Treatment of recurrent severe hepatic encephalopathy in patients with large porto-collaterals shunts or transjugular portosystemic shunt

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Abstract

Patients with hepatic encephalopathy (HE) do not systematically receive priority on the waiting list for liver transplantation. In some patients with cirrhosis, excessive amounts of gut derived ammonia can bypass the liver parenchyma due to large spontaneous portosystemic shunts (SPSS) induced by portal hypertension. A similar but iatrogenic condition can occur after transjugular portosystemic shunt (TIPS) insertion. In these situations HE may develop and can become refractory to standard management.

In patients with preserved liver function, embolization of large SPSS has been shown to control HE mostly without aggravation of other portal hypertensive complications. In case of post-TIPS HE endovascular shunt reduction is able to control refractory post-TIPS HE in the majority of the patients. New strategies to prevent post–TIPS, such as the use of controlled expansion endoprosthesis, are currently explored. (Acta gastroenterol. belg., **2020**, 83, **67-71**).

Key words : cirrhosis, portal hypertension, embolization, shunt reduction.

Introduction

The main event in the natural history of cirrhosis is the development of portal hypertension (PTH) which may evolve into severe complications as ascites, variceal bleeding, and the development of hepatic encephalopathy (HE) (1). HE is a neuropsychiatric syndrome seen in almost 50% of patients with cirrhosis, especially in end stage liver disease. The clinical presentation can range from subtle cognitive slowing to coma. In general, treatment and secondary prevention of HE aims to attenuate gut-derived ammonia production (2) .

A small proportion of patients with cirrhosis presenting with recurrent or persistent HE have a preserved liver function. In these patients, large *spontaneous* portosystemic shunts (SPSS) are frequently found, provided they are looked for by axial imaging. These shunts were formerly considered as an endogenous protective mechanism in the evolving portal hypertensive syndrome giving potential decompression of the portal venous tributary system. Recent data from a multicenter retrospective analysis including 1729 cirrhotic patients conducted by the Baveno Cooperation, however, have shown the opposite. Patients with large SPSS have an increased risk for PTH-related complications such as HE and death (3).

That portosystemic shunting is indeed clinically relevant is illustrated in another condition. Transjugular intrahepatic portosystemic shunt (TIPS) creation has been a well-established interventional method for the management of refractory/recurrent variceal bleeding and refractory ascites for decades (4,5). The downside, however, is the development of refractory post-TIPS HE in 3-8% (6).

In both conditions, the accumulation of plasmatic gut-derived toxins like ammonia leads to alterations in autonomy, consciousness, behavior and psychomotor functions; negatively impacting the autonomy of patients. These patients are frequently admitted with a large impact on quality of life, increased medical costs, but are also exposed to an increased risk of hospital related mortality due to nosocomial infections. Liver transplantation is often the only durable and viable option. However, most of the allocation systems are MELD-based (Model of End Stage Liver Disease) and thus generally discard patients with invalidating hepatic encephalopathy with low MELD from a viable and quality of life restoring intervention.

As a result, in both situations, occlusion or reduction of the spontaneous or iatrogenic portosystemic shunts has been persued as a potential intermediate or definite therapeutic target.

In this review, we outline the current insights and management of HE in spontaneous and iatrogenic portosystemic shunts.

Literature search

A PubMed search was undertaken to identify relevant literature using search terms including cirrhosis, portosystemic shunt, hepatic encephalopathy, embolization, TIPS, shunt diameter, and TIPS reduction. Studies (single and multicenter) with an analysis of at least 10 patients were considered.

Pathophysiologie

The production of NH3 is considered to be the primary pathophysiologic mechanism. Ammonia is produced by

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bacterial metabolism of urea from proteins present in the human diet. Normally, ammonia becomes metabolized by the liver and is mostly cleared by the kidneys. In cirrhotic patients, portal hypertension and the impaired metabolism of NH3 result into shunting of NH3-enriched portal blood to the systemic circulation, crossing the blood brain barrier (Figure 1). Also other factors as inflammatory cytokines, manganese deposition in the basal ganglia, gamma amino butyric acid, microbiota and aromatic amino acids all play their role in functional impairment of neuronal cells (7,8).

Spontaneous portosystemic shunts

Evolving portal hypertension results in the progressive formation of portosystemic collaterals due to dilatation of pre-existing vascular channels but also due to an increased angiogenesis with the formation of new malformed vessels (9-11). These portosystemic collaterals deviate plasmatic gut-derived toxins from the portal vein to the inferior vena cava/systemic circulation. Thus, bypassing the liver parenchyma and as a consequence reducing liver perfusion.

Diagnosis can be easily made by ultrasound and cross sectional imaging by means of CT scan. The most common types of large SPSS are splenorenal (50%) and paraumbilical (25%) (3).

The clinical significance of SPSS has been described previously. Riggio et al showed that 71% of their patients with cirrhosis with recurrent of persistent HE had large SPSS compared to 14% without HE. The group postulated that the development of SPSS had a protective role on the other complications of PTH, since less esophageal varices, portal gastropathy and ascites were observed (12). In a recent retrospective analysis of 1729 patients, it was found that 60% of patient with cirrhosis display the presence of some type of SPSS. The prevalence of SPSS was 42% in MELD 6-9/Child A patients; and 72% in Child C/MELD ≥14 patients (3). In this study, the presence of SPSS was associated with a significantly higher incidence of gastro-esophageal varices and variceal bleeding, ascites and hepatorenal syndrome. Splenorenal shunts were more likely to be linked to gastric varices, whereas paraumbilical shunts were associated with the development of ascites. Also transplant-free survival was decreased in patients with SPSS with a hazard ratio death:liver transplantation of 1.6 (95% CI, 1.33-1.93) compared to patients without SPSS but similar MELD.

Hepatic encephalopathy in patients with preserved liver function and SPSS

In patients with cirrhosis presenting with overt HE but with mild hepatocellular disease and without ascites, the search for the presence of large SPSS needs to be actively persued since several reports have demonstrated that embolization of the shunts improves HE. The lack of clear precipitation of HE as infection, gastrointestinal bleeding or constipation; or the poor effect of medical treatment (*ie.* lactulose or nonabsorbable antibiotics), can be an important clue to diagnosis. In a multicenter European study, the efficacy of embolization of large SPSS was investigated in 37 patients. After 3 months, 60% of the patients was free of HE and was sustained given that 50% was still HE free after 2 years (13). Similar

Table 1. — **Efficacy of embolization of SPSS**

N° patients	Pre MELD / Child score	Type of SPSS	Efficacy	Reference
N= 37	13.2 +/- 0.9	Splenorenal	59% HE free within 100days	(13)
		54%	49% after 2years	
N= 17	MELD: 13	Splenorenal	-2 years HE recurrence rate 40%	(14)
	(11-15)	82%	vs 80% in controls	
			-MELD <15 and no HCC:	
			2 year survival 100% vs 60% in controls	
N=19	Child: 8.7	Splenorenal	-Encephalopathy required	(16)
		100%	hospitalization resolved in 100%	
			-Increase of albumin and	
			improvement of Child score after 3 years	
N= 14	Child: 7-8 64%	Splenorenal	93% disappearance of HE after	(17)
		21%	27 months	
N=20	MELD: 13.1	Splenorenal	Improvement of HE:	(15)
	+/- 3.4	60%	100% after 1-4 months	
			67% avoided HE related	
			hospitalizations in 1 year	
N=21	MELD: 15.7	Splenorenal	Improvement of HE in short and	(18)
		55%	long term	

Child Pugh score ; MELD: Model of End stage Liver disease ; HE: hepatic encephalopathy ; SPSS: spontaneous portosystemic shunt ; HCC: hepatocellular carcinoma.

Table 2. — **Safety of embolization of SPSS**

N° patients	Complications	References
N= 37	Overall procedural related complication rate: 21% (*ie*. infection at puncture site, hematomas, contrast	(13)
	nephropathy, bacteriemia, subcapsular bleeding)	
	No significant development of *de novo* varices and ascites	
N= 17	No serious procedure related complications	(14)
	18% developed ascites, development / worsening esophageal varices 18%	
N=19	No fatal complications related to procedure	(16)
	1 patient died of liver failure after 6 months	
N= 8	No major complication	(17)
	Fever in 71%	
	29% aggravation of esophageal varices after 1 year	
N=20	Overall procedural related complication rate: 10% (*ie.* pain puncture site, bacterial cholangitis)	(15)
	Worsening portal hypertension: 35% within 1 year	
N=21	Local hematoma (n=1), hemoperitoneum leading to death (n=1)	(18)

SPSS : spontaneous portosystemic shunt

data were published by An et al, showing also a 50% 2 year HE-free recurrence rate in comparison to a control group (14). Lynn et al showed in a group of 20 patients immediate improvement of HE in 100% and in almost 70% after 1 year (15). In all of these studies embolization was technically feasible in the majority of the patients. An overview of the efficacy of SPSS embolization is presented in Table 1 (13-18).

Theoretically, embolization of SPSS increases the risk of other portal hypertension related complications; but in the presented studies the complication rates were low. Overall, embolization resulted in the development of *de novo* gastro-esophageal varices in 6% and new onset/ worsening of ascites in 14% (19). In Table 2, procedure related adverse events and overall effect on PTH related complications were summarized.

The success of this intervention, however, seems to depend whether there is sufficient functional liver mass to accommodate redirected portal flow. In the absence of other available biomarkers, we evaluated the MELD score in an earlier collaborative study as a potential discriminating tool and showed – by logistic regression – that a MELD score of 11 could be considered as a surrogate marker herefore (13). Also in the study presented by An et al. analysis of patients with MELD <15 in the absence of hepatocellular carcinoma showed a significant higher survival rate in the embolization group (100% versus 60%) (14). In the study published by Inoue et al. patients with albumin level <2.8mg/dL showed a decreased survival (16). Therefore, only patients with HE and a preserved liver function are candidates for embolization which is however a minority of the patients with HE. Additionally, it needs to be emphasized that SPSS-embolization does not abrogate the need for liver transplantation later on.

Portosystemic shunt due to TIPS

Transjugular intrahepatic portosystemic shunt (TIPS) is a well-established treatment for the management of selected patients with refractory/recurrent variceal bleeding and refractory ascites (4,5). This technique implies the creation of a low-resistance channel between the hepatic and portal veins, bypassing the liver parenchyma. Shunt dysfunction was a problem in the past with the use of bare metal stents in more than 50% after 1 year; since the introduction of expanded-tetrafluoroethylene covered stents, a high primary patency rate is observed being 92% after 1 year and 86% after 5 year; with a 39% reduction in dysfunction compared to bare stents (20,21). The main problem of TIPS nowadays is TIPS-induced HE. Indeed, like in case of SPSS, TIPS may lead to a systemic accumulation of plasmatic gut derived toxins. Especially older age, advanced liver failure, nonalcoholic cause of cirrhosis, increased creatinine and overt HE prior to TIPS, have all been associated with an increased risk of developing

HE after TIPS (22,23). Currently, still 5-10% of patients treated with covered stent experience HE, refractory to standard treatment with lactulose with or without non-absorbable antibiotics. Excessive shunting and hypoperfusion of the liver may even lead to TIPS-induced liver failure in rare cases (24).

Although a previous study could not show a relationship between the diameter of the shunt and the incidence of post TIPS HE, a more recent study compared 8 mm stents with 10 mm in 127 patients suggests significantly fewer spontaneous overt HE incident in the 8 mm group within 2 years with a risk reduction of almost 50% with a similar efficacy (25,26). Recently Rowley et al. suggested that patients with a previous history of HE and low serum albumin would benefit the most with shunt sizes < 8mm in order to prevent the occurrence of post-TIPS HE (27).

In order to balance portal hypertension relief in patients with ascites and the adverse effects associated with excessive shunting, dilatation to 8 mm of the 10 mm stents is commonly practiced. However, under-dilated self-expandable stents may undergo further passive expansion (28-31). Recently, Schepis et al. founded in a prospective non-randomized study that under - dilatation

Table 3. — **TIPS reduction for chronic HE**

N° of patients	Reduction echnique	Outcome	References
N=17	Parallel technique	Improvement or disappearance in 76%	(36)
		4 patients with no improvement died within 25 months	
N=12	Hourglass shaped	Improvement of HE in 100% of which	(37)
	balloon expandable	disappearance in 67%	
	ePTFE stent graft	After follow up of 74 weeks: 50% survival	
N=10	Parallel technique	Improvement of HE in 80%	(27)
Closure n=1		LT-free survival after 1 year: 10%	
Reduction n=9			

TIPS: transjugular intrahepatic portosystemic shunt ; HE: hepatic encephalopathy ; PTFE: polytetrafluoroethylene.

of polytetrafluoroethylene-covered stents (6 mm) resulted in less HE without losing efficacy (32). These data remain to be validated.

Management of TIPS-related HE that is resistant to medical therapy

Endovascular techniques are directed towards reducing the amount of portal venous blood diverted from the liver. In general, these techniques can be categorized into 2 subtypes: complete shunt occlusion or partial reduction of the stent.

Shunt occlusion by insertion of a vascular plug device leads to an immediate increase in portal venous pressure and subsequent high risk of recurrence of the complications of portal hypertension such as variceal hemorrhage.

There are several techniques reported to narrow the intrahepatic shunt (33). All these reports are small and non-controlled trials. Nevertheless all of them reported an acceptable rate of clinical success in controlling post TIPS HE (Table 3). Haskal and Middlebrook described a technique to insert a Wallstent (Boston Scientific Middletown, MA) constrained in its mid-portion with silk suture (34). Gerbes et al described the use of a bare metal stent within the TIPS and injected Ethibloc (Ethicon, Norderstedt, Germany) to obliterate the space between original TIPS and the reducing stent (35). Finally there are reports of TIPS reduction with commercial stent grafts : *i)* insertion of a balloon expandable bare metal stent parallel to a new stent graft within the originally placed TIPS ; *ii)* insertion of a constrained self-expandable stent graft or incompletely dilated balloon-expandable stent graft within the TIPS ; and *iii)* insertion of a tapered stent graft within the TIPS (27,36,37).

However, despite successful reduction of the TIPS diameter, some patients still maintained invalidating HE (Table 3), indicating the unmet clinical need for additional strategies to (ideally) prevent or alleviate post TIPS HE. Such an example is the controlled expansion stent design which is under investigation (38).

Conclusion

Portosystemic shunting is clinically relevant and critically impacts on the outcome of patients with cirrhosis. Although infrequent, the presence of large SPSS needs to be excluded, in particular in case of patients with low MELD and refractory HE, since embolization of these shunts might lead to an improvement of HE (and thus quality of life) and transplant-free survival in a substantial number of these patients.

A major complication of TIPS remains the development of HE due to an excess of portosystemic shunting. In case of therapy resistant post TIPS HE, endovascular shunt reduction can controls HE. However there is still a high number of non-responders, who develop recurrent or severe HE episodes that are hardly controlled by medical therapy. These patients have a poor prognosis and therefore new strategies are urgently needed to prevent this complication of TIPS.

Conflict of interest

Frederik Nevens and Geert Maleux received a speakers fee of Gore. The other authors declare not to have any conflict of interest.

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