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Short Children with CHARGE Syndrome: Do They Benefit from Growth Hormone Therapy?

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Key Words
Short stature · CHARGE syndrome · Growth · Growth hormone treatment · KIGS database

Abstract
Aim: The aim of this study was to evaluate the response to recombinant growth hormone (GH) treatment in short children with CHARGE syndrome. ***Patients:*** We identified 51 children (28 boys and 23 girls) in KIGS (Pfizer International Growth Database). The median chronological age was 7.6 years at the start of GH therapy and 13.2 years at the latest visit. Evaluation for GH deficiency (n = 33) was based on the following: peak GH level 7.3 µg/l and IGF-I level –2.01 standard deviation score (SDS). Sixteen subjects (9 boys) were followed longitudinally for 2 years. ***Results:*** Birth length (median SDS, –0.47) and weight (–0.97) were slightly reduced. At the start of GH therapy, height was –3.6 SDS, BMI –0.7 SDS, and the GH dose was 0.26 mg/kg/week. At the latest visit after 2.7 years of GH therapy, height had increased to –2.2 SDS and BMI to –0.5 SDS. In the longitudinal group, height increased from –3.72 SDS at the start of GH therapy to –2.92 SDS after 1 year to –2.37 SDS after 2 years of therapy (start – 2 years: $p < 0.05$), height velocity increased from –1.69 to 2.98 to 0.95 SDS, and BMI and GH dose (mg/kg/week) 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

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Table 1. Auxological data of the whole group of 51 children with CHARGE at the start of GH therapy and at the latest visit documented in KIGS

	Background	
Birth weight SDS (n = 47)	–0.97 (2.77 to 1.16)	
Birth length SDS (n = 36)	–0.47 (2.30 to 1.40)	
GH peak, μg/l (n = 33)	7.30 (2.70 to 15.5)	
IGF-I SDS (n = 23)	–2.01 (–3.24 to 0.66)	
	At the start of GH therapy	At the last visit
CA, years (n = 51)	7.6 (2.2 to 14.7)	13.2 (4.6 to 18.5)
Children in puberty	3	19
Height SDS (n = 51)	–3.6 (–5.5 to –2.4)	–2.2 (–5.2 to –0.6)
Height SDS corrected with MPH SDS (n = 44)	–3.3 (–4.6 to –1.6)	–1.7 (–3.5 to –0.3)
BMI SDS (n = 51)	–0.7 (–2.6 to 1.3)	–0.5 (–2.6 to 1.7)
GH dose, mg/kg/week (n = 51)	0.26 (0.18 to 0.37)	0.28 (0.18 to 0.36)

Values are presented as medians (10th–90th percentile). MPH = Midparental height.

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. [7] and Verloes [4]. 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 is not due to a hormonal insufficiency. However, growth hormone (GH) deficiency (GHD) 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 body mass index (BMI) in children with CHARGE syndrome.

Patients and Methods

The data of 51 children (28 boys and 23 girls) with the diagnosis of CHARGE syndrome were retrieved from the pharmacoepidemiological survey KIGS (Pfizer International Growth Database) of 2012 [18]. We assume that the diagnosis was made by clinical geneticists according to the criteria defined by Blake et al. [7] and Verloes [4]. Data on molecular confirmation of the diagnosis were not recorded in the database. The children were treated with GH (Genotropin®) by subcutaneous injections on 6 or 7 days per week. The results of a pharmacological GH stimulation test were documented in 33 patients. The median (10th–90th percentile) peak GH level was 7.3 μg/l (2.7–15.5). Fifteen children had a peak GH of <10 μg/l and were considered GH deficient. The median serum IGF-I level was –2.0 standard deviation score (SDS, –3.2 to 0.7). The median chronological age (CA) at the start of GH therapy was 7.6 years (2.2–14.7), with 3 subjects in puberty. At the latest available visit, the median age was 13.2 years (4.6–18.5), with 19 subjects in puberty. The median starting dose of GH was 0.26 mg/kg/week. The median duration of GH treatment was 2.7 years (0.35–8.8). Bone age results were not documented.

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

SDS values for birth data, height, height velocity, and BMI were calculated based on studies from Sweden, Switzerland, and Great Britain [19–21]. The results, where appropriate, are shown as medians (10th–90th percentile) or means (SD). Student's t test was used for comparisons of outcome measures when applicable, otherwise Wilcoxon rang sum test was used, considering differences at <5% level as significant ($p < 0.05$). Statistical analysis was made by SAS (SAS Institute, Cary, N.C., USA).

Results

Cross-Sectional Data of the Total Group

In the total group, median (10th–90th percentile) birth length was –0.47 SDS (–2.3 to 1.4) and birth weight

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

	n	Median	10th percentile	90th percentile	Mean	SD
At the start of GH therapy						
CA, years	16	6.86	2.17	12.5	7.52	4.43
Height, cm	16	99.2	75.5	127.7	102.6	22.4
Height SDS	16	–3.72	–5.63	–2.80	–4.03	1.29
Height – MPH SDS	16	–3.44	–5.79	–1.95	–3.54	1.26
Height velocity, cm/year	4	3.98	2.72	4.82	3.88	0.91
Height velocity 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
GH, mg/kg/week	16	0.23	0.17	0.34	0.25	0.08
First year on GH						
CA, years	16	7.91	3.03	13.6	8.53	4.48
Height, cm	16	106.9	83.2	135.6	111.6	21.6
Height SDS	16	–2.92	–5.17	–1.91	–3.29	1.61
Height – MPH SDS	16	–2.50	–5.35	–1.18	–2.81	1.43
Height velocity, cm/year	16	8.82	6.29	10.5	8.92	2.80
Height velocity SDS	16	2.98	–0.31	6.38	2.93	2.69
Delta height SDS (first year 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
GH, mg/kg/week	16	0.24	0.18	0.35	0.26	0.07
Second year on GH						
CA, years	16	8.87	4.17	14.5	9.52	4.42
Height, cm	16	112.1	93.8	141.9	118.8	20.4
Height SDS	16	–2.37	–4.74	–1.63	–2.89	1.83
Height – MPH SDS	16	–2.11	–4.20	–0.72	–2.40	1.54
Height velocity, cm/year	16	7.19	4.82	9.31	7.28	2.10
Height velocity SDS	16	0.95	–0.88	4.74	1.53	3.19
Delta height SDS (second vs. first year)	16	0.46	–0.28	1.04	0.41	0.49
BMI SDS	15	–1.44	–2.73	0.15	–1.26	1.30
GH, mg/kg/week	16	0.24	0.18	0.36	0.26	0.08

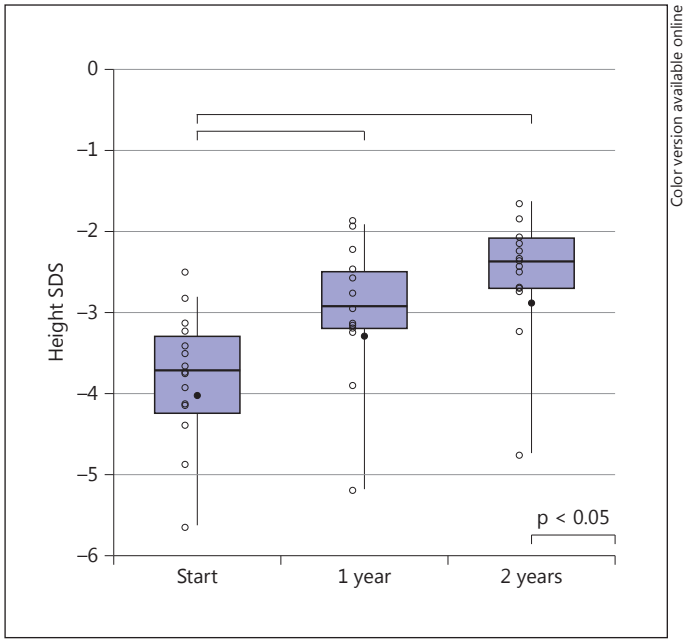
MPH = Midparental height.

was –0.97 SDS (–2.8 to 1.2). Table 1 shows the auxological data of the children at the start of GH therapy and at the latest visit documented in KIGS. At the start of GH therapy, data on height velocity were only available for 10 patients. Median height velocity was 4.4 cm/year (2.3–10.3).

As shown in table 1, the children were very short at the start of GH treatment (height SDS 90th percentile –2.4). On GH, median height 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 years. The first-year height velocity during GH treatment was not different between children with and those without GHD.

Two-Year Longitudinal Data

The longitudinal data of 16 children from the start of GH therapy as well as at 1 and at 2 years 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 without GHD); no information was available for 5 patients. Plotting the peak GH levels versus delta height SDS for 1-year prepubertal growth, a weak and not significant correlation was found ($r = –0.19$). The median (10th–90th percentile) starting dose of GH was 0.23 mg/kg/week (0.17–0.34). Median height SDS increased significantly from –3.7 at the start of GH treatment to –2.4 after 2 years ($p < 0.05$; fig. 1). Height SDS minus midparental height SDS also



Color version available online

Fig. 1. Longitudinal height data (SDS) of 16 prepubertal children with CHARGE syndrome at the start of GH therapy as well as after 1 and 2 years. Box plot with individual height during GH treatment (median value). Box: 25th and 75th percentile; whiskers: 10th and 90th percentile.

increased significantly from –3.4 at the start of GH treatment to –2.1 after 2 years ($p < 0.05$).

During the 2 years of GH treatment, median height velocity SDS increased from –1.7 to 0.95, and the median BMI SDS remained almost unchanged (–1.3 to –1.4). The median change in height SDS was +0.79 in the first year and +0.46 in the second year of GH treatment. The GH dose remained unchanged during the first 2 years of treatment.

Adverse Events

Adverse events were reported in 7 children: upper respiratory tract infection (n = 3), viral gastroenteritis (n = 1), chickenpox (n = 1), headache (n = 1), and kyphoscoliosis (n = 1).

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 of treatment vs. latest visit) of the total group was +1.3 SDS. The age at the start of GH therapy was, however, relatively 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, gastroesophageal reflux, choanal atresia, and/or recurrent hospitalizations [3, 13] and not due to endocrine disorders such as GHD. The low BMI values, both at the start of and during GH therapy, confirm that nutrition is a major problem in children with CHARGE syndrome.

GHD has been documented in children with CHARGE syndrome [12, 13, 16, 17]. Pinto et al. [12] assessed GH secretion in 25 short children with CHARGE syndrome, and 3 had low peak GH values consistent with GHD. Asakura et al. [16] found GHD in 1 of 7 patients with CHARGE syndrome, and Husu et al. [14] reported GHD in 3 of 9 short children with CHARGE syndrome. In the KIGS cohort, a pharmacological GH stimulation test was documented in only 33 patients, with a low GH result (<10 μg/l) in 15 patients. 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 1-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 GHD. Moreover, we have no genetic confirmation of the diagnosis in our subjects.

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

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Disclosure Statemtent

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