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# The Relationship of Autism Spectrum Disorders and Celiac Disease and Gluten-free Diet

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**Abstract** Children with autistic disorders suffer from various gastrological abnormalities more frequently compared to the overall population. Coincidence of autistic disorders and celiac disease is probably a concurrency of two common diseases. However, in order to assess the connection between autistic disorders and non-celiac gluten sensitivity it is necessary to carry out further studies. Gluten-free diet should not be applied in all patients with autistic disorders, but there probably is a group of patients with the diet-related autism phenotype, who can benefit from dietary therapy.

***Keywords:*** *celiac disease, gluten-free diet, intestinal permeability, autism spectrum disorders*

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## 1. Introduction

Autism is a neurodevelopmental disorder, which is clinically manifested by qualitative disturbances of social interaction, verbal and non-verbal communication, and occurrence of limited, repeating stereotypical patterns of activity, behavior and interests. According to the classification proposed in 2013, autism, along with all other previously identified disease entities, is included in a wider category referred to as autism spectrum disorders (ASD) [1,2]. During the last 20 years the prevalence of ASD has increased by more than 10 times [3]. The current prevalence of autistic disorders in the overall population of the United States is estimated at 1 in 88 children. Autism is most frequently diagnosed in early childhood, more often in boys than girls (4:1) [1,2].

Many studies have indicated an increased incidence of gastrointestinal symptoms in autism spectrum disorders. Moreover, cases of association between autism spectrum disorders and celiac disease were reported. It has been also suggested that dietary intervention, specifically the removal of gluten-containing food from diet may impact on the presentation on autism spectrum disorders. However, the results of studies are conflicting and not conclusive. The aim of this review was to estimate the frequency of gastrointestinal symptoms in autism spectrum disorders and examine the association between celiac disease and autism spectrum disorders. Additionally, a review of the medical literature related to the effectiveness of the gluten-free (and casein-free) elimination diet on autism spectrum disorders was conducted.

## 2. The Frequency of Gastrointestinal Symptoms in Autism Spectrum Disorders

The pathogenesis of autistic disorders is still poorly understood and the commonly used psychological, pedagogic and social management does not lead to recovery [4]. It has been suggested that the pathogenesis involves the so-called "leaky gut" (impaired intestinal permeability). However this hypothesis was not confirmed in all studies and it does not pertain to all patients. In the studies by de Magistris et al., abnormal intestinal permeability measured with use of lactulose and mannnitol test was observed in 36.7% of patients with autism, 21.2% of their relatives and in only 4.8% of healthy subjects [5]. In a different study carried out in the same centre, increased intestinal permeability was confirmed in 25.6% of patients with autism and 2.3% of healthy children [4]. Horvath et al. showed increased intestinal permeability with use of the same method in as much as 76% of children with autism [6].

On the contrary to the authors of the previously quoted studies, Dalton et al. did not find any differences in intestinal permeability between children with autism, compared to children with special educational needs but no autism. In two children, one in each of the investigated groups, intestinal permeability was significantly increased, but it was caused by other conditions (celiac disease, status post partial bowel resection) [7]. Similarly, Robertson et al. did not confirm abnormal intestinal permeability in children with autism and gastrological symptoms [8].

Increased intestinal permeability in some patients with autistic disorders allows products of food protein digestion to transfer to the systemic circulation, from where they can pass through the blood-brain barrier, reach the central nervous system and affect child's behavior. High molecular weight proteins, which are suspected of having effect on the functioning of the central nervous system include gliadinomorphin-7 (YPQPQPF; GM7) produced in the process of enzymatic digestion of wheat, α-gliadin hβ-casomorphin-7 (YPFVEPL; hBCM7) and bβ-casomorphin-7 (YPFPGPL; bBCM7) produced in the process of hydrolysis of milk β-casein (human and cow's, respectively). Presence of 2-3 proline residues makes these proteins resistant to further proteolysis. They are ascribed to the group of exogenous opioids called exorphins. The fact that they are similar to morphine and can activate opioid receptors became the basis of the opioid peptide theory proposed by Panksepp in 1979. Activation of μ-opioid receptors induces changes in the EAAT3 expression (excitatory amino acid transporters), which then affects cysteine uptake by mature nervous cells and epithelial cells of the gastrointestinal tract, especially in the distal part of the ileum. In consequence, there is a decrease in the bioavailability of S-adenosylmethionine (SAM), which is a donor of methyl groups in over 200 various methylation reactions. This leads to disturbances in DNA methylation and gene transcription [10].

The presuppositions of the opioid theory in the pathogenesis of autistic disorders are challenged because with use of modern diagnostic methods (LC-MS/MS, Mass Spectrometry coupled with high-performance Liquid Chromatography) it was not possible to detect peptide metabolites of opioid activity in the urine of patients with autism [11]. Moreover, the affinity of exogenous opioids to opioid receptors is low, and in food products there are also peptides of antagonistic action to these receptors [2]. According to Julio-Pieper et al., the data confirming abnormal intestinal permeability in patients with various diseases of the central nervous system, including autism, are limited and the effect on affect neurological and behavioral disturbances by affecting the intestinal barrier requires further studies [12].

An attempt to relate autistic disorders with food elements (especially gluten) is at least partially caused by the high frequency of gastrological symptoms that has been for years reported by many authors. The frequency is by various publications estimated at 22-70% of all patients with autistic disorders [13].

According to the questionnaire carried out among parents of 412 autistic children by Horvath et al., as much as 84.1% of subjects and 31.2% of their healthy siblings presented with gastrological symptoms. They most frequently included: discomfort in the abdominal cavity, flatulence and passing gas and disturbances of the number and/or consistency of the stools [14]. Campbell et al. confirmed occurrence of gastrointestinal ailments in 43% of children with autism and only 4% of their healthy siblings [15]. According to these authors, the data can be understated due to difficulties with verbal and non-verbal communication, being part of the underlying disease [3,14]. In a study by Wang et al., in children with autistic disorders (especially the full autism form) parents significantly more often observed constipation and chronic diarrhea, compared to the healthy siblings. Moreover, the more severe the form of the autistic disorder was, the more prevalent were the gastrological symptoms [16]. According to Pang et al., constipation in children with autism occurs not only more frequently than in the overall population, but also occurs earlier and lasts longer [17]. In the study by Badalyan et al., children with autistic disorders more frequently than their healthy siblings complained about constipation (30% vs 4%), stool incontinence (22% vs 2%), more frequently had atypical food preferences (57% vs 5%) and more frequently refused to eat new types of food (48% vs 8%) [18]. Food selectivity in children with autistic disorders was confirmed by Beighley et al. as well [19]. Ibrahim SH et al. showed that constipation and food selectivity were more frequent in children with autistic disorders than in the control group (33.9% vs 17.6% and 24.5% vs 16.1%, respectively). These symptoms are frequently associated with neurobehavioral disturbances, not the primarily organic gastrological condition. Other gastrointestinal symptoms (diarrhea, vomiting, gastroesophageal reflux, discomfort or flatulence) were equally frequent in both investigated groups [20]. According to parents of children studied in 2013 by Chandler et al., 46.5% of children with autistic disorders, 29.2% of children with special educational needs and 21.8% of normally developing children presented with at least one gastrological symptom in their life. Gastrological symptoms did not correlate with intellectual aptitude, severity of autism and dietary limitations [13].

Literature provides single publications, which contradict more frequent occurrence of gastrological symptoms in children with autistic disorders. Black et al. confirmed occurrence of gastrological diseases in only 9% of children with autism and the same percentage of children without autism [21]. Similarly, Smith et al. did not observe any statistically significant differences in the prevalence of constipation, diarrhea and flatulence in children with autism, compared to healthy children [22]. In a study by Chandler et al., constipations occurred in only 10% of children with autistic disorders, which means they were as frequent as in the overall population [13].

Authors also point to the possibility of occurrence of gastrointestinal pathologies in children with autistic disorders. In 2005 Wakefield et al. confirmed a significantly higher occurrence of lymphatic follicle hyperplasia in the ileum ($p<0.0001$) and the colon ($p=0.0003$), compared to the overall population. Lesions of this type in the ileum were found in 90% of children with autistic disorders, were more severe than in healthy children and did not depend on the type of dietary restrictions applied [23]. Chandler et al. frequently observed macroscopic changes within the upper section of the digestive tract of autistic children. These included reflux esophagitis (69.4% of children), chronic gastritis (41.6% of children) or duodenitis (66.6% of children) and shortening of intestinal villi (5.5% of children) [14].

## 3. The Association between celiac Disease and Autism Spectrum Disorders

Speculations over the connection of behavioral disturbances with gluten sensitivity date from the 50s of the 20$^{th}$ century. Initially, they were mainly ascribed to

celiac disease. This was due to the fact that celiac disease was frequently diagnosed in patients with neurological symptoms such as gluten-dependent ataxia, epilepsy, peripheral polyneuropathy, dementia or depression [24]. Neurological symptoms can occur independently or can be accompanied by gastrological symptoms [1].

Studies on the coincidence of autism and celiac disease are scarce. In a small group of 11 children with autism none was found to have serological markers for celiac disease. Moreover, none of the 120 children with celiac disease had behavioral disturbances confirmed, which are typical for autism [25]. Similarly, in a study by Batista et al., including 147 patients with autistic disorders, did not show higher frequency of gluten-dependent diseases (celiac disease and non-celiac gluten sensitivity), compared to the overall population. Similarly, in a group of 211 patients with histopathologically confirmed celiac disease they did not found higher prevalence of autistic disorders than in the overall population [3]. In a study by Chandler et al. only 1 in 132 children with autistic disorders presented with celiac disease [13]. None of the 36 patients examined by Horvath et al. presented with microscopic lesions in the mucosa of the small intestine that are typical for celiac disease [14]. De Magistris et al. found antibodies specific for celiac disease in 2 out of 162 children with autistic disorders [4]. In a study by Lau et al., involving a total number of 140 children, none of the 37 subjects with autism presented with serous celiac-specific tTG-IgA (IgA class antibodies against tissue transglutaminase) and DPG-IgA (IgA class antibodies against deamidated gliadin peptide). However, children with autism were found to have AGA-IgG antibodies more frequently than their healthy peers (24.2% vs 5.3%; $p<0.01$). Higher concentration of these antibodies more frequently pertained to autistic children with gastrological symptoms [26]. Based on the data obtained from the Swedish registry of patients with celiac disease it can be observed that earlier diagnosis of autistic disorder was not associated with histopathologically confirmed celiac disease (OR 0.93; 95%CI 0.51-1.68) and enteritis (OR 1.03; 95%CI 0.40-2.64), but was associated with over 5-time higher risk of abnormal serological tests specific for celiac disease with no inflammatory changes in the small intestine [27].

However, there are studies which indicate that higher coincidence of celiac disease and autistic disorders is possible. Such conclusions were drawn by Barcia et al., who showed that in a group of children with autistic disorders, celiac disease was more than 3-times more frequent than in the overall population (1:106 vs 1:30, $p=0.014$). After 6 months of a gluten-free diet they achieved some improvement as regards gastrological symptoms in patients who suffered from them, but no behavioral improvement was observed [28]. Based on a questionnaire, Valicenti-McDermott et al. observed that in a group of 100 children with autistic disorders, patients with speech regression more frequently had positive family history of celiac disease and non-specific inflammatory diseases of the intestine than children with no speech regression (24% vs 0%; $p=0.001$) [29].

According to the recommendations of the American Academy of Pediatrics, every child with an autistic disorder and gastrointestinal symptoms should be tested for celiac disease with an assessment of the total concentration of tTG-IgA antibodies with or without antiendomysial antibodies. If gluten-free diet is applied without diagnostic examinations, the patient should undergo a gluten challenge test. Genetical tests for haplotypes HLA-DQ2 and HLA-DQ8 can be useful in exclusion of celiac disease (if the haplotypes mentioned above are not detected) [30].

It is currently suggested that most patients with gluten-dependent disorder do not suffer from celiac disease but a non-celiac gluten sensitivity. In the majority of patients with non-celiac gluten sensitivity IgG class antibodies against native gliadin (AGA-IgG) can be found. Therefore, the finding of isolated AGA-IgG positivity seems to be the most valuable serological marker of non-celiac gluten sensitivity. In the study by de Magistris et al., AGA-IgG and DPG-IgG occurred in children with autistic disorders more frequently than in the healthy population. The concentration of these antibodies was lower in children who were ill but using the gluten-free diet [4]. In a group of 21 children with autism spectrum disorders 1 patient was diagnosed as having histopatologically confirmed celiac disease and next In autism 7 patients were AGA-IgG antibody positive (unpublished personal experience).

The speculations associated with the opioid theory resulted in numerous attempts of application of elimination diets (including gluten-free diet), usually joined with casein-free diet – in order to improve the disturbances of behavior and communication observed in children with autism. Data from the literature indicates that 20-70% of children with autistic disorders make an attempt to apply gluten-free and casein-free diet [2]. Unfortunately, most studies evaluating the effectiveness of such a diet in children with autistic disorders are of low value. This is mainly due to the fact that there is usually no control group, the studied groups are small and the age heterogeneity of the analyzed group is large. Also there is lack of clear inclusion and exclusion criteria. Among all these studies, one publication of 2000 deserved special attention. It included a group of 150 children aged 3.5-16 years, in whom gluten-free diet resulted in a clinical improvement as regards symptoms of autism [31]. In a randomized clinical trial involving 72 children aged 4-10 years, suffering from autistic disorders, Whiteley et al. showed a significant clinical improvement after application of milk-free and gluten-free diet. However, according to the authors, effect of other, diet-independent, factors cannot be ruled out [32]. On the other hand, in a retrospective, randomized, double-blind study of 13 children aged 2-6 years, that was published in 2007, Seung et al., did not observe any differences in verbal and non-verbal communication of subjects on an elimination and general diet [33]. Similarly, in a randomized, double-blind study published in 2010, Hyman et al. did not confirm any differences in the behavior of 30 children aged 30-45 months on an 18-month-long gluten-free, casein-free and general diet [34]. The caregivers of children enrolled in a blinded study by Elder et al., in which a 3-month-long gluten- and casein-free diet was applied interchangeably with a 3-month-long general diet, did not observe any differences in the behavior and development of the children, regardless of the type of diet that was applied [35].

In 2008, Millward et al. made an attempt to perform a meta-analysis assessing the effectiveness of gluten-free

and/or casein-free diet on the improvement of cognitive, social and behavioral functions in children with autism. Unfortunately, they have identified only 2 studies fulfilling the inclusion criteria, based on which they could not formulate any definite conclusions [36]. Similar conclusions were made by authors of later meta-analyses, who concluded that the data confirming the effectiveness of elimination diet in autism is limited and of little scientific value. Gluten-free and milk-free diet should be applied in children with autistic diseases if gluten/milk intolerance or food allergy is diagnosed [37].

## 4. Conclusions

Children with autistic disorders suffer from various gastrological abnormalities more frequently compared to the overall population. Coincidence of autistic disorders and celiac disease is probably a concurrency of two common diseases. However, in order to assess the connection between autistic disorders and non-celiac gluten sensitivity it is necessary to carry out further studies. Gluten-free diet should not be applied in all patients with autistic disorders, but there probably is a group of patients with the diet-related autism phenotype, who can benefit from dietary therapy.

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