



Mini Review

Dysbiosis, small intestinal bacterial overgrowth and biofilms in autism and chronic illness

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Abstract: Recent evidences highlight that alteration of gut microbiota homeostasis could trigger several human pathologies, among them autism spectrum disorders (ASD). This short hypothesis article summarizes the recent literature and offers a novel, complementary and biomedical drugs/natural agents-combined therapy for treating gastrointestinal issues and microbial biofilms in ASD and chronic illness.

Keywords: autism; gut brain axis; gastrointestinal symptoms; biofilms; SIBO

1. Introduction

1.1. Gut microbiota and autism

Recent and emerging evidences well recognized that the composition of gut microbiota is able to influence human normal physiology [1]. Alterations in the gut microbiota homeostasis could drive several diseases. In addition, gut microbiota connects with the central nervous system, thereby influencing brain function and changing behaviors. Dysfunction in gut microbiota takes a role in controlling and regulating stress-related disorders, mental disorders, depression, anxiety, mood, cognition, neurodevelopmental disorders, such as autism, and pain [1,2]. Therapeutic strategies able to modulate the microbiota could represent a novel approach for the treatments of CNS disorders.

Autism spectrum disorders (ASD) are complex, heterogeneous, neurodevelopmental conditions characterized by social and communication impairments, repetitive and stereotyped behaviors and sensory integration dysfunction [3]. ASD are now considered as multifactorial pathologies with

interactions between epigenetic and environmental factors [4]. The gut bacteria brain axis could affect ASD symptoms, development and comorbidities (among them, gastrointestinal symptoms) [5]. Gastrointestinal (GI) symptoms and altered intestinal barrier are most common in autistic people [6]. Greater prevalence of GI symptoms among children with ASD compared with control children has been found [7], with strong positive correlation between GI issues and ASD severity [8]. In addition, higher measures of irritability, anxiety, and social withdrawal are present in ASD children with GI symptoms compared to those without GI symptoms [9]. The possibility to modulate the gut bacteria composition in restoring gut homeostasis could offer improvements also in autistic behaviors [10]; indeed, potential future probiotic and prebiotic based drugs could enhance gut beneficial bacteria against abnormal colonizing bacteria [11]. Gut microbiota takes also a role in immune functions and regulation [12]. Beneficial bacteria are able to repress pathogenic microbial overgrowth, prevent allergy, prevent inflammatory bowel disease and inflammation; in addition, bacterial fermentation produces short chain fatty acids (SCFA), required for a healthy colon [13]. Among beneficial bacteria, several probiotic strains offer therapeutic applications. In example, *Lactobacillus casei*, *L. bulgaricus*, and *L. acidophilus* increase macrophage activity and enhance phagocytosis, decrease gut permeability, exert antimicrobial activities secrete antimicrobial proteins (i.e. activated mucin), increase T helper cells (Th2), decrease Th1, and allergic response, increase anti-inflammatory IL-10, TGFbeta, and *L. reuteri* decreases pro-inflammatory cytokines [14]. Bifidobacterium and Lactobacillus also help against constipation and diarrhea [15]. These strains, as well as others one, could ameliorate ASD-associated dysbiosis. Indeed, ASD is associated with altered composition and function of the gut microbiota [16,17]. This dysbiosis is mainly due to alterations in *Candida* and *Clostridium* levels, as well as increased abundance of *Sutterella* spp. and *Ruminococcus torques* [10,18–20], whereas *Prevotella* and *Veilonellaceae* (typically associated with good colonic health) abundance was found reduced in the intestinal microbiota of ASD children [21]. As proposed mechanisms, toxin production could trigger ASD symptoms [22]. These microorganisms produce several harmful low-molecular-weight bioproducts (propionic acid, PPA, polyamines, polyphenols) by their cellular metabolism. PPA is able to modulate mitochondrial dysfunction and atypical immune activation in autism [23]. It has been demonstrated that anaerobic bacteria of the *Clostridium* genus are able to synthesize 3-(3-hydroxyphenyl)-3-hydroxypropionic acid (HPHPA), found in higher concentrations in urine samples of children with autism [24].

1.2. Small intestinal bacterial overgrowth

Recently, the gut bacteria syndrome, Small Intestinal Bacterial Overgrowth (SIBO), has been correlated with ASD [25]. In this prospective study, the prevalence of SIBO in ASD children was diagnosed by glucose hydrogen breath test; as result SIBO was significantly associated with worse ASD symptoms [25]. However, currently this is the unique study with relatively young samples and needs to be confirmed. SIBO is characterized by the presence of excessive bacteria in the small intestine [26]. The symptoms of SIBO include: Bloating, distention, pain after eating carbs, sugar, legumes, grains, fructose fruits, fructan veggies or fiber; chronic abdominal pain, and gastroparesis. Several causes have been proposed: Abnormal digestion (poor acid and enzyme production); poor motility; overuse of antacids, antibiotics [27]; toxic exposures—glyphosate, metal burden (Pb); celiac disease, alcoholism, hypothyroidism, immunodeficiency (low sIgA); neurological injury, brain injury, vagus nerve impairment; anatomical changes (history or appendectomy), ileitis and ileocecal

valve reflux. The long-term effects associated with SIBO are: Malabsorption of fats and fat-soluble vitamins; malnutrition, low albumin, low globulin (immunoglobulin, sex hormone binding globulin), low hemoglobin, low cholesterol, nutritional deficiencies; poor weight gain; chronic inflammation; chronic pain; increased permeability, leaky gut; food sensitivities; increased enterotoxins. In ASD management, testing for SIBO/dysbiosis could be a good approach. In order to check the presence of SIBO, the gold standard analysis is the duodenal and jejunal aspiration for bacterial counts, but hydrogen and methane breath testing is most commonly done. Other procedures are: The comprehensive stool analysis, aiming to identify overgrowth of bacteria and yeast; malabsorption of fats, low bile acids, low pancreatic enzymes; the urine organic acid test (OAT) to identify bacterial and fungal metabolites of bugs that do not show up in the stool cultures [28]. Treatment options for SIBO include: Antibiotics (Rifaximin, Vancomycin, Bacitracin, Metronidazole), elemental diet, prokinetic drugs (enhance the motility and contractility of the GI tract), serotonin agonists, acetylcholinesterase inhibitors, phosphodiesterase inhibitors, dopamine antagonists [29]. The broad spectrum antibiotic Rifaximin treatment has been proven to be effective and safe for the management of SIBO [30]. This treatment shows some advantages: Not systemically absorbed, works mostly in the small bowel, can increase Bifidobacteria and enhances short chain fatty acids, it is approved for pediatrics. Associated integrative diet-based treatments enhance the antibiotic actions. These diets help in reducing bacterial loads, address the carbohydrate maldigestion (restrictive diets), limit high fiber and fermented foods, improve gut motility. Most common are: Specific carbohydrate diet (SCD), gut and psychology syndrome diet (GAPs), low fermentable oligosaccharide, disaccharide, monosaccharide, and polyols (FODMAP) diet (low FODMAP diet, LFD). In SIBO therapy, these diets are able to enhance antibiotic therapy [31].

1.3. Biofilms

The pathogens *Clostridia* sp., yeast (*Candida*), and Gram-negative bacteria, in autistic GI tract could create chronic infections in the host, when protected by pathogenic biofilm. This biofilm protects the bad bugs from destruction by the immune system [32]. Treatment of pathogenic biofilms can help eradicate dysbiotic flora, restore the normal flora, and improve the symptoms of the neuro-immune-inflammatory conditions associated with autism. The term biofilm indicates a collection of microbial communities of adherent cells enclosed by a matrix of extracellular polymeric substance (EPS) and separated by a network of open water channels. Their architecture is an optimal environment for cell-cell interactions, including the intercellular exchange of genetic material, communication signals, and metabolites, which enables diffusion of necessary nutrients to the biofilm community. The matrix is composed of a negatively charged polysaccharide substance, held together with positively charged metal ions (calcium, magnesium, and iron). The matrix in which microbes in a biofilm are embedded protects them from UV exposure, metal toxicity, acid exposure, dehydration salinity, phagocytosis, antibiotics, antimicrobial agents and the immune system. Biofilms are difficult to diagnose and treat with antibacterial drugs [33]. The European Society for Clinical Microbiology and Infectious Diseases has issued guidelines for the diagnosis and treatment of biofilm infections [34], highlighting the importance for prevention and treatment of biofilm infections and for monitoring treatment effectiveness. Among the biofilm control strategies being researched, there are: Probiotics and prebiotics and synbiotics, NaEDTA (complexes with cations in the extracellular matrix, combined with antibiotics), iron chelating compounds (lactoferrin), mucous/fibrin degrading enzymes, chitosans, surfactants, plant polyphenols (Flavonoids (red wine, red grapes, manuka honey), Quercetin, Fisetin, Kaempferol, and several others [35,36].

1.4. Complementary and biomedical treatments

The True Health Medical Center has developed a gut biofilm approach, comprised of four steps, aiming to kill infections and restore/rebuild the gut lining. The approaches for the treatment of biofilms are based on the prevention and/or on removing the already formed biofilms [37].

The first step uses enzymes, natural iron chelators (green tea, rice bran IP6, curcumin, myoinositol), polyphenol rich nutrients (essential oils, herbs), lactoferrin and fibrinolytics in order to lyse biofilms. In step 2, there is the killing of infective agents: Natural antimicrobials (herbs/oils) firstly, then antibiotics if needed. The choice of the right antibiotic depends on the main colonizing microorganism. Insoluble/soluble fibers (prebiotics), pectin, guar gum, inulin, ground flaxseeds, inulin, zeolites, microsilica and/or activated charcoal help in binding of toxins released from lysis of the biofilm. Rebuilding and nourishing the gut lining, as restoring the damaged gut barrier [38], is a longer process that requires a nutrient dense low glycemic diet that focusing on collagen rich and fermented foods (Kefir, yogurt, sauerkraut), in combination with supportive supplements (chamomile, colostrum, whey protein, prebiotics and probiotics) [37]. Probiotics and prebiotics can modulate gut microbiota to enhance the intestinal immune system [39]. Inulin and oligofructose, components of a low glycemic diet, are able to modulate gut microbiota composition, triggering anti-inflammatory effects and regulating lipid and glucose metabolism [40].

2. Conclusions

Modifications in gut bacteria composition may trigger changes in behaviors, as also seen in ASD. Targeting the altered microbiome could be the future management for these pathologies.

Bacterial/yeast biofilms show great resistance to chemiotherapeutic and antibiotic drugs and disinfectants. A novel approach aiming not only to kill infections, but also to restore/rebuild the gut microbiota, as proposed here, could enhance drug efficacy together with gut good bacteria, in this way alleviating autistic symptoms.

Conflicts of interest

Dr. Usman is owner and director of True Health Medical Center and Pure Compounding Pharmacy.

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