Fecal microbiota transplantation for Parkinson's disease using levodopa-carbidopa intestinal gel percutaneous endoscopic gastro-jejunal tube

Chernova, V.O.; Terveer, E.M.; Prehn, J. van; Kuijper, E.J.; Keller, J.J.; Jong, A.E.V.; ... ; Contarino, M.F.

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Correspondence

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ABSTRACT

We report a patient with a 5-year diagnosis of akinetic-rigid Parkinson's disease under treatment with Levodopa-Carbidopa Intestinal Gel therapy through a PEG-J tube due to motor complications, in which, in the context of a clinical study, we successfully and safely administered fecal microbiota transplant through a PEG-J.

Although Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease, the pathogenesis of PD remains not fully understood and therapeutic options are still limited while effective disease modifying strategies are lacking. For these reasons, innovative therapeutic options are needed.

The pathophysiology of PD has been associated with a perturbed intestinal microbiota which might influence the aggregation of α-synuclein and levodopa pharmacokinetics [1]. Exciting data in animal models demonstrate that microbiota interventions influence progression and symptoms of PD via the gut-brain-axis. Transplanting fecal microbiota of a healthy donor (fecal microbiota transplantation, FMT) with the aim of restoring a PD patients' perturbed microbiota appears a promising approach to slow disease progression and relieve symptoms, or to improve the effect of levodopa.

Currently there are no published clinical trials on FMT for PD, although some case series are available and several studies are already registered and ongoing [2].

In the advanced stages of PD, Levodopa/carbidopa intestinal gel (LCIG) infusion is an effective symptomatic treatment for motor fluctuations unresponsive to conventional oral treatment. LCIG infusion is administered by a portable pomp through a percutaneous endoscopic gastro-jejunal tube (PEG-J) and provides stable levodopa concentrations in plasma throughout the day, thereby reducing motor fluctuations by 38–84%. The number of patients with advanced disease and motor complications who use LCGI is growing. These patients represent an eligible population for experimental treatments such as FMT.

Recently in our center we started the FMT4PD study (Fecal Microbiota transplantation for Parkinson's disease - International Clinical Trial Registry Platform (ICTRP)NL9438). In this prospective, self-controlled, interventional, safety and feasibility donor-FMT pilot study with randomization and double blinded allocation of donor feces we aim to assess the feasibility and safety of FMT in PD patients.

We present a case of a person with PD chronically treated with LCIG infusion to which, in the context of the FMT4PD study, we successfully administered FMT through the same PEG-J tube.

The 49-year old patient had a 5-year diagnosis of akinetic rigid PD and had been treated since one year with LCIG therapy through a PEG-J tube due to motor complications. Despite LCIG therapy, the patient showed progressive symptoms, with persistence of dyskinesia and off periods, associated with apathy, depression and constipation.

The patient fulfilled the inclusion criteria and was included in the study. He received pretreatment with vancomycin, bisacodyl, and domperidone, and lavage with macrogol, according to the protocol.

Instead of infusing the screened healthy donor feces through the working channel of a gastroscope, as by the other participants, in order to avoid the risk of dislocation of the PEG-J tube, we administered them directly via the existing PEG-J tube.

In order to connect the PEG-J tube with the syringes used for infusion, a transition connector (Nutricia, Hoofddorp, The Netherlands; Fig. 1B–C) was used in addition to the usual Luer-Lock adapter (Fig. 1A).

The transplanted material consisted of 198 ml fecal suspension derived from 60 g donor feces filtered with mesh size 0.3 mm, which allows the suspension to be infused via the gastroscope.

The levodopa infusion was shortly stopped before the FMT infusion. The duration of the FMT infusion was not significantly different than when infusing via the gastroscope (approximately 10–15 min). After the infusion, the PEG-J tube was flushed with 100 ml of water to clean the tube, and the levodopa infusion was resumed.

The patient was then observed for 2 hours, during which there were no side-effects except for one bowel movement with watery stool, which is typically observed after this procedure.

Follow-up evaluations were performed 1 week and three months after FMT and telephone interviews were conducted at week 2 and week 6. Three days after FMT the patient experienced mild bloating and mild abdominal pain; no other adverse events were reported during the observation period of three months. There were no malfunctions in the LCGI infusion system or changes of medication dosage across the follow-up.

During the follow-up, the patient reported an improvement of motor symptoms with reduced severity of the off periods and reduced severity and duration of the dyskinesia. The MDS-UPDRS III score was reduced from 22 before to 16 and 14 one week and three months after FMT

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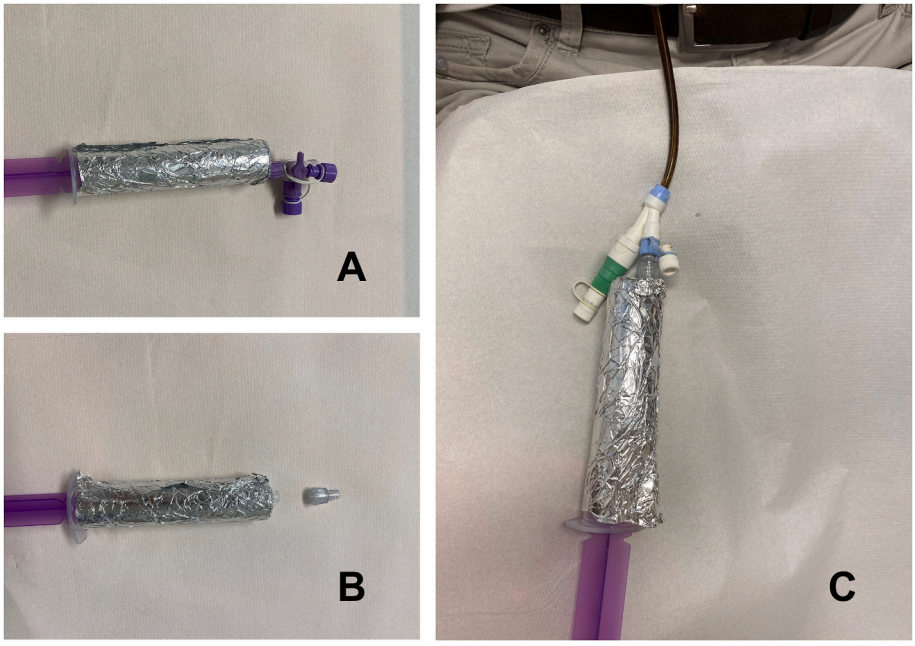

Fig. 1. Illustration of the methods.
A) Standard set-up of Fecal Microbiota transplant administration: the syrinx is connected to a Luer-Lock adapter (purple).
B) Transition connector (transparent) (Nutricia)
C) Complete connection to LCIG PEG-J tube. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

respectively.

The non-motor symptoms were also improved, including slightly improved defecation pattern with softer stool and less anal pressure up to 3 months after FMT. One week and three months after FMT scores in the following scales were reduced with respect to baseline: MDS-UPDRS I (from 6 to 2); MDS-UPDRS II (from 19 to 11 and 8); MDS-UPDRS IV (from 9 to 6 and 5).The procedure described here to administer donor feces via the PEG-J in patients with LCGI is less invasive and easier compared to the administration via a newly placed nasoduodenal tube, gastroscope or colonoscope. Moreover, although procedure-related FMT side effects are rare with administration via the gastroduodenal route (4% of patients report regurgitation or sore throat), some serious adverse events such aspiration have also been reported [3]. The procedure-related adverse events and risk of aspiration could be thus avoided in PD patients with a LCGI by infusing feces via the in situ PEG-J tube; this would also minimize the risk of dislocation of the PEG-J tube.

The PEG-J tube of LCGI has been previously used for enteral feeding by means of enteral nutrition adaptor without complications [4,5]. For FMT we used another adaptor than previously reported for enteral feeding [4]. Of note, there were no problems of potential interference with the efficacy of LCGI, which was stopped only shortly around the procedure, without the patient noticing any change in PD-symptoms. The patient reported only mild and transient gastrointestinal side effects, which fall within what is commonly expected after this procedure.

This case illustrates that infusing FMT through the PEG-J tube is technically feasible, safe, and more patient-friendly, and should be considered in patients with LCIG. Future double-blind, randomized clinical trials on large PD cohorts are needed to confirm the safety and the potential benefits of FMT, also at earlier disease stages.

Author contributions

VOC: acquisition of data, or analysis and interpretation of data; drafting the article, final approval of the version to be submitted.

EMT: interpretation of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

JvP: interpretation of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

EJK: interpretation of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

JJK: interpretation of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

AEvdMdJ: interpretation of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

MPB: interpretation of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

JJvH: interpretation of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

MFC: conception and design of the study, analysis and interpretation of data, revising the article critically for important intellectual content, final approval of the version to be submitted.

Ethical considerations

The Medical Research Ethical Committee Leiden-The Hague-Delft approved the FMT4PD trial and waived the need for an additional formal approval for publication of this case report. The patient provided a written informed consent for participation in the study and additionally for publishing this case report. The study is conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO).

Declaration of competing interest

VOC: no conflict of interest for current work.

EMT: no conflict of interest for current work. Report an unrestricted research grant of Vedanta Biosciences (https://www.vedantabio.com/) and a consultancy fee from Finch therapeutics, all unrelated to this work.

JvP: no conflict of interest for current work. Declares a research grant from MSD (paid to institution), unrelated to this work.

EJK: no conflict of interest for current work. Report an unrestricted research grant of Vedanta Biosciences (https://www.vedantabio.com/) unrelated to this work.

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References

[1] A.H. Tan, S.Y. Lim, A.E. Lang, The microbiome-gut-brain axis in Parkinson disease - from basic research to the clinic, Nat. Rev. Neurol. 18 (8) (2022) 476–495.

[2] K.E.W. Vendrik, et al., Safety and Feasibility of Fecal Microbiota Transplantation for Parkinson's Disease Patients: a Protocol for a Self-Controlled Interventional Donor-FMT Pilot Study, medRxiv, 2022, p. 2022, 05.23.22274942.

[3] E.M. Terveer, et al., Faecal microbiota transplantation for Clostridioides difficile infection: four years' experience of The Netherlands Donor Feces Bank, United Europ. Gastroenterol. J. 8 (10) (2020) 1236–1247.

[4] A. Bernier, et al., Enteral feeding using levodopa-carbidopa intestinal gel percutaneous endoscopic gastrostomy tube, Mov Disord Clin. Pract. 4 (5) (2017) 787–788.

[5] F. Bove, et al., Enteral feeding in Parkinson's patients receiving levodopa/carbidopa intestinal gel, Parkinsonism Relat. Disorders 42 (2017) 109–111.

Vlada O. Chernova
Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands
Netherlands Donor Feces Bank, Leiden University Medical Center, Leiden, the Netherlands

Elisabeth M. Terveer, Joffrey van Prehn
Netherlands Donor Feces Bank, Leiden University Medical Center, Leiden, the Netherlands
Department of Medical Microbiology, Leiden University Medical Center, Leiden, the Netherlands

Eduard J. Kuijper
Department of Medical Microbiology, Leiden University Medical Center, Leiden, the Netherlands

Josbert J. Keller
Netherlands Donor Feces Bank, Leiden University Medical Center, Leiden, the Netherlands
Department of Gastroenterology and Hepatology, Leiden University Medical Center, the Netherlands
Department of Gastroenterology, Haaglanden Medical Center, The Hague, the Netherlands

Andrea E. van der Meulen-de Jong
Department of Gastroenterology and Hepatology, Leiden University Medical Center, the Netherlands

Martijn P. Bauer
Department of General Internal Medicine and Endocrinology, Leiden University Medical Center, Leiden, the Netherlands

Jacobus J. van Hilten
Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands

M. Fiorella Contarino*, on behalf of the
Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands
Department of Neurology, Haga Teaching Hospital, The Hague, the Netherlands

* Corresponding author.
E-mail address: M.F.Contarino@lumc.nl (M.F. Contarino).