

Growth retardation in pediatric inflammatory bowel diseases – pathogenesis and treatment

Zaburzenia wzrastania u dzieci z nieswoistymi zapaleniami jelit – patogeneza oraz możliwości leczenia

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Abstract

Growth retardation is a common complication in children with inflammatory bowel disease. A combination of the following factors results in growth retardation: insufficient food intake, malabsorption, increased catabolism, disease activity, disease extension, complications of disease and the side-effects of treatment. Clinical response to therapy is associated with an improvement in linear growth.

Streszczenie

Zaburzenia wzrastania stanowią ważne, specyficzne dla dzieci z nieswoistymi zapaleniami jelit powikłanie choroby. Do przyczyn zahamowania wzrostu u tych dzieci zalicza się zmniejszoną podaż pokarmu, zaburzenia wchłaniania jelitowego, zwiększony katabolizm, lokalizację, aktywność, powikłania choroby zapalnej jelita oraz niepożądane działania leków. W leczeniu zasadnicze znaczenie ma skuteczna terapia choroby podstawowej, co może stymulować przyspieszenie tempa wzrostu.

Introduction

Inflammatory bowel disease (IBD) onset can occur at any age, but in 25% of patients the disease begins during infancy. The clinical picture of these diseases in children differs from that observed in adults. Inflammatory bowel diseases more frequently have an aggressive and complicated course in the pediatric population. There is a higher tendency for strictures and fissure formation, especially in Crohn's disease, which requires surgical intervention. In ulcerative colitis the extent of the disease is greater than in adults and due to earlier severe exacerbations the inevitability of the surgery emerges not rarely. These differences gave the rationale for the modification of the Montreal Classification of inflammatory bowel diseases and for the elaboration of the new Paris Classification, which takes into consideration the issues specific for children [1-4]. Of great importance is the fact, which particularly distinguishes children with

inflammatory bowel disease, that the disease appears within the period of intense development, influencing its rate and often causing its retardation or even inhibition. This results in growth retardation and in smaller final height, malnutrition, pubertal delay and bone mineralization disturbances in the form of osteopenia and osteoporosis. Growth retardation is considered to be a particularly important complication of the disease, which on one hand points to the high disease activity, while on the other hand, an improvement of the growth rate may be an advantageous sign of the efficacy of therapy. In this period of life growth is one of the important parameters enabling proper identification with the peer group and therefore its retardation has an enormous negative impact on the psychosocial development and on the smooth transition from childhood to maturity. All those elements cause the deterioration of the life quality. The growth process may be defined either as the

maximal height reached at its finishing point or it can be described as the rate of growth or high velocity (HV). In analysis of these processes we are obliged to consider population differences, ethnic and gender (menarche in girls) differences, and to take into account the height of parents and other genetic circumstances.

Etiology and frequency of growth disturbances in children with inflammatory bowel disease

Growth impairment in children with inflammatory bowel disease is a result of malnutrition, which in turn is related to the disturbance of intestinal absorption, restrictions in the diet of ill children and of increased metabolic requirements. The decrease of growth rate is deepened by the detrimental influence of pro-inflammatory cytokines (e.g. IL-6, TNF- α) and by treatment with corticosteroids [5, 6]. Growth retardation is significantly more frequently observed in children with Crohn's disease than in those with ulcerative colitis. The presence of NOD2/CARD15 mutation in this group of patients is linked to the ileo-colonic localization of the disease with more aggressive course, which also may result in malnutrition and retardation or arrest of growth. In patients with NOD2/CARD15 mutation the risk of surgery is 39.5% in comparison to 12.8% in patients free of this defect. In the study of Wine *et al.* it was observed that the presence of NOD2/CARD15 mutation carries a risk of a more severe course of the disease, which in turn may slow down the growth. However, no direct correlation of this mutation with growth retardation has been demonstrated [7]. A similar role is ascribed to IBD5 gene polymorphism, presence of which is associated with growth retardation. In 46% of children with Crohn's disease retarded growth is present before any intestinal symptoms of the disease and only 12% of these children present a proper growth rate at the time of diagnosis. Particularly significant growth retardation is observed when the disease is localized mainly in the small intestine, since up to 19% of these children reach the final height eight centimeters smaller than expected [4]. In the group of children with ulcerative colitis only 3-10% demonstrate a decreased growth rate at diagnosis [4, 9]. Sometimes at the time of diagnosis not only growth retardation and sexual maturation retardation are observed, but also chronic, serious disturbances of bone mineralization in the form of severe osteoporosis, which are the first symptoms of IBD, are present as well [10]. It has been demonstrated that, among others, growth retardation, body mass deficiency, intestinal strictures, young age, male sex and the presence of extra-intestinal symptoms of the disease are factors pointing to an aggressive and complicated course of the disease [11].

Studies on growth and development rate are very difficult and require proper methodology and sophisticated measurement equipment [12]. They are based on anthropometric measurements, calorimetric studies, bioimpedance, isotope studies, radiologic imaging and laboratory studies. It seems that the problem of disturbances of growth due to its interdisciplinary character require collaboration between gastroenterologists and other specialists such as endocrinologists, andrologists and anthropologists, as well as experts from basic sciences. A dietician who has proper experience in pediatric nutrition is also an indispensable member of the therapeutic team [13]. Management of children with inflammatory bowel disease in whom the disease appeared during the period of physiological growth and maturation always require meticulous supervision of growth.

Pathomechanism of growth disturbances in children with inflammatory bowel disease

Many different mechanisms, which frequently occur concomitantly and overlap, should be taken into account in the analysis of pathogenetic factors causing growth disturbances. Hartman *et al.* in a work discussing the nutritional state and methods of nutritional treatment in inflammatory bowel diseases presented causes of malnutrition and pathophysiology of growth retardation taking into account various etiopathogeneses and mechanisms [14]. Pathogenesis of growth disturbances is presented in Tables I and II [14].

Hormonal and inflammatory factors

Inadequate secretion or deficiency of growth hormone (GH) and insulin-like growth factor 1 (IGF-1), GH/IGF-1 axis disturbances as well as tissue resistance to the action of those factors are the main features of hormonal disturbances in children with inflammatory bowel disease [15, 16]. Bioavailability of IGF-1 (somatomedin C) depends on its free fraction and on its serum carriers, namely binding proteins (IGFBPs: IGFBP-1 to IGFBP-6). Binding proteins demonstrate various affinity to IGF-1 and the inflammatory process, and nutritional and caloric restrictions may lead to deficiency of some of them. Growth hormone is responsible for the induction of the precursor cells in the growth plate and on the other hand IGF-1 stimulates differentiation of chondrocytes. The protein STAT5, which is an activator and a factor responsible for transcription and in consequence for GH-dependent growth, is of fundamental importance. STAT5 exists in two forms (A and B) and the STAT5B form participates in growth regulation. The mechanism of inhibition of growth hormone's biological effect consists

Table I. Nutritional deficiencies in patients with inflammatory bowel diseases**Tabela I.** Niedobory żywieniowe u pacjentów z nieswoistymi zapaleniami jelit

Macro- and micro-nutrient deficiencies	Nutrients	Percentage of CD patients with deficiencies
Hypoproteinemia and hypoalbuminemia	Protein (albumin)	17.6
Anemia	Iron deficiency	39.2
	B ₁₂ deficiency	18.4
	Folic acid deficiency	19.0
Electrolyte and trace elements	Zinc	15.2
	Copper	84.0
	Selenium	82.0
Vitamin deficiency (low serum levels)	B ₁₂ deficiency	18.4
	Vitamin A	23.4
	Vitamin B	29.0
	Vitamin C	84.0
	Vitamin D	17.6
	Vitamin E	16.0

According to Hartman et al. [14]

Table II. Pathophysiology of growth failure in children with inflammatory bowel diseases**Tabela II.** Patofizjologia zaburzeń wzrostu u dzieci z nieswoistymi zapaleniami jelit

Etiopathogenesis	Mechanism
Energy and nutrient deficiencies	Deficits of energy, macronutrients and micronutrients
Inflammation (pro-inflammatory cytokines)	Anorexigenic effect
	GH-IGF-1 axis
	Bone metabolism disturbance
	Catabolic effects
Disease severity and disease location	Disease severity
	Jejunal localization
Abnormal bone metabolism	Effect of pro-inflammatory cytokines
	GH-IGF-1 axis dysfunction
	Calcium and vitamin D deficiency
	Delayed sexual maturation
	Corticosteroids
Delayed onset of sexual maturation	Hypogonadism
Abnormal IGF-1 axis	Low IGF-1 and IGF-1BP
	Pro-inflammatory cytokines
Drugs	Corticosteroids

According to Hartman et al. [14]

on the one hand of the decrease of the number of specific receptors (downregulation) and on the other of the increase of suppressor protein levels (upregulation). It happens that children with inflammatory bowel disease, particularly those with Crohn's disease, in whom symptoms of the disease are atypical, are chronically treated with growth hormone according to the regimen of

the treatment of children with somatotrophic hypophysis insufficiency. It is only when the lack of the efficacy of such treatment is observed that further diagnostics are conducted, which indicate inflammatory disease of the intestines as the origin of short stature. Overproduction of pro-inflammatory cytokines, including TNF- α , INF- γ , IL-6, IL-12, IL-17, IL-23, and IL-1 β , plays a key role in the

resistance mechanism of tissue resistance to the action of hormonal factor stimulating the growth process [16-18]. Studies on animals have documented a pivotal role of IL-6, which induces growth inhibition due to the suppression of IGF-1 secretion. In experimental studies, administering anti-IL-6 antibodies to mice provoked significant growth acceleration. It was demonstrated that in patients with Crohn's disease the presence of genotype IL-6-174 is connected with the highest expression and production of this interleukin; hence such studies might be important in the prognosis of the course of the disease [19]. The direct effect of IL-6 on the bone system is established on the stimulation of maturation and activation of osteoclasts on one hand, and on inhibition of osteoblasts on the other, which reduces the growth plate as a final result. Independently of cytokine activity, of importance is chronic exposure to bacterial endotoxins, lipopolysaccharides (LPS) and others, which induce insensitivity to growth hormone activity.

Although chronic use of epinephric hormones during periods of exacerbation of the disease decreases its activity and for a short time stimulates growth, finally it may negatively influence the growth process by its premature termination. Exogenous hormones provoke the state of functional GH deficiency. They also have a weak influence on mucosal healing, which is currently the objective of the therapy. In the group of hormonal factors a certain importance is ascribed to disturbances in steroid hormones and thyroxin secretion, which is observed in exacerbations of inflammatory bowel disease.

Nutritional factors

The influence of nutritional factors is also complex. On one hand, these diseases are accompanied by a significant lack of appetite and restriction in food consumption. It seems that this process is dependent on the action of TNF- α , one of the most important pro-inflammatory cytokines, the overabundance of which causes quantitative and caloric restrictions due to the effect on hypothalamic nervous tracts linked with satiety and appetite. On the other hand, intestinal malabsorption, frequent diarrhea, intestinal passage disturbances, abdominal pain, surgical procedures and increased catabolism cause that even those diminished amounts of nutritional components are not fully utilized. It is worth emphasizing that energetic expenditure in children with remission phases of the disease does not differ from the caloric requirement of healthy children; therefore, efficient management of the disease is a condition of proper development. The recommended special diet is not well accepted due to its taste, especially by the youngest children. Hence, increased energetic

expenditure is accompanied by diminished energetic supply. Therefore, establishment of energetic balance in the planning of nutrition of children with inflammatory disease and current supplementation of energetic losses in exacerbation periods are of significant importance. Gradually, worsening quantitative and qualitative deficiencies result in malnutrition and growth failure.

Treatment of growth disturbances in children with inflammatory bowel diseases

Many practical observations and clinical studies in children with inflammatory bowel diseases indicate a positive correlation between effective treatment and improvement of growth rate.

Biologic treatment of Crohn's disease with anti-TNF- α antibodies is the best documented management of growth rate improvement in children. The pathogenetic mechanism is clear and is linked to inhibition of pro-inflammatory cytokine production by the group of these drugs and indirect effect on the GH/IGF-1 axis. Moreover, it is known that TNF- α may induce reduction of lifespan and death of chondrocytes. In the studies of Malik *et al.*, in patients who responded positively to the treatment with anti-TNF- α an increase in height velocity (HV) from 2.0 cm per year to 6.4 centimeters per year was demonstrated. This process was accompanied by a statistically significant increase in specific bone alkaline phosphatase as a marker of increased osteoblastic activity. In patients who did not respond to the treatment an improvement of growth velocity was not observed [20]. Borrelli *et al.* also demonstrated that the effect of that treatment was significantly better if the treatment was prolonged than if it was limited to induction with three doses of the drug [21]. Biologics directly affect bone metabolism and the reabsorption process in a mechanism independent of anti-inflammatory action [9]. In the studies of Malaise *et al.* it was demonstrated that already after eight weeks of biologic treatment biochemical markers of bone formation (type-1 collagen C-telopeptide, type-1 procollagen, osteocalcin, specific alkaline phosphatase) were normalized in 14-51% of patients [22]. Long-term effects of such treatments are still unknown and they require further studies.

Enteral feeding may be an alternative to steroid hormones and allows clinical remission to be obtained equally effectively as steroid therapy. Nutritional treatment with elementary formulas, semi-elementary formulas and polymeric diets applied temporarily or as a nocturnal alimentation corrects nutritional deficits very effectively, has a trophic effect on the intestinal mucosa, exerts an anti-inflammatory effect and stimulates mucosal healing, which improves high velocity [23].

Such treatment allows remission to be obtained in up to 80% of children with newly diagnosed Crohn's disease, and also is frequently effective (in 58%) in chronically ill patients in whom other forms of therapy were applied [24]. Although earlier studies on enteral nutritional therapy were encouraging and its efficacy was compared to the treatment with steroids in achieving remission, studies from recent years indicate smaller efficacy of nutritional therapy and further studies are necessary to establish its true effectiveness [25]. In certain cases enteral nutrition may be supplemented by parenteral nutrition, especially when oral nutrition is impossible or contraindicated as for example after surgical procedures. Suprarenal hormones inhibit activity of the chondrocyte growth plate, which causes deceleration of the long growth of bones and is the effect of local decrease of IGF-1 expression. The effect of steroids is, therefore, functional deficiency of growth hormone and decreased affinity of IGF-1 within the chondrocyte growth plate. This effect is observable even at a relatively low dose of prednisolone (3-5 mg/m²). Long-term effects of these drugs remain controversial. In the studies of Griffiths *et al.* it was demonstrated that the use of steroids causes decrease of growth rate only in the first year of treatment; however, this reduction was not statistically significant if current activity of the disease was taken into account [26]. In order to diminish potential adverse effects, alternate therapy and selective elimination of the evening administration of the drugs may be the alternative; this allows one to avoid the inhibition of nocturnal secretion of GH. In selected patients the use of budesonide may be an option which allows these adverse reactions to be limited [4]. Budesonide is a drug with small availability due to the "effect of first passage" through the liver, since only 90% of the absorbed amount of the drug is metabolized by isoenzyme CYP3A4 of cytochrome P450 to compounds with low activity.

One of the therapeutic options, especially if growth retardation is accompanied by pubertal delay, is the use of testosterone derivatives. In the studies of Mason *et al.* in a group of boys with inflammatory bowel disease oral or parenteral administration of this hormone caused improvement of growth velocity by more than 50% and appearance of sexual maturation in the majority of children [27].

Efficacy of immunosuppressive drugs, mainly from the thiopurine group (azathioprine, 6-mercaptopurine), is well documented in supporting remission in Crohn's disease. The influence of such therapy on growth rate in children is not known. In a well-conducted randomized study of Markowitz *et al.* it was found that the growth rate in children who were treated with thiopurines from

the moment of diagnosis was faster than in children treated conventionally [28]. Early introduction of drugs from this group diminishes the necessity for suprarenal hormones which delays the process of cartilage ossification and advantageously affects the final growth. A similar positive effect on remission permanence and growth process in children with Crohn's disease as in the case of thiopurines has been demonstrated for methotrexate [29].

Zinc is one of the principal microelements, which is necessary for catalysis of about 100 various enzymes, and its deficiency in inflammatory bowel disease, and in Crohn's disease especially, is one of the main causes of growth deterioration. Appropriate supplementation of this element decrease such risk [30].

Surgical management in children with inflammatory bowel disease is reserved for the treatment of complications. However, in several retrospective studies, in which growth rate in children with inflammatory bowel disease during the pre-pubertal period who underwent surgical local resection of the intestine due to the resistance of the disease to the treatment, has been evaluated and statistically significant acceleration of growth rate has been observed after these procedures [31-33]. These procedures caused an increase of anabolic processes, expressed as increased utilization of nitric compounds already 4 weeks after the procedure. However, in these studies long-term results of such management of the patient and its effect on the final height after puberty were not analyzed.

In the analysis of the Cochrane Database there are only a few methodologically well-conducted and documented therapeutic interventions which influence height of children with Crohn's disease. These interventions include enteral nutrition, intestinal resections in children with disease resistant to therapy during the pre-pubertal period, and currently the most recommended therapy with anti-TNF- α antibodies [34]. In the case of ulcerative colitis there are significantly fewer such observations and they pertain only to the influence of colectomy on growth in disease resistant to treatment [35, 36].

Summary

Growth retardation in children with inflammatory bowel disease is an important, concerning symptom, which, especially in Crohn's disease, may precede the diagnosis. Due to that, the disturbances of growth rate are taken into account in the Paris classification of Crohn's disease. Pathogenesis of growth disturbances in children is complex. Early diagnosis and appropriate management of this disease with the objective of obtaining not only clinical but also endoscopic and histologic remission allows prevention of this complication. Current-

ly the most promising is biologic treatment with anti-TNF- α antibodies, which most effectively inhibits the illness of the intestine [37, 38]. Of enormous importance is constant monitoring of child development since growth inhibition may be one of the important signals indicating inefficient management [39, 40].

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