DOI: 10.17816/KMJ2020-834

Disorders of the gastrointestinal tract and possible mechanisms of their development in autism spectrum disorders

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Abstract

The article presents an analysis of current literature covering general information, as well as clinical and experimental research on autism spectrum disorder. Autism is a complex mental disorder. A growing body of literature suggests the association of autism spectrum disorder with dysfunction of the autonomic nervous system, especially those affecting the gastrointestinal tract and bladder. In addition, there are problems with nutrition, metabolism, immune and endocrine systems, and microbiota. Prevalence of autism has increased significantly over the past 40 years. As more and more children with autism become adults, understanding this condition throughout life is of paramount importance. Although many research has focused on understanding how diagnosis and treatment can help little children, few are focused on adults with autism and how primary care groups can better help these people. Despite significant progress toward identifying the factors influencing the development of autism spectrum disorder, the etiology of the disease remains uncertain. In this regard, scientists are trying to obtain models of autism in rodents to continue further research. Based on the data obtained during clinical and experimental researches, a hypothesis about the possible role of the purinergic system in the pathogenesis of autism spectrum disorder is considered. The results are encouraging, but further research is required. Thus, somatic disorders can worsen the main symptoms of autism, which affect communication and behavior functioning. In this regard, further research is necessary, including in a rodent model of autism spectrum disorder to contribute to identifying the possible causes of the disorder.

Keywords: autism, autism spectrum disorders (ASD), gastrointestinal tract, somatic problems.

For citation: Ivanova D.V., Ziganshin A.U. Disorders of the gastrointestinal tract and possible mechanisms of their development in autism spectrum disorders. *Kazan Medical Journal.* 2020; 101 (6): 834–840. DOI: 10.17816/KMJ2020-834.

Autism spectrum disorder (ASD) represents a complex mental impairment. Many studies have suggested the presence of autonomic nervous system (ANS) dysfunction in patients with ASD [1], especially concerning the gastrointestinal tract (GIT) [1–7], as well as bladder dysfunction [8]. In addition, problems with nutrition, metabolism, endocrine system, and microbiota are noted in children diagnosed with ASD. The prevalence rate of these concomitant problems reaches more than 90% for gastrointestinal tract pathology and nutritional and metabolic disorders, more than 50% for thyroid dysfunction, and up to 100% for microbiota-associated conditions [9].

The incidence of ASD has increased significantly over the past 40 years. Even in the last two decades, its prevalence has increased from 6.7 per 1,000 in 2000 to 14.6 per 1,000 people in 2012 (1 per 59 people) [10]. Moreover, 46% of patients with ASD have an IQ above 85, which means that they have an average or above-average IQ. As more children with autism become adults, understanding the course of this condition throughout their lives becomes paramount. While many studies have focused on understanding how diagnostics and treatment can help young children, few have focused on adults with autism and how primary care groups can provide better treatment to this population [10].

Typical GIT disorders in ASD. GIT disorders represent one of the most common diseases associated with ASD. If left untreated, these diseases can lead to more severe ASD symptoms, other associated clinical manifestations, and decreased quality of life [11]. Literary sources report the occurrence of symptoms in GIT disorders such as intestinal pain, constipation, and diarrhea, which are often associated with an altered composition of the intestinal microbiota [12]. Others have suggested the

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existence of a communication between the microbiota and the brain, which underlies some neurological disorders [1,3,13–19].

Numerous studies have suggested that ANS dysfunction occurs in patients with ASD. The ANS is a part of the brain–gut axis, which consists of a complex interaction between the gut microbiome, mucosal immune system, intestinal nervous system, ANS, and central nervous system [1]. In addition, the gut–brain axis involves endocrine, immune, and neural connections [14,20]. Changes in the gut microbiome and vegetative parameters can serve as noninvasive markers of the state of the gut–brain axis in ASD [1].

Possible mechanisms of the development of GIT disorders in ASD. Increasing evidence presents the effect of vitamin A on the course of GIT disorders in ASD. Vitamin A plays an important role in brain development and GIT functioning. Deficiency of this vitamin increases the risk for gastrointestinal comorbidities and aggravates the main symptoms in children with ASD [21,22]. In addition to vitamin A, children with ASD have vitamin B_1, B_6, B_{12}, and D deficiencies, which may also influence the development of comorbidities [23].

In recent years, diets that can be used as therapeutic intervention for ASD gained growing interest. Selective diet therapy for ASD and brain function has been shown to improve behavioral changes and reduce malnutrition, which appear to be associated with allergies or food intolerance to gluten [24]. Many studies have investigated the effect of gluten-free [12,18,19,25], casein-free, ketogenic, and specific carbohydrate diets [12,19,25,] on ASD symptoms, as well as the addition of probiotics, polyunsaturated fatty acids, and food supplements (vitamins A, C, B_6, and B_{12}, magnesium, and folate) [25]. However, further research is required to assess the effect of diets on the course of ASD symptoms [25,26].

However, opposing opinions disprove the effect of diets on ASD development. Thus, Monteiro et al. conducted a systematic review of studies from 2003 to 2018 and found insufficient scientific evidence to support the efficacy of nutritional supplements or dietary therapy in children and adolescents with autism [27]. Ferguson et al. assessed the relationship between GIT symptoms, intake of ω_3-fatty acids, trace elements, and macronutrients in children with ASD. This study showed that dietary variation did not lead to GIT symptoms in patients with ASD [28].

Recently, zonulin, a new biomarker found, plays a role in altering intestinal permeability. The level of this protein was increased in patients with ASD compared with healthy people and correlated with indicators of ASD severity. Zonulin may be a promising biomarker for a subgroup of children with ASD and GIT problems caused by an impairment of the intestinal integrity. However, not all studies support this hypothesis [29].

Interest in intestinal peptide hormones has also increased over the past decade. Peptide hormones belong to the group of polypeptides derived from the GIT and can perform various physiological functions by binding to specific receptors. Currently, dozens of molecules have been classified into this group, such as cholecystokinin, vasoactive intestinal peptide, pituitary adenylate cyclase activating peptide, YY peptide, secretin, pancreatic polypeptide, and ghrelin. In addition to nutrition and metabolic regulation, the potential role of gut peptide hormones in other behavioral paradigms has emerged in recent decades.

Notably, some intestinal peptides are involved in the regulation of social functions. For example, the absence of secretin in knockout mice leads to a deficit in social interaction, and a vasoactive intestinal peptide is important for the manifestation of social affiliation and aggression. Given that social deficit is one of the main symptoms of ASD, intestinal peptides may be associated with the pathogenesis of ASD. Therefore, further understanding of the role of intestinal peptide hormones in ASD should help to explain better the pathogenic mechanism as well as to develop a potential strategy for ASD management [30].

Several studies have report a possible role of *FOXP1* haploinsufficiency in ASD. It is characterized by autistic behavior, speech and mental deteriorations, as well as gastrointestinal problems. These data were obtained when *Foxp1*$^{+/-}$mice were studied as a model of *FOXP1* haploinsufficiency. Animals were found to have a decrease in body weight and changes in eating behavior with a reduced consumption of food and water. The esophagus and colon had severe muscular atrophy, caused by decreased muscle cell proliferation. Nitric oxide-induced relaxation of the lower esophageal sphincter was impaired, and achalasia was confirmed by manometry in vivo. General gastrointestinal transit was prolonged considerably due to impaired colon contractility. A previously unknown dysfunction (such as achalasia and impaired intestinal motility) was found to explain the gastrointestinal disorders in patients with *FOXP1* syndrome, which could potentially have a broader relevance to autism [31].

At present, emerging evidence confirms the occurrence of bladder dysfunction in patients with ASD. Some studies have reported that urinary incontinence is diagnosed in 85% of adults and 90% of children and adolescents [8,32,33].

Hypotheses have been put forward on the presence of mitochondrial disorders in the pathogenesis of ASD [18,29,34]. For example, the cell hazard response hypothesis states that the underlying cause of autism is a universal cellular response to stress by transforming the normal function of the cell into a new state. Severe and/or prolonged stress causes a redistribution of cellular resources for survival. This universal response to stress is monitored by the mitochondria. Annual scientific data indicate increased levels of oxidative stress, abnormal methylation processes, atypical energy metabolism, mitochondrial dysfunction, and abnormalities in sulfur and amino acid biochemistry in ASD [18].

Moreover, more than half of patients with ASD have immune dysregulation and neuroinflammation. Various clinical trials and experimental animal studies have identified abnormal immune function as a central part of the pathogenesis of autism, at least for a subgroup of patients diagnosed with this condition. Studies have identified chronic inflammatory processes in many fields of the brain and cerebrospinal fluid in patients with ASD, including increased production of inflammatory cytokines and chemokines and sequential activation of the astrocytes and microglia [12,18,34].

Most studies on ASD have focused on young adults, but clinical needs and outcomes in older adults with ASD should be investigated more profoundly [35,36]. Communication impairments have been reported to be an important impediment to diagnosing comorbidities in autism [37,38]. Only one study actually focused on the presence of comorbidities in adults with ASD, while others were based on evaluating patients/caregivers or medical records/registries. The results indicate that each person may have 1–4 comorbidities. Overall, epilepsy was the most common disease, followed by allergic rhinitis and irritable bowel syndrome [37].

Studies have shown also that patients with ASD are more likely to have health problems during childhood, adolescence, and adulthood, which can lead to an increased risk of early death. The frequency, timing, and cause of death in a large cohort of adolescents and adults with ASD (n = 406) over a 20-year period (1998–2018) have been reported. During this time, 6.4% of the patients died at an average age of 39 years. Causes of death were chronic diseases (such as cancer and heart disease), accidents (such as choking when eating and accidental poisoning), and complications of drug side effects [39].

Despite the significant progress in identifying factors that influence the development of ASD, the disease etiology remains unclear. In this regard, scientists are trying to develop rodent models of autism for further research [40–43]. Among the modeling methods, the administration of propionic acid in the postnatal period is the most actively investigated [45–47]; other models involved exposure to air pollution associated with movement, pregnancy, and feeding [48], and chronic prenatal psychological stress caused by ultrasound with a variable frequency of 20–45 kHz [49].

However, prenatal administration of valporic acid (VPA) to rodents is considered the most common method, as an increase in ASD prevalence has been reported in people exposed to intrauterine VPA. VPA administration also induces autistic behavior in rat offspring after prenatal exposure; therefore, it is a model of preclinical disease with high translational value [40–43].

In this model, VPA or isotonic sodium chloride solution was injected subcutaneously to pregnant mice at a dose of 600 mg/kg on day 12–13 of pregnancy [50, 51]. Their adult offspring were assessed in a social interaction test, and only male mice showed a decrease in sociability and a lack of preference for social stimulus over a new object.

Intrauterine exposure to VPA was found to cause a change in the density of astroglial and microglial cells in the cerebellum and dentate gyrus of adult mice. These neuroinflammatory effects were more pronounced in females than in males and manifested themselves in the early stages of development [50].

However, the apparent distinction between rodents and humans poses a significant problem for extrapolating the results of rodent models to humans. For this reason, a primate model of autism was first modeled by VPA administration. Eye-tracking analysis revealed that the offspring exposed to VPA have various manifestations of impaired social interaction, pronounced stereotypy, and greater attention to non-social stimuli. Results from non-human primate models are currently the best evidence for a causal relationship between intrauterine exposure to VPA and developmental defects of nervous system and susceptibility to ASD in humans [52].

Recent studies have highlighted the importance of perinatal risk, in particular maternal immune system activation (MIS), and have shown a strong association with the subsequent onset of ASD in affected children. MIS activation can be simulated in animal models by administering a non-pathogenic double-stranded polyinosinic-polycytidylic acid [poly (I:C)] agent during pregnancy. This report demonstrates the key role of the ligand-ion channel represented by purinergic P2X7 receptor in MIS-induced autistic, behavioral, and biochemical aspects. A study found that genetic or phar-

macological inhibition of P2X7 receptors in both the mother and offspring can reverse compromised brain development and autistic phenotype, which opens up new opportunities for the prevention and treatment of ASD [53].

Impaired functioning of the purinergic signaling system is believed to be associated with ASD, and this may represent a potential therapeutic target in ASD. In this regard, the effect of suramin, a nonselective antagonist of purinergic P2 receptors, on behavioral, molecular, and immunological responses in a model of autism caused by prenatal exposure to VPA was evaluated. Suramin treatment did not affect VPA-induced activation of P2X4 and P2Y2 receptor expression in the hippocampus and P2X4 receptor expression in the medial prefrontal cortex, but normalized the increased level of interleukin-6 [42].

In a clinical study of ten boys aged 5–14 years, all five children who received a single dose of suramin intravenously, compared with five boys who did not receive the drug, had an improvement in all major symptoms of autism, which lasted for 5–8 weeks. Although the authors believed that the results are encouraging, further research is still required [54].

The results indicate a possible important role of purinergic signaling modulation in behavioral, molecular, and immunological disorders characteristic of the VPA-induced model of ASD [42].

Conclusion. Analysis of modern literature has shown that ASD represents a complex disease whose pathogenesis involves the ANS, immune system, and endocrine system. Numerous concomitant diseases have been identified, and gastrointestinal disorders prevail among them, which are based on changes in the intestinal microbiome. Bidirectional interaction between the central nervous system and the intestinal microbiota through neuroendocrine, neuroimmune, and autonomic nervous mechanisms suggests the formation of the microbiota–gut–brain axis. Changes in the composition of the gut microbiota and increased intestinal permeability are proposed to explain the general and gastrointestinal symptoms of ASD.

Thus, disorders in the somatic sphere can aggravate the severity of the course of the main symptoms of autism, which affect communication and behavior. In this regard, further studies are required, including experiments in rodent ASD model, to establish possible causes of ASD.

Author contributions. D.V.I. collected the literature data and prepared the initial version of the article. A.U.Z. was the work supervisor and edited the draft and the final version.

Funding. This work was partially funded by the Russian Foundation for Basic Research and the Government of the Republic of Tatarstan within the framework of scientific project No. 18-44-160009.

Conflict of interest. The authors declare no conflict of interest.

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