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The pre-treatment characteristics and evaluation of the effects of recombinant human growth hormone therapy in children with growth hormone deficiency and celiac disease or inflammatory bowel disease

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Abstract

The aim of the study *was to investigate the coincidence of growth hormone deficiency (GHD) and celiac disease (CD) or inflammatory bowel disease (IBD) in patients referred for short stature, and to evaluate the baseline anthropometric parameters and the effectiveness of recombinant human growth hormone (rhGH) therapy in the first year in those patients (GHD+CD/IBD subgroup) in comparison to patients with GHD without CD or IBD (GHD-CD/IBD subgroup).*

Material and methods: *The study was retrospective and included 2196 short patients (height SDS [Standard Deviation Score] ≤ –1.2). 1454 patients had height SDS ≤ –2. Twenty-nine patients suffered from CD or IBD. GHD was confirmed in 419 patients with height SDS ≤ –2. The coexistence of GHD and CD or IBD was found in seven patients (GHD+CD/IBD subgroup).*

Results: *At baseline the GHD-CD/IBD subgroup did not differ significantly in chronological age, height SDS, height velocity (HV) before rhGH therapy, body weight SDS, and body mass index SDS from the GHD+CD/IBD subgroup. The improvement in height SDS within the first year of rhGH therapy was higher in the GHD+CD/IBD subgroup than in the GHD-CD/IBD subgroup and the difference was statistically significant ($p<0.05$). HV in the first year of rhGH therapy was also significantly higher in the GHD+CD/IBD subgroup than in the GHD-CD/IBD subgroup ($p < 0.05$).*

Conclusions: *In patients with chronic inflammatory disorders of the gastrointestinal tract, especially celiac disease, coexisting with GHD, rhGH therapy could be effective and should be administered together with therapy of primary gastrointestinal disease.*

Key words: *growth hormone/insulin-like growth factor-1 axis, chronic inflammation, growth hormone deficiency, celiac disease, inflammatory bowel disease.*

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Introduction

The associations between the growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis, malnutrition, and chronic inflammation are known but still not fully explained [1-11]. In patients with chronic inflammatory disorders of the gastrointestinal tract, such as celiac disease (CD) and inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis, growth retardation accompanying puberty delay is one of the main extraintestinal manifestations of those diseases [1-5, 8, 12, 13]. Jericho *et al*. [13] reported that the prevalence of short stature in children with CD was 33%. In patients with IBD, growth retardation is more frequent in children with Crohn's disease than in those with ulcerative colitis [3, 5, 14-17]. According to available studies, short stature is present in 10-56% of children with Crohn's disease and in 3-10% of patients with ulcerative colitis at diagnosis [2, 3, 14-18].

The pathogenesis of growth retardation associated with CD and IBD is mainly related to generalised or selective malnutrition resulting from systemic inflammation and a local impact of the affected epithelium on absorption, and to the inflammatory process itself [2, 3, 6, 9, 11, 19, 20].

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Increased levels of proinflammatory cytokines such as interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), and interleukin-1β (IL-1β) lead to changes in secretion and sensitivity of the GH/IGF-1 system, causing partial GH resistance, inhibition of growth hormone receptor (GHR) expression and action, and a decrease in IGF-1 irrespective of GH levels [2-5, 7-9, 11, 20-23]. Inflammatory cytokines may also inhibit linear growth at the chondrocytes level independently of IGF-1 pathways [2, 10, 24].

In patients with CD, after the start of a gluten-free diet (GFD) height velocity (HV) usually increases, especially in the first year of gluten restriction [1, 9, 13, 22, 25, 26]. Anti-inflammatory drugs, immunosuppressants, and biologic agents administered to patients with IBD minimise inflammation and induce prolonged remission of primary disease, but their long-term effects on growth are controversial [3, 18, 27]. Chronic use of glucocorticoid therapy is another factor that adversely impacts linear growth and leads to growth retardation [2, 3, 11, 28]. Patients with IBD, more often than CD patients, had a lack of complete catch-up growth despite advances in primary disease therapy [5, 10, 11, 14, 18, 27-29].

The lack of adequate catch-up growth despite adequate and effective therapy of primary disease in children with CD and IBD could be associated with the coexistence of other comorbidities which could also lead to growth retardation with delayed puberty, including growth hormone deficiency (GHD) [1, 8, 9, 13, 30-33].

The aim of our study was to investigate the coincidence of GHD and CD or IBD in patients referred for short stature to our department and to evaluate the baseline anthropometric parameters and the effectiveness of recombinant human growth hormone (rhGH) therapy in the first year in those patients in comparison to patients with GHD without CD or IBD.

Material and methods

The retrospective study, conducted in the Department of Paediatrics and Endocrinology of the Medical University of Warsaw, included data of 2196 children and adolescents with height standard deviation score (SDS) ≤ –1.2 aged from three to 18 years (911 girls and 1285 boys, mean age 9.68 ± 3.88 years), referred for short stature. Data were obtained by reviewing the medical records of patients from 01.01.2003 to 30.06.2017. Among them, 1454 children and adolescents had height SDS ≤ –2 (615 girls and 839 boys, mean age 9.83 ± 3.93 years). Twenty-nine patients of the whole study group suffered from CD ($n = 22$) or IBD (Crohn's disease $n = 4$, ulcerative colitis $n = 3$). GH release was evaluated in patients with height SDS ≤ –2. Growth hormone deficiency was confirmed in 419 patients (148 girls and 271 boys, mean age 11.17 ± 3.40 years). In 371 of them, data covering the first year of rhGH therapy were available. GHD was defined as growth hormone concentrations below 10 ng/ml in three tests: one test evaluating spontaneous growth hormone secretion at night during sleep and two stimulation tests with different stimuli such as clonidine, insulin, glucagon, or arginine. Maximum growth hormone release in a particular patient was defined as the highest concentration of growth hormone in any of the three tests. We found coexistence of GHD and CD or IBD in seven patients (five girls and two boys, aged 9.67-15.08 years, mean age 13.24 ±1.89 years). In all the patients from this subgroup, CD or IBD was confirmed by gastroenterologists and treated before GHD was diagnosed.

HV at baseline was calculated based on measurements of height taken twice at minimum six-month intervals. Anthropometric measurements included in the analysis were taken at baseline and after 12 months of rhGH treatment. Height parameters were normalised for chronological age, and body weight parameters were normalised for age-for-height. Body mass index (BMI) was calculated and normalized for age-for-height. HV in the first year of rhGH treatment was calculated based on height parameters at baseline and at 12 months of rhGH therapy and presented in cm/year. Improvement in height deficit (delta height SDS) was calculated using height SDS at baseline and at 12 months of rhGH therapy.

The study obtained approval from the Bioethics Committee at the Medical University of Warsaw in accordance with the Declaration of Helsinki.

Statistical analysis

The analysis of the results was performed using Statistica 13.1. Data were reported as means with standard deviation, median, and interquartile ranges, or as percentages, as appropriate. Data normality was checked by Shapiro-Wilk normality test. Comparisons between baseline and treatment values were conducted using the Wilcoxon signed-rank test for non-parametric parameters and *t*-test for parametric parameters. Comparisons between studied subgroups were conducted using the Mann-Whitney *U* test for non-parametric data and the *t*-test for parametric data. A p value < 0.05 was considered significant.

Results

We analysed the data of 2196 children and adolescents with height SDS ≤ –1.2 referred to our department for short stature from 01.01.2003 to 30.06.2017. In 66.21% ($n = 1454$) of them, height SDS was ≤ –2. Among the whole study group, 1.32% ($n = 29$) of the patients suffered from CD or IBD; in the subgroup with height SDS ≤ –2, patients with CD or IBD comprised 1.72% ($n = 25$). Patients with CD or IBD ($n = 29$) were significantly shorter than other studied patients ($n = 2167$) without CD or IBD ($p < 0.05$, height SDS –2.47 ±0.58 vs. –2.22

±0.63), but they did not differ significantly in body weight SDS or BMI SDS. The characteristics of the whole study group and both subgroups without and with CD or IBD are presented in Table 1. GHD was confirmed in 28.82% (n = 419) of patients with height SDS ≤ –2. The coexistence of GHD and CD or IBD was found in seven patients (five patients with CD, one patient with Crohn's disease, and one patient with ulcerative colitis), who comprised 0.48% of the subgroup with height SDS ≤ –2 and 1.67% of patients with GHD. In all of those patients rhGH therapy was initiated. In further analysis we compared baseline anthropometric parameters and the effects of the first year of rhGH therapy between that subgroup (GHD+CD/IBD) and those patients with GHD without CD or IBD, who were treated with rhGH for a minimum of one year during the evaluated period (GHD-CD/IBD, n = 364). Baseline and treatment parameters of both compared subgroups (GHD-CD/IBD and GHD+CD/IBD) are presented in Table 2. At baseline both compared subgroups did not differ significantly in chronological age, height SDS, HV before rhGH therapy, body weight SDS, and BMI SDS. Height SDS increased significantly in both subgroups within the first year of rhGH therapy ($p < 0.05$). HV also increased significantly within the first year of rhGH therapy in both studied subgroups ($p < 0.0001$). After one year of rhGH therapy, height SDS increased from –2.93 ± 0.80 to –1.96 ±0.77 in the GHD+CD/IBD subgroup and from –2.68 ±0.64 to –2.10 ±0.71 in the GHD-CD/IBD subgroup. The improvement in height SDS within the first year of rhGH therapy (delta height SDS at baseline to 12 months of therapy) was higher in the GHD+CD/IBD subgroup than in the GHD-CD/

Table 1. The characteristics of the whole study group (n = 2196) and both subgroups without CD or IBD (n = 2167) and with CD or IBD (n = 29)

Variable	*n* = 2196	*n* = 2167	*n* = 29
Chronological age (years)	9.68 ±3.88	9.68 ±3.88	10.26 ±3.82
Height SDS	–2.23 ±0.63	–2.22 ±0.63*	–2.47 ±0.58*
Age for height (years)	7.46 ±3.29	7.45 ±3.29	7.72 ±3.10
Body weight SDS	–0.26 ±0.82	–0.26 ±0.82	–0.21 ±0.77
BMI SDS	–0.31 ±1.10	–0.31 ±1.10	–0.25 ±0.99

*Data are shown as mean ± SD, *p < 0.05*
SDS – standard deviation score, BMI – body mass index

Table 2. The characteristics of baseline and treatment parameters of both compared subgroups: GHD-CD/IBD (n = 364) and GHD+CD/IBD (n = 7)

Variable	GHD-CD/IBD	GHD+CD/IBD	*p*-value
Baseline parameters			
Chronological age (years)	10.98 ±3.41	13.24 ±1.89	ns
HV (cm/year)	4.75 ±1.41	4.77 ±0.58	ns
Height SDS	–2.68 ±0.64	–2.93 ±0.80	ns
Age for height (years)	8.11 ±2.98	9.93 ±1.57	ns
Body weight SDS	–0.03 ±0.90	0.03 ±0.35	ns
BMI SDS	0.01 ±1.25	0.04 ±0.43	ns
Parameters after 1 year of rhGH therapy			
HV (cm/year)	8.96 ±1.75	9.90 ±0.81	< 0.05
Height SDS	–2.10 ±0.71	–1.96 ±0.77	ns
Age for height (years)	9.54 ±3.12	11.62 ±1.66	ns
Body weight SDS	–0.07 ±0.78	–0.20 ±0.27	ns
BMI SDS	–0.06 ±1.01	–0.36 ±0.30	ns
Δ height SDS	0.58 ±0.42	0.97 ±0.45	< 0.05

Data are shown as mean ± SD
SDS – standard deviation score, HV – height velocity, BMI – body mass index, Δ height SDS = height SDS after the first year of rhGH therapy – baseline height SDS, ns – not significant

IBD subgroup (mean 0.97 ±0.45 vs. 0.58 ±0.42), and the difference was statistically significant ($p < 0.05$). HV in the first year of rhGH therapy was also significantly higher in the GHD+CD/IBD subgroup than in the GHD-CD/IBD subgroup (9.90 ±0.81 cm/year vs. 8.96 ±1.75 cm/year, $p < 0.05$).

Discussion

Pathogenesis of growth retardation in children with CD and IBD is multifactorial [2-4, 6, 8-11, 19, 22, 34-36]. Generalised or selective malnutrition, resulting from reduced food intake, protein malabsorption, increased intestinal protein loss, increased energy expenditure, and chronic inflammation, is considered to be the main cause of short stature [2-4, 6, 8, 9, 22]. Chronic inflammation itself could also lead to growth retardation independently of malnutrition [2-4, 34-36]. Those mechanisms have been confirmed by several authors in humans and in animal models, but some associations still need to be explained [4, 11, 34-40]. Elevated levels of proinflammatory cytokines, resulting from an active disease, such as IL-6, IL-1β, or TNF-α, directly disturb the function of the GH/IGF-1 axis and lead to relative hepatocyte resistance to GH stimulation (relative GH insufficiency), a decrease in IGF-1 secretion by the liver, and impairment of IGF binding proteins (IGFBPs) [4-6, 8, 10, 34, 41-44]. Acquired GH resistance, mediated by both undernutrition and active inflammation, could be associated with two mechanisms: down-regulation of the level of GHR and impaired regulation of GH-induced intracellular signalling pathways [4-6]. TNF-α and IL-1β affected GHR expression. IL-6 is the best described cytokine, which inhibits GHR-mediated signalling by inducing expression of members of the family of suppressor of cytokine signalling (SOCS) [6, 10, 43-47]. Down-regulation of IGF receptors and impairment of local IGF-1 signalling pathways have also been reported [5]. Dysfunction of the GH/IGF-1 axis in children with chronic inflammation is not permanent and may be reversed because of primary disease therapy using GFD in CD and enteral nutrition, infliximab, prednisolone, and surgical resection in children with IBD [5, 22, 48-54]. Growth acceleration is usually observed later than improvement in nutritional status [22]. In children with CD, normalisation of height is usually observed within the first two years of therapy, but in some patients it is incomplete [1, 9, 13, 22, 25, 26, 55]. In patients with IBD, especially in Crohn's disease, catch-up growth could be unsatisfactory despite successful treatment of primary disease, and in about 20% of patients with paediatric-onset Crohn's disease target adult height is not reached [5, 10, 11, 14, 18, 27-29].

The prevalence of CD in short children is estimated to be from 0.63% to nearly 20% in different studies, which possibly depends on different inclusion criteria (studies can include patients from first-, second-, or third-line centres; therefore, some of the studied groups of patients have already been screened by other physicians). Most researchers agree that it is between 2 and 10% [1, 8, 9, 26, 56-62]. Exclusion of CD is recommended in the case of all patients with short stature. It is especially important in children suspected of having GHD before evaluation of GH release in stimulation tests. Active inflammation associated with increased levels of proinflammatory cytokines could lead to impaired GH response and false positive results in GH stimulating tests [4, 8, 9, 26, 31, 63]. Similarly, impaired GH response is observed in patients with IBD [4, 11]. On the other hand, confirmation of CD or IBD in children with short stature does not exclude other possible causes of growth retardation, including GHD. Evaluation for GHD should be performed in children with a lack of adequate catch-up growth after at least one year of a GFD and after confirming seronegativity for anti-tissue transglutaminase and/or anti-endomysial antibodies in CD patients, or one year after initiating IBD therapy in patients with Crohn's disease or ulcerative colitis [1, 2, 9, 11, 18, 26, 27, 31, 63, 64].

In our study, evaluating a large cohort of short children with height SDS ≤ –1.2, CD or IBD was confirmed in 1.32% of patients. In a selected subgroup with height SDS ≤ –2 the prevalence of CD or IBD was 1.72%. We found that children with CD or IBD were significantly shorter than other patients, but they did not differ significantly in nutritional status. For further analysis we included only patients with height SDS ≤ –2; GHD was confirmed in 28.82% of that subgroup, while the coexistence of GHD and CD or IBD was confirmed in seven patients, who comprised 0.48% of patients in that subgroup and 1.67% of patients with GHD. In all of those seven patients idiopathic GHD was diagnosed. Giovenale *et al.* [1], in a multicentre study evaluating more than 7000 short children, confirmed CD in 0.63% of patients, GHD in 9.2%, and the association between GHD and CD in 16 patients (0.23%), including one subject with Down's syndrome and one with Turner's syndrome [1]. The authors indicate that they evaluated an unselected group of patients admitted for short stature, and the prevalence of CD varied in different paediatric outpatient centres included in this study, ranging from 0.31% to 3.77%. However, our study assessed a selected group of children referred to endocrinologists by paediatricians after preliminary screening or by specialists including gastroenterologists, and that is why the prevalence of GHD and CD is higher than in studies comprising unselected groups of short patients. In the study by Bozzola *et al.* [31] among 1066 short children 1.12% of patients had CD, 19.7% had GHD, and coexistence of GHD and CD was confirmed in three boys (0.28%). In all of those cases (two with isolated GHD and one with multiple GHD) the congenital origin of GHD was supported by the congenital abnormalities documented by magnetic resonance imaging (MRI). Nemet *et al.* [32] presented two patients with coexisting GHD and CD – in one of them MRI findings suggested congenital

isolated GHD, in the other patient MRI was normal and idiopathic GHD was diagnosed. Some authors suggest that GHD found in patients with CD could be associated with autoimmune aetiology [63, 65, 66]. Iughetti *et al*. [63] evaluate antipituitary autoantibodies (APA) and anti-hypothalamus autoantibodies in CD children with GHD and poor clinical response to a GFD. The authors confirmed the presence of APA and anti-hypothalamus autoantibodies in four out of five children with CD and GHD, and suggested that impaired GH secretion could result from autoimmune hypophysitis involving the somatotroph cells. MRI of the hypothalamic-pituitary region was normal in all of those patients, which could suggest idiopathic GHD [63]. Delvecchio *et al*. [66] assessed the prevalence and clinical significance of APA in children and adolescents with newly diagnosed CD and reported a remarkable prevalence of positive APA in comparison with healthy subjects (42% of CD patients vs. 2% of control subjects). The authors found that the presence of APA was associated with height impairment and decreased serum IGF-1 concentrations, which suggests an autoimmune pituitary process, which could lead to a linear growth impairment. However, Aguado *et al*. [67] reported the presence of APA in patients with non-gluten-related gastroenteropathies and suggested that it was not associated with a decrease in height velocity, as occurs in CD patients.

In our study we also evaluated the effects of the first year of rhGH therapy in children with both GHD and chronic inflammatory gastrointestinal disorders and compared them with the effects achieved in children with GHD without CD or IBD. The number of studies that report the effects of rhGH therapy in children with GHD and Crohn's disease or ulcerative colitis is scarce. Our study, in contrast to most recently published studies [1, 30-33], includes patients with Crohn's disease and ulcerative colitis as well as patients with CD, but the limitation of our study is the small number of those patients. We found that response to rhGH therapy in the GHD+CD/IBD subgroup was even better than in the GHD-CD/IBD subgroup, which confirms the effectiveness of rhGH therapy in such patients. The above-mentioned study by Giovenale *et al*. [1] also evaluated the effects of the first year of rhGH therapy in children with GHD and CD, and confirmed improvement in height velocity in those patients, but concluded that a longer follow-up is needed to evaluate the true effectiveness of such therapy. In a later study Giovenale *et al*. [30] evaluated the effects of the first three years of rhGH therapy in children with GHD coexisting with CD and in children with isolated GHD, and concluded that the effects of rhGH treatment in GHD patients with coexisting CD seems to be comparable to those observed in children with idiopathic GHD without CD if they comply with a gluten-free diet. Observations of other authors also confirmed the effectiveness of rhGH therapy associated with GFD and the need to initiate such therapy in patients with GHD coexisting with CD [33, 68]. The study by Meazza *et al*. [68] showed that CD children treated for associated GHD reached normal final height. It is important to confirm the utility and safety of rhGH therapy in patients with IBD associated with GHD, possibly in multicentre studies, which make it possible to include higher numbers of patients into analysis. Cooperation between gastroenterologists and endocrinologists should be fostered for better detection of children with both gastroenterological and endocrinological problems.

Conclusions

GHD should be taken into consideration in patients with CD or IBD without adequate catch-up growth despite therapy of primary disease. In patients with chronic inflammatory disorders of the gastrointestinal tract, especially celiac disease, coexisting with GHD, rhGH therapy could be effective and should be administered together with therapy of primary gastrointestinal disease.

The authors declare no conflict of interest.

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