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Review Article

Faecal Microbiota Transplantation (FMT): An Effective Therapeutic Agent for Parkinson's Disease

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Abstract:

Parkinson's disease is an autosomal-dominant neurodegenerative disease of the senior citizens worldwide. The slow progression of the disease affects motor and non-motor functions of the nervous system. Available pharmacotherapy, Surgery, Ayurvedic treatment and FMT only reduces the intensity of the symptoms but not completely wipe out the disease. Among them FMT proves to be the best since the side effects of the antibiotics could be avoided in elders. Few clinical trials as well as studies in animal models give a promising result using FMT. High-quality clinical trials with larger sample sizes demand to qualify FMT as widely recommended therapeutic measures.

Keywords: alpha-synuclein fibrils; pharmacotherapy; surgery; ayurvedic treatment; fmt

Introduction

Parkinson's disease (PD) is a neurodegenerative disease which severely affects quality of life of the patient with a high rate of morbidity expressing four motor defects such as tremor, slowness of movements, stiffness and postural instability. The disease was comprehensively described by James Parkinson in 1817 (An Essay on the Shaking Palsy). But the review of much early literature of Ayurveda dating back as far as 5000 BC would show that syndrome strikingly similar to Parkinsonism mentioned as "Kampa vata", was already known. The non motor defects observed are dysautonomia (constipation, vomiting, orthostatic hypotension, abnormal sweating and dysuria) as well as mental disorders (depression, anxiety disorder, visual hallucination and dementia). Loss of dopaminergic neurons in the substantia nigra leads to motor defects but the non-motor defects are due to loss of neurons in the brain regions affecting non dopaminergic neurotransmitter systems. The above said defects are the result of abnormally aggregated α-synuclein fibrils (Lewy bodies) as well as Lewy neurites in the neuronal cells. Alpha-synuclein "natively unfolded protein"is a small protein made up of 140 amino acids encoded by the SNCA gene found in 1997. A single miss-sense mutation in this gene gave rise to an autosomal-dominant form of PD [1]. α-Synuclein may be modified by phosphorylation, oxidation, nitrosylation, glycation, or glycosylation. This cascade of events, starting from the natively unfolded protein and culminating in the mature fibril formation is collectively termed α-synuclein aggregation [2]. In addition, oxidative stress, autophage dysfunction, proteostasis failure, vesicular trafficking defects and neuroinflammation also trigger loss of these neurons. The synapsis was observed to be the route for α-synuclein fibrils to other neuronal cells. This α-synuclein fibrils could be observed in cerebral cortex, the olfactory bulb, autonomic nervous system, salivary glands, skin and intestine [3]. Several processes have been implicated in PD, including mitochondrial dysfunction, defective protein clearance mechanisms, and neuroinflammation, but the way in which these factors interact remains incompletely understood [4]. In the course of Parkinson's disease (PD), the enteric nervous system (ENS) and parasympathetic nerves are amongst the structures earliest and most frequently affected by alpha-synuclein pathology [5]. Eight million people suffer with age related PD worldwide, but despite more than 200 years of research, its underlying causes are not fully understood [6]. Normally the disease develops after the age of 55, cases of getting the disease in their 30s and 40s is also observed, such as in the case of actor Michael J. Fox, who was diagnosed at age 30 [7]. Our review aims to consolidate the available information on clinical trials and study in animal models till today focussing to use FMT as a treatment modality for this disease and further explore the potential usage of FMT in treating constipation, motor, and non-motor symptoms in patients suffering with PD.

Secondary Parkinsonism

Secondary Parkinsonism is a disorder with symptoms similar to Parkinson's, but medication side effects are the causal factor for different neurodegenerative disorders, illness or brain damage. Quite similar to PD, in the expression of the disease, fortunately the risk of developing secondary Parkinsonism may be minimized by careful medication management, particularly limiting the usage of specific types of antipsychotic medications. At the same time, secondary Parkinsonism does not seem to respond as effectively to medical therapy as PD [7].

Treatments so far available:

Parkinson's patients are treated with medications to relieve the symptoms of the disease by stimulating the remaining cells in the substantia nigra to produce more dopamine (levodopa medications) or by inhibiting some of the acetylcholine that is produced (anticholinergic medications) to restore the balance between the chemicals in the brain. Devising an personalized treatment plan is indispensable and to work closely with the doctor due to vast variations linked with side effects of the class of medication as well as patient. Levodopa, developed more than 30 years ago, regarded as the gold standard for PD therapy though it does not stop or slow the progression of the disease. Side effects may include nausea, vomiting, dry mouth and dizziness. Dyskinesias (abnormal movements) may occur when the dose is increased. In some patients, levodopa may cause confusion, hallucinations or psychosis. Dopamine Agonists that mimic the role of chemical messengers in the brain, generally have more side effects than levodopa, so that is taken into consideration before doctors prescribe dopamine agonists to patients. Side effects may include drowsiness, nausea, vomiting, dry mouth, dizziness and feeling faint upon standing. These common symptoms usually resolve over several days, though some patients, dopamine agonists may cause confusion, hallucinations or psychosis like Levodopa. Entacapone and tolcapone are medications that are used to treat fluctuations in response to levodopa. COMT, an enzyme that metabolizes levodopa in the bloodstream when blocked more levodopa can penetrate the brain to effectiveness of treatment is practiced. Tolcapone is prescribed only for patients when symptoms are not adequately controlled by other medications due to potentially serious toxic effects on the liver. Side effects may include diarrhoea and dyskinesias. Selegiline slows down the activity of the enzyme monoamine oxidase B (MAO-B), the enzyme that metabolizes dopamine in the brain, delaying the breakdown of naturally occurring dopamine and dopamine formed from levodopa. It has been observed that, when taken in conjunction with levodopa, selegiline may enhance and prolong the effectiveness of levodopa. Side effects may include heartburn, nausea, dry mouth and dizziness. Confusion, nightmares, hallucinations and headache occur less often and should be reported to the doctor. Trihexyphenidyl, benztropine mesylate, biperiden HCL and procyclidine blocks acetylcholine whose effects become more pronounced when dopamine levels drop. These drugs are prescribed to solve tremor and muscle rigidity, as well as in reducing medication-induced Parkinsonism. Anticholinergic drugs are generally not recommended for extended use in older patients due to complications and serious side effects. Side effects may include dry mouth, blurred vision, sedation, delirium, hallucinations, constipation and urinary retention. Amantadine an antiviral medication that also helps reduce symptoms of PD (unrelated to its antiviral components) in the early stages of the disease along with an anticholinergic medication or levodopa, proved to be effective in treating the jerky motions associated with PD. Side effects may include difficulty in concentrating, confusion, insomnia, nightmares, agitation and hallucinations. Amantadine may cause leg swelling as well as mottled skin, often on the legs.

Surgery

For many patients with PD, medications are effective for maintaining a good quality of life. Based upon the type and severity of symptoms and the deterioration of a patient's quality of life, surgery may be the next step. stereotactic surgery, pallidotomy, thalamotomy, Deep Brain Stimulation (DBS) are performed depending on the PD patients' condition. Embryonic stem cell research is focussed to produce dopamine neurons from human stem cells in the laboratory for transplantation into humans with PD. The successful generation of an unlimited supply of dopamine neurons may offer hope for PD patients at some point in the future. With this technique researchers are anticipating an ability to prompt these cells, which can theoretically be manipulated into a building block of any of the body's tissues, to replace those lost during the disease's progression. Adult stem cells from bone marrow may be utilized in a similar way to achieve the results. Human studies of so-called neurotrophic factors are also being explored. In animal studies, this family of proteins has revived dormant brain cells, caused them to produce dopamine, and prompted dramatic improvement of symptoms [7].

Ayurvedic treatment for Parkinson's disease

Ayurvedic treatment of PD was mentioned in the literature including its treatment. It includes the treatment with the seeds of a plant containing therapeutic levels of what is today known as levodopa apart from several other preparations. According to Ayurveda, most of the diseases of the Vata are essentially the conditions of degenerative diseases of the nervous system. The treatment of 'kampa vata' consists of both internal and external administration of drugs in different forms aimed to reverse the 'vata' imbalance [8;9].

Pathogenic role of Gut bacteria in PD

In the recent past the gut microbiota is found to be a key regulator [10] of many functions as well as disease conditions leading to the pathogenesis of several gastrointestinal, extraintestinal disorders and also linked to neurodegeneration through the gut microbiota brain axis, opening the possibility for new microbiota-based therapeutic options. A detailed analysis of the gut microbiota revealed the exact degree of gut dysbiosis in about 197 PD patients, and the data were compared to that from 130 healthy controls and the statistical analysis revealed there was significant dysbiosis in patients with PD [11]. Keshavarzian *et al.,* (2015) observed that the microbiota of the faecal material as well as mucosa was significantly different from PD patients compared to controls. Putative, "anti-inflammatory" butyrate-producing bacteria from the genera *Blautia*, *Coprococcus*, and *Roseburia and Faecalibacterium* were significantly more abundant in faeces of controls than PD patients. On the other hand, "proinflammatory" *Proteobacteria* of the genus *Ralstonia* were significantly more abundant in mucosa of PD than controls. The authors also indicated that a large number of genes involved in metabolism were significantly lower in the PD faecal microbiome, whereas genes involved in lipopolysaccharide biosynthesis and type III bacterial secretion systems were significantly higher in PD patients [12]. A study by Sampson *et al*., (2016) tested the role of gut bacteria in the regulation motor symptoms and pathophysiology of PD, more specifically alpha-synuclein (α-synuclein) dysfunction, in a mouse model. In order to find out the link between PD and gut microbiota, FMT was performed from PD patients into mice. To their surprise significant motor impairment was observed in mice. In addition, they also demonstrated that the presence of specific microbes or even microbial metabolites is enough to promote α-synuclein pathology, neuroinflammatory changes, and characteristic motor and gastrointestinal dysfunction in the mouse model [13]. In another study Segal *et al.,* (2021) increased abundance *Akkermansia*, *Lactobacillus*, *Enterobacteriaceae*, *Bifidobacterium* and decreased abundance of *Prevotella Faecalibacterium*, and *Blautia* was observed in PD patients. Inflammation-induced misfolding of α-Syn and development of PD pathology could be due to proinflammatory dysbiosis [14]. Scheperjans *et al.,* (2015) compared the faecal microbiota of 72 PD patients and 72 control subjects by pyrosequencing the V1-V3 regions of the bacterial 16S ribosomal RNA gene. On average, the abundance of *Prevotellaceae* in faeces of PD patients was reduced by 77.6% as compared with controls. The relative abundance of *Enterobacteriaceae* was positively associated with the severity of postural instability and gait difficulty. These findings suggest that the intestinal microbiome is altered in PD and is related to motor phenotype [5].

Factors for the development of α-synuclein aggregation

Recently, the researchers at the University of Helsinki have demonstrated that certain strain of *Desulfovibrio* bacteria that absorbs toxic sulphate are

responsible for the prognosis of the disease [15]. Roughly only 10% is contributed by individual gene mutation. *Desulfovibrio*, genus of gram-negative bacteria is commonly found in aquatic environments with high quantity of organic material as well as waterlogged soils species correlated with the severity of PD. *Desulfovibrio* bacteria produce hydrogen sulphide and lipopolysaccharide, and several strains synthesize magnetite, all of which likely induce the oligomerization and aggregation of α-synuclein protein. The substances originating from *Desulfovibrio* bacteria likely take part in Alpha-synuclein misfolding resulting in pathogenesis of PD [15]. Murros *et al.,* (2021) found that worms *Caenorhabditis elegans* model fed *Desulfovibrio* from AD patients had significantly more and larger alpha-syn aggregates than worms fed bacteria from healthy subjects or worms fed *Escherichia coli* strains. The study group also suggested that by preventing the environmental exposure to the bacterial through a carrier, the disease burden could be reduced**.** They also anticipated that once the *Desulfovibrio* bacteria are eliminated from the gut, α-synuclein aggregates are no longer formed in intestinal cells, from which they travel towards the brain via the vagus nerve like prion proteins. Many people harbour this bacterial in the gut with or without AD. Scientific validation is wanting on the difference between the bacteria harbouring in healthy and PD patients [16; 17].

FMT in the management of PD

Currently, FMT is explored as a therapeutic option for a wide variety of gastrointestinal disorders as well as non-gastrointestinal disorders [18; 19; 20;21]. At present the treatment is limited to pharmacotherapy and surgery with the resurgence of most symptoms discussed earlier in this review. Out of these, FMT has been one of the most promising approaches since, strong evidence for the gut dysbiosis in the pathogenesis of PD is available and it is imperative to consider the various methods that bring about "eubiosis" or restore the normal microbiota of the gut. Jena R *et al.,* (2021) summarised the details of the information on the clinical trials and studies in animal models performed to treat the disease with FMT [22]. Xiao-Yi Kuai *et al.,* (2021) conducted a study with 11 PD patients were found to reduced constipation intensity with FMT treatment [23]. In another study Arik Segal et al., (2021) FMT infused via colonoscopy involving 6 PD patients, was observed to be safe and resulted in improvement of PD motor and non-motor symptoms, including constipation, at 6 months. Further research is needed to assess longer-term maintenance of efficacy and safety, including in large scale randomized controlled trials [14]. DuPont *et al.,* (2023) performed a similar study found from their double-blind placebo-controlled pilot study in 12 PD patients suffering with constipation for 12 months with FMT, increased diversity of the intestinal microbiota that was associated with reduction in constipation and improved gut transit and intestinal motility. Faecal microbiota transplantation administration improved subjective motor and non-motor symptoms also. Significant increase in the selective families within the phylum *Firmicutes* but decrease in the proportion of microbiota belonging to *Proteobacteria* is an observation to focus in treatment of constipation. These conclusions suggests a therapeutic potential for reconstructing the gut microbiota of PD patients and improving their motor and non-motor symptoms [24]. In mouse model also FMT could protect mice against PD via suppressing α-syn expression[25].

Conclusion

With limited clinical trials it was shown that FMT is an effective treatment for PD however, further research is needed to assess longer-term maintenance of efficacy and safety in large scale randomized controlled trials, preferably in patients with moderate to severe PD patients. The outcome of the high-quality clinical trials with larger sample sizes required to qualify FMT as a widely recommended therapeutic measure. It is also needed to establish the routes of administration, standardized protocols and the adverse effect profile of FMT as well.

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