Fecal microbiota transplantation to treat Parkinson’s disease with constipation
A case report
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Abstract
Rationale: Fecal microbiota transplantation (FMT) is recognized as an emerging treatment through reconstruction of gut microbiota. Parkinson’s disease is a neurodegenerative disorder, which is accompanied by constipation. Here we first reported a patient with Parkinson’s disease and constipation that were obviously relieved after FMT.

Patient concerns: A 71-year-old male patient presented with 7 years of resting tremor, bradykinesia (first inflicted the upper limbs and subsequently spread to lower limbs), and intractable constipation (defecation needing more than 30 minutes).

Diagnoses: Parkinson’s disease for 7 years; constipation >3 years.

Interventions: The patient had used madopar, pramipexole, and amantadine for anti-Parkinson and showed partially mitigation while laxative therapy for constipation failed. Finally FMT was performed.

Outcomes: The patient successfully defecated within 5 minutes and maintained daily unobstructed defecation until the end of follow-up. The patient’s tremor in legs almost disappeared at 1 week after FMT but recurred in the right lower extremity at 2 months after FMT.

Lessons: Gut microbiota reconstruction may have therapeutic effects for Parkinson’s disease patients, especially those who have gastrointestinal symptoms and limited treatment choices.

Abbreviations: FMT = fecal microbiota transplantation, OUT = operational taxonomic units, PAC-QOL = patient-assessment of constipation quality of life, PCoA = principal co-ordinates analysis, PD = Parkinson’s disease, TET = transendoscopic enteral tubing, UPDRS = unified Parkinson’s disease rating scale.

Keywords: constipation, fecal microbiota transplantation, gut microbiota, Parkinson’s disease, tremor

1. Introduction
Parkinson’s disease (PD) is a progressive, chronic, neurodegenerative disorder, which always with gastrointestinal dysfunction. Patients with PD often demonstrate gastrointestinal symptoms, such as constipation, which precede the motor sign of PD.<sup>[1]</sup> The etiology of PD is not well understood but like to be the outcome of genetic factors and environmental effects, whereas the concept...
of “gut microbiota-brain axis” has been well established and its dysregulation may lead to neurological disease like PD.[2]

Accumulating evidence indicates a potential bidirectional interaction between gut microbiota and PD. A research showed gut microbiota was involved in motor deficits, microglia activation, and αSyn pathology which play important roles in the development of PD. Moreover, αSyn-overexpressing mice implanted with microbiota from PD-affected patients showed more obvious physical impairment compared to those with microbiota from healthy human donors.[3] Fecal microbiota transplantation (FMT), a technology by transplanting the gut microbiota of healthy people into the patients through the endoscopy channel and fiberoptic enteral tubing (TET) tube (Nanjing FMT Medical, Nanjing, China).[10] Then 200 ml of prepared fecal microbiota suspension was injected through the TET tube. The procedure was repeated for 3 times (once every day). No adverse reaction appeared during FMT. After the FMT treatment, the patient declared the obviously reduced tremor in both lower limbs and the easier and quicker defecation. During a follow-up of 3 months, we recorded the change of tremor, completed several surveys and sampled his fresh stool for 16s RNA microbiota analysis.

During the follow-up, the tremor in legs almost disappeared at 1 week after FMT treatment (see Video, Supplemental Video1-B, http://links.lww.com/MD/D50). Though the resting tremor recurred in the right lower extremity at 2 months after FMT (see Video, Supplemental Video1-C, http://links.lww.com/MD/D51), but its severity dropped compared with that of pre-FMT (see Video, Supplemental Video1-A, http://links.lww.com/MD/D49). In Table 1, the patient’s UPDRS score began to decrease after FMT, and then decrease became significant at 1 week after treatment, but later, the score showed a trend increasing with time. PAC-QOL and Wexner constipation score suggested that the patient’s constipation was significantly alleviated: the time of defecation was shortened from more than 30 minutes to 5 minutes. This effect continued until the end of follow-up. Coupled with the results of fecal microbiota analysis at different follow-up points, FMT could effectively raise the α-diversity of the gut microbiota (Fig. 1A and B). It was found by PCoA analysis that the patient’s microbiota structure was similar to the donor’s at 1 week after FMT, but the structural difference showed up with time went on (Fig. 1D). Using OTUs clustering and weighted unifrac tree analysis method (Fig. 1C and E), we found the abundance of Firmicutes increased while those of Proteobacteria and Bacteroidetes decreased after treatment, and the clustering of bacterial communities showed similarity between donor and patient after treatment. On genus level (Fig. 1F), the relative abundance of Lachnoclostridium, Dialister, Alstonipes, and Unidentified-Ruminococcaceae increased after 1 week; that of Megamonas increased after 1 month, and that of Akkermansia and Faecalibacterium increased after 3 months.

### 2. Case presentation

A 71-year-old male patient presented with 7 years of resting tremor and bradykinesia that first inflicted the upper limbs and subsequently spread to the right lower limb and left lower limb. In addition to the above symptoms, the patient has been plagued by constipation (defecation needing more than 30 minutes) for years. After diagnosis of PD in the local hospital, the patient started to use madopar, pramipexole, and amantadine for anti-Parkinson and showed partially mitigation while laxative therapy for constipation but showed very limited effect. According to the unified Parkinson’s disease rating scale (UPDRS),[6] 13/42; part III (motor examination), 46/142. Patient-assessment of constipation quality of life (PAC-QOL score),[7] and Wexner constipation score,[8] 18 and 16.

The patient was referred to Guangzhou First People’s Hospital in October 2017 after former constipation treatment failed for FMT. We gained written informed consent from the patient. Routine examinations were completed to ensure the absence of contraindications for FMT. During colonoscopy, a transendoscopic enteral tubing (TET) tube (Nanjing FMT Medical Company, Nanjing, China) was inserted into the ileocecal junction through the endoscopy channel and fixed to the intestinal wall. The stool for FMT was obtained from a college student (26-year-old male) who also signed an informed consent form before donation. Stool donor was selected with a well-defined protocol adapted from the published literature.[9] The laboratory and clinical work flow were implemented according to the instruction of automatic purification system (GenFMTer; FMT Medical, Nanjing, China).[11] Then 200 ml of prepared fecal microbiota suspension was injected through the TET tube. This procedure was repeated for 3 times (once every day). No adverse reaction appeared during FMT. After the FMT treatment, the patient declared the obviously reduced tremor in both lower limbs and the easier and quicker defecation. During a follow-up of 3 months, we recorded the change of tremor, completed several surveys and sampled his fresh stool for 16s RNA microbiota analysis.

### 3. Discussion

As a potential modulator of human biology, gut microbiota can directly or indirectly regulate brain neurochemistry through immune, metabolic, or endocrine mechanisms.[11] PD is a huge concern for the aging population. Mounting evidence proves that...
Figure 1. Microbiota analysis. Fecal microbial communities of the patient before FMT, at 1 wk after FMT, 1 mo after FMT and 3 mo after FMT. (A) Alpha diversity of observed species; (B) Venn diagram of shared and independent bacterial OTUs during different periods; (C) Weighted unifrac tree analysis, differences in the clustering of bacterial communities by the UPGMA; (D) PCoA; each dot represents 1 fecal sample; dot closeness indicates the similarity between bacterial communities. (E, F) Relative abundance of fecal bacterial taxa on phylum and genus levels, respectively. FMT = fecal microbiota transplantation, PCoA = principal co-ordinates analysis, UPGMA = unweighted pair group method with arithmetic mean.
the gut microbiota is required for motor deficits and neuroinflammation in a model of PD.\textsuperscript{3,12} In this case, the patient had suffered from serious tremor and constipation. Fortunately, the patient agreed to try FMT, and the outcomes were inspiring. Although this case was the first attempt to treat PD with FMT, the patient’s constipation and tremor was effectively relieved. We also noticed that the patient’s gut microbiota status was significantly associated with the severity of symptoms.

However, several problems needed to be settled. First, the patient’s tremor in limbs was decreased, but other Parkinson-related symptoms such as face and neck stiffness showed no change, even the patient’s tremor disappeared at 1 week after treatment, indicating that the effect gradually diminished with time. Second, Scheperjans\textsuperscript{8,13} sequencing of 72 stool samples from PD patients and healthy controls found the abundance of \textit{Prevotella} in PD patients decreased significantly. Keshavarzian et al\textsuperscript{14} found the abundance of butyric acid-producing bacteria such as \textit{Blautia}, \textit{Coprooccus}, and \textit{Roseburia} reduced in PD patients. But our report found a decline in the abundance of butyric acid-producing bacteria, but not of \textit{Prevotella}. This difference should be illustrated with further research. Third, \textit{Megamonas}, and \textit{Akkermansia} genus increased after FMT treatment, and whether the enrichment of these bacteria was also associated with PD was unknown.

Braak et al\textsuperscript{15,16} inferred that the gastrointestinal plexus was involved in the early onset of PD. Svensson et al\textsuperscript{17} verified that cutting off the abdomen significantly reduced the prevalence of PD, which meant the intestinal activity may associate with PD. Cui B, Li P, Xu L, et al. Step-up fecal microbiota transplantation strategy: a pilot study for steroid-dependent ulcerative colitis. J Transl Med 2015;13:298.

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Acknowledgments

We thank the patient participated in this study and all staff in the Department of Gastroenterology.

Author contributions

HH and HX contributed equally to this work. HH involved in design of the study, recruitment of the patient, and drafting of the article; HX involved in statistical analysis and interpretation of the data, and drafting of the article; QL, JH performed the sample collection and DNA extraction; ML was the attending Neurologist and managed follow-up visits; HC and WT prepared fecal samples into filtrate for administration during the FMT procedure and revision of the article; YZ and YN designed and organized the study, interpretation of the data and revision of the article.

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