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 (µg/L) was 7.3 (2.7 - 15.5). Fifteen children had a GH peak < 10 µg/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 (10^{th} - 90^{th} 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 µg/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; 10^{th} – 90^{th} 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	10th	90th	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	**N**	**Median**	**10th**	**90th**	**Mean**	**SD**
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 (1st 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	**N**	**Median**	**10th**	**90th**	**Mean**	**SD**
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 (2nd yr vs 1st 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

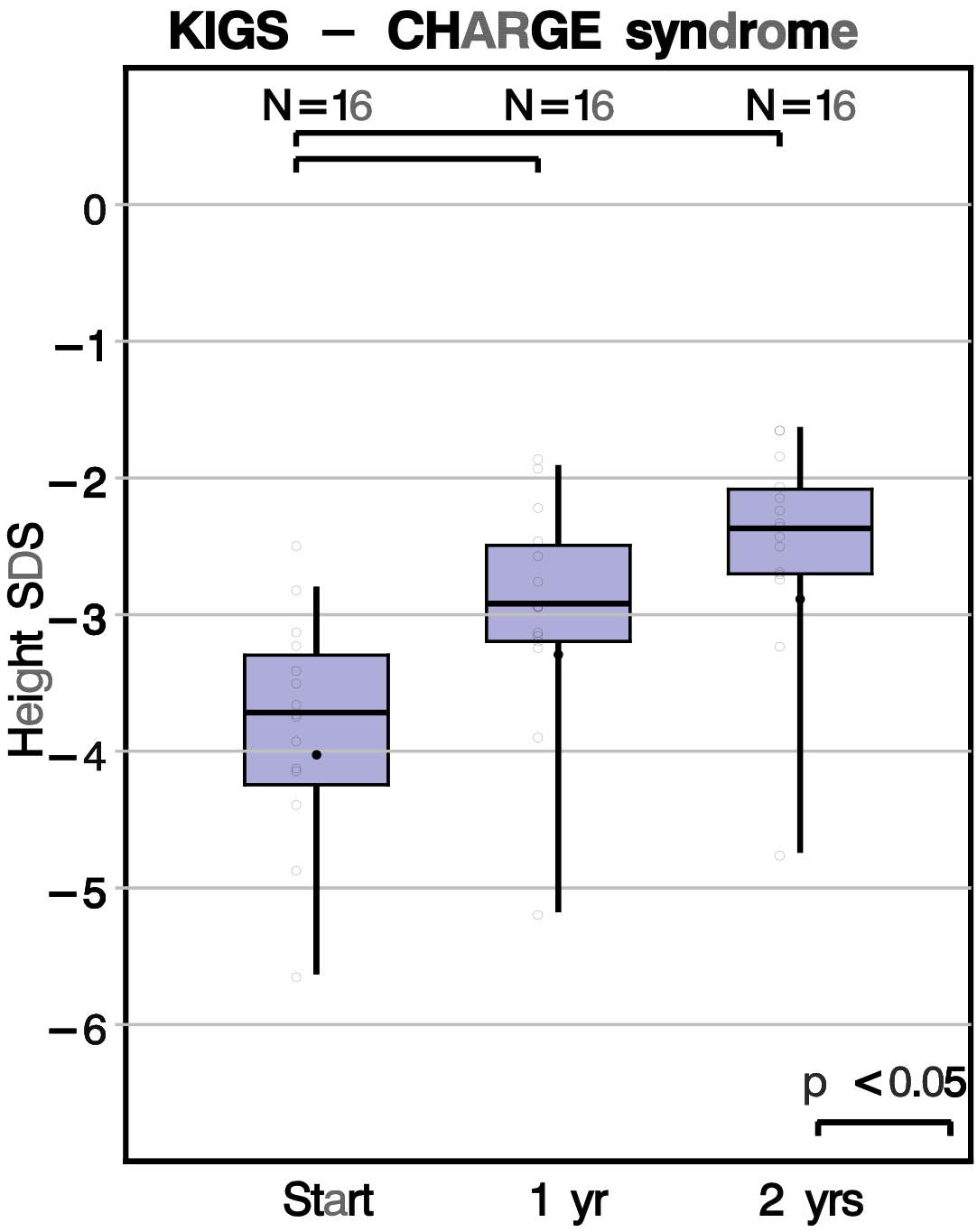
CA = chronological age; H = height; SDS = standard deviation score;

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).



References

1 Pagon RA, Graham JM, Jr., Zonana J, Yong SL: Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: Charge association. The Journal of Pediatrics 1981;99:223-227.

2 Lalani SR, Safiullah AM, Fernbach SD, Harutyunyan KG, Thaller C, Peterson LE, McPherson JD, Gibbs RA, White LD, Hefner M, Davenport SL, Graham JM, Bacino CA, Glass NL, Towbin JA, Craigen WJ, Neish SR, Lin AE, Belmont JW: Spectrum of chd7 mutations in 110 individuals with charge syndrome and genotype-phenotype correlation. American Journal of Human Genetics 2006;78:303-314.

3 Blake KD, Prasad C: Charge syndrome. Orphanet Journal of Rare Diseases 2006;1:34.

4 Verloes A: Updated diagnostic criteria for charge syndrome: A proposal. American Journal of Medical genetics Part A 2005;133A:306-308.

5 Jyonouchi S, McDonald-McGinn DM, Bale S, Zackai EH, Sullivan KE: Charge (coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness) syndrome and chromosome 22q11.2 deletion syndrome: A comparison of immunologic and nonimmunologic phenotypic features. Pediatrics 2009;123:e871-877.

6 Hsu P, Ma A, Wilson M, Williams G, Curotta J, Munns CF, Mehr S: Charge syndrome: A review. Journal of Paediatrics and Child Health 2014;50:8.

7 Blake KD, Davenport SL, Hall BD, Hefner MA, Pagon RA, Williams MS, Lin AE, Graham JM, Jr.: Charge association: An update and review for the primary pediatrician. Clinical Pediatrics 1998;37:159-173.

8 Vissers LE, van Ravenswaaij CM, Admiraal R, Hurst JA, de Vries BB, Janssen IM, van der Vliet WA, Huys EH, de Jong PJ, Hamel BC, Schoenmakers EF, Brunner HG, Veltman JA, van Kessel AG: Mutations in a new member of the chromodomain gene family cause charge syndrome. Nature Genetics 2004;36:955-957.

9 Jongmans MC, Admiraal RJ, van der Donk KP, Vissers LE, Baas AF, Kapusta L, van Hagen JM, Donnai D, de Ravel TJ, Veltman JA, Geurts van Kessel A, De Vries BB, Brunner HG, Hoefsloot LH, van Ravenswaaij CM: Charge

syndrome: The phenotypic spectrum of mutations in the chd7 gene. Journal of Medical Genetics 2006;43:306-314.

10 Issekutz KA, Graham JM, Jr., Prasad C, Smith IM, Blake KD: An epidemiological analysis of charge syndrome: Preliminary results from a canadian study. American Journal of Medical Genetics Part A 2005;133A:309-317.

11 Bergman JE, Bocca G, Hoefsloot LH, Meiners LC, van Ravenswaaij-Arts CM: Anosmia predicts hypogonadotropic hypogonadism in charge syndrome. The Journal of Pediatrics 2011;158:474-479.

12 Pinto G, Abadie V, Mesnage R, Blustajn J, Cabrol S, Amiel J, Hertz-Pannier L, Bertrand AM, Lyonnet S, Rappaport R, Netchine I: Charge syndrome includes hypogonadotropic hypogonadism and abnormal olfactory bulb development. The Journal of Clinical Endocrinology and Metabolism 2005;90:5621-5626.

13 Blake K, Kirk JM, Ur E: Growth in charge association. Archives of Disease in Childhood 1993;68:508-509.

14 Husu E, Hove HD, Farholt S, Bille M, Tranebjaerg L, Vogel I, Kreiborg S: Phenotype in 18 danish subjects with genetically verified charge syndrome. Clinical Genetics 2013;83:125-134.

15 Zentner GE, Layman WS, Martin DM, Scacheri PC: Molecular and phenotypic aspects of chd7 mutation in charge syndrome. American Journal of Medical Genetics Part A 2010;152A:674-686.

16 Asakura Y, Toyota Y, Muroya K, Kurosawa K, Fujita K, Aida N, Kawame H, Kosaki K, Adachi M: Endocrine and radiological studies in patients with molecularly confirmed charge syndrome. The Journal of Clinical Endocrinology and Metabolism 2008;93:920-924.

17 Gregory LC, Gevers EF, Baker J, Kasia T, Chong K, Josifova DJ, Caimari M, Bilan F, McCabe MJ, Dattani MT: Structural pituitary abnormalities associated with charge syndrome. The Journal of Clinical Endocrinology and Metabolism 2013;98:E737-743.

18 Wilton P: Kigs: Structure and organization. ; in Ranke MB, Price, D.A., Reiter, E.O. (ed) Growth hormone therapy in pediatrics - 20 years of kigs, . Basel, Karger, 2007, pp 1-5.

19 Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P: An update of the swedish reference standards for weight, length and head

circumference at birth for given gestational age (1977-1981). Acta PaediatrScand 1991;80:756-762.

20 Prader A, Largo RH, Molinari L, Issler C: Physical growth of swiss children from birth to 20 years of age. First zurich longitudinal study of growth and development. HelvPaediatrActa Suppl 1989;52:1-125.

21 Cole TJ: Body mass index reference curves for the uk, 1990. Arch Dis Child 1995;73:25-29.

22 Searle LC, Graham JM, Jr., Prasad C, Blake KD: Charge syndrome from birth to adulthood: An individual reported on from 0 to 33 years. American Journal of Medical Genetics Part A 2005;133A:344-349.

23 Bergman JE, Janssen N, Hoefsloot LH, Jongmans MC, Hofstra RM, van Ravenswaaij-Arts CM: Chd7 mutations and charge syndrome: The clinical i mplications of an expanding phenotype. Journal of Medical Genetics 2011;48:334-342.

24 Darendeliler F, Karagiannis G, Wilton P: Headache, idiopathic intracranial hypertension and slipped capital femoral epiphysis during growth hormone treatment: A safety update from the kigs database. Horm Res 2007;68 Suppl 5:41-47.