

Short children with CHARGE syndrome – Do they benefit from growth hormone therapy?

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Abstract

Aim: To evaluate the response to recombinant GH treatment in short children with CHARGE syndrome.

Patients: We identified 51 children (28 boys, 23 girls) in KIGS (Pfizer International Growth Database). Median chronological ages (CA) at GH start was 7.6 yr and at the latest visit 13.2 yr. Evaluation for GHD (n= 33): GH peak 7.3 µg/L and IGF-I -2.01 SDS. Sixteen subjects (9 boys) were followed longitudinally for 2 yrs.

Results (median SDS): Birth length (-0.47) and weight (-0.97) were slightly reduced. At GH start, Height (Ht) was -3.6, BMI - 0.7 and GH dose 0.26 mg/kg/wk. At latest visit after 2.7 yrs of GH, Ht had increased to -2.2 and BMI to -0.5.

Longitudinal group (start, 1 yr, and 2 yr): Ht increased from -3.72 to -2.92 to -2.37 (start - 2 yr: $p<0.05$), Ht velocity increased from -1.69 to 2.98 to 0.95, BMI and GH dose (mg/kg/wk) remained almost unchanged.

Conclusions: Our data show a positive effect of conventional doses of GH on short-term growth velocity for the longitudinal as well as for the total group, without any safety issues.

Introduction

CHARGE is an acronym proposed by Pagon et al [1] to describe a syndrome (OMIM 214800) with multiple congenital anomalies such as coloboma of the eye, heart malformations, choanal atresia, retardation of growth and mental development, genitourinary anomalies, and ear malformations [2-6]. CHARGE syndrome is a clinical diagnosis based on major and minor criteria as outlined by Blake *et al.* and Verloes [4, 7]. Mutations of the chromodomain helicase DNA-binding protein gene, *CHD7*, were reported to be a major cause of CHARGE syndrome [2, 8, 9].

Children with CHARGE syndrome have also endocrine disturbances which affect genital development, puberty and growth. Puberty is often delayed or absent due to hypogonadotropic hypogonadism in combination with anosmia [10-12]. Studies show that postnatal growth is disturbed in 37-72% of affected children [13-15]. It has generally been assumed that short stature is caused by recurrent infections, feeding problems, and/or hospitalizations, and not due to a hormonal insufficiency. However, growth hormone (GH) deficiency has been reported in children with CHARGE syndrome [12, 13, 16, 17].

To the best of our knowledge, there are no published data in the literature on the effects of GH treatment in short children with CHARGE syndrome. The aim of the present study was to evaluate the effects of GH treatment on growth and BMI in children with CHARGE syndrome.

Patients and Methods

The data of 51 children (28 boys, 23 girls) with the diagnosis CHARGE syndrome were retrieved from the pharmaco-epidemiological survey, KIGS (Pfizer International Growth data base), in 2012 [18]. We assume that the diagnosis was made by clinical geneticists according to the criteria defined by Blake et al. and Verloes [4, 7]. Data on molecular confirmation of the

diagnosis were not recorded in the database. The children were treated with GH (Genotropin®) by s.c.-injections 6 or 7 days per week. The results of a pharmacological GH stimulation test were documented in 33 patients. Median (10 – 90 percentiles) peak GH ($\mu\text{g/L}$) was 7.3 (2.7 - 15.5). Fifteen children had a GH peak $< 10 \mu\text{g/L}$ and were considered GH- deficient. The median serum IGF-I level was -2.0 SDS ($-3.2 - 0.7$). The median chronological age (CA) at the start of GH therapy was 7.6 yr (2.2 –14.7 yr), with 3 subjects in puberty. At the latest available visit, the median age was 13.2 yr (4.6 - 18.5) and 19 subjects were in puberty. The median starting dose of GH was 0.26 mg/kg/week. The median duration of GH treatment was 2.7 yr (0.35 – 8.8 yr). Bone age results were not documented.

Of the total group, the longitudinal auxological data of 16 prepubertal children (9 boys, 7 girls) who remained prepubertal for at least 2 yrs during GH treatment were analyzed. The median CA at start of GH for those was 6.9 yr (2.2 - 12.5 yr).

SDS values for birth data, height (H), height velocity (HV), and BMI were calculated based on Swedish, Swiss, and Great Britain references [19-21]. The results, where appropriate, are shown as median (10th - 90th percentile) or mean (SD). Student's T-test was used for comparisons of outcome measures when applicable otherwise Wilcoxon rang sum test was used, considering difference at less than 5% level as significant ($p < 0.05$). Statistical analysis was made by SAS (SAS Institute, Cary, NC 27513-2414, USA).

Results

Cross-sectional data of the total group

In the total group, median (P10 to 90) birth length was -0.47 SDS ($-2.3 - 1.4$), and birth weight SDS was -0.97 ($-2.8 - 1.2$). Table 1 shows the auxological data of the children at start of GH and at the latest documented visit in KIGS.

At the start of GH therapy, data on Ht velocity (HtV) were only available for 10 patients. Median HtV was 4.4 cm/yr (2.3 - 10.3 cm/yr).

As shown in Table 1, the children were very short at the start of GH treatment (Ht SDS P90 -2.4). On GH, median height SDS increased from -3.6 to -2.2 SDS at the last documented visit, whereas median BMI SDS remained unchanged. The median duration of GH therapy was 2.7 yr. The first-year HtV during GH treatment was not different between children with and without GH deficiency.

Two-year longitudinal data

The longitudinal data of 16 children from start of GH therapy, at 1 yr, and at 2 yr on GH treatment are shown in Table 2. All children remained prepubertal during the observation period. Peak GH levels were reported for 11 patients (9 with GHD and 2 with non-GHD); no information was available for 5 patients. Plotting the peak GH levels versus delta height SDS for one-year prepubertal growth, a weak and not significant correlation ($r = -0.19$) was found. The median (P10-90) starting dose of GH was 0.23 mg/kg/wk (0.17 - 0.34). Median Ht-SDS increased significantly from -3.7 at the start to -2.4 at 2 yr ($p < 0.05$) (Fig. 1). Ht-SDS minus mid-parental Ht-SDS also increased significantly from -3.4 at the start to -2.1 at 2 yr of GH treatment ($p < 0.05$). During the 2 years of GH treatment, median HV-SDS increased from -1.7 to 0.95, and median BMI-SDS remained almost unchanged (-1.3 to -1.4). The median change in Ht-SDS in the first year of GH treatment was +0.79 and, in the second year, +0.46. The dose of GH remained unchanged during the first 2 yrs of treatment.

Adverse events

Adverse events (AEs) were reported in seven children: upper respiratory tract infection ($n = 3$) and one each with viral gastroenteritis, chickenpox, headache, and kyphoscoliosis.

Discussion

This is the first report showing efficacy and safety data on the growth outcomes and adverse events in GH-treated short children with CHARGE syndrome. All children were found to have a substantial improvement in height SDS and height velocity SDS after 1 and 2 years of GH treatment, while BMI SDS remained unchanged. The gain in height SDS (start vs latest visit) of the total group was +1.3 SDS. Starting age was however relative high and many children entered puberty only after some months on treatment, which could contribute to overestimation of efficacy. However, the same results were found when only a prepubertal subgroup was analyzed.

It has been shown that children with CHARGE syndrome usually have a normal birth weight and birth length [13, 22]. The birth data of our group confirm these results. The majority of children with CHARGE syndrome experience decelerated growth pattern during late infancy [10, 13-15, 23]. It has been speculated that the etiology of short stature is multifactorial due to cardiac malformations, infections, feeding problems, gastro-esophageal reflux, choanal atresia, and/or recurrent hospitalizations [3, 13] and not due to endocrine disorders such as growth hormone deficiency. The low BMI values, both at start and during GH therapy, confirm that nutrition is a major problem in children with Charge syndrome.

Growth hormone deficiency has been documented in some children with CHARGE syndrome [12, 13, 16, 17]. Pinto *et al.* assessed GH secretion in 25 short children with CHARGE syndrome [12] and three had low peak GH values consistent with GHD. Asakura *et al.* found GHD in one of seven patients with CHARGE syndrome [16], and Husu *et al.* reported GHD in three of nine short children with CHARGE syndrome [14]. In the KIGS cohort, a pharmacological GH stimulation test was documented in only 33 patients with a low GH result ($<10 \mu\text{g/L}$) in 15. The high incidence of GHD in our population can

be explained by a recruitment bias, since the data were extracted from a GH database.

The weak correlation between peak GH levels versus delta height SDS for one-year prepubertal growth may indicate that endogenous GH status does not appear to play a role in the first-year height response to GH therapy, but the cohort may be too small to be certain. The reported adverse events are harmless and in parallel to previous reports in other GH indications [24]. In order to recommend treatment with GH in these patients, it is necessary to have long-term data on GH and particularly final height data. However, it is important to carry out a careful evaluation of the hypothalamic-pituitary axis in children with CHARGE syndrome.

Our study has several limitations. There might be a selection bias since only very short-statured patients with CHARGE syndrome were selected for GH therapy. Additionally, there were children who were treated with GH without proven GH deficiency. Moreover, we have no genetic confirmation of the diagnosis in our subjects.

In summary, here we present short-term longitudinal outcome to treatment with GH in children with CHARGE syndrome. GH was effective in improving linear growth over the first years on treatment, also when a prepubertal subset was studied. However, long-term data on GH and final height data are unfortunately lacking.

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Disclosures

Helmuth Dörr, Margaret Boguszewski, Jovanna Dahlgren, David Dunger, Mitchell E. Geffner, Anita Hokken-Koelega, Michel Polak, and Raoul Rooman were members of the KIGS Steering Committee at the time of the study. Anders Lindberg is a full-time employee of Pfizer Inc., Sollentuna, Sweden. This study was sponsored by Pfizer Inc.

Table 1

Auxological data (Median; 10th – 90th percentile) of the whole group of 51 children with CHARGE at the start of GH and at the latest documented visit in KIGS.

	Background	
Birth weight SDS (n = 47)	-0.97 (2.77 - 1.16)	
Birth length SDS (n = 36)	-0.47 (2.30 - 1.40)	
Max GH peak µg/L (n = 33)	7.30 (2.70 - 15.5)	
IGF-I SDS (n = 23)	-2.01 (-3.24 - 0.66)	
	At GH start	At last visit
CA (yr) (n = 51)	7.6 (2.2 - 14.7)	13.2 (4.6 - 18.5)
In puberty	N = 3	N = 19
H-SDS (n = 51)	-3.6 (-5.5 - -2.4)	-2.2 (-5.2 - -0.6)
H-SDS corrected with MPH-SDS (n = 44)	-3.3 (-4.6 - -1.6)	-1.7 (-3.5 - -0.3)
BMI SDS (n = 51)	-0.7 (-2.6 - 1.3)	-0.5 (-2.6 - 1.7)
GH dose (mg/kg/wk) (n = 51)	0.26 (0.18 - 0.37)	0.28 (0.18 - 0.36)

CA = chronological age; H = height; SDS = standard deviation score;

MPH = midparental height; BMI = body mass index; GH = growth hormone

Table 2 Longitudinal data of 16 children with CHARGE syndrome in KIGS who remained prepubertal during 2 yr of GH therapy

	N	Median	10 th	90 th	Mean	SD
At GH start						
CA (yr)	16	6.86	2.17	12.5	7.52	4.43
Height (H; cm)	16	99.2	75.5	127.7	102.6	22.4
H-SDS	16	-3.72	-5.63	-2.80	-4.03	1.29
H – MPH (SDS)	16	-3.44	-5.79	-1.95	-3.54	1.26
Height velocity (HV; cm/yr)	4	3.98	2.72	4.82	3.88	0.91
HV-SDS	4	-1.69	-3.36	0.35	-1.60	1.95
BMI-SDS	16	-1.32	-3.58	0.60	-1.28	1.41
hGH (mg/kg/wk)	16	0.23	0.17	0.34	0.25	0.08
1st year on GH						
CA (yr)	16	7.91	3.03	13.6	8.53	4.48
Height (cm)	16	106.9	83.2	135.6	111.6	21.6
H-SDS	16	- 2.92	- 5.17	- 1.91	- 3.29	1.61
H – MPH (SDS)	16	- 2.50	- 5.35	- 1.18	- 2.81	1.43
Height velocity (cm/yr)	16	8.82	6.29	10.5	8.92	2.80
HV-SDS	16	2.98	- 0.31	6.38	2.93	2.69
Delta H-SDS (1 st yr vs start)	16	0.79	0.45	1.14	0.73	0.43
BMI-SDS	16	- 1.19	- 3.58	0.19	- 1.42	1.45
hGH (mg/kg/wk)	16	0.24	0.18	0.35	0.26	0.07
2nd year on GH						
CA (yr)	16	8.87	4.17	14.5	9.52	4.42
Height (cm)	16	112.1	93.8	141.9	118.8	20.4
H-SDS	16	-2.37	-4.74	-1.63	-2.89	1.83
H – MPH (SDS)	16	-2.11	-4.20	-0.72	-2.40	1.54
Height velocity (cm/yr)	16	7.19	4.82	9.31	7.28	2.10
HV-SDS	16	0.95	-0.88	4.74	1.53	3.19
Delta H-SDS (2 nd yr vs 1 st yr)	16	0.46	-0.28	1.04	0.41	0.49
BMI SDS	15	-1.44	-2.73	0.15	-1.26	1.30
hGH (mg/kg/wk)	16	0.24	0.18	0.36	0.26	0.08

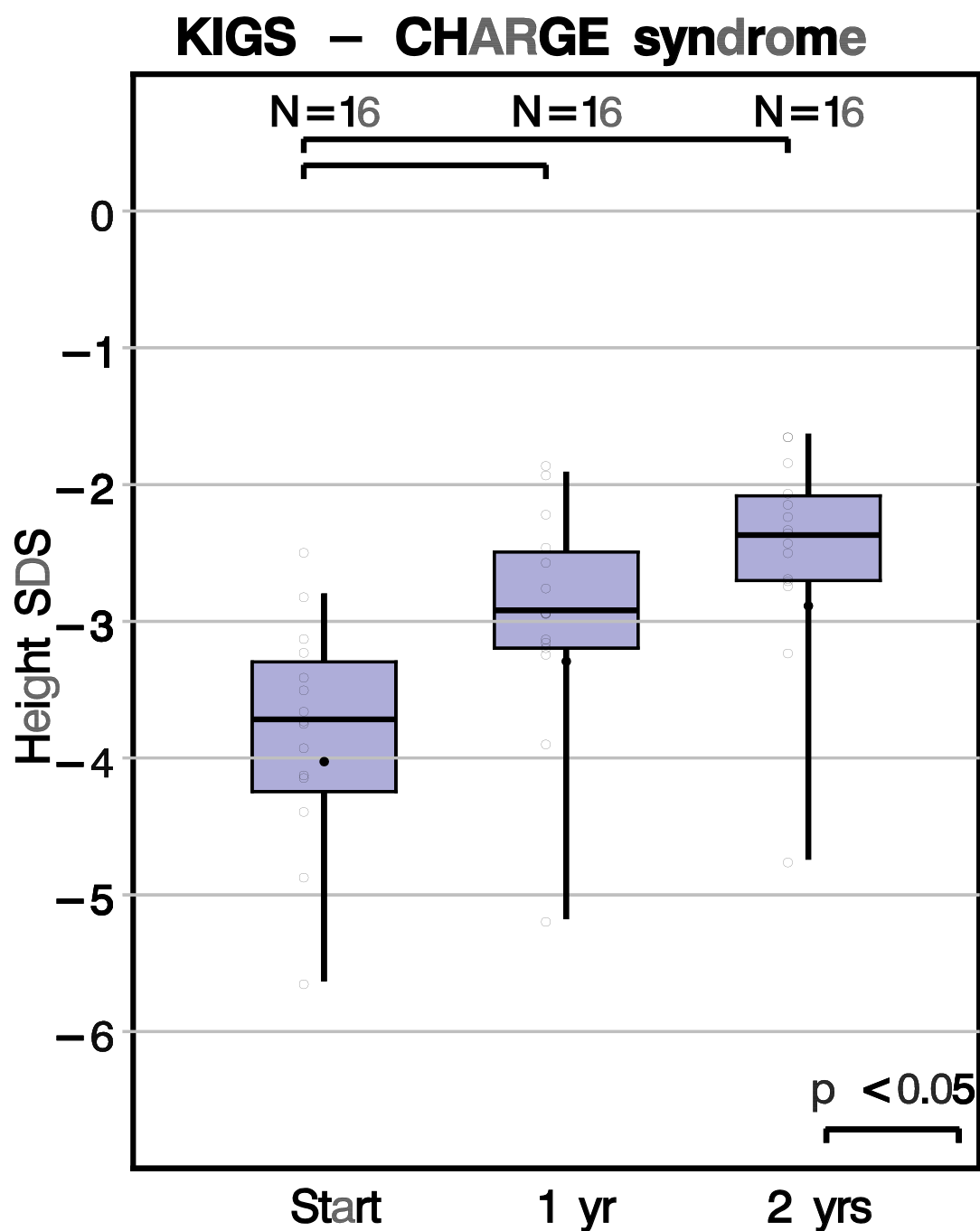
CA = chronological age; H = height; SDS = standard deviation score;

MPH = midparental height; BMI = body mass index; hGH = growth hormone

Fig. 1

Longitudinal height data (SDS) of 16 prepubertal children with CHARGE syndrome on GH therapy at start, at 1. and 2. yr.

(Box plot with individual height during GH treatment; median value, box 25th and 75th percentile; whiskers 10th and 90th percentile).



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