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SOMATIC DEVELOPMENT DISORDERS OF CHILDREN WITH NON SPECIFIC INFLAMMATORY BOWEL DISEASES

ZABURZENIA ROZWOJU SOMATYCZNEGO DZIECI Z NIESWOISTYMI ZAPALENIAMI JELIT

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Abstract

Frequency of inflammatory bowel diseases (Crohn's disease and ulcerative colitis) tends to increase in developing countries. Nearly 25% of cases affects pediatric patients. Inflammatory bowel diseases are often associated with weight loss and stunting in children. Moreover, weight and height deficiencies are often early symptoms. Initially, nonspecific or latent course of disease delays the diagnostic process.

Malnutrition in inflammatory bowel diseases can be caused by disorders of digestion and nutrients' absorption, intestinal loss, increased energy expenditure and appetite impairment. Nutritional deficiencies and inflammatory agents lead to disturbance of tissue metabolism – muscle and bone - and retardation of somatic development of affected children. Thus, deficiencies of muscle mass, bone mineral density and body height are observed. Insufficient normalization of somatic features may be the consequence of recurrent nature of disease and specificity of pharmacological treatment.

Present work deals with the current state of knowledge concerning the somatic development disorders of children with inflammatory bowel diseases. Abnormal nutritional status, bone mineral density deficits and growth failure of patients have been discussed in the context of their relations and dependencies on inflammatory, nutritional and therapeutic factors.

Key words: inflammatory bowel diseases, child development, malnutrition, bone density, growth disorders

Streszczenie

Częstość występowania nieswoistych zapaleń jelit (choroby Leśniowskiego-Crohna i wrzodziejącego zapalenia jelita grubego) wykazuje tendencję wzrostową w krajach rozwijających się. Blisko 25% zachorowań stanowią pacjenci pediatryczni. Nieswoiste zapalenia jelit wiążą się często z utratą masy ciała oraz z zahamowaniem rozwoju somatycznego u dzieci, a niedobór masy i wysokości ciała bywają pierwszymi objawami choroby.

Początkowo niespecyficzny bądź utajony przebieg procesu chorobowego opóźnia rozpoznanie, co sprzyja pogłębieniu stanów niedoborowych.

Za przyczyny niedożywienia w nieswoistych zapaleniach jelit uznaje się zaburzenia trawienia i wchłaniania składników odżywczych, straty jelitowe, zwiększone wydatkowanie energii oraz osłabienie łaknienia. Niedobory pokarmowe oraz działanie czynników zapalnych prowadzą do zachwiania metabolizmu tkanek – mięśniowej i kostnej oraz spowolnienia rozwoju somatycznego chorych. Tym samym wśród młodych pacjentów z nieswoistymi zapaleniami jelit obserwuje się niedobory masy mięśniowej, gęstości mineralnej kości i wysokości ciała. Nieprawidłowości te stwierdzane są już w momencie rozpoznania choroby i mogą pogłębiać się pomimo rozpoczęcia leczenia. Niedostateczna normalizacja cech somatycznych może być skutkiem nawracającego charakteru choroby oraz specyfiki działania środków farmakologicznych stosowanych w jej leczeniu.

W pracy przedstawiono aktualny stan wiedzy na temat zaburzeń rozwoju somatycznego dzieci z nieswoistymi zapaleniami jelit. Nieprawidłowy stan odżywienia, obniżona gęstość mineralna kości oraz spowolnione wzrastanie chorych zostały zaprezentowane jako problem wielowymiarowy, wynikający z działania czynników – zapalnych, żywieniowych oraz terapeutycznych.

Słowa kluczowe: choroby jelit zapalne, rozwój dziecka, niedożywienie, gęstość kości, zaburzenia wzrastania

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INTRODUCTION

Malnutrition and growth retardation are often first signs of chronic disease in children and precede specific symptoms (1). Inflammatory bowel diseases (IBD) is a group of autoimmune diseases of genetic origin and unclear etiology, which includes two main entities – Crohn's disease (CD) and ulcerative colitis (UC). The disease is chronic and extends with periods of relapse and remission. IBD can occur at any age, but the peak of morbidity is observed in the third decade of life. It is known that 25% of newly diagnosed cases of CD an UC are pediatric patients. Moreover, in recent years the incidence of IBD has been increased, which can be linked, among others, to the spread of Western lifestyles in many countries (2). Patients with IBD are at particular risk of malnutrition due to impaired digestion and nutrients' absorption, intestinal losses, dietary restrictions (often unjustified), increased need for protein and energy, and the use of pharmacological agents that cause specific deficiencies (3). Mentioned factors, as well as the direct effect of proinflammatory cytokines interfere with the metabolism of body tissues and the secretion of growth and maturation stimulating hormones.

NUTRITIONAL STATUS OF CHILDREN WITH IBD

Impaired nutritional status is a common complication of IBD and it is also one of the first symptoms. Weight loss before diagnosis is observed in 80% of children with CD and 60% of children with UC (4) that often results in underweight. According to research by Polish authors, weight deficiency affects up to 100% of children with newly diagnosed CD and 47% of children with diagnosed UC (5-7). Foreign studies suggest a lower incidence of weight deficiency among pediatric patients: 22-32% of CD patients and 9% of UC patients (Tab. I) (8-9). The problem of excessive weight gain in children with IBD is insufficiently described in the literature. IBD patients registry by Sładek and Ćmiel indicated the occurrence of overweight or obesity in 6% of children with newly diagnosed CD (7). Registry conducted in North America showed that excessive body weight among children with UC is pronounced in a similar degree as in a population of healthy children (8).

Weight to height ratios are quick, easy and inexpensive methods of assessing nutritional status. Body mass index (BMI) and Cole's index, commonly used in pediatric practice, allow to evaluate body weight in relation to body height, age and sex of the patient. BMI values below the 3rd percentile (or 5th percentile by foreign standards) or Cole's index value below 75% are considered for severe malnutrition (1, 8). These methods, however, do not include the actual composition of the body. Therefore, nutritional status is extended to include measurements of skinfold thickness, arm circumference, densitometry or bioelectrical impedance (10-12). Many studies have shown a significant deficiency in muscle mass in children with IBD with simultaneously normal or slightly reduced fatness (11-13). Rocha et al found a weight deficiency in 14% of patients with CD and in 5,7% of those with UC, while nearly half of the patients were muscle deficient, even those with normal BMI (10). It also appears that the normalization of the body weight in IBD is more related to the increase in body fat than muscle tissue (11).

IBD also contribute to deficiency of vitamins, micro- and macronutrients (Tab. I). Among patients the most frequent is iron deficiency which can affect up to 100% of children with newly diagnosed IBD (14). Causes of this deficit in the course of CD and UC are different. UC is often associated with loss of blood from the gastrointestinal tract (6), in CD an inflammation in small intestine results in nutrients' malabsorption (15). Many studies also showed high prevalence of anemia in IBD children (4, 7, 15, 16). In UC hemoglobin level is negatively associated with activity and duration of the disease (16). In CD the highest frequency of anemia is related with ileal and colonic location of disease. Such location of inflammation is the cause of vitamin B12 malabsorption – vitamin supporting iron incorporation into haem. Incorrect management of this element may also result from folic acid deficiency, which is usually associated with sulfasalazine use in the treatment of IBD (15). A study carried out in United States among newly diagnosed IBD children indicated the proper concentrations of vitamin B12 and folic acid in the serum of patients. Appropriate levels of folic acid in the patients was explained by consumption of fortified foods. High intake of folic acid seems to cover the deficiency of vitamin B12 (17). Among adults with IBD folic acid and vitamin B12 deficiencies are common – 20-60% and 5-48%.

Impaired absorption of fat-soluble vitamins (A, D, E, K) is equally frequent in IBD. The disorder results from a shortage of bile acids and steroids use which impede the absorption of vitamin D (3). In pediatric IBD vitamin A and zinc deficiency is more common than in healthy children. Low concentrations of vitamin D and E have been observed in similar percentage of affected children (62% and 5%) and healthy children (75% and 8%). The difficulty in vitamin D supply is mainly due to the limited number of sources (17). Buenosvaros et al showed that the incidence of vitamins A and E deficiency in IBD children increases with the disease severity and the trend is even more pronounced in CD than in UC (18).

FACTORS AFFECTING NUTRITIONAL STATUS IN IBD

The severity of malnutrition is a result of many factors including the above-described digestion and absorption disorders or intestinal losses (3). Inadequately balanced diet promotes nutrients' shortages. In children with IBD insufficient supply of energy and protein compounds is noted, which is the cause of weight loss. In addition, vitamins and trace elements (especially iron and calcium) appear to be scarce in the daily feeding of most patients (19). These abnormalities may arise from the elimination or restrictions in the diet of important products and ingredients such as dairy or fiber. Dietary restrictions are not always justified by the real necessity (3).

The disease is also associated with a decrease of appetite which affects about 60% of newly diagnosed cases of IBD and is more frequent in CD (4, 20). Stimulation of the anorexigenic peptides secretion by proinflammatory cytokines may be one of the reasons for low consumption. Moran et al found elevated peptide YY (PYY) level in the serum of CD patients before and after the test meal. High concentration of PYY was associated with the occurrence of nausea and bloating in the subjects. However this condition was distinctive only for those with active disease localised in the small intestine (21). In addition, the stricturing disease cause vomiting and reduces food intake, which predispose to weight deficiency (9).

Proinflammatory agents not only affect appetite, digestion and nutrients' absorption. They also interfere directly in tissue remodeling. A study conduced in piglet model with induced colitis indicated a relationship between the severity of the immune response and protein-energy metabolism (22). Similarly, in IBD children body weight deficiency deepens with disease severity (12, 13). The deficit of adipose tissue is rare even in the period of acute inflammation (23).

Cachexia in IBD patients is caused by several factors: impaired tissue metabolism, protein loss and its inadequate supplementation. Muscle mass deficiency is further deepened by the lack (or limitation) of physical activity during the flare of disease. Acute disease prolongs the sleep time which indicates poor physical condition of the affected person (12). Grade fever and arthritis pain are obstacles in performing daily activities (5, 6). Furthermore, physical capacity is weakening due to secondary anemia (24).

THE EFFECT OF TREATMENT ON THE NUTRITIONAL STATUS OF CHILDREN WITH IBD

Weight deficiency mainly concerns children with newly diagnosed disease and the implementation of adequate treatment should improve the nutritional status (9, 11). The use of steroids in the treatment is associated with rapid weight gain. This effect is of short duration and lasts only for the first few months of therapy (25). In this case the body weight gain is due to the increase in body fat (11) which is explained by appetite improvement and intensification of glucose uptake in the gastrointestinal tract (25, 26). Furthermore, the abnormal adipose to muscle tissue ratio may be associated with the increase in anabolic processes and the loss of protein from the body during steroid therapy. Deficiency of muscle tissue is also observed among patients treated with 5-aminosalicylic acid. Burnham et al found that patients taking this kind of treatment were often given simultaneously steroids and they had inflammation in the small intestine. In view of the factors overlap (disease- and treatment-related) it is difficult to determine the actual impact of pharmacological agents on the nutritional status of patients (13).

The new therapy based on anti-TNF-α (tumor necrosis factor α) monoclonal antibodies seems to be highly effective in inducing disease remission and improves the body weight of children with IBD (28, 29). The study by Kim et al suggest that antibodies "top-down" therapy results in a significant weight gain during one year of use (25). Infiximab (trade name of anti-TNF-α antibodies) therapy is not only associated with fat gain, as in the steroid treatment, but this is also seen an increase in muscle tissue (11).

BONE METABOLISM IMPAIRMENT IN CHILDREN WITH IBD

Patients with IBD are at risk of osteoporosis and osteopenia due to the effect of pro-inflammatory cytokines, vitamin D and calcium deficiency and the use of steroid agents. Bone densitometry finds reduced bone mineral density (BMD) in 30-48.7% of pediatric patients with IBD. Impaired bone mineralization occurs more frequently in children with CD than in children with UC (Table I) (30, 31). Low BMD is one of the reason for the weakening of the bone. Another weakening factor is the abnormal bone geometry in children with IBD. Werkstetter et al found a reduction of trabecular mineral density and low cortical thickness of the radius in pediatric IBD. These abnormalities are due to the muscle deficiency - a source of mechanical stimuli forming bone (32). In turn, the abnormal bone metabolism contributes to the slowdown in the growth process (23, 33).

FACTORS AFFECTING BMD IN CHILDREN WITH IBD

Impaired bone metabolism in patients with IBD is largely the result of cytokine secretion deregulation. In CD was

noted an increased production of interferon γ (INF-γ) by T-lymphocytes. This is due to inhibition of osteoclastogenesis and osteoblast activity. In addition, cytokines influence the system osteoprotegrin – RANKL protein (OPG-RANKL), thereby disturbing the process of bone resorption (34). Another study indicates a direct effect of interleukin-6 (IL-6) in bone remodeling. The action of this agent decreases the mineralization of bone matrix and disorganize the osteoblast layer (35). The decrease in IL-6 level in the serum of patients with CD is associated with the increased activity of osteoblasts. Improved clinical status of patients entails an increase in the markers of bone formation (osteocalcin, bone alkaline phosphatase and collagen C-terminal protein). However, it does not improve BMD because of the constant level of bone resorption agents, even in remission of the disease. This indicates a complex and multifactorial mechanism of impaired bone mineralization in IBD (31). El Hodhod et al found elevated levels of fibroblasts growth factor 23 (FGF-23) and parathyroid hormone (PTH) in children with exacerbation of CD which was connected with low BMD. FGF-23 is responsible for the demineralization of bone tissue by induction of hypophosphatemia and suppression of enzyme converting vitamin D to its active form (36).

THE EFFECT OF STEROID THERAPY ON BONE MINERALIZATION IN IBD

Steroid treatment is considered to affect adversely BMD by the function impairment and apoptosis of osteoblast as well as by calcium malabsorption in the gastrointestinal tract. Studies on the effects of steroids on bone mineralization in patients with IBD are inconclusive (37). *Krzesiek* et al observed twice more frequent steroid (Encorton) use in children with reduced BMD compared to children with normal BMD (45% vs. 23,1%). However, the drug use has been associated with severe inflammation (30). Steroid therapy may therefore impair bone mineralization but the inflammation itself results in a decrease in BMD. Walther et al showed comparable prevalence of osteopenia and osteoporosis in children with newly diagnosed IBD (steroid-native) and in patients treated with steroids. There was also no significant difference in the concentrations of vitamin D active metabolite between those groups (38).

Achieving remission seems to be the key factor in improving BMD. *El Hodhod* et al observed a significant improvement of BMD in children with remission of IBD despite three- or four-week steroid therapy previously used in each patient. The frequency of osteopenia or osteoporosis was reduced by about 50% in remission compared to the frequency in the active phase of the disease. The greatest effect was achieved in six patients who had been treated with anti-TNF-α antibodies as an additional therapy (36).

GROWTH IMPAIRMENT IN CHILDREN WITH IBD

Body height and growth velocity are important indicators of child's development accuracy and health status. These parameters may vary due to many factors (eg. health, nutrition, exposure to toxic agents), but the scope of these changes is determined by genetics. Commonly used method of body height assessment by reference to national or regional standard ignores mentioned aspect (1). However, it turns out that growth-impaierd children have lower parental height than growth-nonimpaired children. It underlines the importance of genetic factors as a determinant of body height even in affected children (39).

Short stature (defined as a body height below -2 standard deviation (SD)) affects approximately 9,5% of children with newly diagnosed CD and 6,9 - 8,9% of patients treated for longer than three years. This suggest a slight compensation of patients' growth in spite of the therapy (9, 40). The incidence of body height deficiency among children with UC is about three times lower than in CD (Table I) (39). The disease appearance in the early stages of development and relatively long diagnostic process are risk factors of growth retardation. In children with IBD are frequently reported non-specific symptoms of the disease which delays introduction of appropriate therapy. Rapid therapeutic intervention is so important that a shortage of body height at diagnosis provides final body height deficiency (9, 41). Some studies also indicate that boys with IBD are more prone to the growth inhibition than girls. Short stature at diagnosis and lower growth velocity are noted more frequently in boys than in girls. Consequently, final body height in this group deviates significantly from the estimated target height. The reason for the increased sensitivity of boys on disease-related agents is poorly understood (9, 39, 42).

FACTORS INHIBITING THE GROWTH PROCESS OF CHILDREN WITH IBD

The severity of disease is a key factor of growth impairment in IBD. Related with the severity of disease long hospitalization and the need for use of steroid or immunosuppressive drugs contribute to an increased risk of growth inhibition by 60% relative to primary risk in children with CD (43). Many studies have shown a negative association of C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) with body height and growth promoting factors (40, 42). The main proinflammatory agents in IBD-IL-6, TNF-α and lipopolisacharide binding protein (LPS) – interfere with secretion of hormones and growth factors. In children with active CD decreased insulin-like growth factor 1 (IGF-1) and, simultaneously, an increased growth hormone (GH) resistance are noted. However, there is adequate GH serum concentration in patients despite active disease. The decrease of proinflammatory cytokines results in increased IGF-1 plasma level and in normalization of CD patients' body height. IGF-1 secretion in CD depends not only on the severity of inflammation but also depends on the nutritional status of the organism (11, 42). Inflammation in CD seems to inhibit the growth process stronger in boys than in girls. In this group are found lower concentrations of IGF-1 and insulin growth factor binding protein 3 (IGFBP-3) as well as greater resistance of GH than in girls.

Table I. The frequency of deficiencies in children with Crohn's disease and ulcerative colitis, according to various authors.

Tabela I. Częstość niedoborów wśród dzieci z chorobą L-C i WZJG według różnych autorów.

Deficiencies ***Niedobory***	**Crohn' disease** ***Choroba L-C***	**Ulcerative colitis** ***WZJG***	**Author, year** ***Autor, rok***
Body mass deficiency *Niedobór masy ciała*	22-100%	7-47%	*Kugathasan et al*, 2007 (8) *Toporowska-Kowalska et al*, 2007 (6)
Anemia *Niedokrwistość*	39-63.9%	40-72.2%	*Krzesiek et al*, 2012 (16) *Pytrus et al*, 2013 (15) *Ryżko et al*, 1991 (4) *Sładek and Ćmiel*, 2011 (7)
Hypoproteinemia *Hipoproteinemia*	45%	back of data *brak danych*	*Mierzwa et al*, 2007 (5)
Hypoalbuminemia* *Hipoalbuminemia*	28.1-70%	8.8%	*Ryżko et al*, 1991 (44) *Sładek and Ćmiel*, 2011 (7)
Iron deficiency *Niedobór żelaza*	31.5-100%	do 100%	*Ignyś et al*, 2004 (14) *Sładek and Ćmiel*, 2011 (7)
Zinc deficiency *Niedobór cynku*	40%	30-40%	*Alkhouri et al*, 2013 (17)
25-OH-D deficiency *Niedobór 25-OH-D*	<62%	<60%	*Alkhouri et al*, 2013 (17)
Retinol deficiency *Niedobór retinolu*	20%	<10%	*Alkhouri et al*, 2013 (17)
Osteopenia *Osteopenia*	23.1-43.1%	16.7-38.9%	*Krzesiek et al*, 2005 (30) *Walther et al*, 2006 (38) *Sylvester et al*, 2007 (31)
Osteoporosis *Osteoporoza*	8.6-23.1%	3.7-16.7%	*Krzesiek et al*, 2005 (30) *Walther et al*, 2006 (38) *Sylvester et al*, 2007 (31)
Body height deficiency *Niedobór wysokości ciała*	9.4-27.01%**	9.52**-11.1%	*Lee et al*, 2010 (39) *Malik et al*, 2012 (40) *Wiskin et al*, 2011 (23)

*Low level of albumin is often associated with inflammation, regardless of nutritional status.

**Niski poziom albumin często bywa związany z działaniem stanu zapalnego niezależnie od odżywienia organizmu*

**Frequencies of 27.01% (in CD) and 9.52% (in UC) were estimated after the adaptation of 5th percentile (-1.64 SD) as the limit of short stature.

***Częstości 27,01% i 9,52% zostały oszacowane przy przyjęciu wartości 5 centyla (-1,64 SD) za granicę niedoboru wysokości ciała.*

This is explained by different effects of proinflammatory cytokines on hypothalamus-pituary-gonadal axis in both sexes. It has been observed that the CRP concentration correlates negatively with pituary hormone (luteinizing) and testosterone in males which in turn is associated with low level of IGF-1 (42).

Additional factor of growth impairment that contributes to nutritional deficiencies is the inflammation location. In CD, inflammatory changes may include each segment of the gastrointestinal tract. Therefore, children with CD may be varied in terms of nutritional status and body height (3, 43). Both this features are related to each other by promoting effect of nutrition on growth process even in the case of IBD (22). Studies indicates that inflammatory localised in the illeum and jejunum cause greater body height shortages in children with CD (41, 43). Despite these observations, the location of inflammation appears to be less substantial than the inflammation severity (43).

THE EFFECT OF THERAPY ON BODY HEIGHT OF CHILDREN WITH IBD

The weakening of inflammation often results in catch-up growth, which is an important indicator of the effectiveness of therapy. This process is particularly marked in patients with severe body height deficiency during diagnosis (40, 41). Many studies have shown, however, that children affected by the disease in the early stage of development have difficulty in achieving their developmental path. Therefore, the final body height of IBD patients is often a few centimeters lower than expected despite treatment (9, 39, 40). The long and frequent periods of exacerbation and certain pharmacological agents use are an impediment to the optimal body height achievement (41).

Many studies have shown that steroid use impairs the growth in children with IBD (9, 11, 40). Malik et al reported poor height velocity of CD children in the first

year of treatment when the steroid use was common. But this kind of therapy has been used in patients with more severe disease which could enhance the relationship between steroid use and growth inhibition (40). Described observations are inconsistent with the results of the study by Sawczenko et al. Patients who received at least one series of steroid therapy had standarized body height similar to patients undergoing for other forms of therapy (41). It turns out that the inhibitory effect growth is exerted also by immunosuppressive agents - methotrexate and azathioprine (40, 43).

Increasingly more research points to the effectiveness of biological therapy for the induction of remission, state of nutrition improvement (28, 29) and consequently growth acceleration in children with CD. Growth improvement is only seen in children who responded positively to anti-TNF-α therapy. Malik et al observed this effect even in children who received and completed steroid therapy before the biological treatment or had the dose of steroids only reduced during biological treatment. But increasing the dose of steroid drugs during biological treatment did not accelerate the growth (33).

In special cases, the only treatment is a resection of the affected bowel. Studies does not indicate a slower growth in patients after intestinal surgery compared to patients treated pharmacologically (9, 39). Sawczenko et al reported growth improvement of children with a history of surgery. This may indicate the essential role of inflammation in developmental disorders induction (41).

SUMMARY

Disorder of somatic development in children with IBD is an extremely complex problem. Inflammation, which is the essence of the disease, directly affects the nutritional status by digestion and nutrients' absorption disturbances, increased intestinal losses and appetite weakening. Direct effects of proinflammatory agents also affects the bone formation process. It results in the decrease of bone mineral density and even osteoporosis. Inflammatory factors modulate the function of the IGF-1/GH trial and hypothalamus-pituary-gonadal axis, thus slowing the development of affected children - especially their growing. These abnormalities are deepened by secondary malnutrition. The weakness of physical capacity and malaise (especially in relapse of disease) leads to a decrease in physical activity of children with IBD. Protein-calories shortages and lack of physical activity lead to the loss of muscle mass, and thereby reducing skeletal forming stimuli.

Therapy used in the treatment of IBD is another important modulator of developmental process. The use of steroid preparations and immunosuppressants is associated with the risk of abnormal body composition and growth delay. Of the available therapies biological treatment seems to be the most effective in health, nutrition and growth improvement of affected children. Unfortunately, clear evaluation of the actual impact of pharmacological agents on the development of children with IBD appears to be difficult or even impossible. The value of diagnostic feature is in fact the result of many factors that determine the type of therapy.

Based on the cited literature it can be concluded that pediatric patients with IBD require a multidirectional intervention to improve their health and thus their development. The basis for the management of these disorders should be rapid diagnosis and effective pharmacological treatment. Additionally, nutritional education of parents can prevent the deepening of malnutrition in many cases. Health improvement and well-being of patients is essential in maintaining normal or only slightly limited physical activity. It is also necessary to monitor the course of development using a full range of indicators and standards (including genetic predisposition) in order to assess the effectiveness of the treatment.

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