Gluten-Free Casein-Free Diet for Autism Spectrum Disorders: Can It Be Effective in Solving Behavioural and Gastrointestinal Problems?

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ABSTRACT

Autism spectrum disorder [ASD] is characterized by deficits in communication and social interactions combined with repetitive and restricted patterns of behaviors. Bidirectional changes in brain-gut microbiota are known to be responsible for the pathophysiology of many brain-related disorders, such as autism, as well as well-known gastrointestinal diseases, including gut disorders. Imbalance in the composition of gut microbiota is frequently observed in individuals with ASD. It is therefore believed that this imbalance is significant in the frequent occurrence of gastrointestinal symptoms. The integrity of the intestinal barrier and the blood-brain barrier [BBB] in individuals with ASD is affected. Incompletely digested peptides, toxins, and proinflammatory cytokines cross the BBB by entering the bloodstream and reach the central nervous system. As a result of the accumulation of these elements, brain function is adversely affected. It is hypothesized that incompletely digested peptides acting as opioid agonists reduce pain sensitivity and increase the severity of autism-specific behaviors. However, it is not known exactly how opioid peptides trigger ASD symptoms after they reach the brain. Diet therapies, especially elimination diets, are considered to be an alternative treatment to prevent this condition. Gluten-free casein-free [GFCF] diet is an elimination diet that involves the removal of certain proteins from the normal diet, such as gluten and casein. However, studies that demonstrate the beneficial effects of the GFCF diet on ASD patients and explain its mechanism is limited, which supports the opioid theory. This review aims to investigate the gastrointestinal and behavioral problems that are frequently observed in ASD, the possible action mechanisms of GFCF diets, and the efficacy of these elimination diets.

Keywords: Autism spectrum disorder, gluten-free casein-free diet, opioid peptides, gastrointestinal symptom, gut dysbiosis

Introduction

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental disorder characterized by difficulty in social interactions and verbal and nonverbal communication along with restricted and repetitive movement patterns [1].

The incidence of ASD was 3-4 in 10,000 cases in the 1980s [2]; however, a recent study conducted by the Center for Disease Control and Prevention (CDC) has reported that 1 out of every 59 children suffers from ASD, and in the occurrence is 4 times higher in boys than girls [3]. According to the World Health Organization (WHO) epidemiological data, the rate of occurrence of ASD is 1/160 [4]. It is thought that the increase in awareness and the development of diagnostic criteria are also effective in the increase in its prevalence [5].

Although the cause of ASD is not well-known, pre- and postnatal damage, nutrition, genetic, environmental, and immunological factors are reported to play a role in its pathophysiology [5, 6]. Mitochondrial dysfunction, impaired transmethylation and transsulfuration pathways, oxidative stress, immune dysfunction, gastrointestinal pathology, and nutritional disorders are among the causes of this condition [7]. Genetic changes account for only 10-20% of autism cases [8], and more than 400 genes have been reported to be associated with the development of autism [9].

Individuals with ASD often need intensive care and guidance [10]. Although lifelong educational and behavioral therapies have a low contribution to treatment, they continue to be implemented

Cite this article as: *Baspinar B, Yardimci H. Gluten-Free Casein-Free Diet for Autism Spectrum Disorders: Can It Be Effective in Solving Behavioural and Gastrointestinal Problems? Eurasian J Med 2020; 52(3): 292-7.*

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Received: October 19, 2019
Accepted: January 23, 2019
Available Online Date: June 4, 2020

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DOI 10.5152/eurasianjmed.2020.19230

[9]. Healthcare costs of individuals with ASD are 4.1-6.2 times higher than those without ASD [11]. Treating behavioral and mental problems make up some of these healthcare costs. Early diagnosis, knowledge of the etiology, and prevention of behavioral disorders can reduce the medical expenses and improve the quality of life [6].

Families frequently turn to alternative or complementary therapies as well as medical treatment [11, 12], and in this context, dietary therapies, especially elimination diets, are seen as an alternative [12]. Some studies have shown that behaviors have improved with nutrient elimination, and they have deteriorated when exposed to the same nutrients again [13, 14]. For example, in some studies, gluten-free casein-free (GFCF) diets have been shown to be successful in improving symptoms of autism whereas others have reported that such diets have no effect [15, 16]. The aim of this review is to investigate the gastrointestinal and behavioral problems which are frequently observed in ASD, the possible action mechanisms of GFCF diets, and the efficacy of these elimination diets.

Common Nutritional Problems in Autism Spectrum Disorder

In a recent meta-analysis, many nutritional problems were reported in children with ASD unlike their peers [17]. It is estimated that 46-89% of children with ASD have nutritional problems [18].

Food selectivity [17] and related insufficient food intake [18], food rejection [19], preference for food items of a specific taste, pica, and irregular meal times are common problems [18]. Therefore, the quality of diet for children with ASD is lower than that of healthy children [20]. It is thought that these nutritional problems may arise from biological food intolerances as well as behavioral problems such as obsession with details, fear of innovation, sensory deprivation, and a propensity for difficult situations [21].

Main Points

- Nutritional and gastrointestinal problems are very common in individuals with autism.
- Families turn to alternative treatments to solve these problems, believing that they are harmless.
- There is insufficient evidence for the effectiveness of these frequently used alternative treatments. One of these alternative treatments is the GFCF diet, one of the elimination diets.
- This diet is based on the opioid theory. However, there is insufficient evidence to prove its effectiveness.
- The benefit of this diet is controversial and with long-term administration, it may cause micronutrient deficiencies.

In addition to nutritional problems such as oral motor disorders and chewing problems [18], various uncontrolled immune responses arise in individuals with ASD, including increased natural killer cell activity, presence of autoantibodies directed to brain proteins, and modified cytokine profiles, which cause increased middle ear infections at a young age [22]. Skin diseases such as atopic dermatitis, eczema, asthma, food allergies, and intolerances are frequently associated with autism [23]. It is known that food sensitivities are known to cause abdominal pain, bloating, nausea, vomiting, constipation, diarrhea, asthma, rhinitis, joint pain, and cognitive and emotional disorders [24]; these symptoms are thought to cause an increase in the severity of behavioral disorders in individuals with ASD [6].

Common Gastrointestinal Symptoms in Autism Spectrum Disorder

Gastrointestinal (GI) symptoms are more common in children with ASD than in healthy children [25]. The prevalence of GI symptoms such as constipation, diarrhea, abdominal pain, gastroesophageal reflux, and inflammatory bowel diseases [26] in children with ASD range from 23% to 70% [27]. Furthermore, the severity of GI symptoms correlates with the severity of autism symptoms [28].

Bidirectional changes in brain-gut microbiota are known to account for the pathophysiology of many brain-related disorders such as gut disorders, which are well-known gastrointestinal diseases [29], as well as autism [30], Parkinson's [31], and chronic pain [32]; however, no clear mechanism has been identified.

The signals from the brain affect the signals of microbiota and gut motility and integrity. Therefore, the gut affects brain development and function [30]. Intestinal microbiota and metabolites affect intestinal permeability, mucosal immune function, intestinal motility, and sensitivity [25]. In addition to the release of GI hormones and neurotransmitters from cells [30], enteroendocrine and enterochromaffin play a role in the enteric nervous system [33]. Apart from this, microbiota and their metabolites are responsible for stress-induced behaviors and brain processes [34], emotional behaviors [35], pain modulation [30], and the regulation of brain chemistry [36]. Imbalance in the composition of gut microbiota can frequently be seen in individuals with ASD. For this reason, this imbalance is thought to be effective in the development of GI symptoms [10, 30]. Kang et al. [37] reported that GI symptoms reduced by approximately 80% and autism-related behavioral symptoms decreased in a study in which 18 children with autism underwent fecal microbial transplantation for 8 weeks. The integrity of the intestinal barrier and the BBB is affected in approximately one-third of the individuals with ASD. As a result, due to the permeability of the intestinal membrane and BBB, pathogenic microbiota, food-derived peptides that are not fully metabolized, bacterial metabolites, and other bacterial components can enter the bloodstream [9].

In fetuses with normal development, the gut, which is initially completely permeable, assumes a mucosal tight-junction character at the end of pregnancy, and then becomes less permeable shortly after birth. This is also referred to as gut closure. The gut barrier, which is not fully closed, adversely affects the development of gut in the following years [38]. Incomplete gut closure leads to increased gut permeability and permeable gut syndrome in individuals with ASD [26, 39].

Gluten Free Casein Free Diet

Although it is predicted that diet therapies may improve gut microbiology, composition, and toxin production [10, 31], studies have not clarified this yet . Studies have shown that these specific diets in individuals with ASD will contribute to a better course of the disease. GFCF diet is one of the diets frequently administered in ASD.

It was suggested for the first time in the 1980s that consumption of foods containing gluten and casein might cause autism-like symptoms by altering brain functions [40, 41]. GFCF diet is an elimination diet that involves the removal of some proteins from the normal diet such as gluten and casein [42].

Casein, one of the proteins most frequently causing an immune reaction in children [43], was found to be among the proteins that are most frequently involved in an immune reaction in a study on children with ASD [6]. Celiac disease, a disorder in which the small intestine develops a reaction to gluten, was found to be three times more common in children with autism [44]. The physiological suitability of GFCF diet is defended by high antibodies or reactions to milk, gluten, and casein [45]. In some studies, this has been associated with autoantibody formation or proinflammatory cytokines [12, 45]. In a study, it was determined that children with ASD who are on the GFCF diet had less tumor necrosis factor-a production than those who did not go on the diet [46]. However, the most common theory that is effective in the acceptance of the GFCF diet is associated with the release of neurotransmitters and peptides with opioid activity into the intestines [47] (Figure 1). Opioid peptide species-exogenous

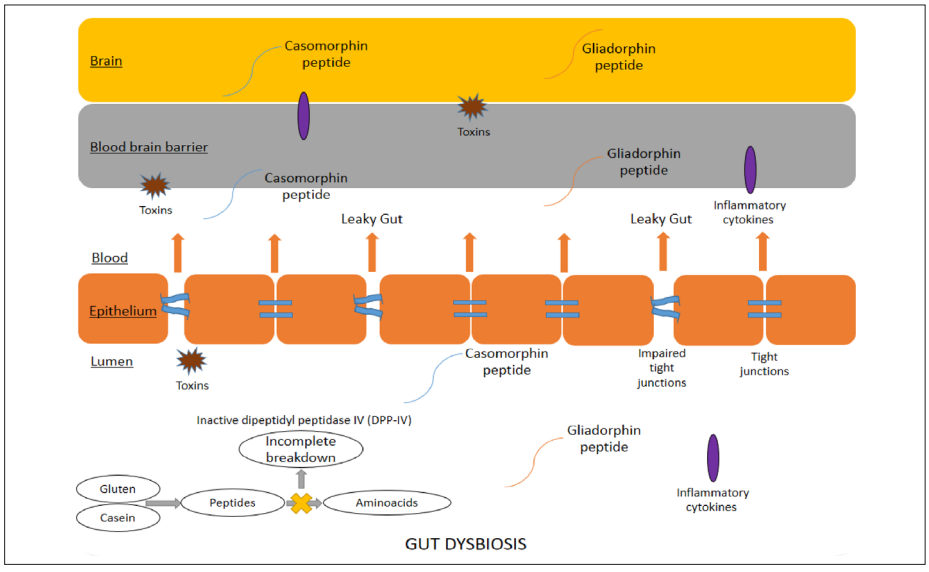

Figure 1. Gut dysbiosis and impaired blood-brain barrier in ASD

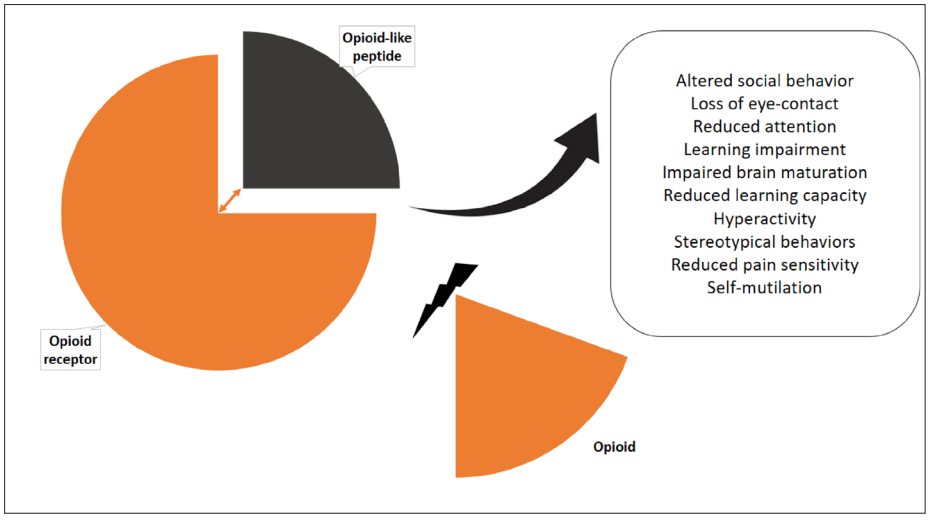

Figure 2. Changes in individuals with ASD due to the binding of the opioid-like peptides to the opioid receptor

neuropeptides [exorphins] such as gluteomorphin and casomorphin-occur by hydrolysis of cereal and milk proteins [47]. The brain has three different opioid receptors: δ, κ, and μ. In addition, the cells of the digestive, immune, nervous, and endocrine systems also contain opioid receptors [48].

The β-casomorphin-7 (β-CM7) released from beta-casein in cow milk is an exogenous opioid [49, 50]. It is known as the μ-opioid receptor [MOR] agonist and can interact with the morphine serotonin system [49, 50]. In addition, gluten-derived opioid peptides (exorphins such as A4, A5, B4, and B537) interact with the δ-opioid receptor in the brain and produce similar effects [51]. Other dietary proteins may include amino acid sequences that exhibit antagonist activity on these opioid receptors [50].

In children with ASD, it is reported that incompletely digested peptides cross the intestinal mucosa of the permeable intestines [47], frequently observed due to the formation of abnormal pores resulting from immunological factors or lesions [39]. These peptides cross the BBB by entering the bloodstream, and they then reach the central nervous system [52] and have negative effects on attention, brain maturation, social communication, and learning (Figure 1). When the peptide level increases, brain functions are affected [34]. Their high levels play a part in the occurrence of symptoms such as loss of eye contact, learning impairment, hyperactivity, stereotypic movements, and self-mutilation [13]. A hypothesis has been proposed that the diets utilized for this purpose can improve learning, social behaviors, cognitive function, and communication skills [16]. Based on this hypothesis, the GFCF diets utilized to reduce ASD symptoms has become an alternative treatment method [9]. It is predicted that the GFCF diet may reduce the common ASD symptoms, such as reduced pain sensitivity and altered social behavior, due to the possibility that the gluten and casein derivatives can stimulate the opioid system (Figure 2) [8]. However, there is no sufficient evidence of this yet.

In a study on rats, an association was found between the abnormal urinary pattern of proteins and abnormal brain chemistry [53]. Peptides and related proteins in the urine are known to be different in ASD from those of healthy controls [54]. When the GFCF diet is administered, urine patterns and levels of peptides change [55]. In a study conducted by Knivsberg et al. [56], it was reported that the GFCF diet was effective in reducing urinary pepdite levels, which is considered an indicator of opioid effect, and that there were improvements in autistic behaviors, non-verbal cognitive, and motor problems. However, in another study, it was suggested that in children with ASD, there was no evidence for any opioid peptides, opioid peptides could not function as a biomedical marker for autism, and that they can not be used to monitor the response to a GFCF diet [57]. In a study conducted by Elder et al. [58], it was found that GFCF diet did not make any difference in urinary peptide levels, which supported the findings of the abovementioned study.

In a study conducted by Salomone et al. [59] in 18 European countries, it was determined that 13% of children with ASD were on the GFCF diet. In reviews conducted on the GFCF diet, it is reported that the existing studies in the literature have various methodological limitations and that the number and quality of the studies are not sufficient [28, 47, 60]. In a study conducted by Winburn et al. [61], parents of children with ASD who were on the GFCF diet stated that at least one gastrointestinal symptom decreased in their children, while some parents said that their children's concentration and attention increased, whereas the repetitive behaviours specific to the disease decreased.

Knivsberg et al. [56] investigated the effects of the GFCF diet on a group (n=15) with ASD. They determined that the behaviors of the individuals improved in the first six months; however, no improvement was observed at the end of a year. A recent randomized controlled trial has reported improvements in the behavior of some children with ASD [62].

Elder et al. [58] administered the GFCF diet to 15 children with ASD for 6 weeks and found no significant differences in the children's behavior. Similarly, in a study conducted by Seung et al. [63], a 6-week GFCF diet did not have any significant effect. In a randomized controlled double-blind study conducted by Pusponegoro et al. [64], biscuits containing gluten, casein, and rice were given to children with autism for a week. It was observed that there was no significant increase in behavioral disorders and GI symptoms of the gluten and casein added group compared to the control group. Johnson et al. [42] argued that the diet should be applied for a longer period of time so that its positive effects can be seen. Likewise, Whiteley et al. [60] argued that the GFCF diet requires at least 6 months of implementation. However, Winburn et al. [61] emphasized that it is more acceptable to apply the elimination diets for three months.

Christison and Ivany [65] reported that there was insufficient evidence about the efficacy of GFCF diet in individuals with ASD. Moreover, a systematic review [66] similarly reported that there was no adequate evidence to suggest the removal of gluten and casein from the diet. In a systematic review, elimination diets were recommended only when there was intolerance or sensitivity to food containing gluten or casein [47].

Safety of Gluten Free Casein Free Diet

Although there is a belief that the GFCF diet is completely harmless [47], there is no clear conclusion that it has no risk at all, especially the nutrient deficiencies that may arise are of great concern. However, this has also not been clarified, yet, either [67].

In some studies, it was found that there was no difference in the intake of macro and micronutrients in children with ASD who were on the GFCF diet [42, 68]. Similarly, in another study, no micronutrient deficiency was observed in patients on the GFCF diet [69]. In a case report by Monti et al. [70], it was reported that the bone mineral density of an 8-year-old autistic child with cow milk allergy decreased and that there were four fractures. In another study, it was determined that calcium intake in autistic children whose diet did not involve milk products was inadequate and their bone density was low [71]. Similarly, Hediger et al. [72] and Neumayer et al. [73] reported low bone mineral density in patients on elimination diets. It is reported that children with ASD have lower serum folate and vitamin B_{12} levels than healthy children of the same age [74]. Inadequate consumption of dairy products [75] and GFCF diets [76] have been found to be associated with high levels of homocysteine. For this reason, homocysteine levels should be evaluated, and appropriate supplements should be added before elimination diets. Long-term elimination diets and lack of proper supplementation can have serious adverse effects on bone health.

Children with ASD have frequently been observed to have picky eating behaviors for specific taste, color, or appearance [77]. It is common for in ASD to have severe picky eating disorders [78] and even prefer only five or less food [79]. The implementation of adequate and balanced nutrition plans with adequate macro and micronutrient elements for this group with picky eating behaviors has become difficult [78]. Therefore, some micronutrient levels have been found to be lower in children with ASD as compared to that in healthy children, and inadequacies have been more frequent [69]. This situation can create a burden on families and increase healthcare costs in terms of the implementation of elimination diets [61].

Care should be taken to establish an appropriate nutrition plan for children with ASD who do or do not an elimination diet and to provide adequate information and training programs to the family. The recommended gluten-free diet for a celiac patient requires at least three hours of education to teach the family. Similarly, dietitians require a long time to adequately describe the GFCF diet. In addition to teaching the requirements of the diet to patients, generally accepted healthy nutrition plans should be applicable by the patients in order to provide an adequate and balanced nutrition [78].

It is inevitable that GFCF diet affects food choices and eating behaviors [47]. For parents, this increases the time and cost of food shopping and preparation [68]. Studies report that gluten-free (GF) products are more expensive (by 240%) compared to the same type of product that contains gluten and that gluten-free products are limited [80]. Therefore, the high cost of elimination diets can be considered as one of the challenges. One of the other disadvantages is that the GFCF diet causes social isolation [81]. In a study by Cornish et al. [68], 75% of the families implementing GFCF diets were found to be more isolated in socializing, eating out, and on holidays. In another study, Sponheim [15] reported that GFCF diet did not reduce autistic behaviors and that it caused social isolation.

Another potential disadvantage of this type of elimination diet is the possibility of delaying the diagnosis of problems such as food allergy, celiac disease, or lactose intolerance [67].

Conclusion

Studies in this field are quite insufficient in terms of quantity and quality. Since the methods of these studies are different from each other, it also made it difficult to interpret. In addition, while evaluating behavior changes, it was adhered to their parents' statements by not using an objective method. Therefore, these are the limitations of this review.

In summary, although the underlying cause of gastrointestinal symptoms in patients with ASD is not exactly known, the most widely accepted one is the opioid theory. There are a few studies that demonstrate that the GFCF diet has a beneficial effect to support the opioid theory. Since the studies are generally applied to a small number of subjects for short periods, the effect of this diet on autistic behavior is not clear. In addition, although dietary interventions are generally considered to be harmless, long-term administration of restricted diets such as GFCF may cause micronutrient deficiencies. It should be taken into consideration that restricted diets may cause an economic burden on families by causing social isolation and having social and psychological consequences. For this reason, in cases where a restricted diet such as GFCF is applied, it should be ensured that a healthy diet plan is established and that the dietary requirements are met.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.B., H.Y.; Design - B.B., H.Y.; Supervision - H.Y.; Resources - B.B.; Materials - B.B., H.Y.; Data Collection and/or Processing - B.B.; Analysis and/or Interpretation - B.B., H.Y.; Literature Search - B.B.; Writing Manuscript - B.B., H.Y.; Critical Review - B.B., H.Y.

Conflict of Interest: Authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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