Autism Spectrum Disorder and Gut Microbiome: A brief review

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Abstract

The human microbiota consists of the 10-100 trillion symbiotic microbial cells harbored by each person, primarily bacteria in the gut. The association of the gut microbiota with human health and disease has been widely studied. A number of human disorders and diseases have been directly and indirectly associated with the microbiome. Children with Autism Spectrum Disorder (ASD) have distinctive gut microbiota compared to neurotypical children. Autism spectrum disorder (ASD) is associated with several oropharyngeal abnormalities, including dysbiosis in the oral microbiota. As there is a correlation between abnormal microbiota and development of autism like behaviour, so, modifying the gut microbiome by probiotics, prebiotics, antibiotics and fecal microbiota transplant (FMT) could be a potential route to improve GI and behavioural symptoms in children with ASD.

Keywords: Microbiome; Autism Spectrum Disorder (ASD); gut microbiota.

Introduction

The intimate association between man and microbe over the course of a lifetime has profound implications on human health, including metabolism, immunity and the gut-brain axis. The human microbiota consists of the 10-100 trillion symbiotic microbial cells harbored by each person, primarily bacteria in the gut. Oral microbiome, by definition, is the collective genomes of microorganisms that reside in the oral cavity (Kolenbrander et al., 2002; Turnbaugh et al., 2007). The human microbiome, or community of microbes and collection of genomes found in and on the human body, is now the subject of renewed, intense study (Relman, 2012).

Oral microbiome and developmental disorders

Many researchers believe that the characterisation of oral microbiome is an essential step in understanding oral health and systemic diseases (Dewhirst et al., 2010, De et al., 2018). A number of human disorders and diseases have been directly and indirectly associated with the microbiome. The association of the gut microbiota with human health and disease has been widely discussed (Walsh et al., 2014, De et al., 2019). Current evidences support that alterations in composition and/or metabolic activity of gut microbiota play pivotal role in the pathogenesis of obesity and related disorders (Musso et al., 2010).

Autism spectrum disorder (ASD)

Autism spectrum disorder (ASD) is a developmental disability that can cause significant social, communication and behavioral challenges. The Diagnostic and
Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) adopted the term Autism Spectrum Disorder (ASD) with a dyadic definition of core symptoms: early-onset of difficulties in social interaction and communication, and repetitive, restricted behaviors, interests, or activities (APA, 2013). ASD is a dynamic disorder with complex changes over time from childhood into adulthood (Lange et al., 2015), and developmental perspective may contribute to interpret some contradictory findings in ASD studies (Uddin et al., 2013).

Prevalence of ASD

The Centers for Disease Control and prevention (CDC), 2018, mentioned that the vulnerability to autism had gone up to 1 in 59 – twice as great as the 2004 rate of 1 in 125. According to 2018 report of the National Autism Spectrum Disorder Surveillance System, 1 in 66 has been diagnosed with ASD in Canada. In Korea, the pervasiveness of ASD amounts to 2.64% in school-age children (Kim et al., 2011). It is found that ASD occurs in males four times more than females (Fombonne, 2005). 1 in 42 males is found to be affected by ASD. 1 in 165 females is diagnosed with ASD. 1% of the world population has ASD (approximately).

Etiology of ASD

An inter-play between genetic and environmental factors, as well as both systemic inflammation and inflammation of the central nervous system is said to have an effect on the etiology of ASD (Karimi et al., 2017, Wu et al., 2017, Siniscalco et al., 2018). Twin studies support genetic and environmental contributions to ASD pathogenesis. It has been observed that about 10%-20% individuals with ASD have gene defects and chromosomal anomalies (Herman et al., 2007; Miles 2011). Siblings of individuals with ASD have a 50 times greater risk of ASD compared to neurotypically healthy individuals having a recurrence rate of 5%-8% (Szatmari et al, 1998). In identical twins, this concordance rate reaches up to 82%-92% compared with 1%-10% in fraternal twins. Point mutations can change developmental pathways of neurones involved in synaptogenesis and axon motility in the uterus (Chang et al., 2015; Geschwind 2011; Voineagu et al., 2011). Autism spectrum disorder (ASD) is associated with several oropharyngeal abnormalities, including dysbiosis in the oral microbiota (Olsen and Hicks, 2019).

Human microbiome and Bio-markers of ASD

Biomarkers will not replace clinical assessments, which characterize the extent of specific deficits, but could potentially change intervention/treatment goals and methods (Walsh et al., 2009). The human microbiome, consisting of the total microbial complement associated with human hosts, is an important emerging area for metagenomic biomarker discovery (Hamady et al., 2007). It has been noticed in less than 5% cases that people with certain errors in metabolic pathways, such as, phenylketonuria, creatine deficiency syndromes, adenylosuccinate lyase deficiency, and metabolic purine disorders may develop autistic symptoms (Clifford et al., 2007).

People having certain genetic conditions, such as, Down Syndrome, Fragile X Syndrome, and Rett Syndrome are more susceptible than others to be affected by ASD. Recent studies suggest that in 40% of ASD cases, there is a positive correlation between mutation in cerebellar developmental patterning gene ENGRAILED 2 and autism (Manzi et al., 2008). Other suspected genes responsible for ASD are UBE3A locus, GABA system genes, and serotonin transporter genes (Gharani et al., 2004).

Different pre-natal, peri-natal, and post-natal factors also contribute to ASD (London et al., 2000). Some of the pre-natal factors were viz exposure to teratogens such as thalidomide, intrauterine stress; maternal anticonvulsants such as valproic acid (Kern et al., 2006; Kolevzon et al., 2007). Some peri-natal factors are Low birth weight, abnormally short gestation length, perinatal depression and birth asphyxia (Kolevzon et al., 2007). Post natal factors include autoimmune disease, viral infection, hypoxia, mercury toxicity, and others (Kern et al., 2006; Ashwood et al., 2004; Courchesne et al., 2011).
**Gut Microbiota & ASD**

The Brain-Gut-Microbiome axis is a concept that refers to the complex interactions between the central nervous system, GI system and the microorganisms of the GI tract. All the microbes in the intestine are called gut microbiota. Collective genomes of gut microbes are called gut microbiome. Gut microbiota, consisted of trillions of microorganisms and modulated mainly by diet (Scott et al., 2012), has recently been recognized as a primary mediator for human health (Cani & Delzenne, 2009; Everard & Cani, 2013). The gut microbiome, which may contain > 100 times the number of genes in our genome, endows us with functional features that we have not had to evolve ourselves (Bäckhed et al., 2005).

Based on variation in 16S rRNA genes, it is assumed that the healthy adult gut microbiota comprises four major phyla that in all can correspond to more than 90% of the total bacterial population: Bacteroidetes (gram-negative -- Bacteroides, Prevotella), Firmicutes (gram-positive -- Lactobacillus, Clostridium and Ruminococcus), Proteobacteria (Enterobacter), Actinobacteria (gram-positive--Bifidobacterium) followed by the minor phyla Fusobacteria and Verrucomicrobia. Intestinal dysbiosis, an imbalance in the beneficial organisms in the gastrointestinal tract and/or an overgrowth of pathogenic organisms, can be seen in many individuals with autism.

The Bacteroidetes phylum chiefly generates acetate and propionate, whereas the Firmicutes phylum has butyrate as its primary metabolic end product. Most bacterial activity takes place in the proximal colon where substrate availability is maximum. Toward the distal colon, the availability of substrate falls and the extraction of free water decreases diffusion of substrates and microbial products. This forms the proximal part of the colon, the key site of fermentation. Typically, non-digestible carbohydrates are fermented in the proximal colon by saccharolytic bacteria. Recent studies demonstrate that the intestinal flora of individuals with autism differs from that of individuals without autism (Finegold et al., 2002, 2010, 2011; Kang et al., 2013). Gut microbiome of children with ASD contains abundance of Faecalibacterium, Bacteroides, Suterella, Clostridium, Lactobacillus, Proteobacterium, Desulfovibrio and scarcity of Bilidobacterium, Veillonella, Streptococcus, Prevotella, Actinobacteria. The fecal matter of children with ASD contains increased amount of acetic acid, propionic acid, lactic acid butyric acid and valeric acid producers.

**The Gut-Brain Connection in individuals with ASD**

The gut microbiota prove to be an important environmental factor that may exert an influence on symptoms of ASD, and children with ASD have distinctive gut microbiota compared to neurotypical children (De Vadder et al., 2012). There is a very close connection between the gut and the brain and for this very connection the gut is often referred to as second brain. Bacteria in the gut effect the central nervous system, that lets for constant communication between the gut and the brain (via this gut-brain axis). After extensive research the gut-brain axis theory, is now well-established and accepted. Studies from several groups now states that the gut and the brain communicate and influence each other (Bienenstock et al., 2015; Mayer et al., 2015; Cryan et al., 2019).

The healthy GI tract imbibes only the small molecules of completely broken down food particles originating from fully digested food. Ideally the intestinal wall should be able to prevent large and undesirable molecules. Children with autism often suffer from a range of GI symptoms, including diarrhoea, abdominal pain, constipation and gastroesophageal reflux. Estimates of the prevalence of such symptoms vary from 9 to 91% across studies (Buie et al., 2010). Intestinal dysbiosis, an imbalance in the beneficial organisms in the gastrointestinal tract and/or an overgrowth of pathogenic organisms, can be seen in many individuals with autism. When insufficient beneficial bacteria are present, pathogenic flora can overgrow. These pathogenic organism may then secrete toxic metabolites that have several negative consequences. These toxins may contribute to the development of altered intestinal permeability and may then enter the
circulation and subsequently have secondary effects on brain functioning.

**Intervention for ASD**

Most experts agree that the intervention for ASD should be individualized. Various educational and behavioral treatments have been the mainstay of the management of ASD. If disruptive behaviours such as aggression, agitation, hyperactivity, inattention, irritability, repetitive and self-injurious behaviour are addressed properly it may allow educational and behavioral interventions to proceed more effectively. Two kinds of interventions have been used for individuals with ASD; focused intervention practices and comprehensive approach. The focused intervention practices include prompting, reinforcement, discrete trial teaching, social stories, or peer mediated interventions. These are designed to produce specific behavioral or developmental outcomes for individual children with ASD, and used for a limited time period with the intent of demonstrating a change in the targeted behaviors. The comprehensive treatment models are a set of practices performed over an extended period of time and are intense in their application, and usually have multiple components (Richards et al., 2012). Children with autism showed a significant increase in the *Firmicutes* to *Bacteroidetes* ratio and elevation of the amount of *Lactobacillus* spp (Tomova et al., 2015).

Children with ASD with more severe symptoms have been shown to have higher levels of *Desulfovibrio* and *Clostridia* than children with milder symptoms. The level of *Clostridium* abundance has been correlated with the disease severity of ASD, as measured using the Childhood Autism Rating score (Iovene et al., 2017). Considering the link between the gut and brain, modulating the gut microbiome by antibiotics, probiotics, prebiotics, and/or fecal microbiota transplant (FMT) could be a viable therapeutic option. Probiotics are helpful live bacteria, such as *Lactobacillus*, *Bifidobacteria*, and *Saccharomyces* that provide support to health and body function. It has been proved that these beneficial bacteria prevent and mitigate many issues, including depression, anxiety, obesity, bowel disorders, and autoimmune issues. Prebiotics are food components that let the growth of beneficial bacteria in the gut. Non-digestible oligosaccharides dietary fibers consist major group of prebiotics. In FMT, a large diversity and number of commensal microbes from a healthy donor are used to transform a dysbiotic gut microbiome into a healthy microbiome.

Probiotics and prebiotics can raise the levels of health-supportive bacteria in the gut acting in close connection and it has been shown that they together ameliorate leaky gut, neurotransmitter production, and other brain function. The most promising treatment for neurobehavioural symptoms and bowel dysfunction is the application of probiotics mostly a mixture of *Bifidobacteria*, *Streptococci* and *Lactobacilli*.

**Conclusion**

The microbiome has emerged as a potential therapeutic target in disorders as diverse as IBS, Parkinson’s disease, ASD and depression (Felice et al, 2016; Yarandi et al, 2016). Many other neuropsychiatric disorders including Alzheimer’s disease, amyotrophic lateral sclerosis, autism, stroke and drug addiction have been linked, in one way or another, to the microbiome (Quigley, 2017). More studies need to be conducted to confirm the effectiveness of the therapeutic tools using microbiota for Autism Spectrum Disorder.

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**Conflicts of Interest:**

The authors declare no conflict of interest.

**References**


