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Fecalmicrobiota transplantation in autism spectrumdisorder–anovel treatment approach

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Abstract

Autism spectrum disorder is one of the pervasive developmental disorders (PDD) category of neurodevelopmental diseases. Microbiota gut brain axis is a complex network and consists of multiple pathways that send signals between microbiota and brain. Autochthonous microbial diversity in the gut microbiota causes a proliferation of bacteria that can create neurotoxins, which at least partially contributes to the autistic illness of these individuals. This paper reviews fecal microbiota transplantation (FMT) procedure which involves obtaining a filtrate of liquid feces from the donor and introducing it to the recipient Gastro-intestinal tract. Delivery techniques for FMT was classified into upper and lower GI routes. Upper GI routes include nasogastric tube, nasoduodenal tube, nasojejunal tube and oral capsules. Lower GI routes include colonoscopy and enemas. Severe adverse effects are not found in the treatment of FMT indicating that FMT is a safe treatment approach for patients with Autism Spectrum Disorder.

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Introduction

Autism spectrum disorder (ASD) is one of the pervasive developmental disorders categories of neurodevelopment diseases. These illnesses are distinguished by three basic deficits such as poor communications, impaired reciprocal social interaction, confined, repetitive, and stereotyped behavioral or interest patterns (Faras H *et al.,* 2010).Frequent GI problems are known to be more common in ASD in children when compared to healthy ones, therefore non-adaptive behavior correlates with GI problems.

There is a correlation of ASD and four ASD subscales such as speech, sociability, sensory or cognitive awareness, physical behavior with GI severity. Children with ASD were most commonly to suffer with Clostridial infections induced by clostridium difficile bacteria (MalyginaD *et al.,* 2022). Male are more prone to ASD than female, ratio of prevalence for male to female is 4:1 (FarasH *et al.,* 2010).

There are two main causes that lead to ASD. Environmental factors such as Maternalobesity, gestational DM are associated with Autism and Genetic factors. Autism is one if the heritable medical conditions. Based on the germ-line, de novo mutation study100 genes have been associated with Autism. Exposure to drugs like thalidomide and valproic acid increases the risk of ASD during prenatal period. Premature infant, C-section deliveries, preterm delivery, uterine bleed have increased risk of ASD (HodgesH *et al*., 2020).

Variations in social communication, alteration in motor development, alteration in sensory processing are observedwith ASD. Early signs of ASD start during infancy, children at an average age of 43 months are diagnosed with ASD (Hadders- Algra M, 2022).Children and adolescents with autism spectrum disorder who also suffer from co-occurring anxiety problems may benefit from cognitive behavior therapy. Appliedbehavioral analysis incorporates explicit intercession targets, combined with encouraging feedback with reiteration of learning-preliminaries a key component. Pharmacological therapy includes atypical and typical antipsychotics, mood stabilizers, IV Immunoglobulin therapy (DeFillipis, M, WagnerK D, 2016).

Role of microbes in ASD

A growing body of research shows that the gut microbiota affects the immune system and metabolism and is directly or indirectly linked to ASD symptoms (De Angelis M *et al*., 2015). Autochthonous microbial diversity in the gut microbiota causes a proliferation of bacteria that can create neurotoxins, which at least partially contributes to the autistic illness of these individuals (MangiolaF *et al*., 2016).

Numerous studies have demonstrated that the use of antibiotics, manner of administration, and early colonization all have a major impact on the gut microbiota and the start of autism (Carding S *et al*., 2015). Several variables, including an improper diet, microbial infection, and metabolic stress, can cause maternal microbiome dysbiosis have an impact on the offspring's aberrant brain development and result in lasting behavioral abnormalities (Buffington S A *et al*., 2016).

Different kinds of short-chain fatty acids (SCFAs) can be produced by fermentation by bacteria of plant-based fiber, and these SCFAs may have a positive or negative impact on the gastrointestinal and brain development of autistic people(Carding S *et al*., 2015). Tetanus neurotoxin which is produced by a particular strain of bacteria, travels from the vagus nerve to the central nervous system and inhibits neurotransmitters by cleaving synaptobrevin, a synaptic vesicle membrane protein, which leads to a variety of behavioral impairments. The presence of Clostridium tetani can be employed as a diagnostic marker for ASD (T sai P *et al*., 2012).

A particular bacterial consortium in the mother's digestive system creates chemicals that affect the fetus brain's growth (Botta P *et al*., 2020). Infants' gut microbiome is influenced by the newborn feeding schedule, which is linked to ASD (Azad M B *et al*.,

2013). Ammonia and toxins released by Candida albicans can lead to autistic behavior (Iovene M R *et al.,* 2017). The neuroendocrine, neuroimmune, and autonomic nervous systems, as well as the creation of micro biotic toxins, all affect how the gut microbiota affects brain function (Grenham S *et al.*, 2011). The increased intestinal permeability, or "leaky gut," of people with ASD is a key component explaining the connections between ASD and the gut (Quigley E M, 2016). The various biochemical communication channels between the GI tract and the CNS, sometimes known as the gut-brain axis, and their potential links to autism spectrum disorder (Kim N *et al.*, 2018).

Microbiota gut axis

Microbiota gut brain axis has a major role in ASD and it is one of the main treatment strategies in ASD. Microbiota gut brain axis is a complex network and consists of multiple pathways that send signals between microbiota and brain. Brain regulates the composition and function of gut microbiota by releasing neuroactive compounds which act on gut microbiota or receptors or by regulating motility and secretory activity of gut (Li Y *et al.*, 2022). Changes in the composition of gut bacteria have been associated with the development of autism-related diseases, primarily driven by inflammation. This mild inflammatory response is a natural defense mechanism against the continuous influence of gut bacteria on the immune system. Numerous studies support the existence of a connection between the brain and gut (Mangiola F *et al.*, 2016).

Afferent and efferent pathways are involved in the two-way communication between the stomach and the brain. The microbiota, intestinal hormones, and cytokines that make up the afferent route where neuro-endocrine and autonomic pathways make up the efferent route autonomic control. Considering ASD, neurotropic Intestinal viruses or bacterial toxins may enter the central nervous system. Either directly through the vagus nerve or through enteroendocrine cells, therefore aggravating the symptoms. More specifically, dysbiosis and the consequent alteration of intestinal permeability led to the production and spread into the bloodstream of a potent pro-inflammatory endotoxin, known as lipopolysaccharide. Lipopolysaccharide 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 (Pradeep Mahajan *et al.,* 2019).

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is a procedure which involves obtaining a filtrate of liquid feces from the donor and introducing it to the recipient GI tract (Thakur A *et al.,* 2023). Fecal bacterio-therapy, a non-pharmaceutical medical procedure, involves processing donor fecal material in a lab and transforming it into capsules. Procedure is suitable for both children and adults (Prosperi M *et al.,* 2022). There is also potential clinical applicability of FMT beyond autism such as pseudomembranous colitis, metabolic syndrome, irritable bowel syndrome, inflammatory bowel disease, multiple sclerosis, cancer, multi-drug resistant infection (Thakur A *et al.,* 2023). Studies show that this approach aids in the normalization of the recipient's gut composition, resulting in therapeutic results and also identification of specific gut microorganisms and their functions (Wang J W *et al.,* 2019).

Procedure

The ideal stool donor should be a healthy volunteer "donate" and who has no risk factors for infectious or other chronic disorders (Kassam Z *et al.,* 2019). In order to rule out infectious diseases that can be transmitted by fecal transfer, prospective donors with permissive medical histories must undergo blood and fecal examinations (Cammarota G *et al.,* 2019).

Serological testing should also be done. Common enteric pathogens should be tested in stool samples. The individual is then approved to donate stool after repeating the screening tests every 8 to 12 weeks if all blood and fecal tests come back negative.

1. Donor should be selected.
2. Stool collection should be done. Stool collection should be done and the passed stool should be used in the first 6 hours itself, in case of any delay it should be chilled.
3. Stool should be diluted with 4% milk or regular saline and should have a liquid or slurry consistency for IV injections.
4. It should be filtered to remove the particulate matter after dilution.
5. There are different pathways to deliver FMT such as upper gut delivery and lower gut delivery (Thakur A *et al.,* 2023).
6. Capsule if found to be the non-invasive technique to facilitate the transfer of microorganisms.
7. For the capsule preparation stool sample should be taken from the donor and centrifugation should be done.

After centrifugation of the sample 10% glycerol should be added to protect against freezing. This fecal material should be placed inthe swallowable capsules and should be frozen at -80°C as the final step.

8. Before administration of capsules by the patient, the prepared capsules should be placed at the temperature of -20°C for 1-2hrs (Pradeep Mahajan *et al.*, 2019).

Delivery techniques

Delivery techniques for FMT was classified into upper and lower gastrointestinal (GI) routes. Upper GI routes include nasogastric tube, nasoduodenal tube, nasojejunal tube and oral capsules. Lower GI routes include colonoscopy and enema. Colonoscopy helps to visualize the entire colon and also enables proper delivery of the stool to the appropriate segments of bowel and has possible better retents of stool and can also deliver more amount of stool per transplant procedure and is linked to high success rate. Enemas was found to be less expensive, easy to perform and invasive. There are more great concerns about stool retention and the possibility that it won't pass-through splenic flexure which may necessitate multiple infusions to be effective. Upper GI delivery routes were found to be well tolerated, faster and economical than colonoscopy. Stool sample is also less required for this procedure to minimize regurgitation and to enhance retention rate. The novel delivery technique is oral capsules. These are less invasive, convenient. It entails delivering stools that have been double or triple encapsulated to protect them from gastric acid and combined with the crypto protectant such as glycerol (Ramai D *et al.*, 2019). FMT using capsules are encouraging and also minimize barriers to further adoption of FMT (Rao K *et al.*, 2017). The decision of the physician regarding route of administration depends on patient compliance, cost effectiveness, comfort of administration level of invasiveness, patients' hospital admission, risk of aspiration, infection, multiplicity of administration required and recurrence rate (Gulati M *et al.*, 2020).

Adverse effects of FMT

Severe adverse effects are not found in the treatment of FMT indicating that FMT is a safe treatment approach for patients with ASD (Zhang J *et al.*, 2023). Adverse events of FMT were categorized as short term and are found to be manageable and are reported to resolve without any therapy. Long term effects can also be seen and includes worsening of the diseased condition, development of metabolic diseases, alteration in weight but the risk is low. Theshort-term adverse effects are abdominal pain, diarrhea, vomiting, fever, bloating, flatulence which will be self-limited (Li Y Wang and Zhang T, 2022). Serious complications include aspiration pneumonia and enhancing symptoms of IBD. No deaths have been reported following FMT in patients and were found to be safe and well tolerated (Chen C C and Chiu C H, 2022).

Patient monitoring and safety issues

FMT represents an innovative therapeutic approach, albeit with distinct safety issues. It is vital to emphasize proper supervision and safety precautions to prevent pathogen transmission resulting from improper handling and insufficient oversight, with an emphasis on maintaining sterility (Green J E *et al.*, 2023). Short-term risks are mainly associated with how it's administered. However, since FMT aims to

increase bacterial diversity, there could be potential risks for individuals with underlying chronic illnesses. There have been reports of bloodstream infections in many FMT cases, especially in patients with weakened immune systems, resulting in severe symptoms. Hence, it is vital to place a strong emphasis on thorough evaluation, adherence to regulations, and following standards, particularly in the screening process, to improve the overall results (Merrick B *et al.*, 2020).

Conclusion

Gut microbiota can be altered by the FMT and improve gastrointestinal and behavioral symptoms which is known to be the promising strategy. FMT is considered as the evidence free, alternative form of medicine to acceptance as an important treatment option with great therapeutic potency. Various FMT techniques are used in the transplantation where colonoscopy is found to be the most effective technique.

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