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How Altering Gut Microbiota Affects Autism Spectrum Disorder (ASD) and its Associated Gastrointestinal (GI) Symptoms

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Introduction

Autism Spectrum Disorder (ASD) is defined as "A biologically-based neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction and restricted, repetitive patterns of behavior, interests, and activities.[1] According to the Federal Agency Centers for Disease Control and Prevention (CDC), 1 in 59 children in the United States are diagnosed with Autism Spectrum Disorder. [2] Not only is ASD common in the United States, it is also a costly disorder. According to the Journal of Autism and Developmental Disorders, the forecasted annual direct medical, non-medical, and productivity costs are projected to be $461 billion dollars in 2025. If the incidence of ASD continues to rise then the projected costs of ASD may even exceed the costs of diabetes by 2025.[3] No treatment is currently available to cure this disorder. [4] Contemporary medications treat only the predominant symptoms. [4] Guidelines in UpToDate™ state that ASD requires a comprehensive treatment approach. Therapeutic interventions include behavioral and educational interventions, pharmacologic treatments for medical or psychiatric comorbidities, and complementary or alternative therapies. Treatment is symptomatic.[1] According to CDC.gov, complementary or alternative treatments, and even dietary approaches are sometimes utilized, but many of these therapies lack scientific support necessary for widespread recommendation. Some may be helpful in one child but not another.

Since ASD has become more prevalent, more research has been devoted to understanding its pathophysiology, which may lead to finding effective therapies. Recent research has found correlations between several types of neurobehavioral disorders, including ASD, and microbial dysbiosis of the intestinal tract. Whether the association between ASD and aberrant gut microbiota is a causal relationship is yet to be determined.[5] Multiple theories and hypotheses have been formed about the connection between ASD and gastrointestinal (GI) symptoms, most

suggesting some aberrancy of the normal flora in the gut of ASD patients. One theory suggests that elevated levels of Clostridium bacteria in the GI system could cause a regressive type of autism. In fact, a ten-fold increase of Clostridium was found in the feces of children with ASD compared to their healthy counterparts. In other research, increased numbers of Sutterella (an anaerobic gram-negative bacterium) and other gastrointestinal bacteria were found in children with ASD. The abnormal gut flora in ASD patients may be related to the neurobehavioral aspects of this disorder or may merely be an incidental or unrelated finding. The role of an altered gut microbiome in the pathogenesis of ASD has not been determined by currently available evidence. [5] Nevertheless, many ASD patients have concurrent GI symptoms such as constipation, stomachaches, abdominal pain, nausea, and diarrhea. In a retrospective study that examined the prevalence of comorbid conditions in ASD patients, data were collected from three general hospitals and one pediatric hospital. Over 14,000 patients under the age of 35 with a diagnosis of ASD were included. A higher prevalence of inflammatory bowel disease (IBD) and other GI disorders were found in ASD patients compared to controls. [6]

If the abnormal gut flora and increased GI symptoms in ASD patients are indicative of a pathophysiologic process causing neurobehavioral disturbances, then perhaps altering the gut flora may improve both the GI and neurobehavioral symptoms. Recent research has explored this possibility and produced findings that are promising for treatment with a different approach, altering the gut microbiome.

Discussion

Although the available research is recent, few studies have addressed the hypothesis that improving the gut biota might remedy ASD. Furthermore, the sample sizes were small. In addition, many studies had high dropout or exclusion rates. These limitations decreased the power and generalizability of this research. Nonetheless, most of the data were obtained in

experimental, rather than observational studies, which strengthened their evidence. Other strengths included very specific treatment regimens, control groups, and verified assessment tools. These studies altered the gut microbiota in ASD patients, each using a different method, and then evaluated the participants ASD-related behavior, GI symptoms, or both.

The first method of treatment utilized vitamin and mineral supplementation along with dietary changes, and then assessed for changes in ASD patient behavior. Specifically, 67 children and adults with ASD, ages 3-58, and 50 non-sibling neurotypical controls of similar age and gender were enrolled in a one-year, single-blind study in which the investigators were blinded. The treatment group was given a vitamin and mineral preparation, essential fatty acids supplements, the amino acid carnitine, as well as digestive enzymes, and treated with Epsom salt baths. Additionally, they were placed on a healthy gluten-free, casein-free, soy-free (HGCSF) diet. [7] In this study, nonverbal IQ increased, social responsiveness was enhanced, and multiple other well-known ASD behavior tests showed improvement in communication, social skills, and autistic behaviors in the treatment group. [7] Several limitations of the study include a small sample size, therefore limited power and generalizability as well as multiple interventions, making it difficult to identify what intervention is responsible for the improvements. Additionally, the study did not look at the participants microbiomes before and after treatment.

The second method of altering gut microbiota in ASD patients utilized prebiotic/probiotic supplements and dietary changes in order to improve GI and behavioral symptoms. In a study by Shaaban et al., 30 Egyptian children with ASD ages 5-9 years old were evaluated in a prospective open-label study. The treatment group received three probiotic strains (*Lactobacillus acidophilus, Lactobacillus rhamnosus,* and *Bifidobacteria longum*). Five grams of this powder were given daily to each participant for three months. GI flora was evaluated by PCR assay

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before and after treatment. The Gastrointestinal Severity Index (GSI) and the Autism Treatment Evaluation Checklist (ATEC), indicating the severity of ASD symptoms, were surveyed. [8] In the treatment group as compared with the placebo group, ATEC scores improved significantly and antisocial behaviors, disruptive behaviors, anxiety, and communication disturbances all decreased. Stool consistency and gut function improved and a reduction in Clostridium species was noted. All other improvements were not statistically significant. [8] In another study, 26 children aged 4-11 years old with a formal diagnosis of ASD participated in a randomized, double-blind, placebo-controlled study. Twelve of the participants had a restricted gluten/casein free diet. In addition, each participant was assigned to either receive prebiotics (Bimuno® galactooligosaccharide (B-GOS®)) or placebo for 6 weeks. GI function and symptoms were assessed via Bristol stool charts, fecal and urine samples. Behaviors were assessed via anxiety and ASD behavior related questionnaires. [9] Significant improvement in antisocial behaviors, reduced stress, improved memory, and changes in the stool micro-organism compositions were found in the groups that had both diet and prebiotic interventions; while the group that received only the prebiotics and no dietary changes did not experience significant changes in GI symptoms or sleep.[9] In another study, prebiotics combined with probiotics were compared with prebiotics alone. This small pilot study consisting of eleven children aged 2-11 years old with ASD and GI symptoms was double-blinded, randomized, and included a cross-over component. Participants were given either the combination of the probiotic B. infantis with the prebiotic bovine colostrum product (BCP) or BCP alone, and then after a 2-week washout period were crossed over. Behavior and GI questionnaires along with fecal biota and chemistries, blood cells and their markers, and urine metabolites were analyzed on all participants.[10] Improvements were reported in all treatment groups. The frequencies of certain GI symptoms and aberrant behaviors

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(irritability, lethargy, hyperactivity) were reduced in the group that only received the prebiotic. Although seventy-five percent of parents reported greater improvement in their children on BCP alone, only 25% of parents reported greater improvement with combination treatment. [10] A major limitation of the study was a small sample size due to only 11 individuals meeting the inclusion criteria, therefore limiting generalizability. Strengths of the study included double blinding of the treatment, therefore reducing bias of results.

A third method of altering gut microbiota in ASD patients was achieved through Microbiota Transfer Therapy, which was shown to improve both GI and ASD symptoms. In an open-label clinical trial study, 18 children with ASD, ages 7-16 years old, were studied to determine the impact of Microbiota Transfer Therapy on gut microbiota composition and GI and ASD symptoms. Participants were given two weeks of antibiotics, followed by a bowel cleanse, and then an extended fecal microbiota transplant. Patients first received a high dose transplant followed by lower maintenance doses for 7-8 weeks. Testing included GI bacteria sequencing on stool samples, blood tests, daily stool records (DSR) from parents, GI symptoms via the Gastrointestinal Symptom Rating Scale (GSRS), and behavior assessment tools. Changes were found in the gut microbiota and in the Parent Global Impressions (PGI-III) and GSRS. [11] GI symptoms decreased by 80% at the end of the treatment. Patients had improvements in diarrhea, abdominal pain, constipation, and indigestion. Eight weeks after treatment, patients continued to experience improvements in GI symptoms. Additionally, the parents noted significant improvements in their children's behavioral symptoms with no reversions after 8 weeks. [11] Strengths of this study included assessment of gut microbiota and behavioral assessments. Limitations of this study included small sample size and short duration of follow up.

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Conclusion

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GI microbiota and ASD do seem to be linked. However, due to small sample sizes in these studies, it is difficult to confidently conclude that altering the GI microbiota of ASD patients will improve their GI symptoms and/or behaviors. The evidence seems to indicate that altering the microbiota may positively influence ASD patients. Additional research is necessary to corroborate these findings. Larger studies are needed to power the experiments and extend their generalizability. Fortunately, an on-going study in Italy should achieve these goals. This double-blind, randomized control trial study of 100 preschoolers with ASD is examining the effects of the probiotic mixture, Vivomixx®, on GI symptoms, autism severity symptoms, affective and behavioral comorbid symptoms, plasma, urinary and fecal biomarkers related to abnormal intestinal function, and neurophysiological patterns. [12] Such studies can provide stronger evidence for more definitive treatment recommendations for ASD patients.

Nevertheless, with the available evidence, clinicians could provide ASD patients or their parents information about microbiota alterations in ASD, the role these abnormalities may play in both the GI and the behavioral symptoms, and the preliminary evidence of improved symptoms achieved by changing the gut microbiome. With the caveat that further research is needed on the efficacy and safety of such treatments, recommendations and suggestions could include the use of prebiotics and/or probiotics, advising specific dietary changes, and exploring other methods of altering the gut microbiome. Except for MTT, these therapies are all complementary and alternative, remedies that may be beneficial and may be preferred by some patients and their families because they are “natural”. Nonetheless, encourage patients to be cautious about complementary and alternative medicine because not all those therapies have been proven to be safe or effective. Furthermore, advise them to inform and work together with their medical providers in order to monitor benefits, adverse effects, and drug interactions.

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