Modifying Microbiome Can Improve Encephalopathy Due to Liver Disease

Fecal microbiota transplantation can help reverse brain impairment in people with liver failure.

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Fecal microbiota capsules, which help restore healthy gut bacteria, led to improvement in hepatic encephalopathy, or cognitive impairment related to advanced liver disease, according to research presented at the 2019 International Liver Congress last week in Vienna.

Over years or decades, chronic hepatitis B or C, non-alcoholic fatty liver disease (NAFLD and NASH), heavy alcohol consumption and other causes can lead to cirrhosis (scarring), liver cancer and end-stage liver failure that requires a transplant.

Decompensated liver disease occurs when the liver can no longer carry out its vital functions as a result of the accumulation of scar tissue and blockage of blood flow. Complications may include ascites (fluid buildup in the abdomen), bleeding veins in the esophagus and hepatic encephalopathy (HE).

HE occurs when the liver can no longer filter out ammonia and other toxins. Symptoms include impaired concentration and thinking, confusion, personality changes and, ultimately, coma. Recurrent HE can lead to lasting brain damage. HE can be debilitating at later stages, but even early symptoms can negatively affect quality of life. Treatments include lactulose, a nondigestible sugar that absorbs ammonia and acts as a laxative, and the antibiotics neomycin and rifaximin.

Treatment with lactulose and antibiotics can change the makeup of bacteria in the intestines, known as the gut microbiome. Some types of gut bacteria produce ammonia, which worsens HE, while others trigger systemic inflammation. Studies have shown that altering the gut microbiome can help prevent or improve HE. For example, research presented at the 2013 International Liver Congress showed that a probiotic supplement reduced ammonia levels, improved cognitive function and prevented HE progression in people with advanced liver disease.

Transplanting gut bacteria from a healthy individual is another way to restore a beneficial intestinal microbiome. Known as fecal microbiota transplantation (FMT), this process involves transferring donor stool via an enema formulation or oral capsules. FMT is most widely used as a treatment for Clostridium difficile infection.

Having already shown that FMT via enema improved cognition and reduced hospitalizations in people with liver cirrhosis, Jasmohan Bajaj, MD, of Virginia Commonwealth University in Richmond, and colleagues evaluated the safety, tolerability and effectiveness of a capsule formulation, which is more convenient and can deliver beneficial bacteria to the small intestine, not just the colon.

This Phase I study included 20 people with cirrhosis and recurrent HE who were already receiving lactulose and rifaximin. Bajaj noted that it was difficult to recruit patients, both because of the nature of the treatment and because some did not grasp that their cognitive problems were related to liver disease and might be helped by changing their gut bacteria.

Participants were randomly assigned to receive 15 FMT capsules or similar placebo capsules, in addition to their existing therapy. The capsules were prepared using stool from a single donor—the same "super pooper" who donated for the enema FMT study—with high levels of beneficial Lachnospiraceae and Ruminococcaceae bacteria species. Bajaj stressed that the capsules "do not smell like poop and do not taste like poop."

At the start of the study, microbial diversity in the stool and in biopsy samples from the small intestine (duodenum) and large intestine (sigmoid colon) was similar in both groups. But after two to four weeks of treatment, people in the FMT group saw an increase in bacterial diversity, with more Ruminococcaceae and Bifidobacteriaceae bacteria and a decrease in Streptococcaceae and Veillonellaceae species. Duodenum biopsy samples also showed a reduction in biomarkers of inflammation.

Cognitive function scores improved in the FMT group compared with the placebo group. Just one participant required hospitalization or died in the FMT group while six did so in the placebo group. The total number of hospitalizations was also lower in the FMT group. Although the study population was small, all these differences were statistically significant, meaning they probably were not attributable to chance. No safety issue arose during the study.

"Fecal microbiota transplant using a single stool donor enriched with bacterial species we know are deficient in this population is a promising approach to the potential treatment of patients with cirrhosis and recurrent HE," Bajaj said. "The way to the brain is through the gut."

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