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Autism Spectrum Disorder, Microbiota And Nutritional Therapy Approaches

Şehriban Duyar Özer[1*], Gülçin Sağdıçoğlu Celep[1]

[1] Gazi University, Faculty of Health Sciences, Department of Nutrition and Dietetics, Ankara

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Abstract

Autism Spectrum Disorder (ASD) is a developmental disorder that causes problems related to communication, social, verbal and motor skills. Due to its increasing prevalence and non treatment, interest in autism is increasing day by day. New approaches to the treatment of autism are being developed by considering the factors and symptoms in the etiology. Today, the intestine, defined as the second brain, has been reported to be associated with changes in the microbiota in autism, as in many diseases. As a result of changes in the brain due to increased intestinal permeability in autism, therapeutic approaches to regulate microbiota composition are being developed. Studies in the literature are mainly directed to probiotics and prebiotics, omega-3 fatty acids, ketogenic diets and gluten-free casein-free diets. The diet consumed is thought to be effective in ASD behaviors and reduce symptoms; however, there is no sufficient evidence-based study to establish medical nutrition therapy. In this review, the differences in intestinal microbiota and current dietary approaches in autism were evaluated.

1. Introduction

Autism is a lifelong developmental disability that affects how the individual communicates with other people and how the individual experiences the world around him (National Autism Society, 2016). Autism is a spectrum disorder and its effects vary from person to person (American Autism Association, 2016). In general, verbal or non-verbal language skills are not available to ensure appropriate social interaction in individuals with autism (American Psychiatric Association, 2013). In addition to the spectrum of behavioral abnormalities in autism; seizures, anxiety, sleep failure and metabolic disorders are also observed (Vuong & Hsiao, 2017). Autism symptoms appear in early childhood and are better defined in later life due to increasing social demand (Murphy et al., 2016). In 2014, the Disease Control and Prevention Centers (CDC) reported that; autism prevalence is increasing day by day, one out of 59 children and boys had 4 times more incidence than girls (Baio et al., 2018).

Immune and neuronal disorders are reported in individuals with autism. Although the underlying mechanism is not fully known, genetic and environmental factors are effective in the etiology of autism (Louis, 2012). Environmental factors include exposure to prenatal or postnatal pesticides, heavy metals, chemicals and drugs, stress, maternal infection and dietary factors (Dietert R, Dietert J. & De Witt, 2011). In addition to genetic and environmental factors, intestinal dysfunction, microbial dysbiosis and immune dysfunction lead to impaired brain development and function (Vuong & Hsiao, 2017).

DSM-5 diagnostic criteria are used in the diagnosis of autism (American Psychiatric Association, 2013). In addition, different scales can be used to evaluate the changes in social behavior and the effectiveness of the treatments applied in the follow-up of autistic individuals (Murphy et al., 2016). Since autism is a lifelong disorder, the difficulties experienced by the individual should be reduced with appropriate care in the treatment and new skills should be provided by developing the strengths (National Institute of Mental Health, 2015).

2. Relationship Between Autism and Microbiota

In patients with autism, gastrointestinal problems such as abdominal pain, gastric reflux, diarrhea or constipation, vomiting, malodourous feces, increased bowel permeability and intestinal epithelial failure are frequently seen (Vuong & Hsiao, 2017; Ding, Taur & Walkup, 2017). These problems associated with autism are thought to develop due to environmental risk factors (Vuong & Hsiao, 2017). These symptoms also led to the idea that microbiota may be associated with gastrointestinal problems in autism.

It is known that intestinal microbiome has a symbiotic interaction with various organ systems in the body and contributes to many functions such as maintaining the integrity of the epithelial barrier, stimulating immune interactions, participating in gastrointestinal motility, and regulating metabolism (Sommer & Bäckhed, 2013). Intestinal bacteria or metabolic end products may have surprising physiological activities in mood, cognition, behavior, depression and brain development as well as in the sense of satiety and intestinal transit. This effect was revealed by the formation of the intestinal brain axis (Tuohy et al. 2014). It is stated that intestinal microbiota can affect

***Corresponding author:** Şehriban Duyar Özer
e-mail address: sehribanduyar@gmail.com

brain functions by different pathways. Short-chain fatty acids and toxin metabolites produced by microbiota can penetrate the leaking intestine and affect brain function (Li, Han, Dy & Hagerman, 2017). *Clostridia, Bacteroidetes* and *Desulfovibrio* increase the production of propionic acid in the intestine. Propionic acid stimulates autism-like behavior by crossing the blood brain barrier. This changes some neurotransmitters such as dopamine and seratonin, causing impaired social behavior (Mitsui, Ono, Karaki & Kuwahara, 2005).

The intestinal microbiota can produce neuroactive compounds (eg, 5-HT and GABA) that affect brain function and initiate abnormal behavior. These compounds can directly affect the hypothalamus pituitary adrenal axis and increase circulating cortisol levels. Metabolites and neuroactive compounds can activate enteric neurons and intestinal immune cells secreting cytokines into the circulation and affect brain function through the vagus nerve (Li et al., 2017). In addition to neuroinflammatory and psychiatric outcomes including abnormal metabolism, cytokine imbalances and varying metabolite levels in autism; increased intestinal permeability, microbial metabolites and elevated serum levels of endotoxin due to changes in the intestine (Vasquez, 2017).

In human intestines, mostly firmicutes, bacteroidetes, actinobacteria and proteobacteria species are found (Evrensel & Ceylan, 2015). When the studies examining the change of intestinal microbiota in individuals with autism were evaluated; *Clostridium Clusters I / II / XI, Beta-Proteobacteria, Sutterella, Alcaligenaceae, Desulfovibrio, Bacillus, Clostridium bolteae, Bacteroides vulgatus, Bacteroides fragilis* species increased and *Bifidobacteria* decreased in autism (Ding et al., 2017). In addition, *Streptococcus, Lactococcus, Staphylococcus, Ruminococcus, Firmicutes, Prevotella, Coprococcus, Enterococcus, Lactobacillus* species are also reported to be decreased in individuals with autism (Rooks & Garrett, 2016). In the study, microbiota examination in mice with autism induced by prenatal valproic acid intervention, it was observed that *Bacteroides* decreased and *Firmicutes* increased in autism. In addition, butyric acid synthesis in the intestine was observed to be higher in those exposed to valproic acid. It has been reported that neurological diseases can be managed by regulating the intestinal microbiome (De Theije et al., 2014). In a review by Louis, (2012), a number of studies were conducted that examined changes in the microbiota composition of children with ASD compared to healthy children, based on both bacterial culture and molecular methods. Because of the contradictory results obtained in the studies and because of the difference in methods, no definite conclusion could be reached. However, it was observed that the microbiota of healthy siblings of children with ASD were affected and this was due to the sharing of the same environment and genetic effect (Louis, 2012).

3. Nutritional Therapy Approaches

3.1. Probiotics and Prebiotics

Microbial colonization initiates signaling mechanisms that affect neural pathways involved in motor control and anxiety-like behavior. Probiotic strains have also been implicated in neurological diseases through the vagus nerve (De Theije et al., 2014). Galactoligosaccharide (GOS) and fructooligacaccharides (FOS) regulate the production of short-chain fatty acids such as acetate and butyrate, as well as increasing the amount of intestinal

***Corresponding author:** Şehriban Duyar Özer
e-mail address: sehribanduyar@gmail.com

Bifidobacteria (Tuohy et al. 2014). In the study with mice, treatment with *Bacteroides fragilis* reduced intestinal permeability, changed the composition of the intestinal microbiota and reduced autistic behaviors in ASD (Hsiao et al., 2013). Tomova el al. (2015), probiotic supplementation including *Lactobacillus, Bifidobacteria* and *Streptococci* was given to children with autism. *Bacteroidetes / Firmicutes* ratio is regulated and *Desulfovibrio spp*. and *Bifidobacterium spp*. were found to be similar to the control (Tomova el al., 2015). In the study, the effect of GOS was investigated, β-GOS increased the amount of *Bifidobacterium spp. in vitro* intestinal model in autism and control groups. Short-chain fatty acid production significantly changed in both groups and the amount of ethanol and lactate increased in the group with ASD (Grimaldi et al., 2017). Although positive effects of probiotics and prebiotics have been observed, there is not enough evidence to determine the amount of strains that can be recommended in autism.

3.2. Omega-3 Fatty Acids

Omega-3 fatty acids and metabolic products are associated with brain structure and function, neurotransmission, cell membrane structure, inflammation, immunity and oxidative stress. Low levels of omega-3 fatty acids have been reported in individuals with autism. This suggests that omega-3 fatty acids may be associated with autism symptoms (Mazahery et al., 2017). Ooi et al. (2015) examined the effect of 1g / day omega-3 (EPA + DHA) supplementation for 12 weeks in 41 children with autism from 7 to 18 years of age and improved symptoms of autism, attention deficit, and social problems (Ooi et al., 2015). In the study of Mankad et al. (2015), 38 children with ASD were divided into two groups and administered 1.5 g / day EPA + DHA and placebo. It was reported that high dose omega-3 supplementation has no effect in early childhood in children with ASD (Mankad et al., 2015). In a study of omega-3 and omega-6 supplementation (338 mg EPA, 225 mg DHA, 280 mg total omega-6) in preterm infants with predisposition to autism, positive effects of polyunsaturated fatty acids were observed in the development of children's language skills (Sheppard et al., 2017). In a randomized controlled trial in children with autism, supplementation of vitamin D (2000 IU / day) and omega 3 (722 mg / day DHA) for 12 months was associated with a reduction in irritability symptoms (Mazahery et al., 2019). In the meta-analysis evaluating the studies on this subject, it was concluded that omega-3 fatty acids may be effective in reducing symptoms due to their long-term tolerance, their role in brain functions and the pathology of autism. However, caution should be exercised in order to complete other treatments (Mazahery et al., 2017). In general, positive results have been observed in studies examining the effect of omega-3 fatty acids. High level of evidence is needed to determine supplementary dose and duration.

3.3. Ketogenic Diet

The ketogenic diet is a diet that contains high amounts of fat and low carbohydrates and enables the body to use fats as an energy source (Napoli, Dueñas & Giulivi, 2014). Ketogenic diet has been reported to reduce total intestinal microbial counts, increase sociability, decrease recurrent ASD behaviors, and improve social communication in ASD (Castro, Baronio, Perry, Riesgo & Gottfried, 2017). In the study, mice treated with ketogenic diet for 3 weeks

***Corresponding author:** Şehriban Duyar Özer
e-mail address: sehribanduyar@gmail.com

showed improvement in autistic behavior. It has been observed that mice have increased sociality, decreased repetitive behaviors, and improved food preference (Ruskin et al., 2013). Another study conducted in mice, ketogenic diet showed antimicrobial effect and decreased total host bacteria count. In fecal and cecal samples ketogenic diet have shown a reduction in *Firmicutes* / *Bacteroidetes* ratio and *Akkermansia muciniphila* (Newell et al., 2016). In the pilot study, 30 children with ASD were treated with ketogenic diet for 6 months. In children, dietary compliance improved according to various parameters and the Childhood Autism Rating Scale. At the end of the study, although the available data are scarce, ketogenic diet may be used as an additional or alternative treatment in reducing autistic behaviors (Evangeliou et al., 2003). In the case-control study comparing the effect of the gluten-free casein-free diet and the ketogenic diet (modified Atkins diet), Childhood Autism Rating Scale and Autism Treatment Rating Test scores were improved in both groups. In addition, better results in cognitive performance and socialization have been achieved in those who consume ketogenic diet compared to gluten-free casein-free diet (El-Rashidy et al., 2017). In a study examining the effect of a gluten-free ketogenic diet enriched with medium chain fatty acids (MCT), autism symptoms were improved after 3 months (Lee et al., 2018). The results obtained support the positive effects of ketogenic diet. Large scale studies should be planned to determine the appropriate dietary protocol for autism.

3.4. Gluten-Free Casein-Free Diet

Dietary gluten-based barley, wheat, rye and products obtained from these cereals and casein-based milk and milk products are based on the extraction. Gluten and casein-derived peptides are thought to trigger an immune response that causes gastrointestinal inflammation (Pennesi & Klein, 2012). It is based on the hypothesis that tolerance to gluten and casein and the absorption of peptides associated with these compounds are reduced due to leaking bowel syndrome in autistic individuals (Hyman et al., 2016). Knivsberg et al. (2002) reported a reduction in the physiological and behavioral symptoms of autism when compared with a gluten-free casein-free diet and placebo for 1 year (Knivsberg, Reichelt, Høien & Nødland, 2002). In a study, families of children with autism who applied gluten-free casein-free diet were questioned and their duration of adaptation to diet was evaluated. Improvement in ASD behaviors, physiological symptoms and social behaviors have been reported in those who achieve complete elimination of diet (Pennesi & Klein, 2012). There are individual differences that modulate the response to a gluten-free casein-free diet, which is an increased intestinal permeability, a more permeable blood brain barrier, and a decreased dipeptidyl peptidase 4 (DPP4) enzyme activity. Individual alterations of toxic bacterial products, pathogenic bacteria and opioid peptides enter the blood stream and into the brain more easily, affecting brain function (Ciéslińska, Kostyra & Savelkoul, 2017). In a systematic review, results regarding gluten-free casein-free diets were reported to be poor. Gluten-free casein-free diet has been shown to be partially effective as shown in several randomized controlled clinical trials of small sample size and can be used when intolerance to allergens develops. However, it is thought that the effect of diet is shown more than by the food industry (Marı´-Bauset, Zazpe, Mari-Sanchis, Llopis-Gonza´lez, Morales- Sua´rez-Varela, 2014). In

***Corresponding author:** Şehriban Duyar Özer
e-mail address: sehribanduyar@gmail.com

conclusion, how much elimination of the foods consumed in the gluten-free casein-free diet and individual responses are important in terms of the effect on symptoms and intestinal permeability of ASD.

4. Conclusion

Autism is a spectrum disorder in which many factors play a role and the patients show heterogeneity. With the increasing interest in autism, factors in its etiology and treatment approaches are among the current discussion topics. Studies have shown that there may be a significant relationship between microbiota and ASD. The information obtained from the literature shows that the regulation of intestinal microbiota can be used to reduce the symptoms of ASD. The diet consumed by patients in autism spectrum disorder significantly affects the change in microbiota. Omega 3 fatty acids, prebiotic-probiotics, ketogenic diet and gluten-free casein-free diet are the most emphasized diet approaches. The effectiveness of these approaches needs to be proved in order to be used in medical nutrition therapy. However, there is not sufficient evidence at this level. Future studies are needed to determine the appropriate nutritional therapy and its interaction with the intestinal microbiota in autism.

Conflict of interest

No conflict of interest was declared by the authors.

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***Corresponding author:** Şehriban Duyar Özer
e-mail address: sehribanduyar@gmail.com

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***Corresponding author:** Şehriban Duyar Özer
e-mail address: sehribanduyar@gmail.com