Boreński Grzegorz, Wójcik Magdalena, Poleszak Julita, Szabat Przemysław, Szabat Marta, Milanowska Joanna. Gut microbiota and autism. Journal of Education, Health and Sport. 2019;9(9):204-212. eISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3395320
http://ojs.ukw.edu.pl/index.php/johs/article/view/7380

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.

Received: 25.08.2019. Revised: 30.08.2019. Accepted: 05.09.2019.

Gut microbiota and autism

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Abstract

Introduction: Autism spectrum disorders (ASD) constitutes a group of brain developmental disorders and is characterized by difficulty with social communication and

restricted, repetitive patterns of behavior, interest, or activities. ASD has no clear etiology and research is still ongoing to find it. Gut microbiota seems to have significant impact on the development of autism.

The aim of the study: The purpose of this systemic review was to collect and analyse available data about the role of gut microbiota and new methods of treatment of ASD.

Material and method: Standard criteria were used to review the literature data. The search of articles in the PubMed and Google Scholar database was carried out using the following keywords: autism spectrum disorder, gut microbiota, probiotics.

Description of the state of knowledge: In the studies we can found that symptoms from gastrointestinal tract occur more often in patients with ASD. Many studies confirm alterations in gut microbiota accompanying autism. The general changes are imbalance between Bacteroidetes and Firmicutes phyla, increased population of Sutterella and higher level of cultured Clostridium species in the feces. Researchers try to find a reason of these microbiota changes and the main cause they indicate is using antibiotics. Restoration of microbial balance in the colon, for instance by probiotics or microbiota transfer therapy may have beneficial effect on treatment of ASD.

Summary: Complicated relationship between gut microbiota and brain needs more studies, but at that point we can find its association with autism and ASD and also with anorexia nervosa, depression and other mood disorders and GI diseases. Among currently available methods of treatment we can distinguish behavioural treatment, pharmacological approach (risperidone and aripiprazole) and complementary and alternative medicine therapies. Understanding the impact of microbiota on autism opens up new paths of treatment, for instance probiotics, fecal microbiota transplantation or microbiota transfer therapy. Although, there is a great need for more researches of their efficacy.

Key words: autism spectrum disorder, gut microbiota, probiotics

1. Introduction

Autism was originally defined by Leo Kanner in 1943 as an innate inability to create normal, biologically determined, emotional contact with others [1]. Autism spectrum disorders (ASD) constitutes a group of brain developmental disorders and is characterized by difficulty with social communication and restricted, repetitive patterns of behavior, interest, or activities. [2]. Except these core symptoms, there are also symptoms such as hyperactivity, anxiety, aggression, insomnia, flatus and gastrointestinal symptoms - diarrhea, constipation,

vomiting, reflux, abdominal pain/discomfort and unusually foul-smelling stools [3,4]. There are several theories about pathogenesis of autism, new ones are still emerging and the unequivocal cause has not been determined. One of the new hypothesis about pathogenesis of autism is that autistic behavior arises from dysfunctions in the midbrain dopaminergic system [5]. However, many aspects of autism remain poorly understood. In last few decades major advances have been made in terms of highlighting the genetic, biological, environmental, and developmental origins of autism [6,7,8].

2. Gut microbiota

In the human gut live 400–1,000 different bacterial species and its weight reaches 1kg [9,10]. There are 10^{11} bacterial cells per 1 gram of colon contents and 100 trillion cells - microbes colonizing humans outnumber host cells and express more unique genes than their host's genome [11,12]. These complex communities of microbes that include bacteria, fungi, protozoa, viruses , bacteriophages and archaea play a fundamental role in controlling physiology of human [13,14]. The most of microorganisms are found in the colon - mostly represented by the Firmicutes and Bacteriodetes phyla, and the least in the stomach and small intestine [15]. Gut microbiota functions are to stimulate innate immunity in the early years of life, but also synthesis and metabolism of certain nutrients, hormones and vitamins, and clearance of drugs and toxic [16]. The other functions of gut microbiota are creating the intestinal barrier, stimulating the regeneration of the intestinal epithelium, producing mucus and nourishes the mucous membrane by producing short-chain fatty acids, functions important for brain processes, such as myelination, neurogenesis, microglia activation, modeling behavior and affecting psychological processes [17,18].

3. Relationship between gut microbiota and brain

There are evidences that bi-directional communication between gut, microbiota and brain occurs regularly. The central nervous system exerts control over the gut microbiome composition through peptides, cortisol secretion via hypothalamic-pituitary-adrenal axis regulates intestinal motility and integrity. Immune and neural pathways - the autonomic nervous system regulates peristalsis, secretion of acid, bicarbonates, mucus and modulates mucosal immune response, which is known to exert control over microbial populations [19,20]. The gut microbiota can also affect brain activities via neural, endocrine, immune, and metabolic mechanisms [21]. One study in mice isolated from their mother shows that early life stress causes changes in the composition of the intestinal microbiota [22]. Another study on mice also confirmed bi-directional gut-brain communication, showing that infection with Campylobacter jejuni elevates anxiety behaviors [23].

4. Autism and gastrointestinal symptoms

The gastrointestinal (GI) symptoms often occur in patients with ASD. In studies we can find that symptoms such as constipation or diarrhea occurs more often in children with ASD than in their unaffected siblings [24,25]. D'Eufemia et al. reported that autistic children have problems with altered gastrointestinal motility and increased intestinal permeability[26]. Another study on 14000 patients with autism spectrum disorder (ASD) shows higher

prevalence of inflammatory bowel disease and other GI disorders in patients with ASD than in controls [27]. Alterations in composition of the mucosal micobiota has been reported in patients with ASD [28,29]. There are reports that patients with ASD and GI symptoms have higher measures of irritability, anxiety, and social withdrawal than those without GI symptoms [4]. Studies also show that GI symptoms in patients with ASD exacerbate the symptoms of autism in all aspects [30].

5. Gut microbiota in patients with autism

In recent years possible role of the gut microbiota in pathogenesis of autism has been depended on studies using animal models. Dysbiosis in patients with ASD is characterized by imbalance of Bacteroidetes and Firmicutes phyla, with an increased presence of Bacteroidetes and other gut bacteria such as Bifidobacterium, Lactobacillus, Sutterella, Prevotella, Ruminococcus genera and Alcaligenaceae family [31,32,33,]. These findings suggest that increased population of Suterella in more than half of the patients with ASD and GI symptoms can play an important role in pathogenesis of autism, because in patients without ASD and with present GI symptoms Sutturella is absent [32]. In studies we observe increased population of Suturella and decreased population of Prevotella [29]. It is believed that Prevotella is an important element of intestinal microbiota and is responsible for the well-being of the colon. An increased Prevotella population may have beneficial effects in many areas, e.g. improving glucose metabolism[20,34]. Sandler et al. suggested that colonization of the colon by bacteria able to produce neurotoxin may contribute to the symptoms of autism. They treated children with autism with antibiotics and they noted short-term improvement at the end of the treatment [35]. In 1998, Bolte reported that significant percentage of patients with autism were once intensively treated with antibiotics, which disrupt protective intestinal microbiota. On this basis, he concluded that the chronic infection of the Tetanus that we observe in some people with autism may be at the root of its pathogenesis [36]. Other studies, also noticed that association. Finding that neurobehavioral symptoms and chronic diarrhea occurred after repeated courses of antibiotics in a subset of children with the regressive form of ASD, was the main factor to suggest that a species of toxin-producing Clostridium may be the cause of autism [20]. Clostridia are Gram-positive, anaerobic, endospore-forming bacteria, incapable of dissimilatory sulfate reduction. Comprising approximately 180 species, the genus Clostridium is one of the largest bacterial genera [37]. Within the Clostridium we can distinguish pathogenic and commensal organisms, which, however, in special conditions can be pathogenic. Clostridium butyricum, a strictly anaerobic spore-forming bacillus, is a common human and animal gut commensal bacterium, and is also frequently found in the environment. One strains of Clostridium butyricum are non-toxigenic, while other strains are involved in pathological conditions, such as botulism in infants or necrotizing enterocolitis in preterm neonates [38].Clostridium perfringens is widely distributed in nature, especially in soil and the gastrointestinal tracts of humans and animals, but it can produce potent toxins that are known to cause a variety of human diseases [20,39]. Clostridium tetani and Clostridium botulinum produce two of the most potent neurotoxins known, tetanus neurotoxin and botulinum neurotoxin. Botulinum neurotoxin has been used therapeutically for disorders such as focal dystonia, spasticity, and chronic migraine [40,41]. In children with autism after 6-week course of oral vancomycin, an improvement in neurobehavioral symptoms was

observed in eight of the ten children, as well as an improvement in gastrointestinal symptoms. All patients after stopping the vancomycin experienced a gradual regression in bowel and behavioral symptoms [20,35]. This effect could be caused by converting Clostridia into the spore-form, which is resistance for antibiotics. For instance the ability of Clostridium difficile to form a metabolically dormant spore is critical for the survival of this organism. This spore form is resistant to a myriad of environmental stresses, including heat, desiccation, and exposure to disinfectants and antimicrobials. These properties of spores allow C. difficile to survive long-term in an oxygenated environment, to be easily transmitted from host-to-host, and to persist within the host following antibiotic treatment [42,43]. In another studies a ten times higher level of cultured Clostridium species were found in the feces of children with ASD with GI symptoms than in controls, and also lack of anaerobic bacteria [44].

6. New methods of autism treatment

At this time, there is no effective treatment for ASD. There are several potential new therapies [45]:

- Probiotics and prebiotics
- Fecal microbiota transplantation
- Microbiota transfer therapy
- Other therapies – diet, antibiotics

Probiotics such as Lactococcin, Lactobacilli, Bifidobacteria and Saccharomycetes, could be beneficial to the host when provided in adequate quantities [45]. There are many studies which show that using probiotics could treat many diseases such as depression, Crohn's disease, obesity [46,46,48,]. Study by Hsiao et al. shows that alterations in composition of gut microbiota in mice resulted in the appearance of autism-like behavior [49]. The probiotic/prebiotic can normalize the gut microbiota, enhance gut barrier and relieve the ASD-like behaviors in animal models or ASD patients. In another study, we observe that daily administration of the probiotic and immune modulator improved GI and ASD symptoms [50]. One cohort study on children with ASD shows that supplementation with Lactobacillus acidophilus twice a day for 2 months improve their ability to follow directions [51].

Fecal microbiota transplantation is a procedure in which we collect intestinal microflora from a healthy donor and implant to the recipient with intestinal dysbiosis. It is highly effective in the treatment of recurrent Clostridium difficile infections [52,53]. There are also evidences that fecal microbiota transplantation could be effective in irritable bowel syndrome and inflammatory bowel disease [54]. Using fecal microbiota transplantation in ASD, its safety and its benefits should be considered. Microbiota transfer therapy is a procedure in which after 14 days of antibiotic therapy, a high dose of human normalized intestinal microflora is administered for 7-8 weeks [45]. It improves GI symptoms, ASD-related symptoms and normalized a composition of microbiota in patients with ASD [55].

7. Summary

Autism and ASD are diseases with complicated etiology. There are evidence of alterations in gut microbiota and its association with autism. Complicated relationship between gut microbiota and brain need more studies, but at that point we can find its association not only with autism and ASD but also with anorexia nervosa, depression and other mood disorders and GI diseases. Research focused on gut microbiota may bring new insights into many diseases and new treatment. At this time there is no treatment for autism except behavioural treatment, pharmacological approach (risperidone and aripiprazole) and complementary and alternative medicine therapies. Use of probiotics, fecal microbiota transplantation or microbiota transfer therapy would be a breakthrough in treating autism. Although, available studies of these new methods seem to be promising, there is a great need for more researches of their efficacy.

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