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P D Gupta *

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Review Article

Promising role of Faecal transplant therapy on Sclerosis

K Pushkala [1], P D Gupta [2]*

[1]Former, Associate Professor, S. D. N. B. Vaishnav College for Women, Chennai, India.

[2]Former Director Grade Scientist, Centre for Cellular and Molecular Biology, Hyderabad, India.

***Correspondence Author:** P D Gupta, Former Director Grade Scientist, Centre for Cellular and Molecular Biology, Hyderabad, India.

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Abstract:

Neurodegenerative diseases are poorly understood, and have practically no treatment options available. It seems gut microbiota play a significant role in management of neurological disorders. It was observed that the composition of the microbiota is altered in sclerosis (MS) patients compared with healthy people and the human gut microbiota regulate intestinal permeability in a multifactorial manner. Recently, when healthy human faecal microbiota was transplant in patients suffering with sclerosis showed promising improvement. Therefore FMT may open new vistas for therapeutics of the MS.

Keywords: multiple sclerosis; amyotrophic lateral sclerosis; gut microbiota dysbiosis; rebiosis

Introduction

Multiple sclerosis (MS)

Neurodegenerative diseases are highly prevalent but poorly understood, and only with few treatment options despite decades of intense research are available. Multiple sclerosis (MS) is an autoimmune, inflammatory, demyelinating disease of the central nervous system influenced by genetic susceptibility and environmental factors such as smoking, geographical location, vitamin D intake, and infection with Epstein–Barr virus[1]. This disabling brain and spinal cord disease attacks the myelin sheath resulting in the impaired communication problems between the brain and the rest of the body due to the permanent damage or of the deterioration of the nerve fibres. Severity of the disease depends on the location of damaged nerve fibre in the central nervous system, for example, some patients have problems with mobility and gait. Long periods of remission without any new symptoms depending on the type of MS are also common. Numbness or weakness in one or more limbs that typically occurs on one side of the body at a time, tingling, electric-shock sensations that occur with certain neck movements, especially bending the neck forward (Lhermitte sign), lack of coordination, unsteady gait or inability to walk, partial or complete loss of vision, usually in one eye at a time, often with pain during eye movement, prolonged double vision, blurry vision, vertigo, problems with sexual, bowel and bladder function, fatigue, slurred speech, cognitive problems and mood disturbances are the common symptoms. MS expresses as a clinically isolated syndrome (CIS) in the beginning with various neurological symptoms for a few days, usually followed by a relapse and remission.

Some patients have a gradual onset and steady progression of signs and symptoms without any relapses early in the disease, called as s primary-progressive MS. On the other hand in secondary-progressive MS at least 20% to 40% of the patients eventually develop a steady progression of symptoms, with or without periods of remission. Within 10–15 years, relapsing-remitting MS (RRMS) typically progresses to secondary-progressive MS (SPMS), as symptoms shift from a pattern of relapses to gradual progression without remission [2].

Currently, permanent therapeutic modality is wanted for cure though, symptomatic treatment is given for relief from the development of primary symptoms and to prevent the subsequent development of secondary or tertiary symptoms. Therefore, potential new disease-modifying treatments are needed. Since, evidence suggests that composition of the microbiome is altered in MS patients compared with healthy people, faecal transplant therapy (FMT) could be taken advantage of in therapeutics, like few other neurological diseases such as Alzheimer's, Huntington's disease, Parkinson's disease, Autism spectrum disorder etc. [3-7].

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is also a neurodegenerative disease resulting in loss of upper and lower motor neurons, leading to gradual loss of motor function and cognitive and behavioural changes associated with frontotemporal dementia. The exact mechanism underlying the disease is still an enigma; though a toxic protein aggregation, mitochondrial dysfunction, excitotoxicity and other cellular and molecular processes have been implicated with its development.

This fatal disease is within 2–4 years of diagnosis and currently has drugs to extend life expectancy by 3–6 months or slow the rate of decline in patients. ALS is associated with altered gut microbiome composition in humans and animal models [8:9]. Only one report of a 48-year-old female with ALS who experienced constipation, gradual muscle fasciculation and amyotrophy in her left leg, later spreading to her right leg and arms is existing. Her long-term treatment plan of washed microbiota transplantation (WMT)—a modified form of FMT improved her bowel function and ALS symptoms. Several months later, she was prescribed antibiotics due to a scalp injury and her condition rapidly deteriorated. However, a promising result was witnessed after a re-introduction of the WMT routine and her ALS symptoms once again stabilized [10].

Gut microbiota and Sclerosis

Evidence suggests that the composition of the microbiome is altered in MS patients compared with healthy people. It has been proposed that these changes may alter gut permeability, allowing toxins to travel outside the gut and trigger autoimmune responses, exacerbating MS symptoms. It has been established that human gut microbiota regulate intestinal permeability in a multifactorial manner. Therefore theoretically, increased intestinal permeability due to perturbed microbiota may allow microbial and dietary antigens to pass through the intestinal epithelium may be responsible for triggering autoimmune responses in the host, and exacerbate MS pathophysiology [11]. Nearly, 20–73% of MS patients show an elevated intestinal permeability [11:12] so modulating the gut microbiota in MS patients has the potential to subsequently improve this aspect of the disease.

The gut microbiota is one such environmental factor that has been implicated in the development and progression of the disease. Past studies have repeatedly demonstrated that MS patients have numerous taxonomic alterations in their gut microbiota composition, including (but not limited to) relative increases in *Pseudomonas*, *Blautia*, *Streptococcus*, and *Akkermansia spp.*, and decreases in *Prevotella*, *Bacteroides*, *Parabacteroides*, and *Clostridia spp*. compared to healthy individuals suggesting an interaction between the gut and brain in MS [13]. Involvement of gut brain axis could be anticipated in MS also through neural, immune, endocrine and metabolic channels similar to other neurological diseases [3-6 and 14].

Efficacy of FMT on Sclerosis

Neurodegenerative diseases are often associated with abnormal gut microbiota compositions [15]. Restoring a dysbiotic gut via FMT and recolonizing the "diseased" gut with normal microbiome could be a promising modality of treatment especially when no cure is possible with the available drugs.

Neurodegenerative diseases are highly prevalent but poorly understood, and with few treatment options despite decades of intense research, attention has recently shifted toward alternate therapeutic strategies. One such mediator is the gut microbiota, which communicates with the brain through the gut–brain axis and has been implicated in various neurological disorders.

FMT is gaining attention for its efficacy in treating both intestinal and extra-intestinal microbiota related diseases in the recent past. Indeed, it has been previously shown to improve elevated intestinal permeability in patients with non-alcoholic fatty liver disease and may have the same beneficial effect in patients with MS [15]. Liu and colleagues made a remarkable discovery that micro-RNA-30d (miR-30d) present in the gut microbiota resulted in increased abundance of *Akkermansia muciniphila*, an anti-inflammatory bacterium that increases regulatory T-cells (Tregs), which in turn ameliorated the symptoms of MS before it could progress[16]. Berer and colleagues used faecal matter from a human MS-discordant monozygotic twin pair as donor material, and showed that mice that received FMT from the MS-affected twin were more likely to develop EAE than littermates that were administered FMT from the unaffected twin [17].

In another study FMT transformed either MS patients or healthy household members into germ-free mice. Six weeks following transplantation, mice were immunized to induce EAE and results showed that disease in recipients of FMT from MS patients progressed faster compared to littermates who were administered FMT from healthy controls, accompanied by an up regulation of genes related to immune response. These results give a suggestion that the gut microbiota of MS patients contributes to a pro-inflammatory state that further exacerbates the disease [18]. Few human trials were done to ascertain the strength of FMT on MS so it could be approved similar to *Closterium difficil* recurrent infection. In 2011, a case series was published by Borody and colleagues [19], detailing the improvements seen in three MS patients following the administration of FMT to treat constipation. They reported an unexpected reversal of major neurological symptoms after FMT. Their study gave a clue for the GI infection may be underpinning these neurological disorders similar to other diseases.

Makkawi et al.[20] reported for the first time a long-term benefit of FMT on MS disease progression in a 61-year-old woman with relapsing remitting MS (RRMS). She was followed up in the Calgary MS Clinic in 1988 (age 33 years) and suffered 7 relapses between 1998 and 2001. The potential short-term efficacy of this procedure also has been reported in MS. In a previous report, three people with MS had significant neurologic symptom improvement after FMT for constipation [21].

Engen and colleagues [22] observed an remarkable increase in the abundance of a butyrate-producing bacteria, Faecalibacterium prausnitzii, a short-chain-fatty-acids (SCFA) producing bacteria in abundance, and α-diversity in the microbiome after 10 FMT infusions in a 48-year-old male with a two-year history of RRMS and difficulty walking .In addition they endorsed a significant, improvement in his walking , including gait, cadence and walking speed even after12-month follow up with no relapses during that study period. In order to find the efficacy of FMT [15] a clinical trial was performed involving nine patients with MS and provided monthly FMTs for up to six months. In their pilot study, nine people, six women and three men, joined and were randomized to either an early (four patients) or late (five patients) treatment group. Patients' mean age was 44, and their average disease duration was 14.6 years. The gut microbiota composition, intestinal permeability, and safety were assessed. Two of five patients had elevated small intestinal permeability at baseline that improved to normal values following FMTs. Significant, donor-specific, beneficial alterations to the MS patient gut microbiota were observed following FMT. Faecal transplants also led to changes in the gut microbiome. At the study's start, MS patients had significantly higher levels of *Bacteroides, Blautia faecis,* and *Bacteroides uniformis* than the two donors, while donors tended to have a higher abundance of Prevotella and *Paraprevotella* species. After FMT *Taxa Blautia* and *Subdoligranulum* was increased endorsing probably exerting beneficial taxonomic alterations. In this study *Parabacteroides* increased previously associated with negatively associated with MS. Enrichment of *Phascolarctobacterium succinatutens* after FMT indicating a promising result since these species utilizes succinate to produce short chain fatty acid propionate since, supplementation of propionate slows MS disease progression. Increase of *Hungatella hathewayi* was also enriched post-FMT. In Mouse model, the depletion of circulating taurine-transporter *tauB* could be increased by supplementation of Hungatella hathewayi that ameliorates MS symptoms. In this study also taurine-transporter *tauB* was found to elevate suggesting a potential role of FMT in modulating the bioavailability of this noteworthy metabolite. Increase of anti-inflammatory electron carrier ubiquinol, menaquinone (Vitamin K)-related gene *menC, HasA*, a gene encoding hyaluronan synthesis was also observed after FMT. Hyaluronan has the capability to enrich the abundance of *Akkermansia muciniphila*, a bacterium which is associated with MS. Strengths of this study are that the microbiota of MS patients was followed for six months without any microbiota intervention, as well as for up to six months following FMT. This pilot longitudinal study about the microbiota of MS patients gave a clue that the gut microbiota composition of MS patients can fluctuate over time without intervention, as has been previously reported in healthy individuals. Repeated FMTs were administered in this study to ensure that changes in the gut microbiota persisted over time [15]. Matheson, and Holsinger [23] reviewed the animal studies as well as human trials on the efficacy of FMT for neurodegenerative diseases in various parts of the world and tabulated the outcomes also.

Conclusion

Overall, the findings from animal studies as well as human trials demonstrate that FMT was a safe and tolerable intervention in MS patients, with the capacity to normalize intestinal permeability and produce beneficial alterations to the gut microbiota in all the studies performed. Further studies with longer follow-up and larger sample sizes

are required to determine if FMT is a suitable therapy for MS. The FMT may exert therapeutic avenue clinically and bestow significant protective and preventive functional alterations to the MS microbiota. There is a hope that the gut microbiota may therefore be an additional target in the search for disease-altering treatments in neurodegenerative diseases.

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