ACTA SCIENTIFIC MICROBIOLOGY (ISSN: 2581-3226)

Volume 2 Issue 7 July 2019

Mini Review

Gut Microbiome and Fecal Microbiota Transplantation in Autism Spectrum Disorder

Pradeep V Mahajan[1]*, Swetha Subramanian[1], Siddhesh C Parab[1] and Sanskruti Mahajan[2]

[1]*CMD, StemRx Bioscience Solutions Pvt. Ltd., Level 3, Seven Hills Hospital, Mumbai, India*

[2]*Cincinnati State University, USA*

***Corresponding Author:** Pradeep V Mahajan, CMD, StemRx Bioscience Solutions Pvt. Ltd., Level 3, Seven Hills Hospital, Mumbai, India.

Received: May 15, 2019

Abstract

Current research on pathophysiology of various diseases has proposed a link between occurrence and severity of symptoms and gastrointestinal disturbances. Dysregulation of gut microbiome has been reported to alter intestinal permeability, mucosal immune function, status of inflammation, and subsequently cause GI symptoms. Gastrointestinal disturbances and microbial dysbiosis have also been reported to aggravate behavioral and cognitive symptoms of Autism Spectrum Disorder. Based on the proposed causal relationship, a new therapeutic approach would be establishment of a healthy gut microflora. Fecal microbiota transplantation appears an effective approach to overcome dysbiosis through a sustained effect on the gut microbiome. This technique has been shown to substantially increase the microbial diversity of beneficial bacteria in the gut, such as *Bifidobacteria* and *Prevotella*, the results of which have been maintained for long periods after completion of the treatment. The present work aims to summarize the role of the gut microbiome and fecal microbiota transplant in Autism Spectrum Disorder.

Keywords: Gut; Microbiota; Autism Spectrum Disorder; Fecal Microbiota; Transplantation

Abbreviations

ASD: Autism Spectrum Disorder; LPS: Lipopolysaccharide; FMT: Fecal Microbiota Transplantation; MTT: Microbiota Transfer Therapy; GI: Gastrointestinal

Introduction

The human gut consists of approximately 10^{14} microorganisms, which have now been shown to influence the functioning of various organ systems [1]. The Human Microbiome Project Consortium (2012) described the abundant and diverse gut microflora to be as unique as the fingerprint of an individual [2]. The composition of this microbiota is influenced by environmental and genetic factors, which begins in-utero and fluctuates throughout the lifetime of an individual [3]. The intestinal microbiome has also been shown to influence development of the brain through modulation of the neuroendocrine, neuroimmune, and autonomic nervous systems. Several hypotheses have been put forth, for example the hygiene hypothesis and old friends hypothesis, explaining the causal relation between indigenous microorganisms and incidence of allergic and autoimmune diseases [4,5]. Advances in lifestyle and healthcare practices have resulted in significant changes in the microbiota, some of which may be responsible for triggering epigenetic modifications, and the subsequent incidence of diseases.

The indigenous gut microflora exerts a protective role by competitive inhibition, metabolizing nutrients required for survival of pathogens, and producing inhibitory molecules that suppress the growth of pathogenic organisms. In addition, in physiological state, the gut microbiota maintains a steady state of low-grade inflammation, by continuous stimulation of the immune system, for defense against pathogens. Disruption in the permeability of the intestinal wall may occur due to changes in the microflora, thereby leading to release of toxic products of pathogenic bacteria into the systemic circulation, which in turn elicits a pathological immune response. Alterations in the microflora leading to localized inflammation or disturbed metabolism is known as 'gut dysbiosis,' which is typically characterized by a low microbial diversity [6].

Gut-Brain Axis

Recently, the role of intestinal dysbiosis has received much attention in the pathogenesis of neurodevelopmental and neuropsychiatric disorders such as Autism Spectrum Disorder (ASD), Alzheimer's disease, depression and others [7]. Studies have reported overgrowth of obligate anaerobic organisms such as *Clostridium* spp. as well as *Vibrio* spp. in children with autism. In addition, lower diversity of gut microorganisms and reduction in the numbers of certain strains of beneficial bacteria, such as *Bifidobacteria* and *Prevotella* have also been reported in children with autism [8].

A bi-directional communication exists between the gut and the brain, which involves afferent and efferent pathways. The afferent pathway includes cytokines, intestinal hormones and microbiota while the efferent pathway includes neuro-endocrine and autonomic regulation [9]. The gut-brain axis plays a role in modulation of body metabolism through regulation of appetite and energy homeostasis as well as behavioral factors such as response to stress and pain, emotions, and attitude. Pertaining to ASD, neurotropic viruses or bacterial toxins from the intestine may reach the CNS through enteroendocrine cells or directly via vagus nerve, thereby causing aggravation of symptoms of the condition [10,11].

More specifically, dysbiosis and the consequent alteration of intestinal permeability lead to the production and spread into the bloodstream of a potent pro-inflammatory endotoxin, known as lipopolysaccharide (LPS). LPS induces the production of pro-inflammatory cytokines, which alter physiological brain activity and modulate neuropeptide synthesis. Neuropeptides are molecules utilized by neurons for communication. Thus, dysregulation of synthesis leads to behavioral and skill-related changes.

Treatment

Based on the above-mentioned relationship between gut microflora and gastrointestinal disturbances, and the increasing evidence of the implications of dysbiosis in other systemic disease conditions, a probable effective therapeutic modality for management of symptoms of ASD would be establishment of a healthy gut microflora. This may be accomplished by supplementation with prebiotics and probiotics as well as fecal microbiota transplant. Among these, fecal microbiota transplantation (FMT) has been shown to be most effective to overcome dysbiosis through a sustained effect on the gut microbiome. Figure 1 is a schematic representation of fecal microbiota transplantation.

Fecal microbiota transplantation, although not a new therapeutic modality, has gained popularity in recent years in the management of Clostridium difficile infections [1]. FMT has been shown to substantially increase the microbial diversity of beneficial bacteria in the gut, such as *Bifidobacteria* and *Prevotella,* the results of which have been reported to be maintained two years after the transplantation. Animal studies have reported increase in levels of anti-inflammatory IL-10 by oral administration of commensal bacteria to germ free rats. Similar increases in the levels of IL-10 have also been reported following administration of Lactobacillus GG to laboratory animals [1]. Oral administration of Bifidobacterium *infantis* was shown to reverse experimentally created anxiety and depression in germ free mice. This bacteria is also present in neonatal intestine and probiotics and is known as "psychobiotic" owing to its antidepressant effect.

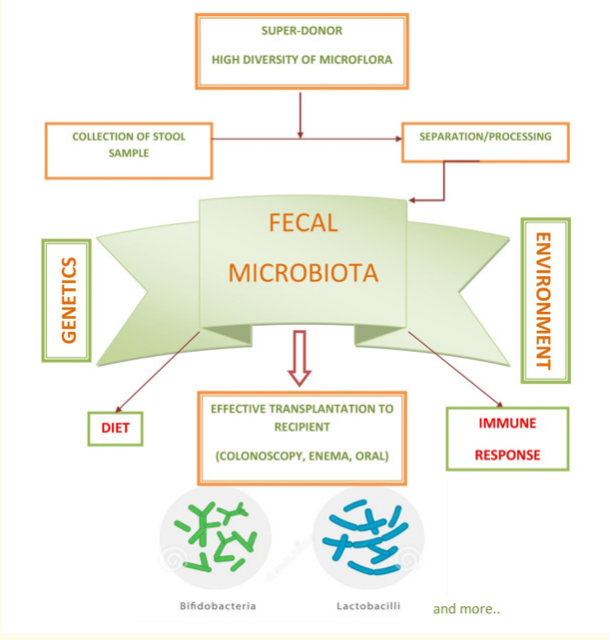

Figure 1: Schematic representation of fecal microbiota transplantation.

Similar studies have also been performed on healthy human volunteers, wherein the subjects were administered Lactobacillus *helveticus* R0052 and Bifidobacterium *longum* or placebo for a month. Decreased stress scores and decreased urinary free cortisol levels were found in subjects who received the probiotic bacteria [12].

The impact of Microbiota Transfer Therapy (MTT) on composition of gut microflora, GI and ASD symptoms was studied in 18 children diagnosed with ASD [13]. The therapy involved a 2-week antibiotic treatment, a bowel cleanse, followed by an extended

FMT regimen using a high initial dose followed by daily and lower maintenance doses for 7–8 weeks. Approximately 80% reduction was observed in GI symptoms, which persisted 8 weeks after treatment. Similarly, clinical assessment revealed improvement in behavioral symptoms of ASD.

Imbalance of Bacteroidetes/Firmicutes ratio, lower levels of Bacteroidetes phylum, Bifidobacterium, Lactobacillus, Sutterella, Prevotella, Ruminococcus genera, Alcaligenaceae family have been reported in ASD [14,15]. Following treatment with MTT, specifically, overall bacterial diversity and the abundance of Bifidobacterium, Prevotella, and Desulfovibrio among other taxa were observed in mice, the results of which were maintained after discontinuation of the treatment. Transplantation of Bacteroides fragilis has beenshow to repair intestinal permeability through expression of tight junction proteins and cytokines, thereby may indirectly contribute to alleviate behavioral symptoms of ASD. Thus, it can be proposed that FMT may provide beneficial results in symptoms of ASD through immunological mechanisms as a result of transplantation of healthy intestinal microbiota on the unhealthy microbiota.

FMT is a reliable procedure with minimal side effects having been reported. Gastrointestinal disturbances, constipation/diarrhea, flatulence, abdominal pain has been reported in some cases for a day or two following the transplantation. These side effects were reported to resolve without the need for any pharmacological intervention. However, a case series conducted on 317 subjects by Gough *et al*. reported significant side effects of upper gastrointestinal hemorrhage, peritonitis and enteritis in three patients, which were managed by conventional therapy [16].

Technique of FMT

Commonly fecal microbiota transplantation has been accomplished via colonoscopy, enema, or nasogastric tube. However, recently, oral route using capsules is being researched in order to facilitate a non-invasive technique for transplantation of the microorganisms. To achieve this, one of the techniques is centrifugation of the stool sample obtained from the donor, followed by addition of 10% glycerol for protection against freezing. The fecal material is then placed in swallowable capsules and is frozen at −80°C. Capsules are placed at −20°C for 1–2 hours prior to the process and are administered to patients orally for the designated number of days. Currently, these capsules are not available for use at home; however, oral application of FMT to regulate intestinal microbiota after antibiotic therapy may soon become a routine procedure [1].

The chief advantage of FMT over other forms of microbial manipulation, for example antibiotics, prebiotics and probiotics, is that FMT provides the full spectrum of microbial organisms from a healthy individual and therefore can treat as yet uncharacterized dysbiotic conditions.

Conclusion

Microbiome-mediated therapies might thus be a safe and effective treatment for ASD. This protocol appears to be a promising approach to alter the gut microbiome and improve GI and behavioral symptoms of ASD. The complexity of the fecal microbiota is actively being defined and recent studies have shown that the pathogenesis of many diseases, both GI and non-GI, result from microbiota-related dysregulation. Thus, FMT is likely to achieve widespread therapeutic benefit for a variety of diseases in the future.

Conflict of Interest

The authors declare that no conflicts of interest exist.

Bibliography

1. Evrensel A., et al. "Fecal Microbiota Transplantation and Its Usage in Neuropsychiatric Disorders".

2. *Clinical Psychopharmacology and Neuroscience* 14.3 (2016): 231-237.

3. The Human Microbiome Project Consortium. "A framework for human microbiome research".

4. *Nature* 486.7402 (2012): 215–221.

5. Perez-Muñoz ME., et al. "A critical assessment of the "sterile womb" and "in utero colonization" hypotheses: implications for research on the pioneer infant microbiome". *Microbiome* 5 (2017): 48.

6. Rook GA., et al. "Mycobacteria and other environmental organisms as immunomodulators for immunoregulatory disorders". *Springer Semin Immunopathol* 25.3-4 (2004): 237-255.

7. Rook GA., et al. "Microbes, immunoregulation, and the gut". *Gut* 54.3 (2005): 317–320.

8. Kriss M., et al. "Low diversity gut microbiota dysbiosis: drivers, functional implications and recovery". *Current Opinion in Microbiology* 44 (2018): 34–40.

9. Wasilewska J., et al. "Gastrointestinal symptoms and autism spectrum disorder: links and risks – a possible new overlap syndrome". *Pediatric Health, Medicine and Therapeutics* 6 (2015): 153–166.

10. Rosenfeld CS. "Microbiome Disturbances and Autism Spectrum Disorders". *Drug Metabolism and Disposition* 43.10 (2015): 1557–1571.

11. Mayer EA., et al. "Gut/brain axis and the microbiota". *Journal of Clinical Investigation* 125.3 (2015): 926–938.

12. Bolte ER. "Autism and Clostridium tetani". *Medical Hypotheses* 51.2 (1998):133–144.

13. Theoharides TC., et al. "Neuro-inflammation, blood-brain barrier, seizures and autism". *Journal of Neuroinflammation* 8 (2011): 168.

14. Messaoudi M., et al. "Beneficial psychological effects of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in healthy human volunteers". *Gut Microbes* 2.4 (2011): 256-261.

15. Kang DW., et al. "Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study". *Microbiome* 5 (2017):10.

16. Li Q., et al. "The gut microbiota and autism spectrum disorders". *Frontiers in Cellular Neuroscience* 11 (2017): 120.

17. Liu F., et al. "Altered composition and function of intestinal microbiota in autism spectrum disorders: a systematic review". *Translational Psychiatry* 9 (2019): 43.

18. Gough E., et al. "Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection". *Clinical Infectious Diseases* 53. 10 (2011): 994-1002.

Volume 2 Issue 7 July 2019