Japanese Journal of Gastroenterology and Hepatology

Research Article

ISSN: 2435-1210 | Volume 10

Growth Hormone Treatment Outcomes in Indian Children with Celiac Disease and Growth Hormone Deficiency

Kochar IS, Ramachandran S* and Sethi A

Consultant Pediatric and Adolescent Endocrinology, Indraprastha Apollo Hospital, New Delhi, India

***Corresponding author:**

Smita Ramachandran,
Consultant Pediatric and Adolescent Endocrinology,
Indraprastha Apollo Hospital, New Delhi, India

Received: 05 Oct 2023
Accepted: 15 Nov 2023
Published: 20 Nov 2023
J Short Name: JJGH

Citation:

Ramachandran S. Growth Hormone Treatment Outcomes in Indian Children with Celiac Disease and Growth Hormone Deficiency. J Gastro Hepato. 2023; V10(5): 1-5

Keywords:

Indian children; Celiac disease; Short stature; Autoimmune; Growth hormone deficiency

Abbreviations: CD: Celiac disease; GHD: Growth hormone deficiency; RGH: Recombinant growth hormone

1. Abstract

1.1. Objectives: To evaluate the final height outcome with growth hormone (GH) replacement therapy during a gluten-free diet in patients with celiac disease (CD) associated with GH deficiency (GHD) in comparison with isolated GHD.

1.2. Method: A retrospective study of 17 pre-pubertal children with Celiac Disease (CD) with isolated growth hormone deficiency and 17 age and sex matched GHD children without any other co-morbidities were included in the study. Their pretreatment and post treatment height and predicted height were evaluated.

1.3. Results: On analysis the mean weight at the start of rGH in GHD was 28.7967 kg and celiac was 27.3731kg, the GHD group was shorter (mean 124.6733cm) than CD (128.4688cm). The height velocity was better in the GHD group of 10.25cm/year and 8.03cm/year in CD which was statistically significant (0.03). The mean final predicted height was hence better in the GHD group 161.8333cm and in the CD group was 158.1875cm. the Z score of final PAH in GHD was -0.1593 (SD 1.07734) and in CD was -0.5625 (SD 0.81394) which was statistically significant (0.001).

The mean weight in GHD was 28.79kg while in CD was 27.37kg, but the final mean weight after treatment was 35.6kg in GHD while 43.6kg in CD (p=0.03).

1.4. Conclusion: GHD and CD is a rare association. In comparison to other studies our children with CD have height velocity less than children with GHD, larger studies are needed from India to ascertain the prevalence of this in the Indian children.

2. What is known

Short stature in celiac disease is due to:

- Poor gluten free diet
- Iron deficiency
- Multi nutrient deficiency

What is new

- the association of CD and GHD is very rare.
- Children on gluten free diet not gaining height should be evaluated for growth hormone deficiency.
- rGH is beneficial in such children in improving height.

3. Introduction

Celiac Disease (CD) is as an immune-mediated enteropathy characterized by a inflammatory reaction to gluten. It is associated with typical changes seen in intestinal biopsies such as blunting of villi, crypt hypertrophy and lymphocyte infiltration of crypts. It is a condition of permanent sensitivity to gluten, and occurs in genetically susceptible individuals (HLA class II haplotype DQ2 or DQ8). Its manifestations can vary from asymptomatic to severely symptomatic including chronic diarrhea, malabsorption, and bloating and growth failure in children. Up to 4% of children seeking medical care due to short stature might have CD and many of them do not have any gastrointestinal symptoms [1].

Short stature and delayed puberty are some of the non- gastrointestinal manifestations in these children, and have an estimated risk of 10-40% for isolated short stature [2]. Short stature in CD is mostly due to malnutrition, iron deficiency and non-adherence to gluten free diet. These children may usually present with reduction of insulin-like growth factor 1 (IGF1), IGF2 and insulin-like growth factor binding protein 3 (IGFBP-3), increase of IGFBP-2 and IGFBP-1 levels, and a blunted GH response to pharmacological stimuli. However, these biochemical parameters are transient and revert once the children adhere to gluten free diet [3].

Children with CD start showing improvement in height velocity and weight when initiated on gluten free diet. However few children with CD do not show any catch-up despite good adherence to gluten free diet. It is in this sub-population that the possibility of growth hormone deficiency (GHD) should be evaluated even as the association of CD and GHD is very rare.

This study was planned to evaluate the association of CD and GHD and the benefit of initiating Growth hormone in such children.

4. Materials and Methods

4.1. Study Design and patients

A retrospective study was conducted from 2010 to 2017 in Indraprastha Apollo Hospital. Data was collected from patient records of children being treated with recombinant growth hormone (rGH) in 2 groups as follows:

1. children with CD having growth hormone deficiency (CD group)

2. children with GHD only (isolated GHD group)

4.2. Inclusion Criteria

17 pre-pubertal children with Celiac Disease (CD) with growth hormone deficiency and 17 age and sex matched GHD children without coeliac disease or any other co-morbidities were included in the study.

4.3. Screening and Diagnosis of Celiac disease

All children with Celiac disease (CD) were screened for CD by anti-ttg IgA antibodies and positive cases were confirmed with endoscopic examination of the upper gastrointestinal tract with at least four biopsies of the distal duodenal mucosa. Only those confirmed patients who did not show catch up growth and continued to have short stature after 12 months of gluten free diet and demonstrated a reversion to seronegativity for anti-ttg antibodies were included in the study.

4.4. Diagnosis of GHD

In all of the patients, the diagnosis of GHD was established when GH response to 2 pharmacological stimuli was <10 ng/mL in the presence of short stature.

4.5. Parameters Assessed

Auxological data of height, weight, BMI, bone age, chronological age was recorded at the time of initiation of growth hormone and at the end of therapy.

- height was measured using a Harpenden stadiometer and expressed as standard deviation score (SDS) for chronological age

- weight to the nearest 0.1 kg (Electro W-No-45).

- BMI was recorded as kg/m2

- bone age was evaluated according to the method Tanner Whitehouse II

- predicted adult height (PAH)

4.6. Other Investigations

- Thyroid and adrenal functions were investigated by evaluating serum total and free T4 and TSH, and morning and evening serum cortisol concentrations, respectively.

4.7. Growth Hormone Therapy

- All patients received treatment with recombinant synthetic human GH for at least 12 months, GH was administered by daily subcutaneous injections at the dose 35μg/kg/day.

4.8. Statistical Analysis

- Height, weight, BMI, predicted adult height was all expressed as standard deviation scores. Independent t-test and paired t-test were used to compare the various pre-treatment and post-treatment data.

The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee. Written informed consent for participation in the study was given by one of the parents of the children and assent was also obtained whenever required.

5. Results

This study analyses the data of 34 children who completed at least 1 year of growth hormone therapy divided into two matched groups of 17 each – one group had celiac disease associated with GHD (CD group) and other group had children with isolated GHD without any co-morbidities (GHD group).

The mean weight at the start of rGH therapy in the isolated GHD group and CD group was 28.79 ± 9.24 kg and 27.37 ± 8.22 kg respectively. The mean height in the isolated GHD group (124.67 cm ± 8.41) was shorter than the CD group (128.46cm ± 10.86).

The mean age of presentation in the isolated GHD and CD groups were 10.3 years and 11.5 years respectively and the mean bone age was more advanced advance in CD group (11.1yr ± 2.18) than the isolated GHD group (9.7yrs ± 1.81) (Table 1- Baseline parameters).

5.1. GH and IGF-1 Levels

The mean growth hormone peak after stimulation was 3.7ng/ml (ranged from 1.19 - 7.0 ng/ml) and the pre-treatment IGF-1 levels were low in all the patients ranging from 29- 45 ng/ml (mean 36.6 ng/ml).

In the CD group, there was a significant increase in the height af-

ter treatment (139.91 ± 9.32) in comparison to before treatment (128.46 ± 10.86). Similarly, a significant weight increase was noticed after treatment (43.62 ± 11.05) than before treatment (27.37 ± 8.22). There was an increase in BMI after treatment which was significant and within the normal range (Table 2- CD group analysis: pre and post treatment).

In the isolated GH group, there was a significant increase in the height and weight post treatment (136.50±9.92 and 35.66±9.50) in comparison to before treatment (124.67±8.41 and 28.79±9.24). However, there was no significant difference in the BMI post treatment (Table 3- Isolated GHD group analysis: pre and post treatment).

Upon comparison between the groups, a numerical increase in the height was observed in the CD group (139.91±9.32) than isolated GHD group (136.50±9.92). However, weight and BMI had significantly increased in the CD group (43.62±11.05 and 22.13±4.411) than the isolated GHD group (35.66±9.50 and 18.86±2.73). The height velocity was better in the GHD group of 10.25 cm/year than the CD group of 8.03 cm/year, which was statistically significant (p=0.03). The mean final predicted height was hence better in the GHD group than the CD group (161.83 cm vs 158.18 cm) (Table 4- Intergroup analysis: post treatment).

There was an improving trend seen in the Z scores of all the auxological parameters assessed within both the groups (Table 5 - SDS of pre and post treatment data of isolated GHD group and Table 6 - SDS of pre and post treatment data of CD group). The Z scores of final PAH in GHD was -0.15 and in CD was -0.56 which were statistically significant.

Table 1: Baseline parameters

Parameter	**CD group** (n=17) (Mean ± SD)	**Isolated GHD group (n=17)** (Mean ± SD)
Age(years)	11.55 ± 1.91	10.30 ± 1.70
Height (cm)	128.46 ± 10.86	124.67± 8.41
Weight (kg)	27.37 ± 8.22	28.79 ± 9.24
BMI (kg/m^2)	16.25 ± 3.03	18.17 ± 3.77
Mid parental Height (MPH)	162.50 ± 5.26	166.20 ± 6.59
Predicted Adult Height (PAH)	153.31 ± 5.77	155.60 ± 7.74
Bone Age (yr)	11.1 ± 2.18	9.7 ± 1.81

Table 2: CD group analysis: pre and post treatment

Parameter	CD group		p value
	Pre treatment	Post treatment	
Height (cm)	128.46±10.86	139.91±9.32	<0.001
Weight (kg)	27.37±8.22	43.62±11.05	<0.001
BMI (kg/m^2)	16.25±3.03	22.13±4.411	<0.001
Predicted Adult Height (PAH)	153.31±5.77	158.18±5.78	<0.05

Table 3: Isolated GHD group analysis: pre and post treatment

Parameter	Isolated GHD group		p value
	Pre treatment	Post treatment	
Height (cm)	124.67±8.41	136.50±9.92	<0.001
Weight (kg)	28.79±9.24	35.66±9.50	<0.001
BMI (kg/m^2)	18.17±3.77	18.86±2.73	0.2
Predicted Adult Height (PAH)	155.60±7.74	161.83±9.62	<0.001

Table 4: Intergroup analysis: post treatment

Parameter	Post treatment		p value
	CD group	Isolated GHD group	
Height (cm)	139.91±9.32	136.50±9.92	0.332
Weight (kg)	43.62±11.05	35.66±9.50	<0.05
BMI (kg/m^2)	22.13±4.411	18.86±2.73	<0.05
Predicted Adult Height (PAH)	158.18±5.78	161.83±9.62	0.208
Height velocity	8.03±2.36	10.25±1.32	<0.05
Height gain	11.45±7.56	11.83±3.9	0.862

Table 5: SDS of pre and post treatment data of isolated GHD group

Parameter	Isolated GHD group	
	Pre treatment	Post treatment
Height (cm)	-1.98±0.85	-1.20±1.00
Weight (kg)	-0.70±1.1	-0.27±0.89
BMI (kg/m^2)	0.33±1.04	0.40±0.72
Predicted Adult Height (PAH)	-1.14±0.83	-0.15±1.07

Table 6: SDS of pre and post treatment data of CD group

Parameter	CD group	
	Pre treatment	Post treatment
Height (cm)	-2.34±0.78	-1.6±0.74
Weight (kg)	-1.67±1.09	0.01±1.05
BMI (kg/m^2)	-0.64±1.14	0.91±1.14
Predicted Adult Height (PAH)	-1.42±1.01	-0.56±0.81

6. Discussion

The prevalence of GHD in CD is a rare entity, whose etio-pathogenesis is not completely clear. Globally, there are only few studies that have been conducted reporting an estimated prevalence of 2.9% to 8.3% [4,5].

A study by Giannattasio reported an incidence of 7% but the sample size was less [4]. However, based on the larger studies, only 16 (0.23%) subjects had both GHD and CD out of the 7066 children with short stature [6].

In our study, the prevalence of CD in children with GHD was only 1.4%. The pathogenesis of GHD in CD is not very clearly understood, even though as per literature it is understood that there is a blunted growth hormone response during the active phase of celiac disease. Growth hormone deficiency secondary to autoimmune hypophysitis, GH insensitivity and low leptin levels are some of the postulated reasons for it [6,7,]. Several studies have documented high levels of anti-pituitary antibodies in celiac children with poor catch-up growth despite gluten free diet. [6, 8]

There are very few studies that have tried to establish the association between CD and GHD [1,5,10,11-13] and only fewer have treated short stature in CD with GHD with rGH and reported the outcomes. [1,11-13]

The dose ranges across different studies were from 0.16 - 0.26 mg/kg/week whereas in our study we had administered rGH by daily subcutaneous injections at a standard dose of 35μg/kg/day.

In a small study by Salardi et al, target height was attained upon treatment with rGH in children with CD and GHD compared to the children who were not given rGH.[11] Giovenale et al had conducted a study with an objective in comparing the final height between children with CD and GHD and children with isolated GHD upon treatment with rGH. It was seen that the improvement in height was comparable in both the groups.[12].

In our study, the Z score of final PAH in the isolated GHD and CD group was -0.15 and -0.56 respectively and was statistically significant. The reasons for this are not entirely clear but it could be interplay of multiple autoimmune mechanisms and hence further studies need to be done to evaluate the same.

All these studies have reiterated that GHD should be borne in mind in children with CD, who have failed to attain appropriate height velocity despite a gluten free diet and sero-negativity for 12months. Though the exact mechanism of this association is not yet fully understood, timely institution of rGH in these children was shown to be beneficial in attaining the target height.

The limitations of our study were the small number of patients and lack of a long term follow up. Hence larger randomized studies need to be conducted to evaluate the association and its effects.

7. Conclusion

This is the first study from India analyzing the association of CD with GHD with a comparison of growth outcomes in these children. Even though the final height outcomes were better in GHD than CD, there was an improvement in the auxological parameters within each group after treatment with rGH. Hence a timely diagnosis along with rGH therapy could be an effective option in this rare association of GHD with CD for rewarding results. This study also warrants the need for future studies with larger sample size and long term follow up.

8. Summary Box

• Height faltering in children in remission warrants further evaluation

• GHD should be considered in such children and evaluated

• Early initiation of growth hormone improves final adult height outcomes

References

1. Giovenale D, Meazza C, Cardinale GM. The prevalence of growth hormone deficiency and celiac disease in short children. Clin Med Res. 2006; 4: 180-3.
2. Tümer L, Hasanoglu A, Aybay C. Endomysium antibodies in the diagnosis of celiac disease in short- statured children with no gastrointestinal symptoms. Pediatr Int. 2001; 43: 71-3.
3. Salardi S, Cacciari E, Volta U. Growth and adult height in atypical coeliac patients, with or without growth hormone deficiency. J Pediatr Endocrinol Metab. 2005; 18: 769-75.
4. Cacciari E, Salardi S, Lazzari R. Short stature and celiac disease: a relationship to consider even in patients with no gastro- intestinal tract symptoms. J Pediatr. 1983; 103: 708–11.
5. Giannattasio A, Di Dato F, Minicucci V, Mariano M, Spagnuolo MI, Macchiaroli A, et al. A retrospective evaluation of the association of celiac disease and growth hormone deficiency: more than a casual association? Minerva Endocrinol. 2017; 42: 24-9.

6. Iughetti L, De Bellis A, Predieri B. Growth hormone impaired secretion and antipituitary antibodies in patients with coeliac disease and poor catch-up growth after a long gluten-free diet period: a causal association? Eur J Pediatr. 2006; 165: 897-903.

7. Maggio MC, Corsello G, Iacono G. Gluten-free diet impact on leptin levels in asymptomatic coeliac adolescents: one year of follow-up. Horm Res. 2007; 67: 100-4.

8. Delvecchio M, De Bellis A, Francavilla R. Anti- pituitary antibodies in children with newly diagnosed growth impairment. Am J Gastroenterol. 2010; 105: 691-6.

9. Sigurs N, Johansson C, Elfstrand PO, Viander M, Lanner A. Prevalence of coeliac disease in diabetic children and adolescents in Sweden. Acta Paediatr. 1993; 82: 748-751.

10. Nemet D, Raz A, Zifman E. Short stature, celiac disease and Growth hormone deficiency. Endocrinol Metab. 2009; 22: 979-83.

11. Salardi S, Cacciari E, Volta U, Santoni R, Ragni L, Elleri D, et al. Growth and adult height in atypical coeliac patients, with or without growth hormone deficiency. J Pediatr Endocrinol Metab. 2005; 18(8): 769-75.

12. Giovenale D, Meazza C, Cardinale GM, Farinelli E, Mastrangelo C, Messini B, et al. Growth hormone treatment in prepubertal children with celiac disease and growth hormone deficiency. J Pediatr Gastroenterol Nutr. 2007; 45(4): 433-7.