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REVIEW

Can probiotics benefit children with autism spectrum disorders?

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Abstract

Children with autism are commonly affected by gastrointestinal problems such as abdominal pain, constipation and diarrhea. In recent years, there has been a growing interest in the use of probiotics in this population, as it hypothetically may help to improve bowel habits and the behavioral and social functioning of these individuals. The gut microbiome plays an important role in the pathophysiology of organic as well as functional gastrointestinal disorders. Microbial modification with the use of antibiotics, probiotics, and fecal transplantation have been effective in the treatment of conditions such as recurrent *Clostridium difficile* infection, pouchitis, and irritable bowel syndrome. The present review presents a number of reported clinical, immunological and microbiome-related changes seen in children with autism compared to normally developed children. It also discusses gut inflammation, permeability concerns, and absorption abnormalities that may contribute to these problems. Most importantly, it discusses evidence, from human and animal studies, of a potential role of probiotics in the treatment of gastrointestinal symptoms in children with autism.

Key words: Microbiome; Gastrointestinal; Inflammation; Functional bowel disease; Probiotics; Autism

Core tip: Important new information has identified an abnormal intestinal microbial community in children with autism, an abnormality reported in many gastrointestinal (GI) conditions, including inflammatory bowel disease and irritable bowel syndrome (IBS). There is a complex interplay in these conditions between GI function (motility, secretion, permeability), the immune system, and the microbiota. Many parents of children with autism complain of GI symptoms, and they administer probiotics, a treatment which has been found to be safe and effective for adults with IBS. Future investigations are needed to determine if

probiotic treatment would benefit the symptoms and behavior of these children.

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INTRODUCTION

The influence of the enteric microbiota on the human body has only started to be unveiled. Its impact is wide, as it has been shown to affect a number of processes including the immune response, metabolism, and neurologic function[1-3]. The disruption of the normal commensal microbial community in humans, also called "dysbiosis", is associated with an increasing number of disorders such as inflammatory bowel disease, irritable bowel syndrome, obesity, hypertension, diabetes, and autism[4-8]. The aim of the present review is to synthetize current data on the association between microbiota dysbiosis and autism, and to assess if its modification could have a beneficial effect in children with autism.

GASTROINTESTINAL ABNORMALITIES IN AUTISM

Autism is a neurodevelopmental disorder which affects social interaction, verbal and non-verbal communication, and behavior. A recent report from the Centers for Disease Control and Prevention indicates a rise in the prevalence of autism in children to one in 68 children in the United States (78% increase since 2007)[9].

Children with autism spectrum disorders (ASD) are among the populations that are most often referred to the Pediatric Gastroenterology clinic. During a two-year period, 3% (121/4013) of children seen by 4 pediatric gastroenterologists for various abdominal complaints in our clinic had an underlying ASD (C. Bearden, U.T. Bioinformatics, personal communication 9-24-2016). The true prevalence of gastrointestinal symptoms (GIS) in ASD is not known, but available data suggest a figure approximately 40%[10]. Wang *et al*[11] reported data obtained from families with children with ASD registered in the Autism Genetic Resource Exchange (AGRE). In their study of 589 affected children, 42% had GIS. Increased autism symptom severity was associated with higher odds of having GIS[11]. Abdominal pain, constipation, diarrhea, nausea, and bloating were the most common symptoms. In the largest study, Mazurek *et al*[12] reported that of 2973 children in an ASD network, 42% reported GIS lasting > 3 mo. A wide range of gastrointestinal (GI) problems have been reported, including feeding abnormalities, gastroesophageal reflux, abdominal pain, diarrhea, fecal incontinence, constipation, and alternating diarrhea and constipation have been reported in one out of three children in the autism spectrum[13,14]. More recently, based on a large epidemiological study, eosinophilic esophagitis in children with ASD and dysphagia has been added to the list of disorders with increased risk in this population, compared to the general population[15]. This group of children with autism reportedly also has severe anxiety, irritability and social withdrawal symptoms, which may overshadow their GI complaints[16].

Some researchers such as Pusponegoro *et al*[17] have reported no differences between children with autism and controls with regard to gastrointestinal symptoms, intestinal inflammation (based on fecal calprotectin), microbiota (based on urinary D-lactate) or intestinal permeability (based on urinary lactulose/mannitol ratio). However, this group reported an increased urinary I-FABP (marker of enterocyte damage) in children with autism who had severe behavioral abnormalities, compared with autistic children with mild maladaptive behavior and compared with normal children[17].

INFLAMMATION HYPOTHESIS

A number of recent studies have suggested that the GIS in ASD may be a manifestation of an underlying inflammatory process. Systemic inflammation has been suggested by an excessive accumulation of receptors for advanced glycation end products (RAGE) in blood and their proinflammatory ligand S100A9 in the plasma of individuals with ASD[18]. The level of S100A9 in plasma correlated with the autism severity score. Another study hypothesized that the inflammation may be pathophysiologically related to an abnormal microbiota. They compared the metagenomic profile of ileal and colonic biopsies in children with ASD, ulcerative colitis (UC), and Crohn's disease (CD). These investigators found that the transcriptome profiles of these tissues of children with ASD segregated apart from normal controls and alongside those with CD and UC when they used principal components analysis, as would be seen with an inflamed colon[19]. However, the authors did not identify why these tissues of ASD children had different transcriptional profiles; for example, they did not look for evidence of inflammation by assessing serum cytokines or fecal inflammatory markers such as calprotectin or interleukin-8. Other groups studying ASD have failed to show changes in gut biopsy cytokine levels[20] or changes in fecal calprotectin[21]. One must keep in mind that these studies were small, and measurable abnormalities were observed in a significant subset of with ASD (approximately 25% of those studied).

Enhanced T cell activation, heightened immunoglobulin and cytokine profiles, as well as histologic changes assessed in intestinal biopsies such as infiltra-

tion of lymphocytes, monocytes, natural killer cells and eosinophils have been described in children with autism[22-26]. These findings can be present in other gastrointestinal conditions such as food allergies and immunodeficiency[27]. In contrast, other laboratory measures of intestinal health, such as fecal levels of calprotectin, lactoferrin, secretory IgA, and elastase have found to be normal in children with autism[21,28]. In addition, reports of intestinal permeability (IP) in children with autism have been conflicting. Studies have reported abnormal IP in these children compared to controls[29,30]. Some have also reported increased IP to occur in first degree relatives of patients with autism *et al*[31]. In contrast, our group as well as others (mostly in small series) have found that the intestinal permeability of children with autism was not different from normal controls[17,32-34].

A recent report indicated that children with autism also have an abnormal carbohydrate digestion based on significant decrease in the expression on their intestinal biopsies of disaccharidases (sucrose-isomaltase, maltase-glucoamylase, and lactase), as well as the hexose transporters (SGLT1 and GLUT-2)[35], a finding which agreed with a previous uncontrolled study[36]. This finding was not supported by extensive observations of Kushak *et al*[37] from a center that performs many intestinal biopsies. These investigators had originally found that more than half of a group of children with autism had low levels of the enzyme lactase in duodenal biopsies[38]. However, in a follow-up study which included neurotypical controls, mucosal disaccharidase activity was not different comparing autistic and nonautistic individuals. Interestingly, even though the disaccharidases were within the normal range, the investigators found that children with ASD had evidence of mucosal inflammation on intestinal biopsy. Standard fecal indicators of gut inflammation, fecal calprotectin and lactoferrin were similar in both groups. A measure of gut permeability, lactulose/rhamnose ratio in urine after oral administration, was also not statistically different in patients with and without autism. Larger controlled studies are required to determine if the gastrointestinal symptoms in children with autism are in fact related to reproducible, "organic" findings, such as intestinal inflammation, to differences in nutrient digestion, or to an abnormal intestinal permeability[27].

FUNCTIONAL BOWEL DISEASE HYPOTHESIS

Gastrointestinal symptoms in ASD may be simply a reflection of sensory over-responsivity to abdominal signals. However, in the authors' opinion, the most common gastrointestinal complaints in children with ASD resemble those of adults and teens with functional bowel diseases such as irritable bowel syndrome (IBS). Irritable bowel syndrome is characterized by symptoms of diarrhea and/or constipation, typically with the relief of pain accompanying the passage of a stool, symptoms which fulfill the Rome Ⅲ criteria[39]. Many children with ASD have diffuse abdominal pain and an irregular stool pattern with either diarrhea or constipation, or alternating diarrhea and constipation. We have postulated that a significant proportion of children with ASD and chronic GIS, have a form of IBS. However, the Rome Ⅲ criteria are validated in adults with normal IQ but are somewhat difficult to apply to normal children, and even more so in those with ASD. When compared to GI symptom scores in ASD, which have been useful but are not validated, there is much broader experience in quantifying autistic behavior changes, such as irritability as measured by the Aberrant Behavior Checklist[40]. As mentioned, studies have shown that the presence and severity of GI symptoms correlate with the severity of underlying autism[11,28,41].

GUT MICROBIOME IN AUTISM

Trillions of microbes and 500-1000 species of microorganisms are natural inhabitants of our gastrointestinal tract, wherein the phyla *Firmicutes*, *Bacteriodetes*, and *Actinobacteria* are the most common. Anaerobic bacteria, yeasts, viruses, and bacteriophages (viruses which reside and proliferate within bacteria) also influence the gut microbial diversity[42,43]. The gut microbiome has a symbiotic interaction with the various organ systems of our body, and it is known to contribute to many GI functions, such as maintaining the integrity of the epithelial barrier, stimulating immune interactions, participating in gastrointestinal motility, and regulating drug and nutrient metabolism[44]. This normal interaction can be disturbed by a number of events, such as infections, gastrointestinal diseases, dietary changes, and neurologic disorders. Drugs such as acid suppressants, antibiotics, and corticosteroids have also been reported to perturb this homeostatic equilibrium. This dysbiosis contributes to the pathophysiology of many gastrointestinal conditions such as inflammatory bowel disease, functional gastrointestinal disease, food allergy, obesity, and liver disease[45].

The enteric microbiome of children with ASD is different from that of typically developed children. Abnormal colonization could be related to diverse factors, including a more restricted diet and exposure to more antibiotic early in life. For example, two studies found that children with ASD were more likely to be treated with antibiotics for otitis media[46,47]. Finegold *et al*[48] reported different levels of bacterial phyla in children with ASD by pyrosequencing. When comparing autistic children with controls there were changes in phyla *Firmicutes* (63% *vs* 39%, respectively), *Bacteriodetes* (30% *vs* 51%), *Actinobacteria* (0.7% *vs* 1.8%), and *Proteobacteria* (0.5% *vs* 3.1%)[48]. In a different study, this same group also reported the presence of non-spore-forming anaerobes and microaerophilic bacteria

in gastric and duodenal aspirates from children with autism, organisms which were not present in control children[48].

As mentioned, a less diverse microbial community in gut of children with autism with lower levels of some genera (*Prevotella, Coprococcus* and *Veillonellaceae*) has been reported. Interestingly, these particular species are known to be versatile carbohydrate metabolizers; and in a controlled trial, reduced colonization correlated with autistic symptoms but not with diet pattern[49]. Other differences in individuals with ASD include the overgrowth of *Clostridium* species, including *Clostridium histolyticum (*linked to the presence of GI symptoms in one study), and low levels of *Bifidobacteria*, a species known to have anti-inflammatory effects[48,50,51].

Overgrowth of other bacteria such as *Desulfovibrio* species has also been found in children with autism and their relatives, compared to controls[52]. Additionally, higher levels of *Caloramator*, *Sarcina*, *Alistipes*, *Akkermansia*, *Sutterellaceae* and *Enterobacteriaceae* were found in children with autism compared with typically developed children[53,54]. Kang *et al*[49] reported a less diverse fecal microbiome by pyrosequencing of 16S rDNA in children with autism. Despite these studies, it should be noted that when bacteria tag-encoded pyrosequencing was used, Gondalia *et al*[55] did not find differences in the gut microbiome, comparing children with autism with their siblings.

Much work needs to be done in determining the metabolic consequences of an abnormal microbiota in ASD. Bacterial by-products are the likely mediators of systemic effects that could lead to alterations in the children's behavior. Some investigators have hypothesized that the abnormal microbiota in children with ASD produces changes in behavior *via* a mechanism involving excessive production of short chain fatty acids (SCFA), such as propionate and butyrate, which represent the major anions of human feces. These SCFA can produce behavioral changes in rodents when injected into the brain ventricles or systemically *via* intermediates such as p-cresol that alter dopamine metabolism[56]. Ongoing investigations have begun to highlight the importance of SCFA in ASD[57,58].

TARGETING THE GUT MICROBIOME AS A POTENTIAL TREATMENT FOR CHILDREN WITH AUTISM

Probiotics

The internationally accepted definition of probiotics is "live microorganisms which when administered in adequate amounts confer a health benefit on the host". Dietary prebiotics are "selectively fermented ingredients that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host well-being and health". The potentially synergistic combinations of pro- and prebiotics are called synbiotics[59]. Functional bowel disorders (including IBS, functional abdominal pain, functional dyspepsia, and cyclic vomiting syndrome) are the most common conditions leading to referral of children to the pediatric gastroenterology clinic[60]. Recent evidence suggests that an abnormal fecal microbiota may play a causal or contributory role to IBS in adults[61] and children[62].

In adults with a functional GI disorders, there is accumulating evidence for a beneficial effect of probiotics. Evidence for probiotic efficacy in IBS now includes 23 randomized controlled trials (RCTs) (2575 patients) and the demonstration of improvement in global symptoms, abdominal pain, bloating and flatulence; however there was heterogeneity among the studies and authors concluded the optimal probiotic has not been identified[63]. In the most recent meta-analysis, which included 21 RCT's, a 1.82-fold (CI: 1.27-2.60) relative rate of improvement *vs* placebo was noted[64]. Fewer studies have been done in children; the only systematic review concluded that 4 probiotics were associated with improvement in symptoms in children with IBS: *L. rhamnosus GG*, *L. reuteri DSM 17938*, VSL#3, and a combination probiotic containing 3 *Bifidobacteria*[65].

The differences in the gut microbiome comparing autistic and typically developed children described in the previous section may provide a clue to the cause for GI symptoms. One early study of vancomycin, a poorly absorbed antibiotic known to destroy *Clostridia* and other gram positive organisms, demonstrated an improvement in diarrhea and more normal behavior, as evidenced by videotape, when vancomycin was given short-term[66]. As mentioned, the gut microbiome can be altered by the use of antibiotics, prebiotics, probiotics, or synbiotics (prebiotics plus probiotics) administered by physicians or parents to ameliorate symptoms in children with ASD[57,67-69].

Virtually all of the GI functions postulated to be impaired in ASD have been shown to be improved by probiotics in animal studies. For example, we previously found that a human breast milk and gut commensal, *Lactobacillus. reuteri,* when fed daily, reduced lipopolysaccharide (LPS)-induced intestinal inflammation[70]. In newborn rat pups, another probiotic, *Bifidobacterium bifidum* reduced gut permeability across the tight junctions that "seal together" the epithelial cells in a model of necrotizing enterocolitis[71]. A recent study by Buffington *et al*[72], which aimed to study mechanisms of abnormal behavior in autism, utilized a maternal high fat diet to induce abnormal social (withdrawal) behavior in the offspring. It is worthy to mention that in humans, too, maternal obesity[73,74], and maternal diabetes[75] been shown to be linked to autism in the offspring. In the mice, high-fat maternal diet produced changes in neurotransmission in the hypothalamus of the newborns. Abnormal behavior was found to be correctable by co-housing "autistic pups" with normal infant pups whose mothers did not take a high fat diet,

Table 1 Evidence supporting a role for probiotics in treating gastrointestinal symptoms in autism spectrum disorders

Clinical symptoms	Ref.
Children with ASD have an abnormal fecal microbiota	[28,35,48,51,54,98-100]
GI symptoms common in ASD are similar to those in IBS	[11,12]
IBS also is associated with an abnormal fecal microbiota	[61,62,101]
Meta-analysis shows IBS symptoms are improved by probiotic treatment. (Preliminary evidence suggests potential benefits in ASD in children and rodents models.)	[65,72,102-104]
Mild inflammation in the GI tact may be seen in children with ASD. (There is evidence to support or refute this contention: abnormal duodenal and ileal biopsies and high plasma S100A9 but normal fecal calprotectin and lactoferrin levels)	[19,22-26,31,37]
Probiotics reduce gut inflammation (Shown in animal models and in human diseases)	[70,105-108]
Systemic inflammation can be also seen in children with ASD	[18,109-111]
Immune modulation of children with ASD may reduce clinical symptoms	[41,112]

ASD: Autism spectrum disorders; GI: Gastrointestinal; IBS: Irritable bowel syndrome.

indicating a microbial effect which was evidenced by a change in microbiota. Following this hypothesis, the authors found that by administering a probiotic, *Lactobacillus reuteri*, the antisocial behaviors and aberrant neurotransmission could be reversed[72].

The lay press and internet have certainly embraced the concept that gut bacteria are linked to autism. A particularly fascinating recent publication from Pärtty *et al*[76] randomized 75 infants at birth to a supplement of *Lactobacillus rhamnosus GG (LGG)* or placebo for the first 6 mo of life and measured microbiota and psycho-behavioral diagnoses 2 and 13 years later. They found no major changes in microbiota. However, at the age of 13, 17% of the children treated with placebo had attention deficit disorder or Asperger's syndrome, compared to none who received *LGG*.

Recent reviews concluded that probiotics should be studied in children with ASD[50,77]. Our interpretation of the rationale for probiotic investigation in ASD is summarized in Table 1. However, it is controversial whether oral probiotics can produce positive effects in such a complex condition. Currently available probiotics are mainly aerobic, derived from milk cultures, not normally a significant part of the human gut microbiome which are primarily anaerobic; and they are short-lived in the human gut. Kristensen *et al*[78] looked at normal humans given probiotics and showed in a meta-analysis of 6 RCTs limited to adults that there was no change in alpha-diversity (number of species) or evenness with probiotic treatment. One trial did show a change in beta-diversity (relative contributions of the various species)[78]; however, virtually all studies which have shown changes in fecal microbial composition during probiotic administration were done in babies, for example preterm infants[79,80]. One study that did show that a probiotic could alter the fecal microbiota focused on older children with cystic fibrosis[81] and another showed changes in adults with alcoholic cirrhosis[82]. Most of these trials used quantitative polymerase chain reaction (PCR), rather than 16S ribosomal RNA gene sequencing. Using 16S rRNA techniques, we[83] and others[78] have not shown differences in microbial composition in adults treated with probiotics. The same lack of effect on the infant's fecal microbiome was observed in a number of studies of infants whose mothers were treated with probiotics before birth and/or during breast feeding[84-86].

Therefore, alternative mechanisms may account for potentially beneficial effects of probiotics in IBS and possibly ASD. An important alternative mechanism by which a probiotic be beneficial is *via* the metabolites that these organisms release in the gut lumen which may reach the circulating blood. A number of studies have shown abnormal fecal metabolites, such as short chain fatty acids (SCFA) related to changes in microbiota[87]. Para-cresol (a phenolic compound) has been suggested to be a urinary marker for autism[88], especially in those with constipation and ASD[89]. In a mouse model of autism induced by maternal immune activation, autistic behaviors such as communication abnormalities, stereotypies, and anxiety behaviors were associated with abnormal serum metabolities produced by the microbiota, including 4-ethylphenyl sulfate (the major metabolite) and p-cresol (to a lesser extent)[57]. These abnormalities and some of the behaviors were improved by giving orally a human commensal *B. fragilis* (not traditionally viewed as a probiotic). In a biomarker discovery study in 52 young children with ASD who were compared to neurotypical controls, a number of plasma markers were found to be altered, many of them were directly related to mitochondrial metabolism. These included elevated succinic acid, aspartate, glutamate, and aminoisobutyrate and decreased citric acid, isoleucine, and creatinine[90].

Despite these gaps in our knowledge regarding "if and why" probiotics may work in autism, in a recent survey of more than 500 physicians who treat children with autism, 19% reported using probiotics[91]. Many autism websites also advocate treatment of children with ASD with probiotics. These recommendations are not evidence-based. A recent review summarized the existing 4 trials of probiotics for ASD[92]. There were methodological difficulties in most; for example, one was a case-control study that had a high risk of selection bias which showed improvement in mental concentration (but not in behavior) in ASD patients treated with *Lactobacilus acidophilus*[93]. Another manuscript which was included as part of a retrospective

case-cohort analysis, reported that probiotic treatment improved an autism treatment evaluation checklist, although the authors did not report which probiotics were given and which dose[28]. A third study was a double-blind placebo-controlled crossover trial which reported reduced disruptive behavior, anxiety and communicative disturbance when the children were on probiotic (*Lactobacillus plantarum)* but is not readily available in reference libraries[94]. A 4th study reported beneficial effects of a 4-mo treatment with a combination probiotic (comprising 3 *Lactobacilli*, 2 *Bifidobacilli*, and 1 *Streptococcus* species). In this latter study, the probiotic increased the qPCR-determined ratio of fecal *Bifidobacilli* to *Firmicutes* and total *Lactobacilli,* while reducing fecal *Clostridia* and fecal tumor necrosis factor (TNF)-alpha levels. This latter study did suggest beneficial effects on the microbiome, although effects of this combination probiotic on autistic behaviors were not reported[77].

Fecal microbiota transplantation

In children and adults with severe gastrointestinal diseases, such as *Clostridium difficile (C. difficile)*-associated colitis or inflammatory bowel disease, fecal microbiota transplantation (FMT) had the potential for more significant and prolonged effects. FMT was effective in many cases of antibiotic-associated *C. difficile* colitis and is now used around the world for severe or multiply recurrent *C. difficile* infection, and it may have a role in the treatment of inflammatory bowel disease (particularly Crohn's disease) and autoimmune conditions. However, fecal transplantation carries many risks, including aspiration, transmission of norovirus, bacteremia, induction of obesity, and possible transmission of autoimmune conditions, including rheumatoid arthritis and Sjogren's syndrome[95,96]. We do not believe this treatment will have a role in the treatment of gastrointestinal symptoms in autism, although there may be successful reductionist approaches, for example combinations of defined communities of culturable commensal organisms, such as those used in the "RePOOPulate" studies in Canada, in which 33 carefully selected isolates from healthy donors were able to eradicate *C. difficile* from patients who had encountered multiple recurrences[97].

CONCLUSION

Gastrointestinal symptoms in children with autism are common and are often linked to the children's abnormal behavior and social interactions. Probiotics are hypothesized to positively impact gut microbial communities and alter the levels of specific potentially harmful metabolites in children with ASD. Whether probiotics improve behavior and these markers has yet to be determined. Although the evidence presented in this review does not confirm benefit of probiotics in this population, it provides a solid rationale for the design of larger prospective trials.

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