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Brief Report

BRIEF REPORT

Deep hyperammonemic hepatic encephalopathy precipitated by fecal microbiota transplantation for fulminant *Clostridioides difficile* infection

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Introduction

Fecal microbiota transplantation (FMT) is highly effective and potentially life-saving for recurrent *Clostridioides difficile* infection (CDI) [1]. Recent pilot trials also reported the use of FMT to revert hepatic encephalopathy (HE) in patients with decompensated liver cirrhosis without infectious colitis [2, 3]. Intestinal microbiota-driven hyperammonemia is central to HE development and most treatments aim to reduce ammonia levels by modulating the intestinal microbiota. However, FMT might lead to increased intestinal ammonia production, as we describe here.

Case presentation

A 70-year-old woman was referred for FMT due to life-threatening, fulminant CDI. The patient presently had stable Child–Pugh B liver cirrhosis from non-alcoholic fatty liver etiology, a history of previous overt HE and variceal bleeding, and partial portal vein thrombosis treated with low-molecular heparin. For 10 weeks, she had been unresponsive to both vancomycin and fidaxomicin treatment, and she had been passing 8–10 watery stools per day. After having confirmed that she was without bleeding or HE, she was administered a single dose of encapsulated FMT, consisting of 50 g of cryopreserved feces from a single donor, processed according to our standard protocol [4]. The procedure was well tolerated without immediate complications and she was discharged.

Thirty-six hours post FMT, the patient was found lying on the floor, disoriented. A few hours beforehand, she had been seen walking around, functionally well, by the home nurse. Upon immediate readmission, she was comatose. Plasma ammonia was elevated at 419 μmol/L compared with near-normal pre-FMT levels (Figure 1A), which was confirmed by a second test. Liver-derived coagulation factors (INR) were normal at 1.2 and bilirubin only marginally elevated (30 μmol/L; reference value, <24 μmol/L). Acute contrast-enhanced computed tomography (CT) ruled out cerebral bleeding and brain edema, and a repeat abdominal CT scan revealed a complete portal vein thrombosis (Figure 1B). Blood-gas values, the concentrations of electrolytes, hemoglobin level, C-reactive protein level, and white-blood-cell counts were all normal. The clinical diagnosis was thus a bout of HE grade IV, precipitated by FMT via acute hyperammonemia. During 12 h of standard corrective

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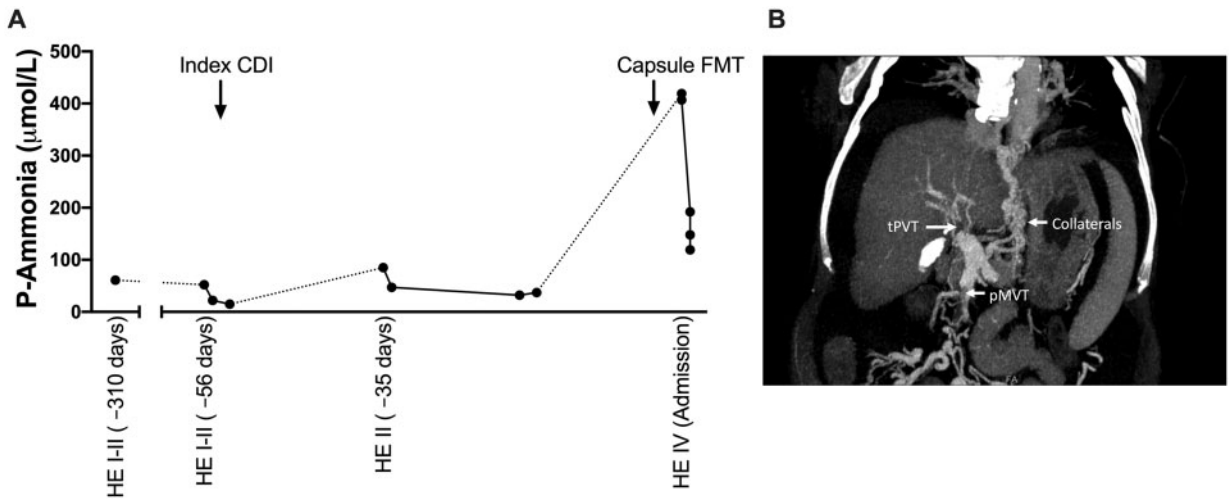

Figure 1. Acute severe hyperammonemia following fecal microbiota transplantation (FMT) for fulminant refractory *Clostridioides difficile* infection(CDI) (A) in a patient with total portal vein thrombosis (tPVT), partial mesenteric vein thrombosis (pMVT), and multiple porto-systemic collaterals (B). HE, hepatic encephalopathy; P-Ammonia, plasma ammonia.

treatment, ammonia levels halved to 192 μmol/L and her cerebral state improved to HE grade II. As part of the clinical management, the insertion of a nasogastric tube was necessary. Although the patient was handled according to procedural guidelines, an uncontrollable nasopharyngeal bleed occurred, from which the patient died the day after admission.

Discussion

This is the first description of deep HE via severe hyperammonemia and precipitated by FMT that was provided for fulminant, refractory CDI.

Previous studies with FMT for patients with or without infectious colitis reported no treatment-related severe adverse events and even found decreased ammonia levels 1 week after FMT HE [2] (Woodhouse CA *et al.*, manuscript in preparation). These patients were stable at baseline and likely had a stable intestinal microbiome, which nevertheless predisposed them to HE. Our case illustrates that FMT provided for CDI in a patient with liver cirrhosis complicated by a portal vein thrombosis is not always safe, even for the patient with a well-preserved liver function. The rapid microbiota correction by FMT seems to require close monitoring.

Hyperammonemia results from increased production or delayed clearance. We suggest that the hyperammonemia in our patient was caused primarily by the rapid shift of a microbiota dominated largely by urease-negative CD to a healthy, intestinal donor microbiota possessing ample urease activity, together with a delayed ammonia clearance because of shunt-related decreased sinusoidal first-passage ammonia metabolism. Engraftment of urease-active bacteria in a patient with portosystemic shunts is described to be able to cause hyperammonemia at levels as observed in our patient [5, 6]. Dehydration from refractory CDI may have further enhanced this. These combined circumstances likely contributed to the developed hyperammonemia and, eventually, HE. The normal INR and near-normal bilirubin indicate that metabolic liver function was preserved before and after FMT and that impaired hepatic function did not contribute significantly to the hyperammonemia. The condition was rapidly reversible on standard corrective treatment and did not cause her death.

The patient was suffering from refractory CDI, which per se is a life-threatening disease carrying a high mortality and a high risk of developing HE in patients with liver cirrhosis. Even though CD is urease-negative, CD is able to produce small amounts of ammonia due to glutamate dehydrogenase activity, limited by the availability of glutamate, and we take this to be an insignificant contribution to her severe hyperammonemia. Importantly, the microbiota of healthy people, who serve as feces donors, comprises urease-active bacteria that cannot be avoided during FMT and may cause acute hyperammonemia.

We suggest that FMT should still be advised in patients with fulminant CDI, liver cirrhosis, and portal vein thrombosis. Particular attention should however be given to securing adequate hydration status. Hospital admission for the FMT may be a necessity until treatment success and clinical stability are assured. Plasma ammonia monitored early pre and post FMT and during follow-up may help to monitor the risk of developing HE in this patient group.

Authors' Contributions

All authors were involved in data collection and interpretation. P.L.E., K.B.F., and C.L.H. treated the patient. L.L.E. and C.L.H. drafted the manuscript. All authors read, revised, and approved the final manuscript.

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The relatives of the patient provided written consent for the publication of this case report.

Conflict of Interest

None declared.

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