



Neuro-Immune Features in Children with a Functional Constipation

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Abstract: The review details current views on the problem of functional constipation in children, discusses immune factors and their relationship with the nervous system that contribute to the formation of constipation. Рассмотрены Current data on the intestinal microbiota, which plays a major role in maintaining the body's immune balance, are reviewed, and pathogenetic and diagnostic principles of functional constipation in pediatric practice are described.

Key words: children, functional constipation, chronic constipation, gastrointestinal tract.

Constipation is one of the most urgent problems of pediatric gastroenterology. Constipation is a symptom complex of general, extra-intestinal and local disorders associated with delayed bowel movement with an increase in the intervals between acts of defecation, compared with the individual physiological norm (usually by more than 32-48 hours) or with systematic incomplete bowel movement [3].

According to American scientists, constipation affects from 30 to 50% of the working-age population in developed countries and 5-20% of children in the general population [12].

Chronic constipation - is a functional disorder of the gastrointestinal tract (GI) that causes serious harm to physical and mental health and affects the quality of life of patients. Its incidence is 2% -27% [30].

In 2016 year by consensus of Rome criteria IV was given new definition of functional disorders of the gastrointestinal tract, which declared that functional disorders represent a violation of the intestinal-brain interaction, which includes a group of disorders, the classification of which is based on the intestinal symptoms interconnected in any combination: impaired motility, visceral hypersensitivity, immune dysfunction, changes the function of the intestinal mucosa, changes of the intestinal microflora, a disorder of the Central nervous system [5].

Neuroimmune interactions play an important role in the digestive system's response to stress, as well as to inflammation as a result of infectious diseases of the gastrointestinal tract. The intestinal microflora is unique, perhaps because there are regional differences in the presence of luminal factors such as nutrients and microbes that play an integral role in the development of intestinal-associated lymphatic tissue (IALT), maintaining mucosal homeostasis, and maintaining normal gastrointestinal motility. Most physiological functions are optimal in a limited range of homeostatic states, and dysregulation of homeostatic states is a sign of disease. The concept that immunological homeostasis

is a goal rather than an actual state offers a more realistic framework for neuroimmune interactions [26].

Bidirectional communication between nerves and immune cells has been maintained throughout evolution and is associated with allostasis, a process that describes continuous adaptation to a constantly changing environment [29].

One of the main roles in the formation of symptoms of chronic constipation is played by insufficient functional activity of the sphincters of the colon. As is known from the definition, morphologically, sphincters play the role of active valves and represent a cluster of circularly located muscle elements of the digestive tube wall with dilatator structures located in its transition region, which performs an anti-reflux function and has functional autonomy [16].

Constipation syndrome in children in 95% of cases is caused by functional constipation (FC). This makes it possible to completely cure the child at the early stages of the disease with proper diagnosis and adequate therapy [1-9].

In infants, constipation rarely appears as an isolated condition. About half of children under 1 year of age simultaneously have a combination of several functional disorders(FD), (for example, infant colic, regurgitation, and constipation) [27].

The peak incidence of constipation in children is observed at the age of 2 to 4 years, when potty training begins [6].

According to Lewis M. L. et al. (2018) children whose parents suffer from similar conditions are more prone to functional gastrointestinal disorders[24].

Quite often, children with FD first seek help from specialists in the emergency department when they experience severe abdominal pain, blood in the stool, anal fissures, functional encopresis, etc. In this case, consultations of various specialists and, often, a large amount of examination are required. Constipation can therefore represent a high cost to the healthcare system. Such an important understanding of the problem of constipation in children is not limited only to the medical side, but can also reduce the quality of life of the child's family [21, 24-25].

Children with constipation often visit a general practitioner or pediatrician. These children are also often hospitalized as an emergency or treated in a hospital. Consequently, constipation is a significant economic problem for the healthcare system [28].

The causes of FD in children include, first of all, alimentary, psychogenic, associated with physical inactivity, drug use, various diseases (central nervous system, gastrointestinal tract, infectious, endocrine), etc. Risk factors for constipation development in children of the first year of life are: artificial feeding, prematurity, morphofunctional immaturity, food allergy [11].

A common cause of the development of chronic constipation is a change in the intestinal microflora due to a violation of the production of specific substances by representatives of the normoflora of the colon that contribute to the formation of stool and support optimal motor activity of the colon [13].

Studies show that the risk of developing FD increases in the presence of a history of intrauterine hypoxia, cesarean section, prolonged conjugation hyperbilirubinemia, and neurological disorders of hypoxic and ischemic origin [4].

Changes in the composition of the microbiota play an important role in the pathogenesis of many functional disorders of the gastrointestinal tract, including constipation. It was noted that the composition of the gastrointestinal microbiota in individuals with constipation is significantly different from those without constipation. Gut function is supported by a number of factors that play an

important role, including the nervous system, the immune system, bile acid metabolism, and the gut microbiota. The causal relationship between changes in the gut microbiota and impaired intestinal motility remains unclear. Some changes in the composition of the gut microbiota may be secondary to slowing down gastrointestinal transit [23].

An analysis of the literature shows that an additional factor significantly aggravating the course of the disease is the development of immunodeficiency states, which develop against the background of chronic fecal intoxication, colitis and intestinal dysbiosis. At the same time, they contribute to the progression of constipation due to synergy in the action of the gastrointestinal tract and the immune system, closing the "vicious circle" of pathogenesis. The most important function of the gastrointestinal tract is proved – its participation in the formation of the local and general immune response. This is manifested by the close interaction of immunocompetent formations associated with the intestine, with the bacteria, viruses and other microorganisms inhabiting it, as well as with foreign molecules with antigenic properties present in the chyme [1].

The development of obstipation syndrome in children may be associated with lifestyle and nutrition features, anatomical features of the colon, the state of the nervous and endocrine systems, pathology of the anorectal zone, etc. Despite the variety of causes, constipation of any origin is accompanied by endogenous intoxication [18].

Constipation in children of the first months of life can be a manifestation of a gastrointestinal form of food allergy. At the same time, foods with a high allergic potential - whole cow's milk, fish, and nuts - are excluded from the mother's diet. FC in children who receive natural feeding are not an indication for transferring a child to mixed or artificial feeding, since this can only aggravate the problem [7].

An important factor is the consistency of the stool. Difficult, often painful defecation, with dense feces and a feeling of incomplete emptying of the intestine are indisputable signs of constipation. Thus, the pediatrician should take into account both the frequency and the density of stool [12].

Chronic constipation is usually preceded by acute stool retention due to various causes, such as anal fissures. Fecal masses are compacted and reduced in volume, their evacuation from the rectum is delayed and accompanied by great effort. If you do not take measures to eliminate constipation, the child begins to deliberately suppress defecation, as it is associated with pain. Fecal masses accumulate in the rectum, which leads to stretching of its ampoule, formation of a functional megarectum, discoordination of the pelvic floor muscles and, as a result, to a persistent violation of the act of defecation [15].

There is objective evidence that with pathological changes in the colon, the regional lymph node is reorganized with a decrease in the area of the paracortex and an increase in lymphoid nodules with a germinal center. The first link of reorganization indicates the suppression of cellular immunity due to endotoxemia accompanying chronic constipation, the second - the formation of a primary immune response of the humoral type [8].

TGF- β belongs to the group of the TGF- β superfamily, which regulates the growth, proliferation and transition of cells along downstream signaling pathways. TGF- β precursors are cleaved by protease hydrolysis to form disulfide -bound active TGF- β dimers and an inactive binding peptide, which binds to the TGF- β -binding protein in an inactive form and is stored in the extracellular matrix. Under certain physiological or pathological conditions, active dimers are released from the complex, activate downstream signaling pathways, and regulate cell proliferation and differentiation [30].

It is quite obvious that the slow transit of feces through the intestine, concomitant dysbiosis and impaired permeability of the intestinal wall due to an inflammatory reaction should lead to pronounced antigenemia, activation of various parts of the immune response, followed by dysfunction and

dysregulation of immune mechanisms. In such a situation, autoimmune reactions are also quite natural. So far, not enough attention has been paid to this aspect. At the same time, it is well known that antineutrophil antibodies are often detected in inflammatory bowel diseases, and they are usually associated with a more severe course of the disease and more severe organic damage [10].

Constipation of functional origin in young children is often associated with immaturity of the gastrointestinal regulatory function due to weak myelination of nerve trunks and insufficient mediators in interneuronal and neuromuscular synapses [9].

FC in older children and adolescents are associated with violations of the regulatory function of the gastrointestinal tract. The causes of constipation can be reduced physical activity, low intake of dietary fiber and water. During adolescence, constipation can be caused by depression. Children with constipation are often diagnosed with autonomic dysfunction syndrome and psychological problems. Often in children with constipation, the tone of the parasympathetic nervous system prevails, and emotionally labile, hysterical, and labile-hysterical types of character accentuation are revealed [2, 14, 20].

According to the materials of the 2016 Consensus on the Diagnosis and Treatment of Functional gastrointestinal Diseases (the so-called RomeCriteria IV), the diagnosis of "functional constipation" in children from 0 to 4 years is established in the presence of at least 2 of the following symptoms that manifest themselves within 1 month:

- 2 or fewer bowel movements per week.
- the facts of taking certain poses or excessive stool retention in the anamnesis;
- defecation, accompanied by pain and straining in the anamnesis;
- a large fecal mass diameter in the anamnesis;
- a history of large fecal plugs in the rectum. For children aged 4-18 years, the diagnostic criteria of the Federal Health Service should include 2 or more of the following symptoms at least once a week for at least 1 month if the criteria for diagnosing irritable bowel syndrome are insufficient:
- 2 or fewer toilet defecations per week.
- at least 1 episode of fecal incontinence per week.
- a history of excessive strong-willed retention of the stool;
- defecation, accompanied by pain and straining in the anamnesis;
- the presence of large fecal plugs in the rectum in the anamnesis;
- large fecal mass diameter in the anamnesis [22].

Identification of risk factors, causes, and their elimination is of no small importance in the prevention of FC. If they are preserved, therapy and prevention of constipation will not be effective enough. In general, the FC – outcome and prognosis of chronic FD are favorable [17].

CONCLUSION

Functional constipation in children, as one of the most common problems that significantly reduce the quality of life of the child population, requires an in-depth study of pathogenetic mechanisms and a personalized approach to therapy.

The etiological factor of constipation varies depending on the age of the patient, as in infants cause of constipation may be a change in the type of feeding the transition from natural to artificial mixed and,

in children of early age – gastrointestinal form of food allergy and the immaturity of the regulatory functions of the gastrointestinal tract in children of preschool age – nutritional factor and potty training, have school-age children and adolescents most often, the syndrome of autonomic dysfunction and depression.

Immune mechanisms of functional constipation are triggered under the influence of antigenemia, due to chronic fecal intoxication, which inhibits cellular immunity, suppresses the proliferation of microbiota and contributes to the development of intestinal dysbiosis, thereby forming a vicious circle.

Discoordination of neuroimmune interactions between intestinal-associated lymphatic tissue, microbiota, and motility, which ensures the transit of intestinal contents, are fundamental links in the pathogenesis of functional constipation.

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