for an elevated ammonia level. His graft was otherwise well functioning with an

albumin of 3.7 g/dL and INR of 1.1. A liver biopsy showed mild periportalcholestasis without duct loss, mild biliary atrophic changes but was negative for acute rejection or viral cytopathic effect. There was no advanced fibrosis or cirrhosis. After administration of lactulose, his ammonia level and mental status improved.

In April 2008, the patient returned to his local hospital with sudden onset altered mental status, and again, the evaluation was normal with the exception of an ammonia level. The graft function was preserved with an albumin of 3.8g/dL and an INR of 1.1. Liver function tests were all normal. The patient was treated with lactulose with subsequent improvement in mental status and fall in ammonia levels within 24 hours. The patient and friends describe these episodes as clinically identical to his pre-transplant hepatic encephalopathy and without obvious precipitating factors. Upon discharge, he was put on a maintenance lactulose regimen.

On his return to our institution, a diagnosis of a spontaneous or persistent portosystemic shunt was entertained. A CT scan was performed (Figure 5) that showed dilated left renal vein, splenic veins, splenic varices and a splenorenal shunt. There was also sluggish flow in the portal vein on Doppler ultrasound. At this point arrangements were made to close the shunt via interventional radiology coil embolization. On the day of the procedure, however, the patient changed his mind and declined the intervention; he elected to remain on maintenance lactulose. The patient has some renal insufficiency and was concerned about the risk of IV contrast renal toxicity. Rifaximin was added to the patient's medical regimen in June 2008; since then, he has been symptom free.

Discussion

The prevailing opinion is that portosystemic shunts should close once portal hypertension resolves after transplant. However, the evidence for decreased portal hypertension and shunt closure in adults is limited. Yanaga et al, observing the reversal of splenomegaly post transplant(4). A study by Ling, et al(5) regarding children who underwent liver transplant showed reversal of portal hypertension by clinical criteria and ultrasound in the majority of patients.

Conversely, there are studies that suggest persistence of portal hypertension. Chezmar, et al(6), showed persistence of portosystemic collaterals by CT scan in 74% and 64% of patients at six months and one year post transplant. One patient had multiple collaterals four years after transplant. Dupuy, et al(7) found 29% of patients who had a CT scan performed up to two years after transplant manifested splenomegaly. These studies were based on radiologic findings that were presumably subclinical.

Hyperdynamic systemic circulation post transplant also hints at persistent shunting. Hadengue, et al(8), studied systemic and splanchnic hemodynamics in seventeen patients before and after liver transplant and compared these patients to controls with normal liver architecture. Cardiac index, azagous blood flow and hepatic blood flow remained elevated after transplant even in the setting of normal portosystemic pressure gradients.

Therefore, portosystemic shunts and portal hypertension may persist in some patients, even years after transplant. The natural history and significance of persistent shunting is unclear. The rarity of such shunt related encephalopathy is likely due to well functioning grafted livers. Nevertheless, portosystemic shunts in the non-cirrhotic setting (trauma, iatrogenic) leading to encephalopathy is well described (2).

Our patients had otherwise well functioning grafts. Although the first patient did not have a liver biopsy, rapidly recurrent hepatitis C is unlikely. She had no significant elevations in

liver enzymes. In particular, there was no cholestatic enzyme pattern suggestive of cholestatic recurrent hepatitis C. Her synthetic function and platelet counts were intact and she had no varices on endoscopy. Most of all she remains well with excellent functional status without anti-viral therapy. If she had severe and rapid recurrence of hepatitis C with cirrhosis within just 4 months of transplant, mere embolization of a shunt would not be expected to stabilize such a rapid decline in graft status. She should be having other manifestations or biochemical evidence of liver failure by now. Detailed MRI imaging studies did not suggest graft outflow obstruction and she had no clinical signs of right heart failure.

In the second case, the presentation was several years after transplant. A liver biopsy confirmed no advanced fibrosis. It remains puzzling as to why he presented so late, but gradual shifting of portal flow to the shunt is speculated. A spontaneous shunt is also a possibility, but equally vexing given the lack of cirrhosis or portal hypertension.

Both patients developed recurrence of their hepatic encephalopathy documented by elevated ammonia levels and response to standard medical therapies. The only other case in the literature involved a 23 year old who received a left lobe from a living donor. Smaller graft volume may have contributed to persistence of shunting and encephalopathy in that case. Our cases are the first involving a whole liver graft from a deceased donor and demonstrate successful treatment by intravascular embolization or medical therapy.

Abbreviations

CT	Computed tomography
AST	Aspartate Aminotransferase
INR	International Normalized Ratio
MELD	Model for End Stage Liver Diseae

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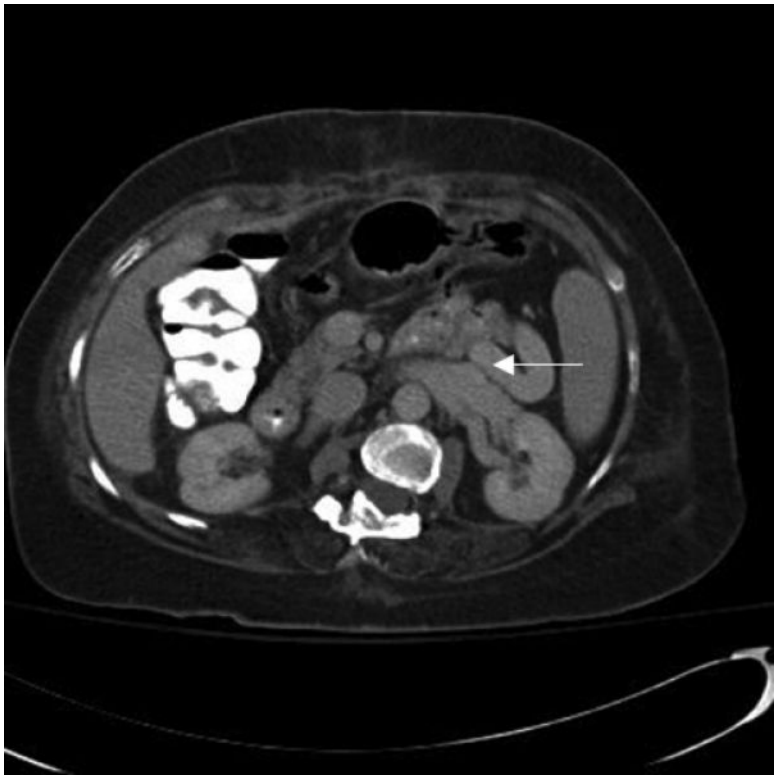

Figure 1.
CT scan demonstrating a left renal vein to inferior mesenteric vein shunt via tortuous gonadal vein (single arrow).

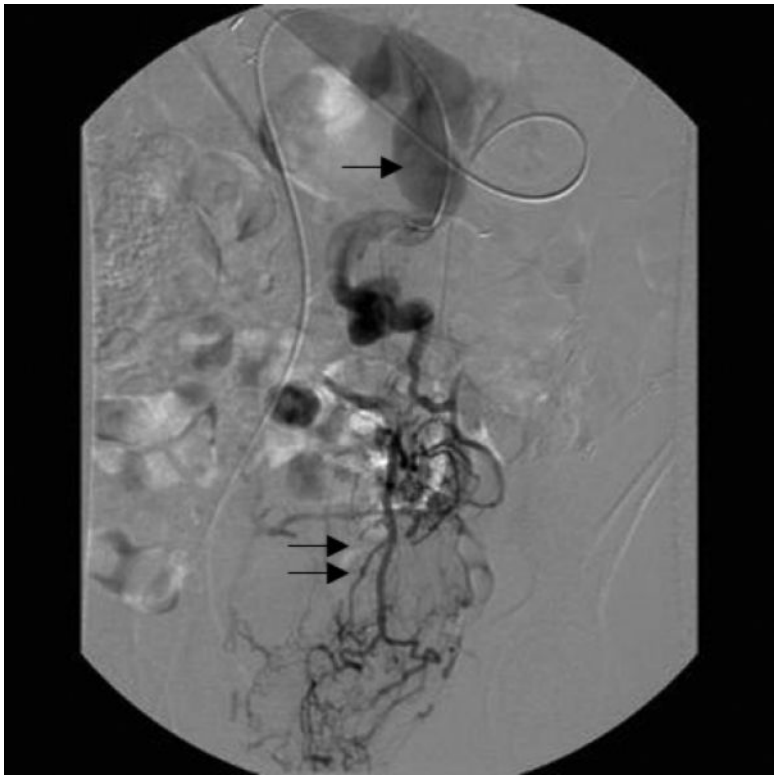

Figure 2.
Fluoroscopy of the porto-systemic shunt. A catheter traverses the renal vein to the gonadal vein varix (single arrow). The contrast flows into the inferior mesenteric vein (double arrow).

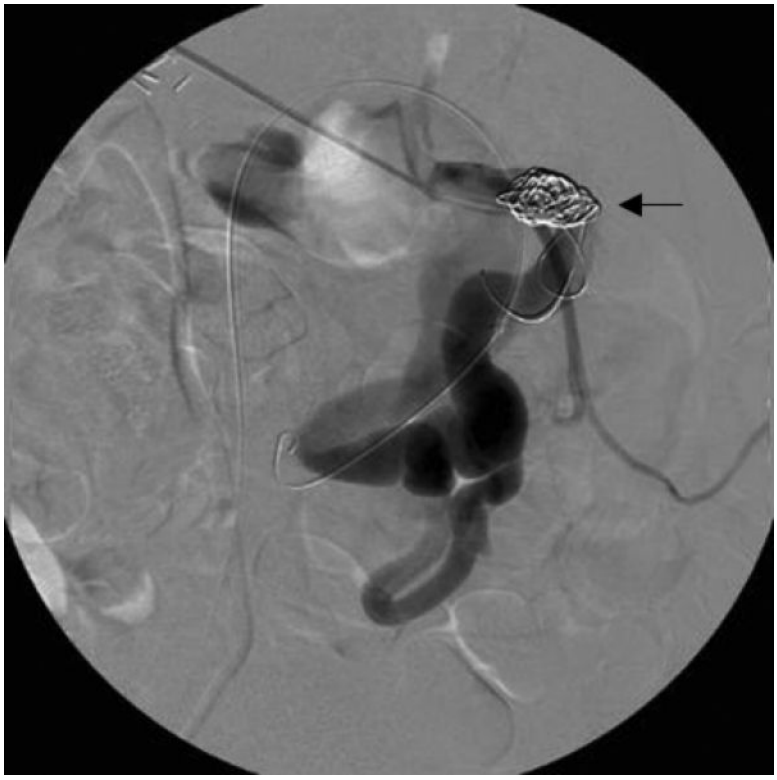

Figure 3.
Coil placement in the gonadal varix (single arrow).

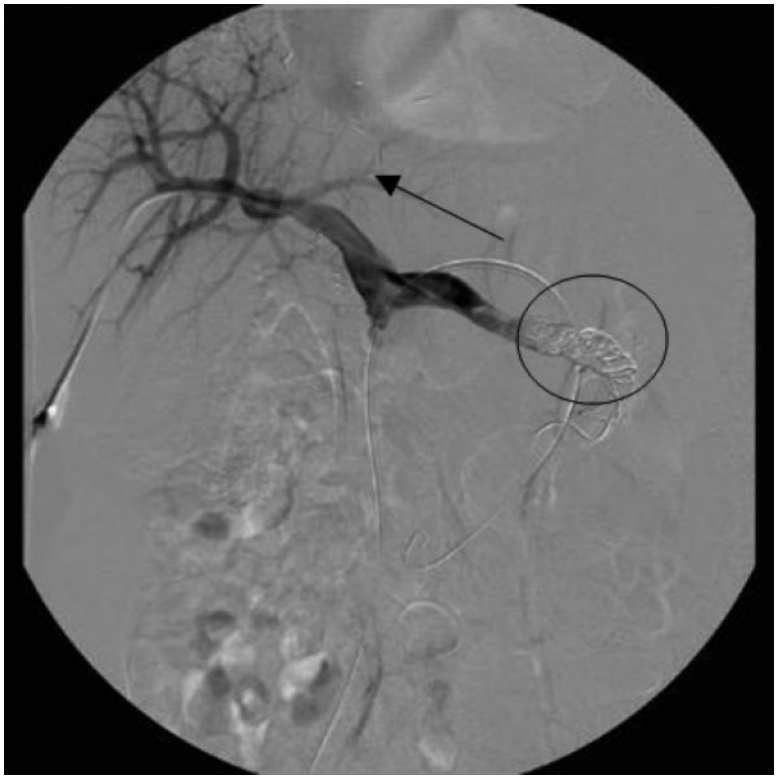

Figure 4.
Shunt obliterated by coils (circled) A trans-hepatic catheter is in the portal vein. Arrow denotes improvement in hepatopetal blood flow

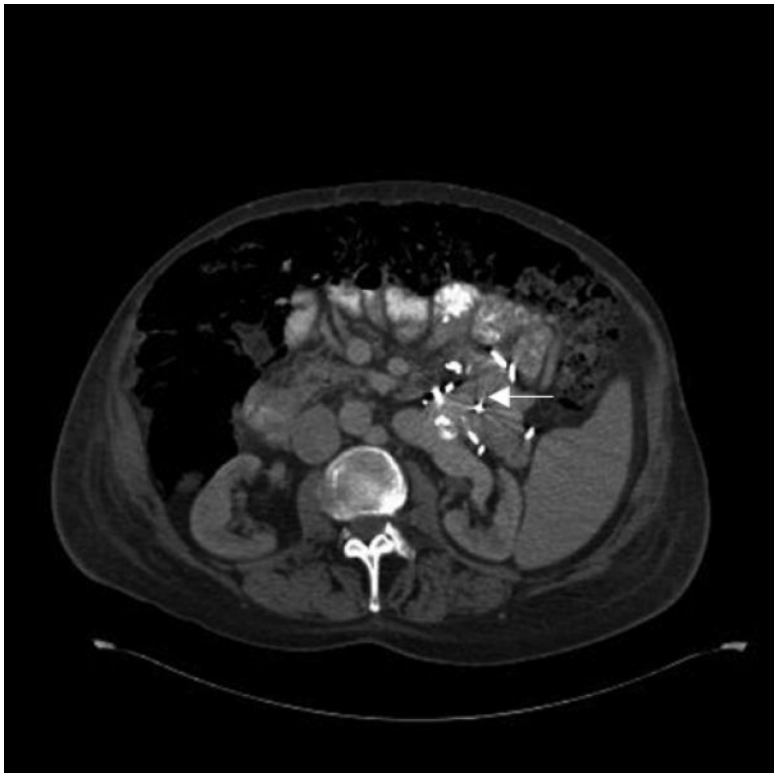

Figure 5.
Case 2. Splenorenal shunt (white arrow). Metallic clips are from original transplant.