Study the Gastrointestinal Flora in Autism Spectrum Disorders (ASDs): Mini Review

Alyaa Abdelhameed¹, Rana Hussein Naser Alqaysi¹, Nada Alharbi²

¹Biotechnology Department, College of Science, University of Diyala, Diyala, Iraq.
²College of Science, University of Princess Nourah bint Abdulrahman, Riyadh, Saudi Arabia.

Email Address: Correspondence should be addressed to Rana Hussein Naser Alqaysi ranaalqaysi@gmail.com

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Abstract

Autism spectrum disorder (ASD) characterized heterogeneous group of behavioural disorder and social deficits. Current research found a scientific evidence that an imbalance of intestinal bacteria a long with excessive inflammation within the brain are responsible for feature associated with ASD and developmental delay in children. The presence of pro-inflammatory cytokines that produced abnormally during pregnancy or vaccinations could trigger the dormant genes that found in autism. Most recently researches found a strong interaction between diet type and ASD. Furthermore, many studies have proposed the role of dietary compound and gut microbiome associated with un-developmental conditions in autistic patients. Patients with ASD exhibited low digestive activity for protein, casein, and nuts. In this review we hypothesized that fragile intestinal microbiome could be result from many factors including immune tolerance, genetic activity, and diet composition, which might contribute to change behavioral symptoms in ASD patients.

Keywords: Intestinal microbiota, Autism spectrum disorder, Inflammatory, diet, nutrient, dysbiosis

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with developmental condition that impact the social interaction, the ASD range from 0.1 to 2% of the global population (1). The causes of this disorder remain incompletely understood. Patient with ASD can suffer from gastrointestinal (GI) problems involved high level of gut immune inflammation that associated with gut dysbiosis (2). It has been noticed that probiotics are able to alleviate GI symptoms as well as improve behavioural issues in children with ASD (3). The etiology behind ASD are an intricate interplay of several genetics, epigenetic and environmental factors. Multiple comorbidities such as psychiatric issues that correlated with anxiety are developed in ASD. There are thousand of bacterial
species commonly seen in GI that affect the patients behaving. Children with ASD presented a high level of propionic acid (PA) that released in brain from probiotics could control the ASD behaviors (4). Other studies demonstrated that ASD has strong genetic basis with several genes such as Oxytocin receptor (OXTR), Gamma-aminobutyric acid (GABA), Beta 3 (GABRB3), and N-methyl-D-aspartate receptor (NMDA)(5). Recent studies presented number of environmental factors, immune systems, and GI that may have a direct link in pathophysiology of ASD. Several studies linked between gut microbiota(6). Research is also conducted that there is a reduction of bifidobacteria spp. and increase Clostridium spp. Desulfovibrio spp., Sutterella spp., and Veillonellaceae with ASD patients (7). A child with ASD might show several symptoms (not speaking or not crawling). A newborn children may a dopt their mother intestinal bacterial community; furthermore, a child’s father may contribute by genes that favor growth probionic acid producing-bacteria (8). Research is also being focused on food toxicity, sensitivity, and diet type (8). The present review aims to highlight the potential role of gut microbiota on the balance of gastrointestinal microbiota on the ASD behavioral traits.

2. Inflammation and Genetic Abnormalities

It quite clear that ASD associated with wide variety of genetic mutations, many genes showed significant behavioral outcomes such as anxiety, psychosis, depression, schizophrenia, and personality disorder (9). The genetics concerns are developed either by new genes that affected individual (such as drug exposure or radiation exposure during pregnancy) or whether the genes were pre-existing, but dormant, in the donor parent from whom they were passed (10). An elevation pro-inflammatory cytokines are capable to activate both new and dormant genes. Systemic inflammation can also impair the ability of stem cells to mature properly and cause DNA miscopied especially when the child is developing within the womb(11).

Furthermore, prior to birth, inflammatory are capable of causing mutations or activating pre-exist genes that are produced within, mother's body, and they can influence the activation or development of unborn child's cellular DNA (12). Researches outlined a process in which combination of abnormal microglia functioning and elevated levels of pro-inflammatory cytokines within central nervous system which plays a significant role in the development of a wide range neurological disorders in the children (13). The abnormal activation of microglia and elevated cytokines are associated with impaired development of fundamental brain architecture (14). Earlier study found that dietary changes also has an effective tool against harmful microglia and help to reduce bacterial overgrowth and pro-inflammatory cytokines (15).

3. Re-Balance Intestinal Bacteria

It is difficult to accept the idea that hundreds of human gut microbiota are causing body and brain many issues. The causes of gut difficulties are unknown, however; few studies have focused on gut microbiota without any consistency in the evaluated parameters (16). The metabolism of gut microbiota has a critical role in the pathophysiology of ASD (17). Earlier studies highlighted the interaction between the gut microbiota and brain function (18). Other studies found that gut microbiota remodelling using specific antibiotics probiotic alleviated symptoms of ASD (19). Additionally, many studies have reported dysbiosis of gut microbiota in individuals of ASD. It has been reported that Bacteriodes sp. were the dominant microflora in children with ASD (20). Other study demonstrated
that pathogenic bacteria such as *Klebsiella pneumoniae* or *Clostridium difficile* are usually accompanied in asymptomatic patients with ASD (21). Some adults or children with intestinal bacterial overgrowth exhibit signs of food intolerance, anxiety, reflux, and heartburn (22). Autism is the consequence of excessive brain inflammation in addition to a toxic encephalopathy from the overproduction of propionic acid from intestinal bacterial overgrowth (23). literature service revealed that *Clostridium spp.* were the major bacterial group found in patients with ASD as a comparison with unrelated healthy children (17). The main etiology of ASD remains unknown, the infection with viral pathogens. One of the case – control study was examined the titres of HHV6 and measles antibodies in the blood serum of 48 ASD patients and age matched controls. The result showed a significant correlation between serology and brain autoantibodies only in ASD samples (24). It has been shown that the comparison of Varicella zoster virus (VZV) antibodies between children with ASD and controls were significantly higher in autistic children (*p*=0.04) (25). An immunological examination was performed on ASD participants with the controls (3-12 years of age) against nine different antigens using IgG, IgM, and IgA antibodies, the results showed highly significant differences. These antibodies may cross the BBB and combine with brain tissue antigens to form immune complexes and reflect further damage in neurological tissues (26).

### 4. Consideration Before and During the Pregnancy

Prenatal maternal factors such as nutritional status, exposure to tobacco smoke, periodontal diseases, and lifestyle have been shown to be associated with higher risk of ASD. Pro-inflammatory cytokines are capable to cause mutations through crossing the placenta and causing many pregnancy complications (27). The best strategy is to reduce the general inflammation levels in order to improve autonomic nervous system. Earlier study found that rifaximin medication is the best chose before pregnancy to re-balance gut microbiota (28). The reduction of inflammation could improve fertility rates and reduce the complications during pregnancy such as miscarriage and pre-eclampsia. Furthermore, inflammation reduction may also improve the health of autonomic nervous system and resilience of mother against the potential injury and microbial strain that might happen during the delivery. During the pregnancy the high levels of pro-inflammatory cytokines (including intestinal bacterial imbalance of mother) might play role on the level of severity of autism (29). However, an excessive pro-inflammatory cytokines after the birth of a child can cause disruption of neuronal development and inhibit the brain from repairing injuries and penetrating the blood brain barriers via paraventricular organs (30).

Other study found that obesity and maternal diabetes are associated with pro-inflammatory cytokines with disrupted immune mechanisms that contribute to the pathogenesis of ASD in new birth child (31).

### 5. Vaccination Considerations

Vaccinations are designed to trigger an effective part of immune system depending on the brain health of the person vaccinated. They are the best way to protect the children from specific diseases that have no antibiotic treatments such as measles, mumps, rubella, and polio. There are many theories about the vaccinations direct and indirect consequences on autism (32). Many studies have recommended to delay the vaccine for a few months for the children that have intestinal bacterial overgrowth and developmental delay. The excessive production of propionic acid is the main
result of bacterial overgrowth. High levels of unhealthy pro-inflammatory cytokines that resulted gut bacterial overgrowth could combine with pro-inflammatory cytokines from vaccine and produce a negatively target the brain functions (33). Furthermore, vaccines capable to impair the function of autonomic nervous system and increase the inflammatory surge of pro-inflammatory cytokines. The pro-inflammatory cytokines can release naturally with healthy immune reactions such as that triggered by influenza, also they release under the specific circumstance such as chemical or toxic exposures. Omega-3 fatty acids from fish, powdered inulin, probiotics, and prebiotics are the best supplements to re-balance intestinal in the children with suspected bacterial overgrowth (34). Children with autism need to balance the vaccinations timing with the recover from intestinal bacterial overgrowth by using the simple nutrition tools that may be an approach to be considered in the future.

6. Diet Considerations

Patients with ASD are pikey eaters, to prevent gut microbiota overgrowth and improve autonomic nervous system, it is important to define trigger food items and follow a restriction diet. Abnormal gastrointestinal function in autistic patients could result from the toxic levels of propionic acid that produced from intestinal bacterial overgrowth and affect the intestinal permeability values such as digestive capacity (35). Many studies recommended the nutritional supplements to re-balance the gut microbiota. Using probiotics supplements are used to improve the ASD behavioral, these supplements could increase the number of *Bifidobacterium* spp. and *Lactobacillus* spp. (7). However, these live microorganisms can be affected by human body environments such as stomach acids, duration, and temperature with the limitation of size. Furthermore, the addition of probiotic may add unknown strains that increase the patient’s inflammation and other psychological symptoms (36). An alternative way is to enable gut microbiota would be the use of prebiotics. These compounds do not lose potency with human body factors and increasing dietary intake. Inulin prebiotics are natural plants fiber that found in many types of food such as oatmeal, onion, garlic, artichokes, and in wide variety of other vegetables (37). Inulin fiber works as fertilizer by nourishing healthy bacteria in the small intestine to control bacterial overgrowth. It used with omega-3 fatty acids from fish oil in a specific dose to reduce propionic acid toxicity (34). Several research groups found that, corn oil, soybean oil, sunflower oil, peanut oil, and cotton seed oil are not allowed because they have high linoleic acid oils as ingredients because they increase brain inflammations (38). The patients with ASD also have gluten and a complex protein sensitivity, gluten-free, casein-free (GFCG) diet could normalize gut microbiota and prevent developmental deficiencies or brain injuries or worsening symptoms of ASD (39).

7. Conclusion

Nowadays a global issue with one or two generations of autistic children that are experiencing increasing rates still unexplained. Autism is the result of brain inflammation combine with overproduction of propionic acid. Many pro-inflammatory cytokines are produced within the brain and excessive levels of propionic acid are released from intestinal bacterial overgrowth that might increase brain damage. The excessive consumption of linoleic acid intake and carbohydrates, abnormal intra-abdominal fat, and exposure to tobacco. The alternative food supplements such as probiotics and prebiotics, microbiome colonization, and immune development during perinatal period could reduce the ASD symptoms. Further research in this area should be designed to highlight the relationships
between all these factors. Furthermore, all these studies have broad implications to detect many disease that correlated with gastrointestinal functions.

**Conflicts of interest**

The author(s) declare that there are no conflicts of interest

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## 8. References


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