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Chapter 5

Fecal Microbiota Transplants as a Treatment Option for Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disease with an unknown cause, high prevalence, and no effective therapy. Alterations in gut microbiota composition and function have been found in PD, which could influence the gut-brain axis. Several mechanisms have been proposed and are investigated to explain the link between gut microbiota and PD. In model systems and in individual case reports, modulation of gut microbiota has been associated with improvement of PD. A safe and effective way of gut microbiota manipulation is fecal microbiota transplant (FMT). FMT is used successfully for treatment of recurrent gastrointestinal infections as well as other indications. We advocate randomized clinical trials with FMT as a treatment option for PD.

Keywords: Parkinson's disease, gut microbiota, fecal microbiota transplantation, clinical trial

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease which is accompanied by gastrointestinal dysfunction in 80% of patients [1]. PD has a high prevalence, affecting almost 2% of people over the age of 80 [2] and is currently incurable, although a variety of therapies are available to treat the symptoms [3]. In the last decade, the hypothesis has gained support that PD starts in the gut and spreads through the sympathetic and parasympathetic nervous systems to the substantia nigra and the central nervous system [4, 5]. More recently, it has been recognized that these brain-gut axis interactions in PD may be essentially influenced by gut microbiota.

In this opinion paper we want to encourage the design and initiation of clinical trial using fecal microbiota transplantation (FMT) as a therapeutic intervention for PD. We first elaborate on the evidence for the role of gut microbiota in PD, followed by a short discussion of FMT, and conclude with arguments to support the setup of clinical studies.

2. Alterations in gut microbiota composition in PD patients

A causal link between *Helicobacter pylori* infections and PD has been suggested for a long time [6, 7]. Even before the discovery of *H. pylori*, the connection between PD and gastric ulcers has already been reported [8, 9], and it was found that duodenal and gastric ulcers often preceded the onset of PD by many (10–20) years. Since then, numerous studies have reported that the incidence of small intestinal bacterial overgrowth is higher in PD patients than in healthy controls [10–13] that PD patients have higher *H. pylori* antibody levels [14] and that *H. pylori* infections are more prevalent in PD patients than in control groups [15, 16].

Several recent studies show that PD is also preceded or accompanied by changes in the abundance of other bacterial groups. It thus has been found that PD patients harbor lower concentrations of *Prevotella* bacteria [17–21], and the number of Prevotella bacteria is negatively correlated with the severity of PD symptoms [20]. Increased numbers of Enterobacteria are found in PD patients [17, 22], and the relative abundance of Enterobacteriaceae is positively associated with the severity of postural instability and gait difficulty [20]. In another study, significantly altered abundances of the Bifidobacteriaceae, Christensenellaceae, (Tissierellaceae), Lachnospiraceae, Lactobacillaceae, Pasteurellaceae, and Verrucomicrobiaceae families were found in PD patients [23]. In PD patients, *Lactobacillus* numbers were found to be higher and *Clostridium coccoides* plus *Bacteroides fragilis* numbers were lower compared to healthy controls, all contributing to a distinct composition of gut microbiota in PD [23]. Concentrations of hydrogen-producing bacteria were also higher in PD patients [24]. It has been suggested that cyanobacteria can be a source of neurotoxins that are related to PD [25, 26]. Molecular analysis of the gut microbiome has shown that 48 operational taxonomic units (OTU's) of the gastrointestinal microbiota have differential abundancy in PD patients versus healthy controls. Some of these OTUs were significantly related to motor symptoms and depression in PD patients. Functional analysis of gut microbiota also shows differences between PD patients and controls. Increased urinary indoxyl sulfate, a marker of intestinal dysbiosis, is found in PD patients [27].

Besides gut microbiota, microbiota at other ecological niches may also differ. The oral microbiota of PD patients and control subjects had differences in beta diversity and abundances of individual bacterial taxa [28].

3. Mechanistic link between gut microbiota and PD

Various studies suggest that gut microbiota do not just correlate with PD but that PD may actually start within the gut, with gut microbiota as a causative agent. The fact that

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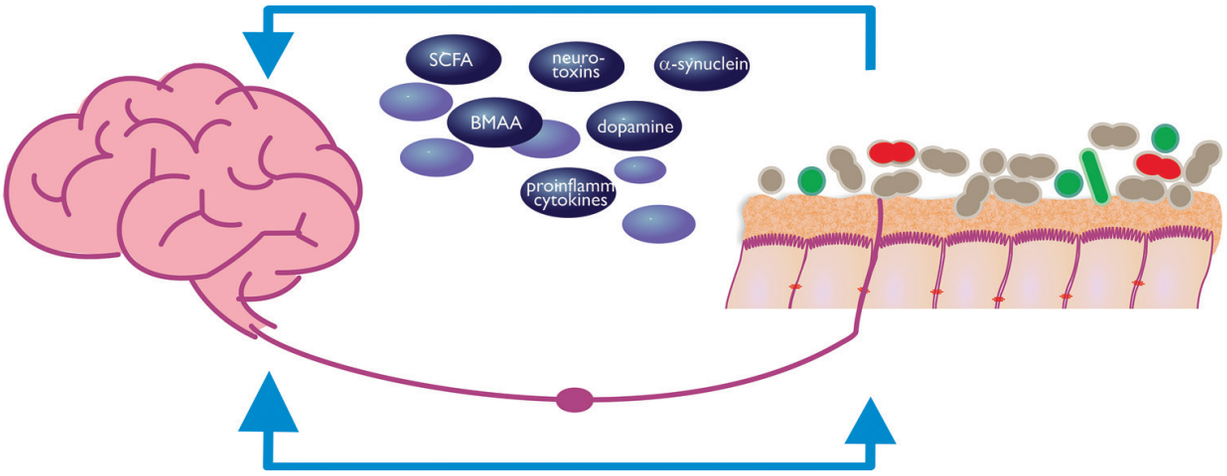

Figure 1. Potential mechanisms of interaction between gut microbiota and the brain in Parkinson's disease.

gastrointestinal dysfunction often precedes motor symptoms by 10–15 years already strongly suggests a role for gut microbiota. In addition, epidemiological studies in Sweden show that gotomy drastically reduces the risk of developing PD [29, 30], suggesting the nervus vagus as vagotomy a route via which PD may travel from the gut to the CNS (see also **Figure 1**). Sampson and co-workers found that fecal microbiota transplants from human PD patients in a mouse model of PD enhances physical impairments, compared to microbiota transplants of healthy donors [31]; a finding which may indicate that alterations in the human microbiome represent a risk factor for PD.

Various mechanisms and mediators have been proposed for the relation between gut microbiota and development of PD (**Figure 1**). PD may be initiated by toxins produced by the gut microbiota or because of a failure to produce key essential neuronal dopamine specific nutrients or enzymes, which are required by dopamine-producing cells [32]. For example, decreased numbers of *Prevotella* are linked to decreased production of important micronutrients like short chain fatty acids, thiamine and folate [19], whereas gut microbes like *Bacillus* spp. are known to produce dopamine [33]. Cyanobacteria are believed to produce the excitotoxin β-N-methyl amino-L-alanine (BMAA) which has been found to be increased in the brain of PD patients [26].

Since PD is assumed to be characterized by synucleinopathy, another potential mechanism may be that alpha-synuclein produced by gut microbiota spreads upwards from the gut along vagal nerve fibers [34, 35].

It has also been suggested that gut dysbiosis leads to chronic low-grade inflammation in the gut, which may ultimately trigger blood-brain barrier leakage, immune cell activation and inflammation, and ultimately neuroinflammation in the CNS [36]. Increased intestinal permeability has been described in PD, resulting in penetration of ***E. coli*** in the intestinal mucosa as well as oxidative stress and increased enteric α-synuclein levels [37].

A more general explanation which has been suggested is that the composition of the gut microbiota changes over the human lifespan, which may play a role in age-related diseases [38].

4. Therapeutic interventions in the microbiome as a treatment option for PD

The effect of interventions in the microbiome on PD has been demonstrated in mouse models. Administration of the antibiotic minocycline prevents nigrostriatal dopaminergic neurodegeneration in a mouse model of PD [39]. Sampson et al. have reported that antibiotic treatment of gut microbiota ameliorates physical impairment, whereas microbial recolonization, or the oral administration of specific microbial metabolites, promotes pathophysiology in a mouse model of PD [31].

In addition, a number of recent clinical studies in human patients show that various treatments of either gastrointestinal dysfunction or gut microbiota composition have a beneficial effect on PD. For example, maintenance laxative usage was associated with apparent stemming of the temporal increase in rigidity in PD [40]. PD patients who were treated for *Helicobacter pylori* infections experienced prolonged (2–3 years) improvement of motor symptoms compared to a control group [41–43]. Furthermore, *H. pylori*-positive PD patients have significantly poorer clinical scores as compared to *H. pylori*-negative PD patients [16]. Twelve weeks after treatment of the *H. pylori* infection, improvements in levodopa onset time and effect duration were observed, as well as better scores in motor performance and quality of life measures [16]. A single non peer-reviewed case study described a PD patient that became symptom-free after receiving a fecal microbiota transplant [44].

Other (non-PD related) effects of gut microbiota composition on the nervous system have also been reported. For example, a case report of three MS patients records dramatic improvement of neurological functions after fecal microbiota transplantation [45]. Significant improvement of myoclonus dystonia symptoms was observed in a female patient after receiving fecal microbiota transplantation [46]. Microbiota management via probiotic supplementation significantly reduced overall cognitive reactivity to sad mood in healthy participants of a placebo controlled, randomized clinical trial [47]. Finally, it has been demonstrated that gut microbiota from depressed patients could induce depression-like behavior in microbiota-depleted rats [48].

5. Fecal microbiota transplantation

Given the evidence described above, modification of the gut microbiota could be a valid and attractive treatment option for PD. The most powerful way to modify the gut microbiota is via a fecal microbiota transplantation (FMT). FMT is a relatively new treatment option for gut dysbiosis-related diseases; mainly *Clostridium difficile* infections, for which it is highly successful with cure rates of over 90% [49, 50]. FMT involves transfer of stool (containing both microbes and the bioactive molecules they produce) from a healthy donor to a patient (see [50] for a review). More recently, the therapy is also offered via orally administered capsules containing a screened sample of donor microbiota in freeze-dried form, which makes the treatment even safer and less invasive.

As of December 2017, nine stool banks have been installed worldwide [51]; the most recent ones being in Madrid and Hong Kong. One of them, OpenBiome, founded by Harvard and MIT microbiologists, also offers treatment via capsules (www.openbiome.org). For the time being, the stool banks only offer treatments to patients suffering from recurrent *C. difficile* infections. However, they also cooperate in studies on other diseases. FMT is considered the most cost-effective treatment option in the treatment of recurrent *C. difficile* infections [52].

FMT is a safe treatment, provided it is performed in a clinical setting and with the use of screened donor feces. Several clinical studies report mild side effects or no side effects at all [49, 53–57]. Even in high-risk groups, FMT was found to be safe: no adverse effects were found in cancer patients [58] as well as in solid organ transplant recipients [59]. A review by Baxter and Colville [60] on the adverse events associated with FMT concludes that "The vast majority of adverse events of FMT appear to be mild, self-limiting and gastrointestinal in nature." As for every new treatment, potential long-term negative effects are unknown.

It is important to note that outside clinical settings, there are risks associated with FMT. There is a growing "do it yourself" movement around FMT, where many people are experimenting with FMT as a last resort option for incurable diseases like PD. The Internet is teeming with discussion fora on which people exchange the best DIY techniques, which may involve kitchen blenders and various pumping devices. In a recent review of information regarding FMT on social media, it is concluded that "there is a vast amount of information available about FMT through social media that has the potential for causing harm" [61]. Donor screening does not take place if and when people perform the treatment themselves. This may lead to patients being put at risk to infections or perforations as a result of unprofessional treatment. For example, it has been reported that a child developed aspiration pneumonia as a result of the entrance of fecal matter in the bronchial system after the parents performed FMT without medical supervision [62]. Another case study describes a patient who developed a cytomegalovirus infection, after performing home FMT using unscreened donor feces [63]. These examples underline the importance of FMT to be provided in a clinical setting under controlled conditions.

6. Arguments in favor of an RCT

Given the above considerations, there are strong arguments for initiating a clinical study on the effect of FMT on PD patients.

a. FMT could potentially provide a treatment option for a disease that affects millions of people worldwide, is currently incurable, and is expected to become more prevalent as a result of an aging population. Given the idea that age-related diseases may be related to aging of the gut microbiota [38], using material from young donors may be especially beneficial.

b. FMT is considered safe, even in high-risk groups.

c. FMT is inexpensive

d. Safe, screened donor feces material can easily be obtained via one of the existing stool banks. A control group can be treated with autologous feces. Alternatively, OpenBiome offers the possibility to assist in designing a setup and provide orally administered capsules.

e. The best way to stem the DIY movement and prevent dangerous situations as a result of people experimenting with FMT, is to offer a safe and controlled alternative in a hospital setting or to develop safe protocols for home-administered fecal transplantations in a health care setting [49, 56].

So far, only one clinical trial has been initiated (ClinicalTrials.gov Identifier: NCT03026231) [64]. However, we argue that more clinical trials are warranted. The argument that the mechanism via which microbiota affect PD is still poorly understood [65–67] should not block further application of FMT. Aspirin, for example, has been effectively applied for centuries before the mechanism was finally elucidated in the 1970s. Likewise, levodopa has been used for the treatment of PD for decades before its mechanism was unraveled. It may take years before the pathways via which gut microbiota affect the brain are unraveled, and meanwhile a potentially promising treatment option remains unexplored. Given the relative ease and safety of the treatment and the fact that it is already applied on a routine basis to *C. difficile* patients, including these in high-risk groups like cancer patients or organ transplant recipients, we advocate more clinical studies. Moreover, a clinical study on FMT in PD could lead to a better understanding of the relation between microbiota and the nervous system.

Finally, several authors have already pointed out that FMT is a very promising treatment option for PD. As stated by Mulak and Bonaz: "The close relationship between gut dysbiosis, intestinal permeability and neurological dysfunction suggests that the gut microbiota modification may provide a promising therapeutic option in PD" [68]. Fang also stated that "Microbiota-based interventions that play a regulatory role in the gut microflora exhibit therapeutic potential" (for PD) [69]. Finally, Scheperjans in 2016 comments in an opinion article: "If this endeavor is successful, we may end up with completely new therapeutic approaches that could hopefully turn the ship around toward effective disease modification or even prevention" [70].

It took a long time before FMT was generally accepted as a treatment option for *C. difficile* infections because physicians were skeptical about this "19th century technique" or wary of any adverse effects [71]. It is unknown how many people died (or are still dying) unnecessarily from otherwise untreatable *C. difficile* infections or had their colons removed, while it was already known that FMT could cure them. The prognosis has finally changed for the betterment for these patients. In 2010, a study on the effect of FMT on recurrent *C. difficile* infection in Amsterdam was prematurely terminated because the data and safety monitoring board of the hospital considered it unethical to withhold the treatment from the control group [55]. FMT thus is on the way to becoming a standard treatment for recurrent *C. difficile* infections in most developed countries.

Given the fact that FMT is a very promising treatment for PD, is safe, not invasive (especially using orally administered capsules) and inexpensive, and people are exposing themselves

to risks by performing the treatment themselves without medical supervision, it could be argued that not starting a trial on the effect of FMT on PD would be similarly unethical. The roadmap is clear, and it now just needs to be taken.

Conflict of interest

The authors have no conflict of interest to declare.

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