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From Gut to Brain: The Role of Microbiome in Autism and Its Clinical Applications

Angela Thomas[1], Ranasinghe Arachchige Dona Kashmira Nawodi Weerasekara[1]

[1]Faculty of Medicine, Tbilisi State Medical University, Tbilisi, Georgia

Corresponding Author: Angela Thomas

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ABSTRACT

Gastrointestinal symptoms are common comorbidity in patients with autism spectrum disorder (ASD). The underlying mechanisms are known to be idiopathic, but recent studies have acclaimed the relationship between the components of the microbiome and the brain. Dysbiosis is associated with handful of diseases, including inflammatory bowel disease (IBD), ASD and mood disorders. Microbiome-mediated therapies might be a safe and effective treatment for ASD.

Autism is a neurological disorder that affects the brain development. The fermentation of different types of short-chain fatty acids (SCFAs) by microorganisms acts as an aid in the autistic subjects. This review sums up the bidirectional connection between our gut and brain, with particular emphasis on the portrayal of the microorganisms that contribute to ASD and outline the promising approaches to restore the healthy gut microbiome balance which can treat autism associated symptoms.

Keywords: Autism Spectrum Disorder, Gut Microbiome, Microbial Therapeutic Treatments, Gut dysbiosis, Gut-brain axis.

INTRODUCTION

Autism spectrum disorder (ASD) is a complicated heterogeneous disorder characterized by extensive neurodevelopmental dysfunction. ASD's clinical features include limited interests, repetitive behaviour, and difficulties with social interaction and communication [1]. ASD is usually diagnosed before the age of three and typically manifests early in childhood. Numerous studies undertaken in Asia, Europe, and North America. According to reports, gender ratios, which can range from 2:1 to 5:1, are more common in men than in women [1]. It is clear that ASD intervention has grown to be a critical public health necessity in order to address the high expense and complexity of medical care. Unfortunately, there aren't many FDA-approved medications that can effectively treat the primary symptoms of ASD because of the disease's complex underlying pathogenesis mechanism and the scarcity of animal models. The onset and development of ASD-related behaviour are currently thought to be caused by a variety of different mechanisms, including a decline in neurogenesis, an imbalance in excitation/inhibitory neurotransmitter, and dysregulated immune response. ASD has also been associated in recent years with a variety of environmental variables, including food, infections in mothers, intestinal dysbiosis, stress, medicines, pesticide exposure, and the use of antibiotics during pregnancy [2,3].

Understanding the rise in the incidence of ASD can be aided by looking at these environmental links.

Microbial imbalances and digestive issues are common in children with ASD, it is possible that these issues contributed to the disorder's development. This bibliometric study looked at Scopus-based studies on the gut microbiota and ASD highlights areas of current research interest and prospective future research hotspots [3]. It is believed that the gut microbiota makeup has a significant impact on immune development, physiological homeostasis, amino acid metabolism, glutathione metabolism, and other activities in humans. Thus, it is clear that the gut-brain axis plays a role in ASD. Given the known bidirectional contact between the gut and the brain, known as the "gut-brain axis," there has been a recent focus in science on examining the possible role of gut microbiota composition as a co-factor in the development of ASD [4]. Researchers interested in the association between gut microbiota and ASD may find the current study to be a useful resource as it makes a substantial contribution to the corpus of research in this area. This technique has the potential to yield benefits such as identifying research gaps, offering recommendations for future study areas, and assisting in the development of innovative solutions. Furthermore, an increasing body of research indicates that gut microbial dysbiosis plays a role in the pathogenesis of a number of illnesses, such as ASD, obesity, coeliac disease, allergies, asthma, metabolic syndrome, and inflammatory bowel disease. The relationship between ASD and the gut microbial population is the main topic of this review. In this review, the role that gut microbiota and its metabolites play in the aetiology, development of ASD, and therapeutic interventions aimed at modifying gut microbiota in individuals with ASD will be discussed [5].

MATERIALS & METHODS

This literature review involved a comprehensive search through databases such as Pub Med and Google Scholar using the keywords- “Autism”, “Gut Microbiome”, “Microbial Therapeutic Treatments”, “Gut Dysbiosis”, “Gut-brain axis”, “Probiotics”.

RESULT

Dysbiosis in gut leading to ASD

Studies on animals have suggested significant changes in gut flora result in behaviour resembling ASD. In models of environmental risk factors like valproic acid (VPA) exposure, maternal immune activation (MIA), maternal high-fat diet (MHFD) and p-Cresol exposure, idiopathic model for autism (BTBR mice), and mono-genetic mutation mouse models of autism like Shank3 KO mice, NLGN3R451C mutants, and EphB6 KO mice, the composition of gut microbiota in rodents exhibiting features of ASD was identified [6]. Mice exposed to VPA during pregnancy showed changes in the makeup of their gut microbiota, including an increase in Clostridiales and a decrease in Bacteroids, Deltaproteobacteris, and Erysipelotrichales [6].

Increased amounts of Alistipes, Enterorhabdus, Mollicutes, Lactobacillales, and Erysipelotrichalis were found in males, indicating a gender effect on the gut microbiota composition of VPA in utero-exposed mouse offspring. Rats exposed to VPA also showed sex-specific changes in the composition of their gut microbiota. Rats exposed to VPA showed a decrease in microbial diversity and an increase in the number of Rikenellaceae, Staphylo-coccaceae, Eubateriaceae, and α-Proteobacteria [7].

According to research on animals, proteobacteria create lipopolysaccharide (LPS), which has the ability to lower the antioxidant glutathione (GSH) levels in the brain [8,9]. The primary generator of propionate in the gut, Bacteroides, is another significant gut microbe. There is a high correlation between the amount of Bacteroides in faeces and propionate levels in autistic patients [10]. In people with autism,

there is an increase in the concentration of Clostridium, the primary producer of propionate, which is subsequently utilized for gluconeogenesis in the liver. Propionate and endotoxins produced by Clostridium may be linked to the intensity of symptoms associated with ASD. Certain Clostridium species have been shown to produce p-cresol, which has been linked to GSH decrease and may be a urine biomarker for autism [11]. The CNS's amygdalae are responsible for controlling emotions and behaviour. It was discovered in the autistic subjects that these areas can be modulated by production and spread of a potent proinflammatory endotoxin, specifically, LPS due to increased intestinal permeability or leaky gut prompted by dysbiosis. Furthermore, it can alter the normal brain physiology and modulate neuropeptide synthesis through the inflammatory cytokines production from the immune cells [12].

Claudins (CLDN-1, CLDN-3, CLDN-5, CLDN-12) are tight junction proteins present abundantly in the brain. It's interesting to note their overexpression can be interpreted as a disruption of the blood brain barrier (BBB). Fiorentino et al., demonstrated both the gut barrier integrity and BBB were impaired in individuals who had autism. This is evidenced by the increased expression of claudin CLDN-5, CLDN-12 in the brain, decreased amount of CLDN-1, and increased levels of pore forming CLDN (CLDN-2, CLDN-10, CLDN-15) in autistic patients as compared to controls[13].

Numerous reports compared the composition of the gut microbiome between autistic subjects and healthy controls, and suggested the former had elevated abundance of Proteobacteria, Lactobacillus, *Bacteroides*, Desulfovibrio, *Clostridium* while levels of Bifidobacterium, Blautia, *Dialister*, Prevotella, Veillonella and *Turicibacter* were consistently lower in them relative to healthy controls [14].

Candida albicans, a type of yeast present in the gut, is liable for absorption of carbohydrates and releases toxins. It can contribute to dysbiosis through interaction with the community of microorganisms [15]. Strati et al. discovered Candida in individuals with ASD was double that found in those without the condition. It is hypothesised Candida overgrowth can produce various byproducts, including ammonia. Ammonia reacts with propionic acid to form beta-alanine, its structure is similar to that of GABA, an important inhibitory neurotransmitter in the brain. Since beta-alanine can cross the blood-brain barrier, it functions as a partial antagonist to GABA. In order to compensate, the brain maintains homeostasis by overproduction of GABA. The neurotransmitter plays a critical role in regulating brain activity, and an imbalance could potentially influence neurological development and behaviour, hence the hypothesis suggests an association between overproduction of GABA and ASD [16].

Microbiome-Based Therapies

➢ Additive therapy

Years of research have led to the prediction that the human gut microbiome is at risk from antibiotics used for therapeutic purposes because of the microorganisms' resistance to the drugs as well as their lack of efficacy and specificity. Additive therapy is the extraction of a mixture of beneficial bacteria from a healthy human body and their introduction into faecal microbial transplantation (FMT) or probiotic ingestion. Probiotics are good, non-pathogenic bacteria that are added to the body to help the gut microbiome rebalance. Examples of these microorganisms are Lactobacillus and Bifidobacterium [17]. During FMT, the intestinal microbial community is fully restored in the patient with a gastrointestinal ailment. The gut microbial homeostasis and the host immune system are regulated by bacteria, fungus, viruses, and archaea (bacteriophage) in this alternate approach to probiotics and antibiotic treatment [18].

- **Reductive therapy**

Reductive treatment targets gut infections without harming other bacteria in the environment by employing synthetic bacteriocins and bacteriophages that exhibit promising antimicrobial efficacy. Compared to the use of antibiotics, which eventually leads to antibiotic resistance, this is a far better choice. Peptides called bacteriocins, which are produced in the ribosome, attack undesirable microorganisms by releasing poisons, stopping breathing, rupturing membranes, and causing cell death. A study using a mouse model showed that the intestinal wall was shielded and certain strains of E. Coli and L. monocytogenes were not able to proliferate due to the bacteriocins produced by Lactobacillus casei L26 LAFTI [19]. The probiotic strain Lactobacillus johnsonii LA1 releases a specific bacteriocin that prevents the growth of the bacteria Helicobacter pylori, which causes ulcers [19].

- **Modulatory therapy**

On the other hand, modulatory therapy,modifies antibiotics, exercise, and food, may considerably restore a healthy balance in the gut microbiota. This promotes the colonisation of beneficial bacteria over pathogens. Depending on the quantity, kind, and balance of the major dietary macronutrients (carbohydrates, proteins, and fats), as well as micronutrients like vitamin D, a nutritious diet is critical in determining the composition of the gut microbiome [20]. Research examining the impact of dietary fat consumption revealed that consuming a lot of fat lowers the concentration of butyrate, a short-chain fatty acid, and the quantity of bifidobacteria[21]. On the other hand, a high-fat diet decreases intestinal inflammation but increases the circulation of lipopolysaccharides and plasma indicators of inflammation. By increasing the synthesis of bacterial metabolites like SCFA, it increases microbial diversity and raises the Bacteroidetes–Firmicutes ratio, which lowers the risk of gastrointestinal and metabolic diseases[21].

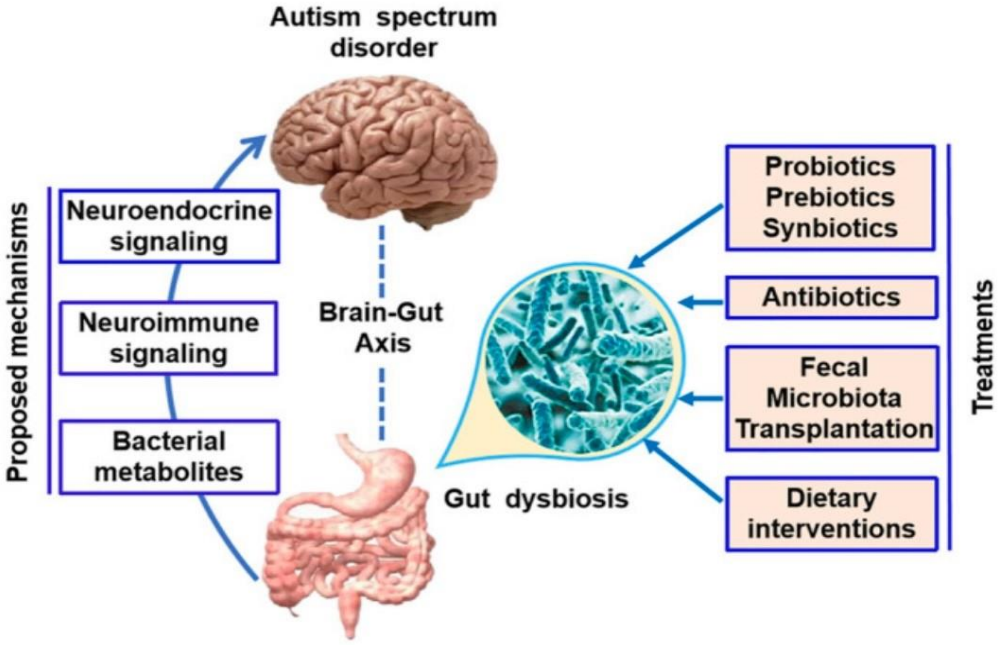

Figure 1. Microbial-based therapeutic interventions in ASD. The gut microbiota has been found to affect brain function through the neuroendocrine signalling, neuroimmune signalling, and bacterial metabolites. Potential microbial-based therapeutic interventions in ASD include prebiotic/probiotic/synbiotic, antibiotics, faecal microbiota transplantation, and dietary interventions[22].

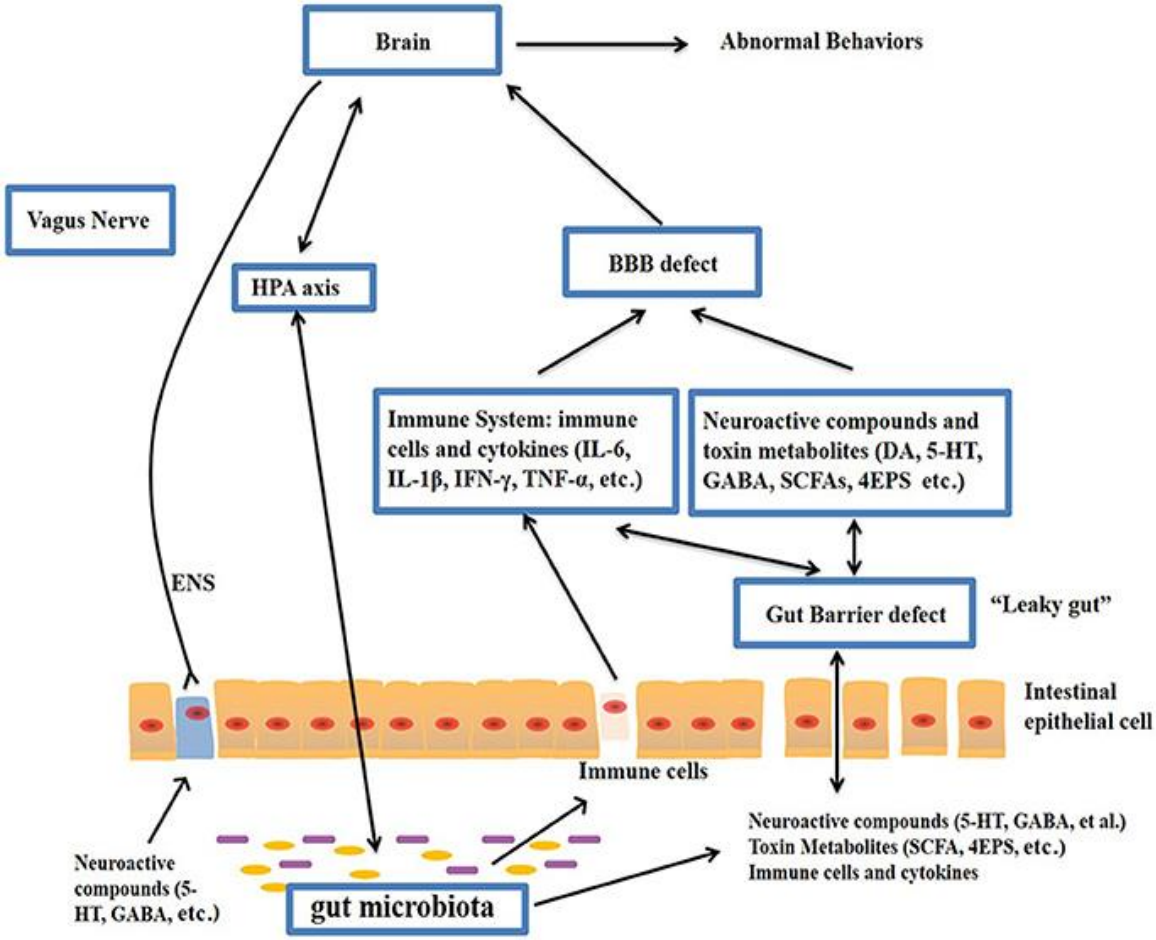

Figure 2. Potential relationships between the microbiota and ASD (the gut-brain axis). 4-EPS, 4-ethylphenyl sulfate; 5-HT, serotonin; HPA, hypothalamic–pituitary–adrenal; SCFAs, short-chain fatty acids; BBB, blood-brain barrier; 5-HT, 5-hydroxytryptamine; ENS, enteric nervous system; GABA, γ-aminobutyric acid; DA, dopamine [22].

DISCUSSION

Microbiota–Gut–Brain Axis

Latest studies on the gut–brain axis suggested the gut forms the enteric nervous system (ENS), considered as a second brain in most people [23]. The components of the gut-brain-axis comprise of the ENS and the central nervous system (CNS), mainly connected to each other via the vagus nerve. The gut-brain axis communicates through nerves, neurotransmitters, hormones, and immune signals [24].

A variety of microorganisms incorporated in the human gut that aid in metabolites production and transportation and maintaining the gut homeostasis. It is also involved in immune system maturation and dysbiosis leads to immune system dysregulation in ASD patients. Chemokines and cytokines such as interleukin-1β (IL-1β), interleukin-6(IL-6), interferon-γ (INF-γ), tumour necrosis factor-α (TNF-α) are released by the activated immune system and cross the blood-brain-barrier (BBB). These mediators bind to endothelial cells of the brain and induce immune responses in the brain. Ashwood et al., investigated cytokine levels in plasma in the typically developing children and ASD affected children, In comparison, elevated levels of cytokines were found in ASD group[25].

Additionally, it's also responsible for production of neurotransmitters such as serotonin [26],[27]. Tryptophan, an essential amino acid found in food is considered a precursor for serotonin [28], and is converted by bacteria such as Bifidobacterium infantis, thus regulating emotions and behaviour. This indicates the dysregulation of this axis may contribute to the

pathogenesis of disorders associated with altered anxiety and cognition[29].

Various pathogenic bacteria such as Clostridium bolteae can lead to gastrointestinal problems [30], [31]. Moreover, the presence of Clostridium in the colon indicates higher risk and severity of ASD [31], [32]. The bacteria is known to produce tetanus neurotoxin (TeNT), a neurotoxin, which reaches the CNS via the vagus nerve, blocking the neurotransmitters and precipitating a whole range of behavioural deficits. Hence aiding in the diagnosis of ASD, with its presence [33].

Maternal Risk Factors Regulating Gut Microbiome

Several experimental and epidemiological studies have revealed the interplay between maternal infection and the development of ASD in the offspring. A newborn infant's gut microbiome framework depends on the mode of delivery primarily colonized by the maternal microbiota. Thus, an imbalance or the dysbiosis of the maternal microbiome due to environmental stress or genetic risk can affect the offspring at the time of birth [34]. Consumption of a high fat diet and exposure to stress during gestation period increases the risk of neurodevelopment and behavioural disorders in offspring [35].

Animal studies observed variation in the gut microbiome during the prenatal stage leads to lifelong neuropathology and altered behaviours in the offspring [36],[37].

CONCLUSION

The relationship between the gut microbiome and ASD is a topic of growing interest, with increasing evidences that the former can facilitate the development of neurobehavorial disorders in ASD individuals. Factors such as colonization patterns of gut bacteria, microbiota dysbiosis, the method of delivery at birth, the use of antibiotics, and exposure to stress can impact gut health and thereby brain function.

Dysbiosis, an imbalance in the microbiota can lead to proliferation of harmful bacteria which in turn induces the production of neurotoxins, that may affect the brain function. A possible link between gut microbiome and ASD was established when certain strains of Clostridium were detected in few ASD children.

Short-chain fatty acid (SCFA) such as butyrate produced by the microbiome aids in brain health by enhancing brain function and supporting cognitive health through inhibition of histone deacetylases. In contrast, propionate, another SCFA produced by microbiota can influence brain function and behavior, potentially affecting traits seen in ASD, such as aggression and other behavioral changes.

Microbial Therapeutic Treatments (MTT), which aim to restore a balanced gut microbiome, have shown promise in managing autism-like symptoms. Recent clinical trials reported improvements in gastrointestinal symptom with minimal adverse effects in children receiving MTT for ASD. A majority of researches have been conducted on animals, however, those conducted on human have shown significant limitations including small sample sizes, lack of proper randomization or control groups, affecting the overall reliability and validity of the results.

Current advances in microbiome studies have progressed from animal studies to clinical studies, highlighting a potential breakthrough in ASD treatment. Researchers by delving deeper the molecular interactions between the gut microbiome and brain function pave the way for innovative therapies that could potentially improve the quality of life and offering new avenues for future treatment in individuals with ASD.

Declaration by Authors

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