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ABOUT COVER

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EDITORIAL

Fecal microbiota transplantation in the treatment of hepatic encephalopathy: A perspective

Arghya Samanta, Moinak Sen Sarma

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Abstract

Due to its complex pathogenesis, treatment of hepatic encephalopathy (HE) continues to be a therapeutic challenge. Of late, gut microbiome has garnered much attention for its role in the pathogenesis of various gastrointestinal and liver diseases and its potential therapeutic use. New evidence suggests that gut microbiota plays a significant role in cerebral homeostasis. Alteration in the gut microbiota has been documented in patients with HE in a number of clinical and experimental studies. Research on gut dysbiosis in patients with HE has opened newer therapeutic avenues in the form of probiotics, prebiotics and the latest fecal microbiota transplantation (FMT). Recent studies have shown that FMT is safe and could be effective in improving outcomes in advanced liver disease patients presenting with HE. However, questions over the appropriate dose, duration and route of administration for best treatment outcome remains unsettled.

Key Words: Fecal microbiota; Dysbiosis; Hepatic encephalopathy; Cirrhosis

Core Tip: Hepatic encephalopathy (HE) remains one of the most dreaded and difficult-to-treat complications in patients with cirrhosis. Alteration in the number and diversity of microorganisms in the human intestinal tract appears to have profound effect in the pathophysiology of HE in cirrhotic patients. Targeting gut dysbiosis by fecal microbiota transplantation is a promising therapeutic modality.

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INTRODUCTION

Hepatic encephalopathy (HE) is a common and grave complication of advanced liver disease[1]. Approximately 30%–40% of patients with cirrhosis experience overt HE during the course of the disease[2]. HE manifests as a broad spectrum of neuropsychiatric abnormalities, from subclinical (minimal cognitive impairment) to marked disorientation, confusion, and coma. It leads to impaired quality of life, increased morbidity and mortality[2,3]. The economic burden is also substantial as it leads to frequent hospitalization[4].

Various chronic liver diseases like alcohol-related liver disease, non-alcoholic fatty liver disease, chronic viral hepatitis, primary sclerosing cholangitis and primary biliary cholangitis can all affect the brain through mechanisms independent from those caused by liver failure[5,6].

THE GUT-LIVER AXIS AND THE ROLE OF THE GUT MICROBIOME

The constituents of the normal gut microbiome include bacteria, fungi and viruses, particularly bacteriophages[7,8]. The gut microbiota is involved in many normal physiological processes and maintains a state of homeostasis called eubiosis [9].

Multiple clinical and experimental studies have proven that various liver diseases disturb this equilibrium- the number and variation of beneficial organisms are severely diminished while pathological organisms thrive[5,6,10-13]. Various causes of dysbiosis in patients with cirrhosis have been hypothesized: (1) Reduced levels of bile acids and short-chain fatty acids (SCFA); (2) small intestinal bacterial overgrowth (SIBO); and (3) immune dysregulation[14-17]. In addition to killing the pathogenic organisms[14,15], bile acids have also been involved in the regulation of innate and adaptive immune signaling pathways in the gut by modulating the differentiation of Th17 and T_{reg} cells[18]. Cirrhotic patients have lower levels of bile acids due to poor hepatic synthetic function[14,15]. SIBO is commonly seen in cirrhosis, which has several downstream effects including changes to intestinal permeability[17,19,20]. SCFAs are by-products of carbohydrate metabolism by intestinal bacteria, which is essential for maintaining luminal pH, intestinal motility and enterocyte structure[18]. Intestinal lymphoid tissue expresses pattern recognition receptors like toll-like receptors, which recognize commensal bacterial antigens, and this leads to a cascade of signals that ultimately lead to the differentiation of naïve T cells[18].

GUT-LIVER-BRAIN AXIS AND HE

The gut microbiota produces certain metabolites that can exert beneficial or harmful effects on the host central nervous system. Some recent studies have shown that basal non-toxic levels of SCFAs can preserve intestinal barrier integrity, protect the blood brain barrier (BBB) from oxidative stress, and positively regulate the expression of tight junction proteins[21,22]. Braniste *et al*[23] found that treatment of germ-free mice with sodium butyrate recovered the destructed BBB after visualizing the level of Evans blue in the frontal cortex. In another interesting study by Wu *et al*[24], the treatment of rhesus monkeys with antibiotics decreased the SCFAs-producing phyla in the gut microbiota and impaired the permeability of the BBB in the thalamus. These findings were corroborated in many clinical studies where a lower amount of propionate, butyrate, and acetate was found in the fecal samples of cirrhotic patients with HE compared to those without HE[25]. The study by Bajaj *et al*[5] in cirrhotic patients with HE revealed a significant decrease in protective organisms like *Clostridiales* XIV, *Ruminococcaceae*, and *Lachnospiraceae* with a significant increase in pathogenic organisms like *Enterococcaeae*, *Staphylococcaceae* and *Enterobacteriaceae*, compared to healthy controls.

THERAPEUTIC IMPLICATIONS

With the understanding that gut dysbiosis may contribute to the pathophysiology of HE, newer therapeutic interventions that target gut dysbiosis and its metabolites gained widespread attention. Modulation of gut dysbiosis by use of prebiotics, probiotics, and antibiotics has been tried in multiple studies[26-28].

In an elegantly done study by Bajaj *et al*[29], use of Rifaximin, a gut-specific antibiotic, was found to be improving cognitive function and endotoxemia in adult cirrhotic patients with minimal HE (MHE) with concomitant alteration of gut bacterial linkages with metabolites without significant change in microbial abundance. In a recently published phase 2 placebo-controlled, double-blind randomized clinical trial by Bajaj *et al*[30], rifamycin SV MMX (RiVM), a nonabsorbable rifampin derivative with colonic action, was effective in reducing ammonia, inflammation, brain oxidative stress, and sarcopenia-related parameters but without significant improvement in cognition. A recent meta-analysis of 9 randomized control trials (RCTs) involving 776 MHE patients by Wibawa *et al*[31] indicated that probiotics were more effective in the reversal of MHE and reduced serum ammonia levels in patients with MHE compared to placebo or no treatment, but not more effective than lactulose or l-ornithine-l-arginine (LOLA). Available evidence on the efficacy of probiotic and prebiotic therapy showed mixed results. In a meta-analysis of 14 RCTs involving 1152 cirrhotic patients in 2016, Saab *et al*[32] found that probiotics decreased hospitalization rates in patients with cirrhosis and HE and prevented progression to overt HE in patients with underlying covert HE, similar to lactulose. However, there was no difference in the mortality rates. A Cochrane systematic review by Dalal also supported these findings. However, most of the included

studies were of poor quality and had significant heterogeneity[33]. Hence further studies are needed for reaching a reasonable conclusion.

FECAL MICROBIOTA TRANSPLANTATION IN HE

Wang *et al*[34] and Luo *et al*[35] have demonstrated in animal models that FMT is effective in improving intestinal barrier function, by regulating the expression of tight junction proteins (claudin-1, claudin-6, and occludin) and thus improving HE. The use of FMT in treating HE in humans was first reported by Kao *et al*[36] which demonstrated that the use of FMT led to obvious improvement in cognition in a 57-year-old cirrhotic patient with grade 1-2. With this encouraging result in the background, the first randomized clinical trial in 2017 by Bajaj *et al*[37] showed that FMT can reduce the length of hospital stay in patients with HE and improve their cognitive ability and quality of life. Further studies in germ-free mouse models of HE indicated that FMT can prevent damage to the gut mucosal immune barrier function and liver necrosis and reduce serum levels of ammonia by enhancing hepatic clearance and gut epithelial permeability[34]. In 2018, the effect of FMT on HE was highlighted in the British Society of Gastroenterology guidelines for use of FMT[38]. Although the potential of FMT to alter the course of HE is promising, the lack of basic research has led to a lack of understanding about the limitations of FMT[39].

A recent meta-analysis by Gao *et al*[40] comprising 21 RCTs and 1746 cirrhotic patients found that FMT significantly reversed MHE [odd's ratio (OR): 0.41, 95%CI: 0.19-0.90, $P = 0.03$], reduced development of overt HE (OR: 0.41; 95%CI: 0.28-0.61, $P < 0.00001$) and the frequency of serious adverse events (OR: 0.14, 95%CI: 0.04-0.47, $P = 0.001$), meanwhile decreased ammonia, neurocalcitonin level and hospitalization rates, compared with placebo/no treatment.

These encouraging results have been associated with the enrichment of supposedly beneficial taxa. However, the understanding of how and why certain taxa are beneficial remains unknown.

Antibiotic resistance is a common complication of cirrhosis that leads to poor outcomes. FMT offers a promising therapy that may reduce the population of multidrug resistance organisms. Bajaj *et al*[41] in a recent study evaluated the expression of the antibiotic resistance gene (ARG) in patients with decompensated cirrhosis before and after FMT. They found that beta-lactamase, vancomycin and rifamycin ARGs were significantly lower at 4 wk post-FMT compared to placebo. A reduction in rifamycin ARG in the interventional group was associated with cognitive improvement. These interesting data suggest that ARG abundance is largely reduced after FMT in decompensated cirrhosis.

CHALLENGES OF FECAL MICROBIOTA TRANSPLANTATION USE

Infections with pathogenic organisms remain a serious concern, especially in patients with cirrhosis due to their compromised immune status. Multiple retrospective case series have reported serious adverse events in patients receiving FMT due to a lack of proper donor screening[42]. Shah *et al*[43], in the current issue, have meticulously discussed about the challenges of FMT in the management of HE in patients with cirrhosis. The authors concluded that though FMT seems to be effective in preventing the progression of HE, more robust data on the adequate dose, duration and safety of FMT is needed before it is incorporated in the routine clinical care in patients of cirrhosis.

FUTURE PERSPECTIVES

Firstly, as patients with cirrhosis are immunocompromised and have increased intestinal permeability, the potential risk of transmission of other pathogenic organisms that are not routinely screened for, remains. The need for careful selection of donor and recipient cannot be overemphasized with FDA updating their protocol on FMT in 2019 mandating that donors be screened for multidrug-resistant organisms. More body of evidence is needed on the safety of FMT before it is incorporated in our daily practice.

Secondly, Recent evidence suggests that cognitive improvement in HE in response to FMT appeared to vary by donors. A study by Bloom *et al*[44], a first of its kind, found that FMT donors did not vary by age or diet type but did vary in their effect on recipient cognitive changes, secondary to primary bile acid ratios, and total normalized SCFA levels. Further, well-designed studies with larger cohort of patients are needed.

Thirdly, whether patients need to be sterilized with antibiotics prior to pre-FMT and whether antibiotics need to be withheld after FMT, is the dilemma that requires further clarity. Current evidence does not recommend for or against the use of antibiotics prior to FMT.

Fourthly, cirrhosis is a chronic disease, and gut dysbiosis in cirrhotic patients may persist for a long time and thus may require long-term maintenance treatment. However, most microbiome therapeutics are currently short-term therapies. Optimal duration for adequate treatment response is another area of further research.

Lastly, so far, the majority of clinical and experimental studies have solely studied the bacterial component of gut microbiota. Along with bacteria, it may be prudent to explore the mycobiome and virome composition through metagenomic and metatranscriptomic studies to identify specific taxa and metabolites that can be associated with HE and act as potential biomarkers or therapeutic targets.

CONCLUSION

The relationship between gut dysbiosis and HE is a complex and dynamic process that needs more research for better understanding. Despite several limitations, emerging evidence suggests that targeting gut dysbiosis with fecal microbiota transplantation can be a promising strategy for the prevention and treatment of HE.

FOOTNOTES

Author contributions: Samanta A did the literature review and wrote the original manuscript; Sen Sarma M did critical analysis, reviewed and revised the manuscript; All authors approved the final version of the manuscript.

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