RESEARCH BRIEF

Growth of Short Children Born Small for Gestational Age and Their Response to Growth Hormone Therapy

***HEMCHAND KRISHNA PRASAD, VAMAN V KHADILKAR, SHASHI A CHIPLONKAR AND ANURADHA V KHADILKAR**

*From the Department of *Endocrinology, Bharati Vidyapeeth University Medical College; and Growth and Pediatric Endocrine Unit, Hirabai Cowasji Jehangir Medical Research Institute, Jehangir Hospital; Pune, Maharashtra, India.*

Correspondence to:
Dr Anuradha V Khadilkar,
Hirabai Cowasji Jehangir Medical Research Institute, Jehangir Hospital, 32 Sasoon Road, Pune 411 001, Maharashtra, India. akhadilkar@vsnl.net
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Growth hormone [GH] is licensed for use in children born small for gestational age (SGA) who fail to catch-up. We retrospectively compared the response of twenty children born SGA (who satisfied the auxological criteria) to growth hormone (Group I) versus randomly selected age and sex matched controls from a group of SGA children with growth related complaints, not treated with GH (Group II). After 2 years of GH therapy the HAZ increased from -2.8 to -1.6 in Group I, compared 2.2 to -1.7 in group II (*P*-value < 0.05). The percentage of pubertal children rose from 55% to 65% in cases versus 60% to 75% in the controls (*P*>0.05). GH resulted in increase in growth velocity Z-score during the first year and (4.3±0.5 in Group-I versus -0.5±0.6 in Group-II, *P*<0.05) second year of treatment (1.7±0.4 in cases versus -0.6±0.7 in controls, *P*<0.05).Thus, GH improves height of short SGA children without accelerating pubertal progression.

Key words: *Growth, Growth hormone (GH), Small for Gestational age (SGA)* .

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Children born small for gestational age (SGA) are shorter that normal children during infancy, childhood and adolescence and reach adult heights that on an average are approximately 1 SD lower than the mean [1]. Therapy with growth hormone (GH) often augments growth potential in short children born SGA [2].

The Food and Drug Administration (FDA) in 2001 and the European Agency for the Evaluation of Medicinal Products in 2003 officially recommend GH therapy in children born SGA who fail to catch-up. There are no Indian studies that describe the usefulness of GH in short children born SGA.

We conducted this study to describe the growth pattern of children born SGA from a pediatric endocrine clinic where they presented with growth related complaints and to assess the efficacy of GH in increasing height of children born SGA with growth failure.

METHODS

This retrospective study is based on data retrieved from case records of 81 SGA children who had been on regular follow-up in a pediatric endocrine clinic for growth related complaints from 2005-2010. Details pertaining to anthropometry, clinical parameters and investigations were collected from the case records. Children presenting with growth related complaints had been assessed using a standard protocol and anthropometric tools [3]. Children with birth weight Z-score <-2 for their gestational age were included in the study. Children with any major congenital malformations, syndromic features or sequelae of intrauterine infections were excluded. All the study subjects underwent GH stimulation tests to rule out GH deficiency.

These children were followed up every six months for monitoring of growth. The anthropometric measures were converted into Z-scores based on our earlier study on affluent children [4]. Pubertal status was assessed by a pediatric endocrinologist [5]. Growth velocity was converted into Z-score using references published by Tanner, *et al*. [6] for pubertal children and Rikken, *et al*. [7] for pre-pubertal children. Subjects were counselled for growth hormone therapy if either the height for age Z-score <-2.5 or annual growth velocity was below the mean for the corresponding age and sex or Height SDS > 1 SD below midparental height SDS. Our hospital ethics committee approved the study.

The subjects were divided into two groups:- Group I children satisfied the auxological criteria and received growth hormone in a dose of 35 µg/kg/day as a daily bedtime injection by the sub-cutaneous route for a minimum period of two years. Group II children did not receive growth hormone owing to logistic reasons.

Analysis of anthropometric and clinical parameters were carried out using SPSS 16.0 (for windows), 2001. The changes in anthropometry and growth velocity parameters of the two groups were compared using the student *t*-test.

RESULTS

We reviewed the case records of 81 children (mean age 7.6 ± 0.4 years, 30 boys) who satisfied the study criteria and were followed up for a minimum period of two years. Finally we compared 20 SGA children who received GH and 20 age and sex matched children who did not receive GH. Baseline characteristics of the two groups are compared in ***Table* I.**

The results of the effect of GH on treated subjects versus 20 controls are described in ***Table* II.** Growth velocity of boys and girls from group I and II are depicted in ***Web Fig.*** 1 (*a*) and 1 (*b*), respectively, in comparison with 50th percentile of available reference data for height velocity. It was observed that the velocity curves of group II children (untreated) largely fell below while those of group I children (treated with GH) were above 50th percentile of reference population.

DISCUSSION

Children born SGA who received GH for 2 years demonstrated a catch-up of +1.2 height SD score. The height velocity of untreated short SGA children remained below the 50th centile. Growth Hormone therapy was not associated with any significant adverse effects or acceleration of pubertal process.

Longitudinal studies on growth of SGA infants from German [8], Belgium [9] and Spain [10] using country specific growth charts demonstrate that SGA children have mean growth velocity Z-score of -1.4, -1 and -2.1, respectively. The mean growth velocity in a study on Argentanian children was 5.4 ± 1.7 cm [11]. The growth velocity curves on cross sectional data of our children are in line with these international studies.

There was a short term increase in height SDs in our study group by + 1.2 from -2.8 to -1.6 after two years of GH therapy. Our results are in line with previous reports [12-

TABLE I BASELINE CLINICAL AND ANTHROPOMETRIC CHARACTERISTICS

	Group I (GH) (*n*=20)	Group II (Control) (*n*=20)
Age (y)	7.7± 3.4	8.5 ± 3.4
Sex (M:F)	7:13	7:13
Birthweight (kg)	1.8 ± 0.3	1.8 ± 0.4
Gestational age (wks)	39 ± 1	38.5 ±1
Target height (cm)	156.7 ± 8.1	158.1 ± 8.7
Target height Z-score	–1.07 ± 0.7	-0.9 ± 0.6
Height (cm)	108.1±20.9	104.9 ± 25.4
Height for age Z-score	–2.8 ± 1.3	–2.2 ± 1.7
Weight (kg)	17.8 ± 8.8	20.05 ± 10.3
Weight for age Z-score	–2.5 ± 1.5	–2.2 ± 1.9
Body Mass Index (kg/m^2)	14.3 ± 2.4	14.9 ± 4
Pubertal status	11/20	12/20

All values are expressed as mean ± SD. Pubertal status indicates testicular volume > 4 mL in boys or Tanner Breast stage 2.

TABLE II CHANGE IN ANTHROPOMETRIC AND PUBERTAL STATUS ON GROUP I CHILDREN (TREATED WITH GH) *VERSUS* CONTROLS IN GROUP II

	Group I (n=20)		*Group II (n=20)*	
Growth velocity in the first year (cm/year)*	10.0 ± 2.1		5.8 ± 2.3	
Growth velocity in the second year (cm/year)*	7.9 ± 1.6		5.5 ± 2.4	
Growth velocity Z-score (1st year) *	4.3 ± 0.5		0.5 ± 0.6	
Growth velocity Z-score (2nd year)*	1.7 ± 0.4		0.6 ± 0.7	
	Baseline	Endline	Baseline	Endline
Height (in cm)*	108.1 ± 20.9	125.3 ± 18.8	104.9 ± 25.4	116.2 ± 19.7
Height for age Z-score*	-2.8 ± 1.3	-1.6 ± 1.2	-2.2 ± 1.7	-1.7 ±1.1
Weight (in kg)	17.8 ± 8.8	19.3 ± 7.6	20.05 ± 10.3	30.1 ± 15.7
Weight for age Z-score	-2.5 ± 1.5	-2 ± 2.8	-2.2 ± 1.9	-1.6 ± 1.9
Body Mass Index (kg/m^2)	14.3 ± 2.4	13.2 ± 2.2	14.9 ± 4	19.3 ± 3.3
Pubertal status	11/20	13/20	12/20	15/20

**P value <0.05.*

WHAT THIS STUDY ADDS?

- Indian children, born SGA, who satisfy the auxological criteria (height for age Z-score <-2.5 or annual growth velocity was below the mean for the corresponding age and sex or Height SDS > 1 SD below midparental height SDS) are likely to benefit from growth hormone therapy.

14]. There was no acceleration of puberty in children treated with GH versus the non-treated group in our study. This is in agreement with previous reports that in the majority of short SGA children treated with GH during childhood, pubertal development begins on time and progresses normally [15]. However, longer follow-up is required to establish whether all of our children will start puberty at an appropriate age and whether the overall duration of puberty is altered.

Birth length has not been used to classify as SGA as it could not be reliably retrieved from many records. Also, the limitations in cross sectional data in assessing longitudinal growth are well known. The effect on glucose metabolism in subjects treated with GH could not be assessed. Also, our children need to be followed up till they reach adult height to see if the catch-up is maintained and there is an increase in the final attained height. Further, predicted height could not be calculated as bone age is not a good predictor of final height in SGA children. However, our results suggest that, anthropometric parameters need to be monitored regularly in children born SGA. GH is likely to be useful in augmentation of height and height velocity in Indian children who are born SGA when they do not catch-up.

Contributors: VVK and AVK were involved in management of the children and collection of data. The study was conceived by AVK. Statistical analysis was done by SAC, AVK and HKP. All authors were involved in drafting the manuscript and VVK will act as the guarantor of the study.

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