Research Article

Evaluation of Growth Hormone Deficiency in Children with Cystic Fibrosis

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Abstract

Background: Due to chronic respiratory and gastrointestinal problems, growth failure is a common issue in patients with cystic fibrosis (CF). The present study aimed to investigate the prevalence of growth hormone deficiency (GHD) in CF children with stable gastrointestinal and respiratory conditions. **Materials and Methods:** In this study, the growth indicators of all 4–16-year-old children referred to two CF clinics were monitored over 3 years. Children without severe gastrointestinal or pulmonary symptoms with weight <3% percentile or whose height increase were two standard deviations below their expected height growth over 6 months were selected for the growth hormone (GH) stimulation test by clonidine and L-dopa test. Some of the children without CF, who were also referred for height growth disorders and matched the CF group, were considered the control group. They underwent the GH stimulation test, and the results were compared. **Results:** From 150 patients with CF, growth failure was observed in 24 patients with stable gastrointestinal and respiratory conditions; in 10 of them, the GH stimulation test was deficient. The prevalence of GHD was 6.6% in CF patients. In the control group of 30 children without CF, but with growth failure, the GH was deficient in nine cases, implying no significant difference with the case group (P = 0.37). **Conclusion:** In our study, the prevalence of GHD was 6.6% in CF patients, whereas the prevalence GHD in the normal population of childhood is <1%. Therefore, further studies should be designed to investigate the cause of GHD in CF patients.

Keywords: *Cystic fibrosis, growth hormone, height, weight*

Introduction

Cystic fibrosis (CF) is a complex and systemic disorder which is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The absence of CFTR and the cAMP-regulated anion channel results in the manifestation of disease, such as failure to thrive and malnutrition.[1,2] Growth is a major indicator of health status in children with CF,[3] such that according to the annual report of the CF Foundation, the median values for weight-for-length and body mass index (BMI) percentile are above the recommendation of 50th percentile. However, the evidence suggests that infants' and children's growth is below what is expected for the U. S. population.[4]

Even though the poor growth in CF patients may be associated with some severe clinical symptoms, such as the long-term decline in lung function, malabsorption, and diabetes mellitus,[5,6] asymptomatic CF infants have growth deficits too and are usually shorter than normal infants. Therefore, it seems that other factors are involved in the growth deficit of these patients.[7,8]

The human growth hormone (HGH) is a proteohormone secreted by the pituitary gland, which operates through binding to the HGH receptor. It acts either by inducing direct effects or initiating the production of insulin-like growth factor I (IGF-I), which is the key mediator of HGH effects. Growth hormone (GH) stimulates the height growth in children and adolescents; however, it has also key metabolic functions during adulthood.[9]

It seems that in addition to known complications of the CF, GH and related factors such as IGF-I are also affected by this disease, such that low levels of GH in CF patients have been reported in several studies.[10-12] Furthermore, many studies gave evidence for the efficacy of treatment with GH led to an improvement of clinical symptoms, growth indicators, and quality of life in children with CF.[2,13-15] However, in most of these studies, it was not reported whether the children under treatment had GH deficiency (GHD) before

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the therapy. The administration of this hormone for patients without deficiency may not be recommended, and there are concerns that taking this hormone may aggravate the cystic fibrosis-related diabetes (CFRD).[16]

Due to chronic respiratory and gastrointestinal problems, growth failure is a common disorder among CF patients. However, we visit CF patients with growth failure, despite having satisfactory gastrointestinal and respiratory conditions. Therefore, the present study aimed to investigate the prevalence of GHD in children with CF with stable gastrointestinal and respiratory conditions who were referred to the CF special clinics in two cities of Tehran and Isfahan.

Materials and Methods

In a cross-sectional study, the growth indicators of all 4−16-year-old children referred to the two CF clinics located in Esfahan (Imam Hossain children's hospital) and Tehran (Children's Medical Center, Tehran University of Medical Sciences) cites in Iran, were monitored from 2017 to 2019. The study was approved by ethical committee of the Isfahan University of Medical Sciences Tehran University of Medical Sciences, and adequate informed consent was obtained from all parents of patients before starting the study. The inclusion criteria consisted of (i) Normal caloric intake without steatorrhea; (ii) without severe pulmonary disease Forced expiratory volume in 1 s >60%); (iii) Who were not on high-dose steroids (defined as prednisolone >1 mg/kg daily) for longer than 1 month during the previous 6 months; (iv) no evidence of CF-related diabetes mellitus, gastroesophageal reflux, or allergy to milk protein.

From enrolled patients with CF, whose height was below the 3% percentile or whose height increase was two standard deviations (SD) below their expected height growth over 6 months, were included in the GH stimulation test study (case group). Besides, some children without CF also referred for growth disorders who matched the CF group were considered as the control group. They underwent the GH stimulation test, and the results were compared.

The GH stimulation test was done using the clonidine test while patients fasted. The patients received 0.15 mg/m^2 clonidine orally, and a blood sample was taken after 0, 30, 60, and 90 min. When the level of the GH was below 10 ng/mL, the second test was done after the administration of levodopa and taking blood samples at the same intervals. The levodopa dosage in this study was determined by the patient's body weight. In this way, patients <15 kg weight received 125 mg, patients between 15 and 30 kg received 250 mg and patients more than 30 kg weight received 500 mg levodopa. GH levels in blood samples were measured by electrochemical luminescence assay. When at this step the hormone level of the child was still below 10 ng/mL, the patient was recorded as a GHD case.[17]

Statistical analysis

The continuous data are presented as mean (SD) and qualitative data with a number (%). Two study groups were compared in terms of sex, age, height, weight, BMI, and GH level using the independent-samples *t*-test and Chi-squared (χ^2) tests. To compare the adjusted mean, we applied the analysis of covariance. The Pearson correlation was used to examine the relationship between the growth indicators and demographic parameters with the level of GH. The *P* value below 0.05 was considered statistically significant. We used the SPSS software version 20.0 for the data analysis and Microsoft Excel for visualization.

Results

From 150 CF patients enrolled with stable gastrointestinal and respiratory conditions, 24 patients had growth failure. In this study, 24 children with CF and 30 children without CF were enrolled for GH stimulation test. Demographic and growth parameters (including weight, height, BMI, level of GH, and frequency of low level of GH) characteristics are presented in Table 1. The two studied groups were age and sex matched. There were not significant differences between studied children in two groups regarding their growth parameters ($P > 0.05$). Mean (SD) of GH and frequency of low level HGH were not different significant ($P > 0.05$).

The prevalence of GD was 6.6% (10/150) in CF patients. The mean (SD) level of HGH was not significant between case and control groups ($P > 0.05$). After adjustment for age, weight, height, and BMI, the difference was not significant ($P > 0.05$).

In the control group of 30 children with growth failure but without CF, the GH stimulation test was deficient in nine cases, implying no significant difference with the case group ($P = 0.37$).

The correlation between the GH level with age, weight, height, and BMI in the two studied groups is provided in

Table 1: Demographic and growth parameters characteristics in children with (case group) and without cystic fibrosis (control group)

Variables	Case group (*n*=24)	Control group (*n*=30)	*P***
Sex (female/male), *n* (%)*	12 (50)/12 (50)	14 (46.7)/16 (53.3)	0.81
Age (years)	8.9±4.4	10.1±3.3	0.27
Weight (kg)	20.4±7.9	24.3±9.3	0.11
Height (cm)	115.5±21.6	122.6±19.6	0.21
BMI (kg/m^2)	14.8±1.5	15.6±2.1	0.11
GH (ng/mL)	13.5±6.6	13.2±9.9	0.82
Frequency of low level of GH (<10 ng/mL), *n* (%)*	10 (41.7)	9 (30)	0.37

*All variables except sex are presented as mean±SD, **P-value was calculated based on the independent *t*-test, except for *n* found by the Chi-square test. BMI: Body mass index, GH: Growth hormone

Table 2. Results of the Pearson correlation test indicated that except BMI, the other factors have a significant positive correlation with the level of GH in the case group. In the control group, there was not a significant correlation between the level of GH and other studied variables.

The mean level of GH was higher in boys than in girls, in both case and control groups. However, there was no significant difference between the two sexes on the level of HGH in any of the groups.

Discussion

In this study, we evaluated the prevalence of GHD and factors related to the level of GH in patients with CF. Our findings indicated a 6.6% prevalence of GHD. Level of GH was associated with the age, weight, and height of children with CF, whereas there was not such as association in the control group.

Results of many studies indicated that, despite significant improvement in the management and follow-up of children with CF, they had delayed linear growth. Some studies reported that linear growth impairment in these children is related to their weight and not height.

The results of a recent systematic review and meta-analysis indicated that, in patients with CF, weight is significantly associated with severity of the disease and pulmonary function. It is suggested that the pathophysiology of growth delay in this group of patients is multifactorial and factors such as chronic malnutrition, inflammation, malabsorption, and suppression of GH-IGF-1 axis are the potential causes.

Some recent studies evaluated the outcome of recombinant GH therapy on somatic growth. Some indicated that the therapy could improve anthropometric parameters in children with CF. Some other studies demonstrated that the impact of this therapy was less clear and limited in height and linear growth. Given the above-mentioned evidences, it seems that evaluation the GHD would more helpful both for growth evaluation and GH therapy.[3,18,19]

Table 2: The correlation between the growth hormone level and age, weight, height, and body mass index, in the case (with cystic fibrosis) and control (without cystic fibrosis) groups

Groups	Parameter	GH level	
		Correlation coefficient	*P*
Case group	Age (years)	0.386	0.03**
	Weight (kg)	0.372	0.04**
	Height (cm)	0.498	0.007*
	BMI (kg/m^2)	−0.238	0.13
Control group	Age (years)	−0.137	0.47
	Weight (kg)	−0.157	0.41
	Height (cm)	−0.136	0.48
	BMI (kg/m^2)	−0.079	0.68

*Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level. BMI: Body mass index, GH: Growth hormone

In this study, the mean of three growth indicators, weight, height, and BMI, had no significant difference between the children with CF and the children without CF. Therefore, we may conclude that the CF disease cannot be the only factor affecting the growth. However, since the mean of studied growth parameters was numerically, but not statistically, lower in the case group with CF children than the control group. It seems that for achieving more precise conclusion in this field, a larger study population is needed. In a study by Karami *et al*.,[10] the mean of height, weight, and BMI in a population of 60 Iranian CF children were reported, respectively, equal to 116 ± 20 cm, 22.8 ± 8.8 kg, and 15.9 ± 2.3 kg/m^2, which are pretty similar to our study population.

In this study, we found the prevalence of GHD to be 6.6% in CF patients, whereas the prevalence GHD in the normal population of childhood is <1%.[20] Therefore, further studies should investigate the cause of GHD in CF patients.

Growth deficit is common in children suffering from CF, but the cause is complex.[1] Severe complications of the CF, such as the long-term decline in lung function, malabsorption, and diabetes mellitus, are considered associated with growth deficit; however, some patients with no severe complications are still diagnosed with growth deficits.[7,8] In the current study, we evaluated the variation of the GH secretion in CF patients. We found no statistically significant difference between the level of GH in the CF group and the control group, similar to the results of the study by Laursen *et al*.[21] who reported no significant difference in both the stimulated and the spontaneous GH levels between the CF patients and the control (normal) group. They also indicated a significantly declined IGF-I and IGF-binding protein-3 (IGFBP-3) in CF patients. They suggested that the combination of decreased IGF-I and IGFBP-3 and a normal GH release may be because of a relative GH resistance or a disturbance in the pituitary axis in patients with CF.

Some other studies also reported a decreased or disordered GH in children and adult with CF.[22] Ciro *et al*.[23] studied 285 children with CF. From studied population, 18 patients underwent GH stimulated test and 12 out of them had GHD.

The rate of GHD in their study was 4.2%. Our findings were also similar to this study. They suggested that GH deficiency in these patients may be an independent cause of growth impairment in this group of children.

In another study on pigs with CF, it was found that the CFTR malfunction affected the somatotropic axis, which resulted in decreased GH release.[12]

We observed a significant correlation between the age, weight, and height with the GH level in CF patients; however, it was not seen in the control group. Explain this observation is difficult because various factors affect the growth process, especially in patients with CF. However,

it can be a confirmation of the effectiveness of GH therapy in patients with this disease, which discussed in several studies.[2,24] The negative correlation between the BMI and GH level (although not significant in this study) matched some previous studies.[25] This can confirm that with weight gain in CF children, the GH secretion is declined, which reduces the rate of growth in these children.

Sex is one of the parameters affecting the GH. In this study, despite the lower mean level of GH in girls compared to boys, this difference was not statistically significant in any group. In a study on mice with CF, the GH deficiency was significant in female mice, but not significant in male mice.[26]

The limitations of this study were small sample size and lack of term follow-up in studied patients.

Conclusion

Considering the findings of the current study, CF does not appear to affect, on its own, the GH level in children of both sexes, and the growth failure in these patients may be because of other clinical and hormonal factors. However, the significant correlation observed between the height and weight with the level of GH in patients with CF underlines the important role of this hormone in the growth parameters. Hormone therapy in these patients should be administered after measuring the level of GH. It is recommended to plan further prospective studies in this field.

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Conflicts of interest

There are no conflicts of interest.

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