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THE BRAIN-GUT-MICROBIOME AXIS MANIPULATION AS A POSSIBLE THERAPY FOR PATIENTS WITH AUTISM SPECTRUM DISORDER

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Abstract

Autism is a developmental disorder characterized by a delay in the development of social and language skills, as well as different patterns of repeated behavior. While it is exclusively a neurogenic disorder, it is accompanied by a wide spectrum of medical comorbidities of which GI associated problems are among the most common. The GI tract is home to more than 100 million neurons that form the Enteric nervous system (ENS). It communicates with the central nervous system (CNS) mainly through the *vagus* nerve and this connection forms the basis for the bidirectional regulation and integration between the CNS and ENS defined as the gut-brain axis. Even though research in this area is still new, major advances have been made in connecting the brain-gut-microbiota axis and ASD. Experiments done on mice and humans have shown promising results in the treatment and management for this exceptionally hard to treat set of disorders.

KEYWORDS: ASD, autism, brain-gut-microbiome axis, clostridium, serotonin

INTRODUCTION

Autism (or autism spectrum disorders, ASD) is characterized by antisocial behavior and communication difficulties, as well as repetitive and restricted manners that can vary in severity between people. In the last 50 years it has progressed from a strictly defined, rare childhood diagnosis to a well-publicized, recognized, and researched lifelong disability that is now acknowledged as a widespread and extremely diverse condition.[1] Although the diagnosis of ASD is predominantly neurobehavioral, ASD is associated with many comorbidities that are often much more prevalent in autistic children than in typically developing children. Among these co-occurring disorders, gastrointestinal (GI) problems are the most common.[2] This article will aim to assess the possible correlation between ASD and GI problems among these patients as well as examine possible treatments.

WHO SUFFERS FROM ASD?

Based on a paper that examined 99 estimates from 71 studies it has been found that the median range for ASD diagnosis to be 100/10,000(Range 1,09/10,000 to 436,0/10,000 depending on the study)[3], The World Health Organization, citing this paper as a source, estimates that ASD affects 1% of the general population.

The epidemiology of ASD is inconsistent across cultures, possibly due to the fact that it is a spectrum disorder and as such contains within itself a broad array of symptoms that themself affect the diagnosis criteria. Alternatively, variable levels of awareness across countries, differences in culture and diagnostic criteria, as well as differences in sampling and evaluation, also contribute to inconsistent epidemiology findings. A study in Sweden found that while the number of children aged 2-17 years diagnosed with ASD increased 3.5-fold, the traits exhibited did not increase over time, leading to the conclusion that changes in diagnostic criteria may be the reason for increased prevalence.[4] Gender is an important factor influencing the prevalence of ASD, with men four times more likely to be affected than women. One possible explanation is that girls diagnosed with ASD have a more developed lexicon as well as fewer abnormalities in communication and social skills than boys. Furthermore, the repetitive and stereotyped activities girls exhibit also differ from ones present in the male population. These improved social and communication capabilities can assist women in adapting to social situations, disguising some of the main symptoms of ASD and leading to wrong or late diagnosis.[5] However, despite all these findings, it is still difficult to determine if the number of people diagnosed with ASD is rising strictly due to the everchanging categorization criteria or if the number affected is increasing due to

some other factor that contributes to the etiology of the disorder. Despite this, it is widely accepted in the medical world that the occurrence of the condition is 100/10,000 in the general population.

THE CONNECTION BETWEEN ASD AND THE GUT MICROBIOTA

ASD is accompanied by a wide array of medical comorbidities which range from neurological to physiological. Recognizing these co-occurring problems is important because many of them can stimulate or exacerbate the abnormal behaviors seen in children with autism. Additionally, since most of these conditions are curable, proper diagnosis and treatment can greatly improve the quality of life for children and families given that usually the agitated behavior stops once the associated symptoms subside. However, comorbidities in children with ASD are not always easily identifiable due to a variety of factors, including communication impairment, symptom ambiguity, deviation from the general population, and changes over time.[6]

Many symptoms and behaviors commonly attributed to autism may reflect the presence of other organic disorders.

Table 1. Comparison of prevelance of GI symptoms for children diagnosed with ASD, delayed development(DD) and typical developing children (TD).

Source: Chaidez V, Hansen RL, Hertz-Picciotto I. Gastrointestinal problems in children with autism, developmental delays or typical development. *J Autism Dev Disord*. 2014;44(5):1117. doi:10.1007/S10803-013-1973-X
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	ASD n=499	TD n=324	DD n=137
GI symptoms[c]	%	%	%
Abdominal pain	5.1%	1.6%	3.9%
Gaseousness/bloating sensation	11.0%	2.0%	2.3%
Diarrhea	13.0%	1.6%	6.1%
Constipation	15.5%	3.5%	15.8%
Pain on stooling	6.2%	1.6%	5.5%
Vomiting	2.9%	0.3%	6.2%
Sensitivity to foods	31.0%	4.5%	11.1%
Difficulty swallowing	4.2%	0.3%	4.6%
Blood in stools	0.4%	0.3%	0.8%
Blood in vomit	0.2%	0.0%	0.0%
Presence of related issues[d]			
Food allergies Y/N	23.0%	11.1%	13.5%
Food restrictions Y/N	37.4%	10.4%	21.6%
Food dislikes Y/N	63.5%	34.0%	34.6%
GI diagnosis Y/N	7.5%	1.9%	22.9%

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3981895/

For example, head banging could be caused by headaches or pain when frustrated, as well as an inability to communicate these symptoms. If the child fidgets frequently, he or she may be suffering from constipation. The presence of pain and the child's inability to communicate about his or her condition may also be associated with aggression and self-injurious behavior. Pica (an eating disorder in which a person eats things not usually considered food) could also be a sign of nutrient deficiencies, particularly iron deficiency, which is relatively common in autistic children. Food refusal may be related to the high food selectivity observed in autistic children, but it could also be due to the presence of food allergy or intolerance. It could be due to a more local cause, such as the presence of dental problems that hinder their ability to properly chew and digest food.[7]

Further contributing to the problem in diagnosing these individuals lies in their inability to properly communicate which is further exacerbated by the fact that for those diagnosed with ASD the occurrence of pathological conditions is greatly amplified as opposed to the general population. As such, 84% suffer from anxiety, 26% from depression and 5-38% from epilepsy depending on age (compared to 31%, 7% and 1% respectively in general population).[8-10] When examining non-neurological co-occurring conditions, the ones that have the highest correlation with ASD are Gastrointestinal (GI) problems. It is important to note that some of these problems can be inferred as a direct result of the increased sensitivity to foods as well as different eating habits and desires present in people diagnosed with ASD. Even taking that into account, GI problems are far more common in children with Autism and developmental delays than those in neurotypical children. As presented in Table 1, children with ASD are approximately six to eight times more likely to report frequent gaseousness/bloating, constipation, and diarrhea than typically developing children.[2] Coupled with the fact that children with GI problems show agitated behavior that disappears once the underlying problem is treated, it is assumed that the gut microbiota and the symptomatology of ASD are somehow connected. Still, more research needs to be done to examine if this is a direct cause and effect relation or a byproduct of some other unknown condition that affects them both.

THE BRAIN-GUT-MICROBIOTA AXIS

Recent studies on the gut–brain axis suggested that the gut contains 200-600 million nerve cells (roughly equal in number to the spinal cord), eventually forming an extensive network called the enteric nervous system (ENS). The ENS and the central nervous system (CNS) are mainly connected via the vagus nerve and this connection forms the basis for the bidirectional communication between the CNS and ENS defined as the gut-brain axis.[11] The complex relationship can be examined in figure 1.

Communication within the gut-brain axis is regulated via the autonomic nervous system, the enteric nervous system, neurotransmitters, hormones, and immune responses. Neurotransmitters produced in the gut influence our emotions by modulating the gut-brain axis. The

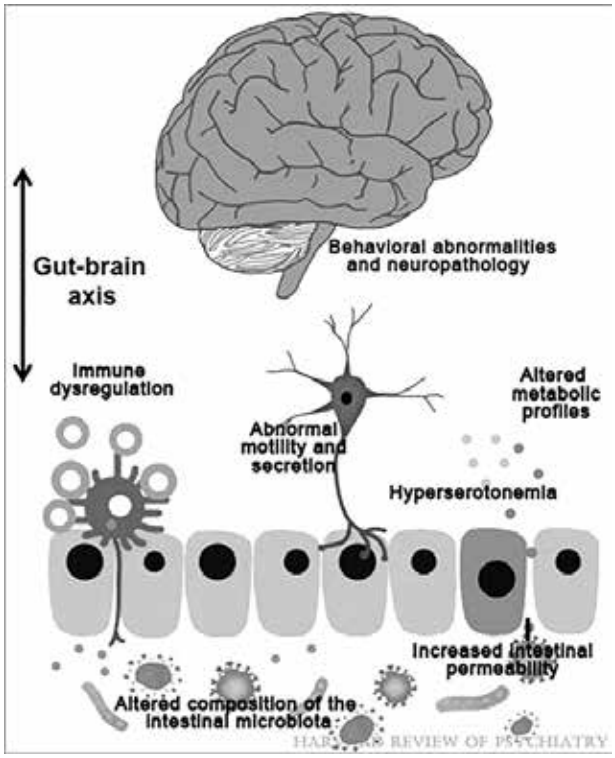


Figure 1. Gastrointestinal influence on symptoms of autism spectrum disorder.

Gastrointestinal abnormalities, such as increased intestinal permeability, altered intestinal microbiota composition, and dysregulated gastrointestinal motility and secretion, have been described in subsets of ASD patients. Overall, changes in the gastrointestinal tract can influence higher-order behavior and brain function via the gut-brain axis, driven by direct connections of the intestinal epithelium to the brain stem and secondary projection sites via the vagus nerve, and by indirect connections of the gut to the brain via alterations in immunity and metabolism.

Source: Hsiao EY. Gastrointestinal issues in autism spectrum disorder. *Harv Rev Psychiatry*. 2014;22(2):104-11. doi: 10.1097/HRP.0000000000000029. Copyright © The Author(s) 2014.

neurotransmitter serotonin (5-hydroxytryptamine) is mainly produced in the gut (about 90%) and promotes mucosal growth, maintenance of neurogenesis, liver regeneration and inhibits osteoblast proliferation.[12] As 5-HT impacts the development of both central and enteric nervous system it could play an important role in both brain and intestinal anomalies associated with ASD. A study found that 30% of individuals with ASD have increased levels of 5-HT in the blood (hyperserotonemia).[13] Hyperserotonemia in this subset of ASD patients may therefore be indicative of dysregulation of gastrointestinal 5-HT secretion. Alternatively, serotonin can be regulated by its reuptake transporter (SERT). Five different gene encoding variants of this transporter have been found to be overexpressed in ASD patients. Each variant was a gain-of-function mutation that conferred to hyperactivity of SERT. The most common of these variants, SERT Ala56, has been found to be associated with increased serotonin levels in blood, as well as altered social and repetitive behavior in mice.[14] SERT Ala56 mice also have abnormal ENS development which contributes to their abnormally slow in vivo and in vitro motility of the whole intestine, as well as reduced frequency and speed of colonic peristaltic contractions.[15] Interestingly, modulation of the 5-HT4 receptor may circumvent the defects caused by SERT-Ala56 mutations. Administration of prucalopride, a highly selective 5-HT4 agonist, during critical periods of neurodevelopment normalized intestinal neuron numbers and prolonged colonic motility recovery in SERT-Ala56 mice.[16] Furthermore, 5-HT4 receptor is located in the parts of the brain involved in learning, memory, depression, anxiety, and feeding behavior. Studies show that hypomethylation of the genes encoding this receptor are associated with greater risk of ASD.[17] Despite these promising findings further human testing is needed to determine the safety and efficacy of using 5-HT4 agonists in a clinical setting.

Another possible link between the Brain-gut-microbiota axis and ASD lies in the microbiota of GI tract and the presence or lack of certain bacteria in it. One study found that in ASD brains, the expression of genes associated with blood-brain barrier integrity may be altered, leading to increased neuroinflammation and impaired intestinal barrier integrity.[18]

The role of the gut microbiota in ASD was first questioned when anecdotal reports emerged of young children who developed regressive ASD after repeated exposure to antibiotics for chronic otitis media. The clinical course described in this subset of children included the development of chronic diarrhea after administration of antibiotics, followed soon afterwards by loss of language and social skills. The first hypothesis, put forward in part by Ellen Volte, involved anaerobic bacteria, namely Clostridia, due to their ability to produce neurotoxins. This particular bacterial strain produces tetanus neurotoxin (TeNT) which travels through the vagus nerve to the CNS and blocks neurotransmitters through proteolytic cleavage of synaptobrevin, a synaptic vesicle membrane protein, causing numerous behavioral disorders. This suggests that the presence of B. tetanus can be used as an indicator for ASD diagnosis.[19,20] To test this hypothesis, 11 children with regressive autism participated in an intervention study using vancomycin, an oral, minimally absorbed antibiotic. Multiple psych evaluation tests were performed by a psychiatrist before and after treatment, and short-term improvement was seen in 8 of 10 children tested. Unfortunately, these benefits were significantly diminished at follow-up.[21] Another study performed on mice showed that colonization of the maternal microbiota with Clostridium-dominant spore-forming bacteria leads to decreased fetal brain gene expression and thalamocortical axon formation which connect the thalamus and cerebral cortex. One possible therapy for this is fecal transplant as it can restore the healthy microbial composition inside the maternal mice. By increasing the relative abundance of Bacteroides species by 95%, Clostridium difficile's relative abundance was reduced to 5%.[19] Further testing is required to see if this will prove to be a viable therapy option in humans.

CONCLUSION

Summarizing all the growing evidence reveals a relationship between the gut-brain axis and ASD. There has been a rapid advancement in the knowledge base of the gut microbiome and the technologies used to study it. However, considerable effort is still needed to study the Brain-gut-microbiota axis in adults with ASD, as almost all research in this field has focused on pediatric populations. Despite this, it is strongly implied that exploring the gut microbiome in the pathogenesis and advancement of ASD will aid in finding promising pharmacological agents as well as developing novel microbially mediated treatments. Experts are hopeful that those findings will deliver new hope for the treatment and management of this exceptionally hard to treat set of disorders.

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MANIPULACIJA CRIJEVNO-MOZGOVNE OSOVINE KAO POTENCIJALNA TERAPIJA ZA PACIJENTE DIJAGNOSTICIRANE SA POREMEĆAJIMA AUTISTIČNOG SPEKTRA

Sažetak

Autizam je razvojni poremećaj koji karakterizira zaostajanje u razvoju socijalnih i jezičnih vještina, kao i različitih ponavljajućih obrazaca ponašanja. Iako je isključivo neurogeni poremećaj, popraćen je širokim spektrom medicinskih komorbiditeta od kojih su jedni od najčešćih problemi vezani uz probavni trakt. Unutar gastrointestinalnog sustava nalazimo složenu mrežu više od 100 milijuna neurona koji zajedno komuniciraju i čine enterički živčani sustav (EŽS). On komunicira sa središnjim živčanim sustavom (SŽS) preko *nervusa vagusa* koji čini osnovu za dvosmjernu regulaciju i integraciju između EŽS-a i SŽS-a koji zovemo crijevno-mozgovna osovina. Unatoč činjenici da su istraživanja ovog područja nova, postignuti su veliki napredci u povezivanju crijevno-mozgovne osovine i autizma. Istraživanja na miševima, a i ona ljudima pokazala su obećavajuće rezultate u poboljšanju simptoma ovog skupa iznimno teško izlječivih poremećaja.

KLJUČNE RIJEČI: autizam, ASD, crijevno-mozgovna osovina, klostridije, serotonin