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"SINGLE MICROBIOTA TRANSPLANTATION FOR TREATMENT OF PERSISTENT HEPATIC ENCEPHALOPATHY: A NOVEL CLINICAL APPROACH"

Gastroenterology

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ABSTRACT

Hepatic encephalopathy (HE) is a common neuropsychiatric disorder most rooted from end-stage liver cirrhosis or portosystemic shunting. Ammonia is not the driver for HE; there is strong evidence for other drivers such as systemic inflammation, electrolyte imbalance, and microbial dysbiosis. It has been shown that patients with HE are occupied with potentially pathogenic bacteria. Current conventional therapy changes microbial function and milieu. The considerable amount of patients with HE are unresponsive to current conventional therapy, our patient was one of them. We tried a novel clinical approach for management of persistent HE by microbiota modulation through fecal microbiota transplantation (FMT) from sibling stool donor. The patient improved his sensorium, cognitive function and reduced ammonia level after single FMT. No adverse events or infectious complications related to FMT were observed after transplantation.

KEYWORDS

Fecal microbiota transplant; Persistent hepatic encephalopathy; Alcoholic liver cirrhosis, Dysbiosis

INTRODUCTION

Hepatic encephalopathy (HE) is serious neurological complication. It manifests as a wide range of neuropsychological abnormalities varies from subclinical alteration to coma (Ryan & Shawcross, 2015). It occurs as a consequence of an end – stage liver disease or portosystemic shunting. Cirrhotic patients have 60 – 80 % risk to develop HE (Gow, 2017). It increases the burden on health care due to high morbidity and mortality (Gow, 2017). Rifaximin and lactulose are current first-line agents for management of HE. These agents change gut microbial functionality and milieu (Bajaj et al.,2017). Unfortunately, approximate 20% cases of HE are unresponsive to first line agents (Wang et al., 2017[1]. Hence novel treatment approach needs to be explored. Fecal microbiota transplant (FMT), implantation of faeces from a healthy donor to the gastrointestinal tract of a recipient, is a promising approach to treat HE by restoring altered gut dysbiosis.

FMT is very effective therapy for chronic gastrointestinal infections, inflammatory bowel disease (IBD) and *Clostridium difficile* infection. Moreover, it also gained attention for its therapeutic potential for cardiometabolic, autoimmune and other extra-intestinal condition that were not previously considered to be associated with the intestinal microbiota (Bajaj et al., 2017). FMT is being rapidly accepted due to its viability, safety, and effectiveness (Bajaj et al., 2017). In this case report, we present a novel paradigm of a single FMT in persistent HE as a consequence of alcoholic liver cirrhosis.

CASE REPORT

A 37-year-old male patient presented in unconscious state. He was a known case of liver cirrhosis (secondary to alcohol abuse) with portal hypertension. His caregiver gave history of lethargy, slurred speech, pedal oedema, and altered behaviour since two months. Moreover, the patient did not pass stool since last two days. On physical examination, he had normal vitals with increased pulse rate (111/min) and scleral icterus. His Glasgow coma score was 3-6. Moreover, his model for end-stage liver disease (MELD) score was 23; HE grade 4, type C and Child Turcotte Pugh (CTP) class – C (Table: 1). Cardiovascular examination revealed sinus tachycardia.

Table 1 Laboratory investigation before and after FMT

Laboratory test	Before FMT	After FMT	Normal range
Haemglobin	8.3	8.3	13.5-17.5 gm/dl
Total white blood cells	6500	4000	4000-10000 cu/mm
Platelet count	54000	56000	150000 - 45000/cu mm
Total bilirubin	7.16	6.56	< 1.2 mg/dl
AST	65	14	<40 U/L
ALT	28	45	<40 U/L
ALP	201	115	44/147 U/L
GGT	19.4	14.6	<30 U/L
Creatinine	0.6	0.6	0.8 – 1.3 mg/dl
Sodium	136	137	135-145 mmol/L
Potassium	4	3.9	3.5-5 mmol/L
Total protein	5.8	6	6-8.3 gm/dl
Albumin	1.9	2.2	3.5-5 g/dl
Prothrombin time	26.3	24	11 – 13.5 sec
INR	2.33	2.12	<1
Ammonia	165	109	15-45 µg/dl
MELD	23	22	

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferase, INR: International normalized ratio, MELD: Model for end – stage liver disease

He had been conservatively treated with the first-line agent rifaximin (550mg BID) and lactulose 30 mg/ 5 ml TID, but was unresponsive. Then, L-Ornithin-L-Aspartate (LOLA; 5 gm TID) was added. But the addition of LOLA did not made any recovery. Hence, a novel treatment approach FMT was suggested in view of restoring dysbiosis. He was treated with single FMT from sibling stool. The donor was also prescribed Albendazole (400mg, BD) for two days. Twelve hours before FMT, antibiotic treatment was stopped to the patient. Sibling microbiota was introduced in the right colon of recipient by colonoscopy. He was discharged with improved sensorium and cognitive functions. On discharge, laboratory examination revealed ammonia level (109µg/dl), normal level of ALT, AST, and ALP and

MELD 22. The patient was followed up weekly for two months. We observed improvement in sensorium and cognitive functions. After two months of FMT, arterial ammonia level was 56 µg/dl and MELD score was 19. He was conscious and oriented with good cognitive functions and stable behaviour. No adverse events or infectious complications related to FMT were observed during the hospital stay and on the follow-up.

DISCUSSIONS

To our knowledge, this is the first report of treating persistent HE with single FMT. In this case, the dramatic clinical improvements following single FMT are very encouraging.

Alcohol consumption decreases intestinal barrier strength by increasing permeability of the protective layer mucus. It allows direct contact of bacteria in the epithelial cell of by translocation. It triggers systemic inflammation and microbial dysbiosis (Ferrere et al., 2017). Thus in our case, alcohol abuse was a causative factor for the development of HE.

The pathogenesis of HE is multifactorial and complex. Ammonia plays a crucial role in the precipitation of HE. Hyperammonaemia results from an accumulation of glutamine in astrocytes, which create an osmotic pressure that causes astrocyte to take water and swell. It further develops cytotoxic brain oedema (Ryan & Shawcross, 2015). Ammonia is not the only driver for HE; there is strong evidence for other drivers such as systemic inflammation, electrolyte imbalance and microbial dysbiosis (Shen et al., 2015). Microbial dysbiosis, an abnormal and pathogenic state of human microbial flora in the gut, has emerged as a critical driver in the development of HE. It promotes systemic pro-inflammatory milieu, resulting in neuroinflammation and neuronal dysfunction including HE (Shen et al., 2015; Wang et al., 2017). HE patients were increased with pathogenic *Enterobacteriaceae* and reduced relative abundance of short – chain fatty acid producing beneficial families such as Ruminococcaceae, *Bifidobacteriaceae* and *Lactobacillaceae*. This microbial profiles are linked with poor mental status and cognitive dysfunction (Bajaj et al., 2017). Microbiota modulation can improve cognitive dysfunction (Bajaj et al., 2017). Thus, we hypothesized to modulate microbiota through FMT.

Bajaj et. al. treated 20 recurrent HE patients with FMT and reported that FMT recovered MELD score but did not improve AST, ALT, WBC count, albumin or hemoglobin. Moreover, they also reported FMT improve cognitive function (Bajaj et al., 2017). Another study by Wang et. al. reported data of preclinical study which reported FMT can improve AST, ALT, ammonia level as well as reduce systemic inflammation, protect the intestinal integrity, improved learning and memory functionalities (Wang et al., 2017). In our case, MELD score was also reduced to 19 that improve hepatic functionality. Most importantly, after FMT, his serum ammonia level reduced with improved cognitive function and stable behaviour. No adverse events or infectious complications (related to FMT) were observed during the hospital stay as well as on follow-up which indicated good safety profile. Thus, FMT holds promising approach in the management of persistent HE.

In conclusion, our case – report provides an evidence of safety and efficacy of single FMT for treatment of persistent HE. It revealed the protective mechanism of FMT in persistent HE. Thus, we provide a base for potential clinical application of FMT in persistent HE as a new paradigm.

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