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REVIEW ARTICLE

The effect of intestinal microbiome on autism spectrum disorder

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Abstract:
In recent years the gut microbiome has been identified as a major regulator of many organism systems normal function. There is also data showing that gut microbiome is involved in brain development, as it affects synaptogenesis, development of dopamine system and blood-brain barrier permeability. On the other hand, the intestinal microbiome presents significant changes between children with autism and normal children and by-products of gut microbiota seem to be correlated with certain aspects of autistic phenotype, although findings tend to be controversial among different studies. Modification of intestinal microbiome could alleviate some symptoms of autism, but controlled clinical trials are not available, yet.

Keywords: *microbiome; autism; gut-microbiota; gut-brain axis*
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1. The role of gut microbiota in humans

It is estimated that approximately 3.9*1013 bacteria are found in the colon of a "reference man" and approximately 0.9·1011 bacteria are detected per gram wet stool [1]. With regard to species that compose gut microbiota, Firmicutes and Bacteriodetes phyla, the kingdom of Archaea and eukaryotes, as well as many viruses and bacteriophages are most frequently identified [2,3]. The role of gut microbiota in human physiology is manifold. Gut microorganisms contribute to energy production from the fermentation of undigested carbohydrates and the subsequent absorption of short-chain fatty acids (butyrate, propionate, acetate). Moreover, they play a role in vitamin synthesis, in metabolism of bile acids, sterols and xenobiotics and establish a natural intestinal barrier, providing protection from invading species. They also stimulate epithelial regeneration, exert a trophic action on the mucous membrane and suppress pathogenic microbial growth. It should also be noted that gut microbiome is involved in the maturation of the immune system, as it stimulates innate immunity (maturation of the gut-associated lymphoid tissue-GALT) and acquired immunity (local and systemic immune responses) [3,4].

In recent years gene-microbiota interactions are increasingly proposed to be a special case of gene-environmental interaction and the gut microbiota is regarded as a reservoir for environmental epigenetic factors [5].

2. Gut microbiota and brain-gut axis

Alterations in the gut microbiome are strongly considered to modulate significantly brain development and behavior. The proposed underlying mechanisms have been mainly identified through studies in germ-free (GF) mouse models (devoid of any microbiota throughout development) and include effects on synaptogenesis and on the development of the dopamine system, changes in blood-brain barrier permeability, as well as the effect of metabolic by-products of the gut microbiota on brain circuits [6]. However, the relationship between gut microbiome and CNS is bidirectional, as the CNS is able to continuously alter the composition of microbiota, as well as gut permeability, modulating motility and secretion through the activation of the hypothalamus pituitary-adrenal (HPA) axis and the autonomic and neuroendocrine system [7]. In literature there is evidence of clinical and basic research that gut microbiota may be involved in a variety of neurologic disorders (autism spectrum disorder, schizophrenia, dementia, mood disorders).

3. The intestinal microbiome in autism spectrum disorder

According to literature, the intestinal microbiota in children with autism presents significant differences in comparison to normal children. In general, studies conducted during the last 15 years in fecal samples of autistic children have demonstrated that a large amount of species under the Clostridium genus, as well as an imbalance of Bacteroidetes and Firmicutes phyla, with an increased presence of Bacteroidetes and other gut commensal such as Bifidobacterium and Lactobacillus [3,8-10].

More specifically, Tomova, et al. (2015) have shown a significant decrease of the Bacteroidetes/Firmicutes ratio, as well as an elevation of the amount of Lactobacillus spp in the fecal microbiota of autistic children compared to normal sibling and healthy children. They have also shown a trend in the incidence of elevated Desulfovibrio spp in children with autism along with a very strong association of the amount of Desulfovibrio spp with the severity of autism [11]. On the other hand, Kang, et al. (2013) compared fecal DNA samples between autistic and healthy children and found less diverse gut microbial compositions and a significantly lower abundances of the genera Prevotella, Coprococcus and unclassified Veillonellaceae. The above findings were correlated with the presence of autistic symptoms rather than the severity of gastrointestinal symptoms and were not affected by different diet patterns [12].

Moreover, recent studies have shown increased levels of short chain fatty acids in stool samples from children with autism. As short chain fatty acids (especially acetate, propionate, butyrate) consist metabolic by-products of gut microbiota, differences in their levels in feces may be an additional evidence of altered gut microbiome in children with autism [13]. Abnormalities in fatty acids profile (lower docosahexaenoic, eicosapentaenoic, arachidonic acid and ω-3/ω-6 ratios) have also been identified in the serum and red blood cells of children with autism compared to controls [14]. Similarly, in adolescent rat models augmented concentrations of specific lipopolysaccharides (lipoglycans or endotoxins), which consist products of enteric bacteria have been correlated with altered behavior and development of autistic features, while serum levels of lipopolysaccharides were also significantly higher in autistic patients compared to heath individuals and inversely correlated with socialization scores [15,16]. In this way the hypothesis of an altered gut microbiota in patients with autism spectrum disorder is strengthened.

4. Pathophysiological mechanisms

A potential mechanism by which the changes in gut microbiome can predispose to autism is an alteration in the pattern of synaptogenesis. GF mice have been found to present higher expression of synaptic-related proteins and a subsequent hypermyelination in certain brain areas. This may be an evidence that gut microbiota play a role in brain development. As accelerated brain growth during the first years of life has been associated with neurodevelopmental disorders accompanied by disturbed brain connectivity patterns (such as autism), the effect of the intestinal microbiome may be a linking factor [17,18]. In the same mice models microglia (cell population regulating immune response in CNS) have been shown to display altered immune phenotype, thus leading to an attenuated response to infectious challenges [6,19]. The diminished immune response may also be a result of the decreased blood-brain barrier permeability observed in GF mice in comparison to healthy mice [6].

With regards to metabolic by-products of the gut microbiota, lipopolysaccharides seem to significantly affect the function of specific brain areas (e.g. amygdala), as well as the production of inflammatory

cytokines [20,21]. In addition, some of the short chain fatty acids are believed to modulate host gene transcription and as a result overexposure to them during crucial periods can negatively affect neurodevelopment (e.g. milestones achievement) [13].

Besides, the gut microbiota exerts a significant influence on serotonin synthesis, metabolism and availability. On the other side, studies have inversely correlated high plasma serotonin levels with low serotonergic neurotransmission in patients with autism spectrum disorder, thus providing a complementary mechanism by which gut dysbiosis could adversely affect brain development. Moreover, the maternal gut microbiota can also affect fetal neurodevelopment in a prenatal level by influencing levels of circulating serotonin. In turn, serotonin regulates fetal neuronal cell division, differentiation and synaptogenesis and its depletion results in altered CNS development [22].

The above findings support the hypothesis that gut microbiota has a strong effect on brain development and imply that altered microbiome composition is an underlying factor contributing to the development of some of the autistic traits. It is also a fact that many children with autism exhibit a variety of gastrointestinal symptoms including periodical abdominal pain, food selectivity, gases, constipation with some of them presenting a correlation with certain aspects of the disease. However, further screening of these children reveals objective findings similar to children without autism [23,24].

On the other hand, it should be mentioned that circumstances and practices predisposing to changes in intestinal microbiome (Caesarean section, infant formula instead of breastfeeding) have not always been proven to increase the risk for autism spectrum disorder or other neurodevelopmental disorders (e.g. attention deficit hyperactivity disorder), as other confounding factors (family, environment) seem to exert significant influence, too [25-27]. Under this view more studies in human populations are needed to further confirm a possible etiological link between gut microbiota and autism spectrum disorders in children.

5. Therapeutic interventions

The relationship between gut microbiome and autism could also permit the application of new therapeutic strategies. Hsiao, et al. (2013) have shown that administration of Bacteroides fragilis probiotic alleviates certain symptoms of autism (particularly mood disorders) in an animal model [28]. Controlled studies in humans are generally few and have controversial outcomes. Mixture of probiotics has been found to improve psychological distress, but the study was conducted in healthy subjects [29]. In a pilot study by Tomova, et al. (2015) probiotic diet supplementation normalized microbiome profile in feces of autistic children, but the study did not include any control group (evidence level 4) [11]. Future rigorous clinical trials are anticipated to evaluate more safely the impact of treatments with probiotics on clinical, as well as neurophysiological patterns in children with autism [30]. Moreover, an additional potential therapeutic aim of probiotics/synbiotics administration in this pediatric population could be the alleviation of gastrointestinal symptoms, as no effective treatments for these symptoms exist [31]. With regards to fecal microbiota transplantation, although the efficacy of this method has been investigated in other disorders (metabolic syndrome, inflammatory bowel disease), data in children with autism is poor [32,33].

6. Conclusion

Recent data in literature shows that alterations in gut microbiome can play a role in the pathogenesis of autism spectrum disorders through a variety of mechanisms and among additional predisposing factors. Future and more controlled studies in humans may provide clues to underlying mechanisms and to the effects of potential therapeutic strategies, which target the intestinal microbiota profile.

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Conflicts of interest: None

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