Case Report

Journal of the International Society of Physical and Rehabilitation Medicine

OPEN

Fecal microbiota transplantation in patients with spinal cord injury with recurrent *Clostridioides difficile* infection: a case report

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Objective: Fecal microbiota transplantation (FMT) is an emerging treatment for *Clostridioides difficile* infection (CDI) through reconstruction of the gut microbiota, but its impact in people with spinal cord injury (PWSCI) is limited. The aim of this paper is to report the use of FMT in a PWSCI with CDI.

Methods: The FMT was conducted on October 30, 2019.

Results: A 72-year-old man with T8 complete paraplegia from compression of the spinal cord due to an epidural hematoma was referred. He has known severe pancreatic enzyme insufficiency, malabsorption, and a history of recurrent CDI. Despite intensive dietetic treatment (probiotics, enteral nutrition, and parenteral nutrition), and multiple courses of antibiotics (vancomycin and fidaxomicin at various doses and durations) for CDI, he continued to be CDI-positive. His CDI was successfully treated after 2 colonoscopically delivered FMTs. At the 24-month follow-up, he remains CDI-negative and reports improved independence. Although there has been considerable variability in the criteria for the FMT and its mode of delivery, FMT can be an option to treat recurrent CDI.

Conclusion: This case report reports a PWSCI with recurrent CDI who has been successfully treated with FMT and remains in long-term remission. It supports the consideration of FMT in PWSCI with CDI when antibiotic treatment has been unsuccessful.

Keywords: Spinal cord injury, fecal microbiota transplant, microbiota, *Clostridioides difficile*

Introduction

Spinal cord injury (SCI) affects about 2500 people in the UK annually[1]. SCI causes dysfunction of multiple systems, including bladder, bowels, and the respiratory system; making these individuals more susceptible to recurrent infections requiring repeated courses of oral antibiotics[2]. Recurrent antibiotic use increases the risk of antibiotic-associated diarrhea (AAD) and *Clostridioides difficile* infection (CDI). After antibiotic treatment, dysbiosis occurs, which allows either endogenous or introduced toxigenic *Clostridioides difficile (C. difficile)* into the gastrointestinal tract, causing an illness that may be severe, recurrent, or, if not adequately treated, fatal. In the past, the standard of care was focused on treatment with antibiotics to reduce the presence of pathogens. However, recurrences were common, which is not surprising, as further use of antibiotics often worsened the underlying dysbiosis. In addition, diarrhea can delay SCI rehabilitation, increase the risk of developing pressure ulcers, delay wound healing, and reduce overall quality of life.

Fecal microbiota transplantation (FMT), a technology involving transplanting the gut microbiota, is also considered as a treatment for recurrent CDI[3,4]. Evidence concerning the relationship between the microbiome and the effects of SCI in humans is sparse. Animal studies demonstrate gut dysbiosis and raised inflammatory cytokines after SCI, and that premorbid dysbiosis leads to poorer neurological outcomes and neuropathological findings after SCI[5]. After a SCI, there is a constellation of dysfunctions in intestinal transit, expression of nutrient transporters, and mucosal barrier changes. These alterations lead to microbiotal dysbiosis in the gut, which leads to the development of a systemic inflammatory response. Maintenance of the integrity of the intestinal mucosal epithelium is multifactorial, but the gut microbiome most probably plays an important role, along with intraluminal contents, pancreatic enzymes, hepatobiliary factors, and the enteric and central nervous systems. An unstable gut microbiome after SCI is associated with an increased risk of infection[6]. In this case report, we report the first UK case in which FMT has been used to treat CDI in a patient with complete paraplegia who also had severe pancreatic insufficiency. Written consent was obtained from the patient before this case report.

Methods

A 72-year-old man was transferred to a tertiary SCI centre on April 9, 2019. He sustained a T8 complete (American Spinal Injury Association Impairment Scale: A) paraplegia on January 16, 2019, secondary to an epidural hematoma causing spinal cord compression. He has a history of thrombocytopenia and chronic pancreatitis leading to severe pancreatic enzyme

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Journal of the International Society of Physical and Rehabilitation Medicine (2024) 7:71–74

Received 7 September 2023; Accepted 11 April 2024

Published online 7 May 2024

http://dx.doi.org/10.1097/ph9.0000000000000033

insufficiency and malabsorption. Before transfer to the SCI centre, he had a history of CDI after his SCI, which had been treated by oral vancomycin. His bowels remained loose on admission to the SCI centre. He complained of nausea with associated vomiting and, therefore, his appetite was minimal. Due to chronic diarrhea, his nutritional and hydration intake was supplemented by a combination of enteral (~10% of his need) and parenteral (~75% of his need) nutrition. Tests (*C. diff* toxin A and toxin B) for

CDI became positive again shortly after transfer in April 2019. During his episodes of CDI, he complained of nausea, loss of appetite, and intermittent episodes of bloating and loose stools. His observations demonstrated a raised temperature to around 38 °C and tachycardia to around 105 bpm at the time of his acute CDI. On examination, his abdomen was soft, and bowel sounds were present and normal, although his abdomen was slightly distended and tympanic. A computed tomography scan of his abdomen was performed which demonstrated thickening of the ascending colon, sigmoid, and rectum with moderate amounts of free fluid consistent with the history of CDI. A colonoscopy was performed and unfortunately, due to inadequate preparation, the mucosa was only reviewable up to the level of the descending colon but no alternative pathology was demonstrated. During his CDI flare-up, his white cell count was raised to 13.5×10^9 (normal range: 3.7–11) and his C-reactive protein was up to 113 mg/L (normal range: 0–5; Table 1).

Several dietary interventions (low fat, peptide-based formula, and probiotics) and pharmacological protocols were tried (including vancomycin and fidaxomicin) at different doses and durations in accordance with microbiological guidance (Table 2). These were not able to resolve the CDI or the patient's symptoms. The patient remained CDI-positive and symptomatic over a 5-month period after his admission (CDI tests May 10, 2019; July 7, 2019; and September 26, 2019). One of the "recurrences" matched the criteria of severe CDI with *C. difficile* colitis. The treating team considered a trial of FMT through colonoscopy on October 30, 2019.

The FMT material was obtained from a licensed facility regulated by the Medicines and Healthcare products Regulatory Agency following strict guidelines[2]. The donor reported no antibiotic treatment in the last 3 months before the procedure. Additional testing for infectious disease (anti-hepatitis A virus, anti-hepatitis B core, hepatitis B surface antigen, anti-hepatitis C virus, human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, and *Treponema pallidum*) in the serum, and 3 independent fecal samples, were negative *for C. diff* toxins A and B, campylobacter spp., Shigella, Salmonella, Yersinia, pathogenic *Escherichia coli*, adeno, rota and norovirus, parasites, cryptosporidium, and microsporidium.

Before FMT, the patient's antibiotic treatment was omitted for 1 week, and a bowel lavage with enemas was performed[2]. A portion of 150 g of donor stool was weighed and homogenized with isotonic sodium chloride in a sterile flask. The homogenate was filtered repeatedly through sterile gauze pads to remove as much particulate matter as possible. A colonoscopy was then performed. The endoscopic findings were normal. The stool slurry was administered into the proximal transverse colon without any other preparation.

Table 1

Baseline and follow up characteristics

	April 2019	June 2019	August 2019	October 2019	June 2021
Weight (kg)	—	60.4	61.5	62	82
Body mass index (kg/m^2)	—	20.9	21.3	21.5	28.3
C-reactive protein (mg/L)	33	9.5	5.9	6.4	4.4
Total protein (g/L)	48	61	58	59	68
Serum albumin (g/L)	27	34	31	31	40
Correct calcium (mmol/L)	2.35	2.34	2.34	2.27	2.22
Hemoglobin (g/L)	100	128	114	111	143
White blood count (10^9/L)	2.7	5.7	3.9	5.0	6.4
Total cholesterol (mmol/L)	3.4	—	—	2.0	—
HDL cholesterol (mmol/L)	0.9	—	—	0.7	—
Cholesterol/HDL ratio	3.8	—	—	2.9	—
Alanine transferase (U/L)	22	77	39	50	20
Alkaline phosphatase (U/L)	103	102	182	199	126
Magnesium (mmol/L)	0.81	0.75	0.8	0.94	—
Inorganic Phosphate (mmol/L)	1.0	1.0	1.2	1.3	—
Sodium (mmol/L)	137	126	135	138	139
Potassium (mmol/L)	2.8	4.2	4.3	4.7	4.0
Urea (mmol/L)	4.2	6.1	6.0	6.3	6.2
Creatinine (umol/L)	41	33	28	35	37
25-hydroxy vitamin D (nmol/L)	26.3	—	—	38.4	72.7
B12 (pg/mL)	—	—	601	674	—
Folate (ng/mL)	—	—	4.4	9.5	—
Iron (umol/L)	—	—	8.6	6.1	—
Transferrin (g/L)	—	—	2.03	2.03	—

HDL indicates High density lipoprotein.

Results

Three days after the initial FMT, the patient experienced loose bowels again (Bristol Stool Scale, type 7×5 times a day). A second FMT was arranged on November 13, 2019, according to the local FMT protocol. In the following weeks, the patient's bowel pattern continued to improve with no recurrence of watery diarrhea or CDI-like symptoms. His appetite improved and his feeding (percutaneous endoscopic gastrostomy) tube was removed on March 11, 2020, before discharge from the SCI centre on April 6, 2020. Due to the coronavirus disease 2019 pandemic, his first 2 follow-ups were conducted through tele-consultation (in July 2020 and January 2021) and face-to-face 20 months after discharge. The patient reported that he no longer had episodes of loose bowels and had an established daily bowel regime to manage his neurogenic bowels. He mobilizes daily in his wheelchair for several hours a day. His appetite improved and his weight increased. In addition, a stool test for *C.diff* toxin A/B was negative.

Discussion

The gut is known to be a target organ for various kinds of stress triggered by sepsis, shock, trauma, and infection[6]. Considering that SCI is a stressor altering a number of physiological processes, research has hypothesized that bowel dysfunction and altered colonic transit time after SCI could lead to significant changes in the composition of the gut microbiota[7]. Gut microbiota are critical for normal digestion, nutrient absorption, metabolism, and cell function. Common additional causes of gut dysbiosis include antibiotic use, prolonged stress, and gastrointestinal dysfunction[8]. After SCI,

Table 2

Antibiotic treatment before fecal microbiota transplant procedure.

Date	Episode	Antibiotic regimen	Dose/frequency	Administration route	Duration (d)
April 10, 2019	1	Vancomycin	—	—	14 April 11 to April 24
May 10, 2019	2	Fidaxomicin	200 mg/bd	Orally	10 May 10 to May 20
July 7, 2019	3	Vancomycin	250 mg/QDS	NG	17 July 7 to July 23
Vancomycin	—	—	125 mg/QDS	NG	7 July 24 to July 30
Vancomycin	—	—	125 mg/TDS	NG	7 July 31 to August 6
Vancomycin	—	—	125 mg/BD	NG	7 August 7 to August 13
Vancomycin	—	—	125 mg/OD	NG	7 August 14 to August 20
Vancomycin	—	—	125 mg OD alt day	NG	7 August 21 to August 27
September 26, 2019	4	Vancomycin	125 mg/QDS	PEG	20 September 27 to October 16
October 30, 2019	—	FMT	—	—	—

BD indicates two times daily; FMT, fecal microbiota transplantation; NG, nasogastric tube; OD, one time daily; PEG, percutaneous endoscopic gastrostomy; QDS, four times daily; TDS, three times daily.

people with spinal cord injury (PWSCI) often requires antibiotic treatment due to pulmonary infections or urinary tract infections. The use of antibiotics also affects the healthy gut microbiome[7]. In addition, newly injured PWSCI not only have a higher risk of upper gastrointestinal hemorrhage but also usually require anticoagulation therapy to prevent venous thromboembolism. Given these additive risks, most patients are prescribed gastric protection, with a proton pump inhibitor (PPI). However, PPI exposure is also a risk factor for AAD/CDI.[9] Current evidence on the use of probiotics in preventing AAD/CDI in PWSCI who take PPIs regularly remains unclear, as the use of probiotics is strain, dose, and disease-specific, and uncertainty remains as to when and if probiotics should be administered and the durations to be considered[10,11].

In this case, the second FMT was administered as the patient remained symptomatic after the initial FMT (the patient developed loose stools within 3 d of his first FMT). Indeed, Allegretti et al (2018) report that at least 25% of patients will fail to respond to FMT within 1 week after an initial treatment, supporting a view that repeat FMT may need to be considered for refractory symptomatic CDI[12].

The literature also suggests that FMT is a feasible intervention in the treatment of recurrent CDI in PWSCI. To the best of our knowledge, there are only 2 previous case reports of FMT in patients with SCI for CDI management[13,14] [n = 2 case report; n = 2 SCI (n = 1 tetraplegia[14]; n = 1 paraplegia[13]) patients]. There was considerable variability in FMT selection criteria (n = 2: recurrent CDI, ineffective, multiple antibiotic use), mode of delivery (n = 1 colonoscopically[14]; nasoduodenal tube placement[13]), donor [wife[13]; son[14]) and follow-up period (12 wk[14]; 10 mo[13]; Table 3]. Nonetheless, both studies reported that FMT can successfully treat CDI in PWSCI without adverse events.

Although FMT is increasingly common in treating recurrent CDI, there is limited evidence in PWSCI[13,14], probably due to neurogenic bowel dysfunction[15]. The present study reports a PWSCI with recurrent CDI who has been successfully treated with FMT and remains in remission 24 months after his last FMT. The present case study presents a total resolution of CDI, with the absence of diarrhea 8 weeks after the second FMT and he remains in remission 24 months after the FMT. It supports the provision of FMT as an option to consider in people with SCI diagnosed with recurrent or refractory *C. diff* infection.

This study has some limitations. First, there are currently no standard inclusion criteria for FMT in treating recurrent CDI in PWSCI. Therefore, other Health Care Professionals might select and perform FMT differently, which may mean these findings might not be applicable in other PWSCI with

Table 3

Studies evaluating FMT in patients with spinal cord injury.

Author(s)/Journal	Study type/ sample size	Country	FMT selection criteria	FMT source/ donor	FMT delivery method	Volume of FMT	Follow-up period
Veling/J Spinal Cord Med[7]	Case report n = 1	United States	Recurrent CDI; ineffective antibiotic use	Wife	Nasoduodenally	50 mg stool liquefied in sterile saline and filtered to produce 400 mL solution	10 mo
Brechmann et al/World J Gastrroenterol[8]	Case report n = 1	Germany	Recurrent CDI; ineffective antibiotic use	Son	Colonoscopically	160 g stool homogenized with isotonic sodium chloride and filtered in sterile gauze pad	12 wk

CDI indicates *Clostridioides difficile* infection; FMT, fecal microbiota transplantation.

recurrent CDI. However, our data provides a baseline for future comparisons. Second, substantial heterogeneity in both selection and analytic methods, as well as the small number of patients, preclude meta-analysis in this area. Therefore, an additional case/observation study would help clinician to obtain precise estimates with corresponding CIs in using FMT in treating recurrent CDI in PWSCI.

Due to global concerns around antibiotic resistance, an evidence-based nonantibiotic intervention is highly desirable to improve the quality of life in PWSCIs through reducing antibiotic use, antibiotic-associated complications, and CDI. Further research is warranted to characterize selection criteria for FMT and to confirm that FMT is effective in treating recurrent CDI in PWSCI.

Ethical approval

Formal ethical permission to conduct the study was not required by the hospital review board because this was a retrospective case study. Patient written consent was obtained prior to this case report write up.

Source of funding

No funding support was received for this work.

Author contribution

S.W.: data collection, data interpretation, and manuscript preparation. A.F. and A.N.: data interpretation and manuscript revision. N.K.: data collection, data interpretation, and manuscript revision.

Conflicts of interest disclosure

S.W. has received funding support from Yakult Honsha Co Ltd for conducting ECLISP trial. A.F. has received honoraria from Fresenius Kabi, Takeda, and Dr Falk Pharma. The remaining authors declare that they have no financial conflict of interest with regard to the content of this report.

Research registration unique identifying number (UIN)

None.

Guarantor

None.

Data availability statement

The data sets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Acknowledgments

The authors thank all medical and nursing staff for facilitating stool specimen collection. Also, Dr Vicky Blackwell, Dr Jean O'Driscoll, and Dr Sujata Biswas who supported the FMT review and delivery.

Declaration of generative AI and AI-assisted technologies in the writing process

No AI tools or services were used during the preparation of this work.

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