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Fecal microbiota transplantation cured epilepsy in a case with Crohn's disease: The first report

Zhi He, Bo-Ta Cui, Ting Zhang, Pan Li, Chu-Yan Long, Guo-Zhong Ji, Fa-Ming Zhang

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Author contributions: He Z wrote the paper; Cui BT and Zhang T joined the clinical work; Li P performed the lab work; Long CY collected the clinical data; Ji GZ was the attending doctor of this group; Zhang FM designed and organized the study and edited the paper.

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Abstract

Fecal microbiota transplantation (FMT) is a promising strategy that involves reconstruction of gut microbiota. Recently, it has been considered as a treatment of Crohn's disease (CD) and certain neurological diseases. Here, to the best of our knowledge, we report the first case that used FMT to achieve remission of intestinal and neurological symptoms in a girl with CD and a 17-year history of epilepsy. During the 20 mo of follow-up, FMT has proved its efficacy in preventing relapse of seizures after withdrawing the antiepileptic drugs. Furthermore, this finding highlights the role of microbiota-gut-brain axis and inspires a novel treatment for epilepsy through remodeling gut microbiota.

Key words: Fecal microbiota transplantation; Epilepsy; Crohn's disease; Gut microbiota; Brain-gut axis

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Core tip: We report a case of 17-year history of epilepsy which fortunately showed improvement as a result of fecal microbiota transplantation (FMT) treatment for

Crohn's disease. This is the first report that FMT has been used in epilepsy treatment to our knowledge. This case might open a new window into disease mechanism focusing on the microbiota-gut-brain axis and inspire a novel treatment for epilepsy through remodeling of gut microbiota.

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INTRODUCTION

Considerable evidence has shown the effects of microbiota on neuropsychiatric disorders^[1]. However, very few studies have reported the clinical use of microbiota in brain diseases. Fecal microbiota transplantation (FMT), the most effective strategy for reconstruction of the gut microbiota, has been considered as a treatment of *Clostridium difficile* infection^[2], inflammatory bowel disease^[3-5], constipation and other diseases^[6]. In this study, we report the first case that used FMT as a treatment of long-term epilepsy in a patient with Crohn's disease (CD). FMT showed positive response of more than 20 mo seizure free without using antiepileptic drugs.

CASE REPORT

A 22-year-old girl, with a 17-year history of epilepsy, was referred to the Second Affiliated Hospital of Nanjing Medical University in May 2015 because of unsuccessful CD treatment. The initial presentation was at the age of 6 years, with generalized seizures of loss of consciousness and unexplained chronic diarrhea. The patient had more than 120 seizures every year between the ages of 6 to 13. After that, she was diagnosed with epilepsy by typical electroencephalogram (EEG) and started to take sodium valproate. That treatment achieved extended stabilization in the seizures, but she still experienced 2-3 generalized seizures every year if she had forgotten to take the antiepileptic drug. Diagnosis of CD was made at the age of 17, and at that time she started treatment for the chronic diarrhea and achieved symptom improvement after oral mesalamine. She had growth retardation, mild malnutrition and started the first menarche at age 17, which was followed by menstrual cycle disorder.

After administration, abdominal/pelvic magnetic resonance imaging (MRI) showed severe strictures in sigmoid colon and anus with perianal fistula; brain MRI was normal. CD activity index (CDAI) was 361 points. The patient underwent endoscopic balloon dilation for

the intestinal strictures, and then was administered the first FMT through mid-gut by gastroscopically (Trial: NCT01793831) under anesthesia^[7]. The stool for FMT was obtained from a primary school girl and scanned after signing an informed consent from her parents. The laboratory protocol and clinical work flow were noted in our recent report^[8].

The 200 mL fresh fecal microbiota suspension was prepared under an automatic purification system (GenFMTer; FMT Medical, Nanjing, China) in our fecal microbiota bank system. After the FMT, the patient was given professional food instruction related to CD. In addition, she was given oral mesalamine at 3.0 g per day during the follow-up. She underwent the second endoscopic balloon dilation for colonic stricture before her third FMT. Based on our initial expectation on the role of FMT in epilepsy, we decided to stop sodium valproate after the first FMT and getting her informed consent. Since then, the patient never had recurrence of epilepsy during the entire 20 mo of follow-up and has remained in seizure-free without antiepileptic drugs up to the date of this submission. Importantly, a male infant was born by normal spontaneous vaginal delivery before this final approval for this article. Therefore, there was no need for EEG during the follow-up.

The clinical response of CD to the FMT was evidenced by decreasing CDAI to 104 points after 12 mo, and this remission maintained after the third FMT until the end of 20 mo follow-up. In addition, the patient showed sustained improvement of quality of life and started to work. More interestingly, her menstrual cycle after FMT tended to shorten and became regular every 6 wk, with normal menstruation quantity during each cycle. The key clinical parameters before and after the FMT were shown in Table 1.

DISCUSSION

Epilepsy entails a major burden in seizure-related disability, mortality, comorbidities, stigma and costs^[9]. Although the number of available antiepileptic drugs has increased substantially during the past 20 years, about a third of patients remain resistant to medical treatment^[10]. Despite the development of surgical procedures, epilepsy surgery is still done in a small subset of drug-resistant epilepsy cases. Here, we report a case of 17-year history of epilepsy which fortunately showed improvement as a result of FMT treatment for CD. Although the patient never took any antiepileptic drugs after the FMT, she had a more than 20-mo seizure free and this status is maintained to date.

Unfortunately, in this case report, there is no confirmed focal pathology, no potential pathogen identification, no microbiome analysis, and no gene mutation detection. There are very few reported cases in the literature on epilepsy comorbid CD^[11,12], which may be the key reason that the mechanism linking intestinal microbiota, intestinal inflammation

Table 1 Clinical parameter changes of the patient during follow-up

Parameter (normal range)	Before the 1 st FMT	After the 1 st FMT					
		1 mo	3 mo	6 mo	12 mo	15 mo	20 mo
CDAI score	361	174	158	87	104	112	131
Body weight in kg	42	42	43	47	49	50	52
Hemoglobin (110-160) in g/L	95	99	120	117	113	103	111
CRP (0-10) in mg/mL	8	3	7	10	1	3	10
ESR (0-20) in mm/h	59	51	27	30	36	21	61
Album in g/L	39.6	ND	47.7	39.7	45.5	48.4	41.5
Total cholesterol (≤ 5.2) in mmol/L	4.08	ND	4.98	ND	ND	5.71	ND
Triglycerides (≤ 2.3) in mmol/L	1.68	ND	1.03	ND	ND	0.32	ND
HDL-C (≥ 0.9) in mmol/L	0.7	ND	1.2	ND	ND	1.8	ND
IgA (0.70-4.00) in g/L	5.71	ND	5.47	4.39	ND	ND	5.4
Menstrual cycle length in d	60-75	ND	45	45	45	45	30

CDAI: Crohn's disease activity index (remission: < 150 ; moderate: 150-450; severe: > 450); CRP: C reactive protein; ESR: Erythrocyte sedimentation rate; FMT: Fecal microbiota transplantation; HDL-C: High density lipoprotein-cholesterol; LDL-C: Low density lipoprotein-cholesterol; ND: No detection.

and epilepsy remains unclear. CD with associated nutrient deficiencies could have symptoms like tetany and seizures, which may be related to the deficit of magnesium and/or calcium^[12]. However, the present patient in this report was diagnosed as epilepsy at the age of 13 and only had mild malnutrition.

Although it has been mentioned that FMT might be helpful for certain neurological diseases^[6] and CD^[7], as far as we know, this article is the first report of successful epilepsy treatment using FMT. We are conducting a randomized controlled clinical trial (Trial: NCT02889627) to investigate the efficacy of FMT for epilepsy. It is notable that the level of blood lipid of the patient returned to the almost normal level after FMT. In our previous studies^[7,13], we also found similar results, showing that the gut microbiota could affect host lipid metabolism. These evidence suggested that FMT may be one of the therapeutic options for metabolic diseases.

Although there has been an at least 1700-year old history of using FMT in human diseases^[14], to the best of our knowledge, no previous report on using FMT in epilepsy is present in the publicly available literature. This interesting finding might open a new window into disease mechanism focusing on the microbiota-gut-brain axis and inspire a novel treatment for epilepsy through remodeling of the gut microbiota.

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COMMENTS

Case characteristics

A Chinese girl with long-term epilepsy was referred to our hospital because of unsuccessful treatment for Crohn's disease (CD).

Clinical diagnosis

Clinical symptoms showed chronic diarrhea, growth retardation, mild malnutrition and menstrual cycle disorder.

Differential diagnosis

The differential diagnosis included intestinal tuberculosis and viral infection.

Laboratory diagnosis

Laboratory evaluation revealed low hemoglobin and elevated erythrocyte sedimentation rate.

Imaging diagnosis

Magnetic resonance imaging confirmed the severe strictures in sigmoid colon and anus with perianal fistula, and negative finding in brain.

Pathological diagnosis

The patient was diagnosed definitely with no pathological examination, although this was important.

Treatment

The patient underwent three fecal microbiota transplantations and two endoscopic balloon procedures during the 12 mo after her first visit.

Related reports

There is no report on fecal microbiota transplantation for epilepsy.

Term explanation

Fecal microbiota transplantation involves infusing healthy donor microbiota into the intestines of a patient to restore the intestinal microbiota.

Experiences and lessons

This case highlights the disease mechanism, focusing on the microbiota-gut-brain axis and possibly inspiring a novel treatment for epilepsy through remodeling of the gut microbiota.

Peer-review

The paper is well written. The nutrient deficiencies associated with CD is usually subclinical but, occasionally, can cause weight loss, growth retardation, anemia and, even, tetany and seizures.

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