Portosystemic Shunt Syndrome and Endovascular Management of Hepatic Encephalopathy

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Abstract

The term "portosystemic shunt syndrome" was coined by Kumamoto et al referring to reduction of the hepatic reserve (reflected by progression of the Child–Pugh score) over 5 years compared with portal hypertensive cirrhotics without gastrorenal shunts or with prior history of obliterated gastrorenal shunts. Saad et al elaborated on this term further by describing a complete syndrome with clinical findings (including worsening liver failure and hepatic encephalopathy [HE]) and imaging findings (including hepatic atrophy, portal vein thrombosis, and paucity of intrahepatic portal vein radicles). This article discusses the syndrome in detail. In addition, the article describes the types of HE and the endovascular management of shunt-related HE.

Keywords
- hepatic encephalopathy
- portosystemic shunt
- portal hypertension
- interventional radiology

Objectives: Upon completion of this article, the reader will be able to discuss the diagnosis and treatment of portosystemic shunts that lead to hepatic encephalopathy.

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Hepatic encephalopathy (HE) is defined as an alteration in personal autonomy/independence, consciousness, behavior, and psychomotor and cognitive function.[1–4] It is due to the accumulation of toxins due to hepatocellular dysfunction and/or portosystemic shunting.[1–4] HE is classified into two forms: encephalopathy related to hepatic failure (synthetic HE) and encephalopathy related to portosystemic shunts (whether man made like transjugular intrahepatic portosystemic shunts [TIPSs] or spontaneous portosystemic shunts [SPSS]).[1–4] The latter is referred to as Type-B or bypass HE, and is largely uncommon but causes considerable morbidity to the patient and expense to the health care system. Type-B HE accounts for only 0.33% of all hospital admissions but costs the health system 4.5 billion US dollars annually.[3,4] The incidence of SPSS in patients with HE is 46 to 71%,[2,3,5,6] and most patients with recurrent or persistent HE are recalcitrant to conservative and medical therapy.[3] Moreover, Type-B encephalopathy is usually (especially early in its course) associated with preservation of the liver function (relatively low Model for End-Stage Liver Disease [MELD]), which keeps the suffering patient from not receiving a timely liver transplant.[3]

The term "portosystemic shunt syndrome" was coined by Kumamoto et al, and refers to a reduction of hepatic reserve (reflected by progression of the Child–Pugh score) over 5 years, as compared with portal hypertensive cirrhotics without gastrorenal shunts or with prior history of obliterated gastrorenal shunts.[7] Saad et al elaborated on this term further by describing a complete syndrome with clinical findings (including worsening liver failure and HE) and imaging findings (including hepatic atrophy, portal vein thrombosis, and paucity of intrahepatic portal vein radicles).[8]

Portosystemic Shunt Syndrome

Clinical Syndrome

The term "portosystemic shunt syndrome" originally was used to describe the gradual decline of hepatic function (hepatic reserve) as reflected by an increasing Child–Pugh

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Table 1 Portosystemic shunt syndrome

	Hepatic encephalopathy	Hepatic function	Hepatic atrophy	Vanishing portal branches	Portal vein thrombosis
Early stage	X	Relatively preserved	–	X	–
Late stage	XX	Reduced	X	XX	X
End stage	XX[a]	Poor[a]	XX	XXX	XX

[a]In end-stage portosystemic shunt syndrome, both types of HE may exist: the bypass type (associated with the spontaneous portosystemic shunt) and the synthetic type (due to the poor hepatic function).
Source: Modified from Saad et al.[8]

score over time (5 years to be specific).[7] The term has now been expanded and describes a constellation of symptoms and findings (clinical and imaging findings) constituting a complete syndrome[8] (►**Table 1**). Moreover, Saad et al defined stages to the syndrome (early-stage, late-stage, and terminal stage)[8] (►**Table 1**). The syndrome, especially in the early stages, is a triad of Type-B HE, no ascites, and a relatively preserved hepatic reserve (a relatively low MELD score). In the later stages, there is hepatic failure (hepatic atrophy and portal vein thrombosis) and a combination of both types of HE (Type-B and synthetic type—see below)[8] (►**Table 1**). Thrombocytopenia has also been commonly (more than 90% of patients) described in portal hypertensive patients with spontaneous gastrorenal shunts.[9]

Pathogenesis and Hemodynamics

Liver cirrhosis causing portal hypertension eventually leads to the formation of SPSS in at least 10 to 20% of portal hypertensive patients.[10,11] These SPSS act as "release valves" to reduce the portal pressure, but also act as bypasses to normal liver flow. As portal hypertension progresses, these SPSS grow and shunt more portal blood into the systemic circulation. At one point, the shunt becomes large enough that it starts contributing to the progression of the liver disease; in other words, the liver disease, portal hypertension, and portosystemic shunt become an enclosed vicious cycle. Once the cycle is complete, the portal vein becomes diminutive and flow within it becomes hepatofugal; the portal vein may even thrombose in the end-stage, resulting in the portosystemic shunt becoming the only outflow of the splanchnic (splenic and mesenteric) circulation (►**Table 1**).[8] The amount of portosystemic shunting that is significant is unknown and is probably variable from one patient to another and one portal circulation to the other. However, anecdotally and in reference to TIPS flow, the threshold of significance is probably portosystemic shunting/blood flow of 500 to 700 mL/min. The causes of variation in the significance of a SPSS includes, but is not limited to, the degree of underlying liver disease, the location of the shunt, the compliance of the portal circulation, the compliance (peripheral resistance) of the hepatic parenchyma, the presence of other portosystemic shunts (existing or potential), and size and length (resistance) of the spontaneous shunt itself.[11]

SPSS can be associated with esophageal or ectopic varices, or can be shunts that do not pass through walls of viscera and are not associated with ectopic varices.[11] A typical (most common) example of a shunt with ectopic varices is a gastrorenal shunt that is associated with isolated gastric or gastroesophageal varices. Gastrorenal shunts, from a hemodynamic standpoint, are considered splenorenal shunts (they shunt blood from the splenic vein to the left renal vein).[11]

Imaging

Cross-sectional imaging (computed tomography or magnetic resonance imaging [MRI]) is very important for collaborating the diagnosis of portosystemic shunt syndrome. The imaging findings include a SPSS with or without varices (see above), disappearance of intrahepatic portal vein branches/radicles, diminution of the portal vein, and in the later stages thrombosis of the portal vein.[8] If there is portal vein thrombosis, it is less likely to have cavernous transformation than other causes of portal vein thrombosis. Portal vein diminution with or without thrombosis occurs with left-sided (prehepatic) portosystemic shunts and not recannulated paraumbilical veins (right-sided or intrahepatic shunt). In splenic shunts (such as splenorenal and gastrorenal shunts), there is dilation of the splenic vein and diminution of the portal vein, thus reducing the portal vein-to-splenic vein diameter ratio.[2] There is commonly splenomegaly, and thrombocytopenia is seen in more than 90% of patients with large SPSS.[9] In the late stages, there is also significant hepatic atrophy as well as splenomegaly.[8,9]

In the setting of prehepatic SPSS (which are the most common type), Doppler ultrasound demonstrates sluggish (< 20 cm/s) hepatopetal portal blood flow in the main portal vein with a paucity of portal vein branches intrahepatically. With time the flow becomes bidirectional, then reverses (hepatofugal) with a diminutive portal vein, and then finally a thrombosed or collapsed portal vein is commonly noted but is seen without cavernous transformation. However, in the setting of an intrahepatic portosystemic shunt (recanalized paraumbilical vein), the portal vein flow is always hepatopetal with high velocities unless there is a coexisting prehepatic shunt. However, the intrahepatic portal vein radicles (especially on the right side) still vanish in the presence of a significant recanalized paraumbilical vein. In the setting of HE, findings on MRI of the head can be found that are suggestive of the diagnosis of HE (see below).[1,2]

Hepatic Encephalopathy

Clinically, morbid HE related to liver cirrhosis is classified into recurrent or persistent HE[1–3]; both recurrent and persistent

HE are formally referred to as chronic.[1–3] HE has a poor prognosis with a 1-year and 3-year survival rates after the initial encephalopathy episode of 42 and 23%, respectively.[12,13] HE is usually overlooked, possibly because initially it is accompanied by relatively good hepatic function, and therefore is usually diagnosed a year after its onset.[3] HE is due to systemic accumulation of intestinal-derived neurotoxins (such as ammonia), due to impaired (hepatocellular dysfunction) and/or bypassed (portosystemic shunting) liver detoxification.[14–17]

Types

Clinically, morbid HE related to liver cirrhosis is classified into recurrent or persistent HE. Recurrent HE is defined as frequent episodic neurologic impairment ($>$ 2 episodes/year), and persistent HE is defined as contiguous neurologic and cognitive deficits.[2,16] From a pathogenesis standpoint, there are two types of HE: HE related to hepatic synthetic function (associated with hepatic failure, or terminal HE) and HE associated with portosystemic shunting (Type-B or bypass type). Both types can theoretically coexist in end-stage portosystemic shunt syndrome (►**Table 1**).[8] The bypass type can be further classified according to the location and types of shunts. These two types are intrahepatic (recanalized paraumbilical vein, or a TIPS) and prehepatic (which are the majority of spontaneous portosystemic shunts).[3,4] The association between HE and recanalization of the paraumbilical vein is controversial.[3,18,19] However, like Laleman et al,[3] the current author believes that large dilated paraumbilical veins are associated with HE Type-B just like TIPS. The current author believes that occluding right-sided or intrahepatic shunts (TIPS or paraumbilical veins) for encephalopathy carries a higher risk of portal vein thrombosis compared with prehepatic portosystemic shunts such as splenorenal and gastrorenal shunts.

Brain Imaging (Magnetic Resonance Imaging)

The findings by brain MRI in patients with HE include pallidal hyperintensity on T1-weighted spin echo sequences.[2] However, these MRI findings are not specific to HE.[2] MRI is, however, still important for ruling out other organic causes of neurologic and cognitive deficits clinically similar to HE.

Clinical Testing and Evaluation

Clinically, chronic HE (former definition) is now defined as recurrent or persistent HE (see above) and can be precipitated by infection or acute disease. Laboratory evaluation includes serum (arterial and venous) ammonia levels. Serum ammonia levels correlate significantly with recurrent or persistent HE and have been found to be inversely correlated with hepatic volume.[2] Psychometric testing for evaluation of HE includes digital symbol test, number connection test "A" and "B," serial dot test, and line tracing test.[1]

Endovascular Management

Endovascular management is an evolving treatment that is receiving interest internationally. If the SPSS is associated with a patent portal vein and varices (typically a gastrorenal shunt with gastric varices), the shunt and the varices should be obliterated with the balloon-occlusion retrograde transvenous obliteration (BRTO) technique.[8,10,11,20,21] Bland occlusion of the shunt with coils and/or vascular plugs may pressurize the varices and may cause significant (even catastrophic) bleeding. If the portosystemic shunt is not associated with ectopic varices, then bland embolization with coils and/or vascular plugs can be performed. Regardless of whether the shunt is directly related to ectopic varices or not, all patients must undergo upper endoscopy for diagnosis and preemptive/prophylactic management of esophageal and ectopic varices (even if not directly related to the shunt). This is because partial or complete closure of the portosystemic shunt is expected to increase the portal pressure and thus increase the risk of variceal bleeding, particularly if the patient is going to be anticoagulated. Long-term outcomes (2- to 5-year follow-up) carries a risk of variceal bleeding of 25 to 30%.[4,22] As a result, careful imaging and endoscopic planning and management are needed before embarking on the management of HE.

One of the greatest concerns in closing large and significant SPSS, even in the presence of a patent portal vein, is where will the additional portal blood flow redirected back to the portal circulation go. The additional portal flow is accommodated usually by compliance of the portal vein, other smaller collateral shunting, and hepatic sinusoidal compliance. These, especially the latter, are unquantifiable in a meaningful manner by current technology. If the liver does not accommodate the increased blood flow directed toward it, there will be stagnation of portal flow, which potentially may increase the risk of portal vein thrombosis. As a result, careful postprocedural Doppler evaluation is required to evaluate for portal vein flow stasis or thrombosis. The concern for portal vein thrombosis and increased variceal bleeding have both given the endovascular occlusion of these spontaneous shunts a "high risk label associated with the procedure."[3,23,24]

Historically, BRTO for HE has had excellent response with complete resolution of HE, albeit utilizing subjective criteria.[25] Recently, a multicenter study by Laleman et al ($n = 37$) demonstrated good results with objective criteria and reduction in ammonia levels. Complete resolution of HE and improved HE was 75 and 50%, respectively, of patients up to 24 months after bland occlusion of the portosystemic shunts.[3] However, these authors suggested that complete resolution may worsen gradually over time.[3] In a separate study, Mukund and coworkers evaluated 20 patients who underwent BRTO specifically for HE[20,21]; the clinical response was 80% at 24 months with a statistically significant reduction in the serum ammonia level. Clinical success is defined as improvement in HE (preferably by objective psychometric/cognitive criteria), reduction in serum ammonia levels, and reduction of, if not independence from, medications (purgatives/antibiotics) used to manage HE.

Conclusion

In conclusion, portosystemic shunt syndrome is a clinical triad of HE, no ascites, and a relatively low MELD score. By

imaging, there is a portosystemic shunt, diminution of the portal vein, and disappearance of the intrahepatic portal vein branches. In the late stages, there is diminution or thrombosis of the portal vein and reduced hepatic reserve. HE is of two types: Type-B, which is the bypass type and is associated with portosystemic shunts (early stages of portosystemic shunt syndrome), and synthetic type, which is associated with hepatic failure. Endovascular management of HE by occluding the portosystemic shunt has the risk for developing portal vein thrombosis, but is largely safe with an objective improvement in HE by 50 to 80% at 18 to 24 months.

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