Abstract
Hepatic encephalopathy (HE) is a syndrome that occurs in patients with severe liver dysfunction or a portosystemic shunt. In patients with refractory HE caused by a portosystemic shunt, interventional closure of the shunt vessel is essential. Currently, transcatheter embolization is recognized as a less invasive and highly effective procedure, and it is considered as a first-choice method for the occlusion of shunt vessels. In this review, we discuss the role of a portosystemic shunt in the development of HE and describe the procedure and significance of transcatheter embolization of a portosystemic shunt.

Key words: hepatic encephalopathy, portosystemic shunt, transcatheter embolization

(Interventional Radiology 2017; 2: 51-58)

Introduction
Hepatic encephalopathy (HE) is generally observed in patients with liver cirrhosis or fulminant hepatic failure in which hepatic function has severely deteriorated.

However, HE may develop in patients who underwent a trans-jugular intrahepatic portosystemic shunt (TIPS) or those who exhibit a large portosystemic shunt without significant liver disease. Although the latter situation is extremely rare, a large portosystemic shunt is sometimes seen in cirrhotic patients who present with HE. If HE is considered to be caused by portosystemic shunts and the efficacy of medical treatment is insufficient, interventional approach should be considered. Currently, transcatheter embolization is widely accepted as a first-choice interventional therapy for treating portosystemic shunts.

We describe an outline of the morbidity of HE caused by portosystemic shunts. Then, recent progress in transcatheter embolization as a treatment for portosystemic shunts is discussed in detail.
duced. As the level of ammonia increases in general circula-
tion, brain function is affected as a result of this toxicity.
Otherwise, a portosystemic shunt through spontaneously oc-
curring collateral circulation or a medically constructed
shunt may cause elevated ammonia in the systemic circula-
tion because ammonia-rich portal blood does not pass
through the liver.

The severity of HE is graded from grade 1 to grade 4 ac-
cording to the West Haven Criteria [2]. Grade 1 includes
modest symptoms of encephalopathy, which is defined as an
imperceptible lack of awareness and/or euphoria or anxiety,
including shortening of attention span and an impaired abil-
ity to perform addition or subtraction. Grade 2 to grade 4
are defined as follows: grade 2, lethargy or apathy, minimal
disorientation in time or space, subtle personality change,
and inappropriate behavior; grade 3, somnolence to semi-
stupor, but responsive to verbal stimuli, confusion, and gross
disorientation; grade 4, coma. Although HE of grades 2 to 4
is more easily recognizable, grade 1 HE is often overlooked.
Therefore, a set of neuropsychological tests are required for
the diagnosis of minimal HE.

In addition to grades, HE is classified into one of the fol-
lowing three types: type A (acute liver failure), HE associ-
ated with acute liver failure; type B (shunt), HE associated
with portosystemic shunt without distinct hepatocellular dis-
ease; and type C (cirrhosis), associated with cirrhosis, which
is accompanied by portal hypertension or portosystemic
shunts [2, 3]. The pattern of chronic HE (type B and type C)
can be further subdivided into episodic or persistent en-
cephalopathy. Type C HE is the most common, whereas
type B occurs more rarely.

The distinction between types B and C is often rather du-
bious. In type B HE, mild hepatic fibrosis or a history of
significant amounts of alcohol consumption may be ac-
nowledged. In these situations, minimal portal hypertension
can be evoked by non-cirrhotic liver disease, and the forma-
tion of a portosystemic shunt is accelerated. Therefore, mi-
nor chronic liver disease can involve the generation of a
shunt in type B HE. Conversely, in cirrhotic patients with
type C HE, HE arises not only because of impairment in the
hepatic urea cycle, but also by the generation of a portosys-
temic shunt.

Portal hypertension commonly occurs in cirrhosis. To re-
duce high portal pressure, collateral veins develop. In an ex-
reme case, a large portosystemic shunt develops, thereby re-
directing most portal blood into systemic circulation; thus,
the portosystemic shunt contributes to the development of
type C HE. Therefore, the genesis of type C HE is compi-
cated. Two factors (deterioration of the urea cycle in hepato-
cytes and portosystemic shunt) participate in the etiology of
type C HE in various degrees.

The first choice of treatment for type B HE is the re-
moval and/or ligation of the shunt vessels. In type C HE, HE is frequently induced or aggravated by secondary
predisposing factors [3]. Thus, correction of these secondary
factors, including excessive nitrogen load, electrolyte and
metabolic disturbances, drugs and medications, and oppor-
tunistic infections, is the basis of treatment.

Subsequently, administration of therapeutic drugs is the
next step of therapy, even if a large portosystemic shunt is
found in type C HE. Supplementation of branched-chain
amino acids [2, 4], oral administration of probiotics, and ad-
ministration of lactulose or lactitol [4] are the first-line
medications for type C HE. Lactulose and lactitol are non-
absorbable disaccharides that can reduce the generation and
absorbance of ammonia. Orally administered antibiotics [5]
( rifaximin or neomycin) are recommended to suppress intes-
tinal ammonia-producing bacteria. Moreover, concomitant L-
orinine and L-aspartate administration are used to stimu-
late the urea cycle [2].

If the efficacy of medication is not sufficient, another
treatment option should be considered. Specifically, in the
case of type C HE with a large portosystemic shunt where
the HE is caused by the portosystemic shunt, an interven-
tional approach should be considered. Surgical intervention
(shunt ligation, shunt removal, or liver transplantation) or
transcatheter embolization of the shunt vessel are the next
treatment options. The traditional approach to treating a
shunt vessel is surgical removal or ligation [6]. However,
transcatheter embolization of the causative vessel has been
widely accepted and rapidly used worldwide because of its
less invasive nature [7]. In addition, the development of en-
dovascular devices, such as microcatheters, balloon occlu-
sion catheters, metallic coils, and vascular plugs, have en-
abled safe and certain embolization. Currently, transcatheter
embolization is considered the first choice for interventional
treatment for portosystemic shunts.

Development of Spontaneous Portosys-
temic Shunt

Among animals, congenital portosystemic shunts are more
frequently observed in dogs than in cats [8]. In dogs, porto-
systemic shunts may be present congenitally or acquired
later in life. Congenital shunts are the result of anatomical
abnormalities of the portal tracts or the persistence of fetal
vessels. The shunts are located outside (extrahepatic) or in-
side (intrahepatic) the liver, and congenital extrahepatic
shunts are more common than congenital intrahepatic
shunts. Acquired shunts develop as a result of portal hyper-
tension, which is accompanied by diffuse liver disease [9].
Excessive portal pressure is believed to provide an opening
in embryonic, nonfunctional vascular communications. Hence, sustained portal hypertension promotes further ex-
pansion of the acquired shunt vessels.

In humans, although both intrahepatic and extrahepatic
congenital shunts have been observed, a congenital portosys-
temic shunt, which accounts for HE, is very rare [10, 11]. In
contrast, an acquired large portosystemic shunt is observed
occasionally in patients who exhibit portal hypertension. The
mechanism of formation of an acquired portosystemic shunt
is similar to that observed in dogs. Of these, a lienorenal
shunt is the most commonly observed and known [12].

**Indications and Contraindications of Transcatheter Embolization**

The first-line treatment of type B HE is transcatheter embolization of the shunt vessel. In type C HE, transcatheter embolization should be considered if the HE is thought to be caused by a portosystemic shunt that is difficult to treat by medication alone. In the majority of patients, type C HE caused by a portosystemic shunt resolves spontaneously or with standard medical treatments. However, in a small proportion of patients, occlusion of the shunt is required for the management of symptoms.

Furthermore, even if a large portosystemic shunt is detected in patients with type C HE and severely deteriorated liver function, occlusion of the portosystemic shunt is not expected to be effective. In addition, shunt occlusion leading to a rapid increase in portal pressure may induce serious complications, such as variceal bleeding and intractable ascites [13]. Thus, contraindications for transcatheter embolization include not only severe hepatic failure, but also uncontrolled variceal bleeding, refractory ascites, and severe coagulopathy.

**Approach Routes of Transcatheter Embolization**

Depending on the positon of the portosystemic shunt, transcatheter embolization can be performed with antegrade or retrograde techniques. An antegrade technique is performed through two access routes: percutaneous transhepatic obliteration (PTO) and trans-ileocolic vein obliteration (TIO) [7, 14]. The advantages of using an antegrade technique are that the portal pressure can be monitored directly, and the global image of portal venous systems, including the details of collateral vessels, can be clearly demonstrated by injection of contrast medium.

TIO is the most invasive among these procedures because it requires an abdominal incision under general anesthesia and/or epidural anesthesia. Therefore, TIO might be performed on patients with special hemodynamic situations, such as multiple intrahepatic portosystemic shunts [7].

PTO is an intermediately invasive technique that does not necessarily require deep sedation or general anesthesia. Percutaneous puncture of the intrahepatic portal branch is relatively easy to perform under sonographic guidance. The procedure is similar to percutaneous transhepatic cholangiography. However, puncture of the intrahepatic portal branch may be difficult in patients who have a large extrahepatic portosystemic shunt because the intrahepatic portal vein in these patients exhibits substantial narrowing (Figure 1).

Retrograde embolization of portosystemic shunts generally means balloon-occluded retrograde transvenous obliteration (BRTO). BRTO is a technique popularized in Japan since it was first reported by Kanagawa et al. [15] in 1991 for the treatment of gastric varices. BRTO is less invasive than TIO and PTO, and it can be performed with local anesthesia in almost all patients. While the most common major drainage vein accessed for BRTO is the left renal vein (splenorenal shunt or gastrorenal shunt), relatively uncommon major drainage veins, such as the phrenic vein, pericardial vein, gonadal vein, azygos vein, epigastric vein, iliac vein, and vena cava, can also be accessed. Because of its procedural manageability and safety, the transfemoral approach is more popular than the transjugular approach, particularly for access to the left renal vein [16]. When the left renal vein makes an acute angle with the inferior vena cava, transfemoral catheterization of the left renal vein is difficult. Thus, catheterization in this setting is more favorable via a transjugular approach.

**Procedure of Transcatheter Embolization (Focusing on Devices and Embolic Agents)**

Generally, embolization techniques for portosystemic shunts are roughly divided into two methods: BRTO with sclerosing agents, such as ethanolamine olate (EO), and embolization with coils or plugs alone or in combination with a gelatin sponge/glue (n-butyl-2-cyanoacrylate). The majority of congenital portosystemic shunt cases without liver cirrhosis can be treated by the latter technique [17-23]. For these cases, all parts of the portosystemic shunt do not require occlusion by BRTO with sclerosing agents.

There are advantages and disadvantages to each technique. For BRTO with sclerosing agents, advantages include a high rate of complete occlusion and a lower risk of recurrence. Meanwhile, this method requires a longer procedure time (including the balloon dwell time) as well as carries a higher risk of pulmonary embolism and thrombosis of the portal venous system [24]. Advantages and disadvantages of embolization with coils or plugs are the opposite of those observed with the BRTO method using sclerosing agents.

Sheath introducers of various French sizes, lengths, and shapes are available and are selected depending on the situation [25].

In both antegrade and retrograde techniques, a balloon occlusion catheter is necessary to control the shunt flow. A coaxial double balloon catheter system (Candis, Medikit, Tokyo, Japan), which consists of 9 Fr and 5 Fr balloon catheters, is available in Asia [26]. This system allows good occlusive control of vessel flow. Therefore, we prefer to use this system for BRTO (Figure 2).

Liquid or foamy embolic substances, including EO (Oldamin; Asuka Pharmaceutical, Tokyo, Japan), sodium tetradecol sulfate (STS; Sotradecol, AngioDynamics, Queensbury, NY), polidocanol (Polidocasklerol, Zeria Pharmaceuti- cal, Tokyo, Japan), or n-butyl-2-cyanoacrylate (NBCA; His- toacryl, B.Braun, Melsungen, Germany), have been used in the transcatheter embolization of portosystemic shunts [25,
Metallic coils and vascular plugs can be used in antegrade or retrograde occlusion of the shunt vessel. Additionally, these devices can be used as an adjuvant for embolic substances (e.g., EO mixed with iopamidol). Reinforcement by metallic materials can reduce the time of balloon indwelling in portosystemic shunts.

Metallic coils have a variety of shapes, lengths, and diameters and are made of steel or platinum [28]. In order to insert a coil at a particular place, pushable or detachable coils have been invented [29]. When the shunt diameter is large and blood flow in the shunt is rapid, detachable coils are more suitable than pushable coils for the prevention of coil migration [20]. Metallic coils are also used for the embolization of shunt vessels in order to prevent leaking of sclerosant mixture during the BRTO procedure (Figure 3).

Vascular plugs are vascular devices made of expandable nitinol wire mesh [28]. Although a vascular plug is relatively expensive, it may reduce the number of coils needed, thereby potentially saving both time and reducing costs [28]. Hence, plug-assisted retrograde transvenous obliteration (PARTO) is a therapeutic option for HE caused by portosystemic shunts [30, 31].

Efficacy and Safety of Transcatheter Embolization

Several authors have reported the safety and efficacy of transcatheter embolization of portosystemic shunts in patients with refractory HE [13, 32-38]. In addition, in the previous 10 years, many case reports on HE due to portosystemic shunts that were successfully treated by transcatheter embolization have been published [17-23, 39-42].

The details and outcomes of the reviewed studies are listed in Table 1[13, 32-38].

Efficacy

The technical success rate of portosystemic shunt transcatheter embolization for HE ranges from 86% to 100% [13, 32-38]. These data are equal to or slightly higher than previously reported technical success rates of BRTO for gastric varices (77%-100%) [43].

Regarding the clinical success of portosystemic shunt embolization for HE, the reported short-to-intermediate-term improvement rates of the condition range from 85.7% to 100% [13, 32, 33, 36]. Laleman et al. [35] performed a
A large splenorenal shunt in a 65-year-old woman with liver cirrhosis and refractory hepatic encephalopathy. A. Celiac angiography showing a large tortuous splenorenal shunt. B. Retrograde transvenous venography during occlusion of the exit of the splenorenal shunt by the larger balloon showing poor visualization of the distal shunt vessel because of drainage via the intercostal vein (arrow). C. A smaller balloon catheter inserted deeply over the intercostal vein. Moreover, the microcatheter advanced coaxially into distal side, and then 17 ml of 5% EO was injected. D. Celiac angiography after overnight balloon inflation showing complete disappearance of the splenorenal shunt, and hepatopetal portal venous flow was clearly seen (arrowhead). The level of serum ammonia decreased immediately.

multicenter study involving 37 patients and found that 59.4% of patients were free of HE within 100 days after embolization of portosystemic shunts, and 48.6% of those patients remained symptom free over the long-term (mean follow-up period of 697 ± 157 days). They also reported that the model for end-stage liver disease (MELD) score ≥ 11 was a strong positive predictor of HE recurrence [35].

The recurrence rates of HE in clinical studies with a relatively large number of cases and comparatively longer follow-up periods range from 7.1% to 39.9% [32-35]. An et al. [34] reported that the 2-year HE recurrence rate was significantly lower in patients treated with embolization than in those treated without embolization (33.9% vs. 79.9%, respectively), and the 2-year overall survival rate in patients with a MELD score < 15 without hepatocellular carcinoma was significantly higher in the embolization group than in the non-embolization group (100% vs. 60%, respectively).

In addition, portosystemic shunt embolization may improve liver function by increasing the portal flow to the liver [34]. However, the degree to which portal hypertension was exacerbated after the procedure and the amount of residual hepatic function differs considerably from patient-to-patient. Hence, not all patients benefit from shunt embolization [13, 35].

Safety

Apart from EO-related complications, such as renal tubular disturbances, cardiogenic shock, pulmonary edema, and disseminated intravascular coagulation [44-46], early complications after embolization of portosystemic shunt include puncture site hematoma, intra-abdominal bleeding, infection, fever, hepatic failure, migration of embolic agents (non-target embolization), and contrast-induced nephropathy [24, 32, 35]. Late complications include aggravation of gastroesophageal varices, rupture of gastroesophageal varices, portal hypertensive gastropathy, an increase in as-
Figure 3. A large splenorenal shunt in a 40-year-old woman who had liver cirrhosis with refractory hepatic encephalopathy. A. Balloon-occluded retrograde venography showing leakage of contrast media via the intercostal vein (arrowhead). B. The intercostal vein was embolized with metallic coils. C. Good retention of 5% EO was seen after embolization of the intercostal vein, and then the splenorenal shunt was completely thrombosed.

Table 1. Summary of Published Reports of Transcatheter Embolization of Portosystemic Shunts for Hepatic Encephalopathy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Procedure</th>
<th>Embolic Material</th>
<th>Technical Success Rate (%)</th>
<th>Short-to-intermediate-term HE Improvement Rate (%)</th>
<th>Follow-Up Period</th>
<th>HE Reoccurrence Rate (%)</th>
<th>Overall Survival Rate (%)</th>
<th>Major Early Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lany et al. [32]</td>
<td>2016</td>
<td>20</td>
<td>BRTO</td>
<td>Cells AVP</td>
<td>100</td>
<td>100 (1-4 months)</td>
<td>Vodan 33</td>
<td>N/A</td>
<td>None</td>
<td>Aschoft (n=6)</td>
</tr>
<tr>
<td>An et al. [34]</td>
<td>2014</td>
<td>17</td>
<td>BRTO PTO</td>
<td>Cells + BCBA Cells or combination</td>
<td>100</td>
<td>N/A</td>
<td>Vodan 19</td>
<td>39.9</td>
<td>None</td>
<td>Aschoft (n=18)</td>
</tr>
<tr>
<td>Nakahira et al. [33]</td>
<td>2014</td>
<td>14</td>
<td>BRTO</td>
<td>EO, BCBA, Cells, or combination</td>
<td>92.9</td>
<td>100 (24 hours)</td>
<td>Vodan 2</td>
<td>7.1</td>
<td>None</td>
<td>Eoschiald varices (n=4)</td>
</tr>
<tr>
<td>Zakren et al. [35]</td>
<td>2013</td>
<td>37</td>
<td>PTO BRTO</td>
<td>Cells, AVP, matrix, or combination</td>
<td>100</td>
<td>N/A</td>
<td>Mean 697 days</td>
<td>36.4</td>
<td>N/A</td>
<td>Aschoft (n=6)</td>
</tr>
<tr>
<td>Nakai et al. [36]</td>
<td>2012</td>
<td>7</td>
<td>BRTO</td>
<td>STS</td>
<td>86</td>
<td>85.7 (24-48 hours)</td>
<td>Mean 4 months</td>
<td>0</td>
<td>N/A</td>
<td>None</td>
</tr>
<tr>
<td>Chikamori et al. [37]</td>
<td>2000</td>
<td>5</td>
<td>BRTO</td>
<td>ED</td>
<td>100</td>
<td>N/A</td>
<td>17-74 months</td>
<td>0</td>
<td>None</td>
<td>Eoschiald varices (n=3)</td>
</tr>
<tr>
<td>Zaff et al. [38]</td>
<td>2001</td>
<td>7</td>
<td>BRTO PTO</td>
<td>Cells + BCBA Cells</td>
<td>100</td>
<td>85.7 (1-90 days)</td>
<td>100 (1 month)</td>
<td>0</td>
<td>None</td>
<td>Severo epis (n=11)</td>
</tr>
<tr>
<td>Saittshimori et al. [39]</td>
<td>1997</td>
<td>7</td>
<td>BRTO BRTO</td>
<td>Cells</td>
<td>100</td>
<td>N/A</td>
<td>3-6 months</td>
<td>28.6</td>
<td>None</td>
<td>Venous bleeding (n=2)</td>
</tr>
</tbody>
</table>

Note: HE=hepatic encephalopathy, HEH=hepatic encephalopathy, BRTO=balloon-occluded retrograde transvenous obliteration, PTO=percutaneous transhepatic obliteration, AVP=Amplatzer vascular plug, GB=gelatin sponge, EO=ethanolamine oleate, BCBA=butyl-2-cyanoacrylate, STS=Sodium tetradecyl sulfate, N/A=not available
cites, portal vein thrombosis, and spontaneous bacterial peritonitis [24, 43]. In clinical studies with a relatively high number of cases and comparatively longer follow-up periods, the incidence of esophageal varices after portosystemic shunt embolization ranges from 5% to 28.9% [32-35]. A multicenter study by Laleman et al. [35] showed that 2 of 37 patients (5%) developed esophageal varices after embolization of a portosystemic shunt, of which one patient (2.5%) experienced nonfatal variceal bleeding.

For successful portosystemic shunt embolization, it is essential to select patients who will sufficiently benefit without serious complications. In addition, patient follow-up with upper gastrointestinal endoscopy and contrast-enhanced computed tomography after transcatheter embolization is necessary for detecting complications related to portal hypertension.

Conclusions

We have described the pathogenesis, classification, and treatment of HE caused by portosystemic shunts. In particular, we focused on treatment via transcatheter embolization. In the case of type B HE and type C HE caused by a portosystemic shunt, transcatheter embolization should be considered when conservative treatment is not effective. Technical approaches of transcatheter embolization include PTO, TIO, and BRTO. A variety of devices and embolic agents can be used depending upon the needs of the patient. Transcatheter embolization is a safe and highly effective therapy if applied properly in patients presenting with HE.

Conflict of interest: The authors declare that they have no conflicts of interest to report.

References


