



## Growth Hormone Outcomes in RSS and SGA Children: Indian Tertiary Care Study

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### Abstract

**Objectives:** The aim of the study was to evaluate the efficacy of growth hormone in improving the predicted adult height in children with RSS and SGA in the Indian population.

**Method:** A retrospective study of 56 children with RSS and SGA with short stature, who had taken rGH for duration of minimum 12 months were included. Their pretreatment and post treatment height and predicted height were evaluated.

**Results:** The pre-treatment mean height was -2.618 SDS which improved to -0.010 SDS after one year of treatment. The difference between the Z score of height and weight, pre-treatment and post-treatment were statistically significant (<0.001).

**Conclusion:** A significant height improvement occurred in both RSS and SGA children after 1year of GH treatment. There were no significant side effects noted in during this period. Children initiated at age less than 8 yrs fared marginally better than when started at a later age group.

### What is known

- Children born small for gestation (SGA) are known to have short stature.
- Etiopathogenesis for which is extremely heterogeneous, attributed to multiple genetic factors, environmental, maternal nutrition and health, drugs, infections.
- The SGA children who are below -2 SDS at 4 yrs of age are highly unlikely to catch up.

### What this study adds

- Indicating benefit of growth hormone therapy in short stature in children with RSS and SGA.
- This is the first Indian study of children with RSS and SGA with statistically significant height benefits with growth hormone.
- Children initiated at age less than 8 yrs fared marginally better than when started at a later age group.

**Keywords:** Indian RSS; SGA; Short stature; Growth hormone

### Introduction

Children born small for gestation (SGA) are known to have short stature and the etiopathogenesis for which is extremely heterogeneous, attributed to multiple genetic factors, environmental, maternal nutrition and health, drugs, infections. However 90% of these children catch up the deficit by 2 yrs but about 10% of these children fail to achieve this [1]. The SGA children who are below -2 SDS at 4 yrs of age are highly unlikely to catch up and generally tend to remain short throughout the rest of their lives [2].

The prevalence of SGA babies is about 41.5% in South Asia and is around 30% in India as compared to a 5% to 7% in the developed nations [3].

Russell Silver Syndrome (RSS) is a genetic condition associated with prenatal and postnatal growth retardation. RSS has a prevalence of about 1:30,000 to 1:100,000 worldwide [4]. Short stature associated with RSS is one of the most severe categories of growth impairment in SGA children. These children continue to remain short during their life causing considerable distress and impairment [5].

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**Table 1:** Z score of Auxological data.

	Auxological Data Z Score	
	Pre-treatment	Post-treatment
<b>Height Z score</b>	2.2898 (1.22890)	-1.3509 (1.27469)
<b>Weight Z score</b>	-1.7391 (1.24824)	-0.9782 (1.25442)
<b>BMI Z score</b>	-0.9864 (1.29047)	-0.3827 (1.54716)

Short stature is the hallmark of RSS, these children however do not achieve the catch up growth seen in SGA children, hence remain short despite sometimes having normal growth velocity. Children with RSS have abnormal growth hormone pulsatility which coupled with absent catch growth makes the child remain below the 3<sup>rd</sup> centile for height [6].

There are several studies of children with SGA and RSS from various parts of the world, however there are no studies about the use and effect of growth hormone in these children from India. The cost of long-term therapy has a key role in the duration of treatment in our country, as the entire cost of treatment is borne by the family of these children.

This study aims to evaluate the effect of growth hormone in children who are SGA and RSS, in the India population.

## Patients and Methods

A retrospective study was planned from 2010 till 2017, where all the data was collected from the patient records.

### Diagnostic criteria

**SGA:** Children with birth weight Z-scores <-2 for their gestational age included in the study (SGA), with no evidence of catch up growth till 4 yrs of age.

**RSS:** RSS was diagnosed by the Netchine-Harbisson clinical scoring system.

- All children less than 18 yrs were included in the study.
- Children on growth hormone for 1 yr.
- Results of growth hormone stimulation tests were not part of the exclusion criteria.

All the data of small for gestation children were retrospectively evaluated, those fulfilling the Netchine-Harbisson clinical criteria were assigned as RSS and the rest were included in SGA.

### Netchine-Harbisson scoring system [6]

- Prenatal growth retardation (birth weight and/or length -2 SDS for gestational age).
- Postnatal growth retardation (height SDS for calendar age, ≤ 2.0 according to national reference).
- Relative macrocephaly at birth (head circumference at birth at least 1.5 SDS above birth weight and/or length SDS according to Usher and McLean).
- Prominent forehead (defined as a forehead that projects beyond the facial plane on a side view as a toddler).
- Body asymmetry (defined as leg length discrepancy of ≥ 0.5 cm or arm asymmetry or leg length discrepancy ≤ 0.5 cm with at least two other asymmetrical body parts, with one being a nonface part).
- Feeding difficulties during early childhood. Patients were

classified as clinical SRS if at least four of these six factors were present.

## Patient Characteristics

### At the start of treatment

Birth data were obtained from patient discharge records, Height was measured to the nearest 0.1 cm (Harpenden stadiometer) and weight to the nearest 0.1 kg (ElectroW-No-45). BMI (WT in kg/HT in metre<sup>2</sup>).

### At the end of treatment

Patient parameters recorded were height, weight, BMI, tanner stage, growth velocity (cm/yr). Parents and most participants gave informed consent for participation in the study, which was approved by the ethical committee.

## Puberty

Onset of puberty was defined as breast stage 2 according to Tanner for girls and testicular volume > 4 mL for boys bone age was determined once a year according to Tanner and Whitehouse RUS. Bone age delay was calculated as calendar age minus bone age in yrs. Five of the children were pubertal and hence were not included in the statistical analysis, but their data was computed separately. The ethical committee of the hospital approved the study. We have complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects and/or animals.

## Growth Hormone

All patients received treatment with recombinant synthetic human GH for at least 12 months, GH was administered by daily subcutaneous injections at the dose 40 ug/kg/day. The Z scores were calculated using Microsoft excel using macros.

Height, weight, BMI, predicted adult heights were 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.

## Results

The study enrolled 61 children over a period of 3 yrs, 5 of them were pubertal and hence were not included in the statistical analyses. The data of 56 children were computed, 30 children were SGA and 26 were diagnosed RSS.

31 were males and 25 females. The mean age of starting treating treatment was 7.1 yrs ranging from 5 yrs to 12 yrs. The Z score of height, weight, BMI are detailed in Table 1, and the mean of the auxological data are presented in Table 2.

The mean bone age at the start of the therapy was 6 yrs and increased by a mean of 1.3 yrs at the end of therapy.

In our study the height gain in children between 5 to 8 yrs was 13.9 cm and 12 cm in children aged >8yrs at the start of treatment depicted in Table 3, however it was not statistically significant.

The difference between the Z score of height and weight, pre-treatment and post-treatment were statistically significant (<0.001),

**Table 2:** Auxological data mean [SD].

	Pre-treatment	Post-treatment
Age in years	7.1596 (2.154)	8.4668 (2.1999)
Bone age in years	6.0321 (2.239)	7.3971 (2.371)
Predicted adult height in cms	156.7911 (6.299)	162.6679 (7.004)

**Table 3:** Height gain in different age groups.

Age (yrs)	N	Mean Ht Gain	Std. Deviation	t-value	p-value
4-8	39	13.9103	6.11249	1.005	0.32
>8	17	12	7.464		

but was not significant in BMI. The mean predicted adult at the start of rGH therapy was 156.7 cm and improved to 162.6 cm predicted adult height at the end of 1 yr of treatment (Figure 1). The mean increment was 5.9 cm.

There were no significant side effects resulting in any dropouts.

There was no significant difference in the height velocity of children on growth hormone in the RSS and SGA children.

## Discussion

SGA and RSS are conditions in which the benefits of using growth hormone have been established in several studies from the world over, however there is a paucity of such data from India. In a large study from Andhra Pradesh, 96 children of stature on growth hormone treatment were evaluated, but had only 4 SGA and one case of RSS [7].

This is the first Indian study with a large number of children to evaluate the effects of growth hormone in Indian children with RSS and SGA.

Some studies have compared the benefits of growth hormone in RSS and SGA, a study by Smeets et al. [8] compared the growth outcomes in RSS and SGA on growth hormone and found out that RSS children responded equally well in gaining height as SGA, and idiopathic RSS benefitted the most in their study.

In our study both RSS and SGA responded equally well to rGH therapy and there was no statistical difference in their outcomes.

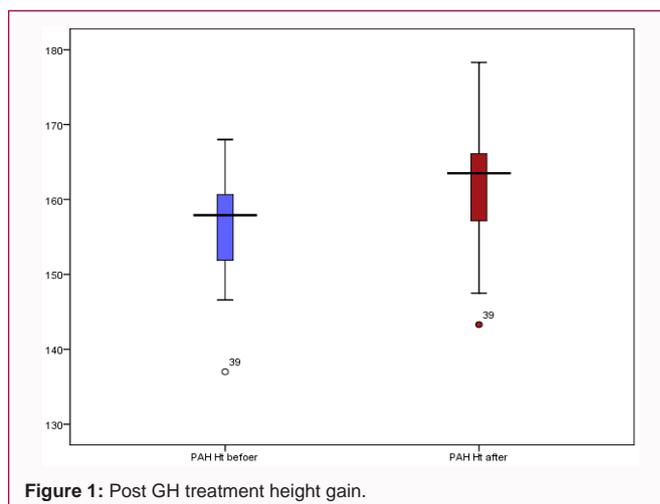
It has been stated that the earlier the age of starting growth hormone better are the outcomes in final height. In a study by Boguszewski et al. [9], they compared the height gain SGA children between 2 to 4 yrs and 4 to 6 yrs, and found out that median height SDS increased from -3.9 at the start to -2.2 at 3 yrs in the 2 to 4 yr old group and from -3.4 to -2.0 in the 4 to 6 yr old group.

But in another study from Spain the response to growth hormone was not very satisfactory and they attributed this to the later mean age ( $8.10 \pm 2.75$  yrs) of starting growth hormone therapy [10]. Argente et al. [11] reported in his study that the children under 4 yrs of age on growth hormone have a greater increase in height and weight than children older than 4 yrs.

We noted that that even though the children between 5 to 8 yrs at the start of treatment responded marginally better than children above 8 yrs at initiation, but the final outcomes were not statistically significant.

The mean dose of recombinant growth hormone administered to the children with RSS or SGA in various studies have been between 0.035 mg/kg/day to 0.04 mg/kg/day [8-10]. However there is evidence that these children benefit maximum by using the higher dose within the therapeutic range [12,13]. Some studies advocate the use of higher doses of growth hormone 0.055 ug/kg/day for extremely short (less than -3 SD) prepubertal children and in pubertal children [14].

We had included 5 pubertal children in our study out of which 1

**Figure 1:** Post GH treatment height gain.

opted out due to financial constraints. We continued the same dose of 0.040 ug/kg/day for these children.

The studies with growth hormones showing maximum improvement in adult height have been where growth hormone has been used continuously for long duration ranging from 3 to 10 yrs [8,9,14].

In a long term study by Toumba et al. [14] there was a concurrent increase in weight, BMI also and marginal improvement in the lipid profile. They also reported greatest increment in height was achieved by the onset of puberty, the shorter individuals showed a better response to GH treatment, and they also reported better outcome in boys than girls but it was not statistically significant. Interestingly their study did not show any positive correlation between the height gain and the age of initiation of treatment, as opposed to the studies mentioned above.

One of the drawbacks of our study was the cumulative data for 1 year was limited, much of the dropouts due to financial constraints on the parents. Larger studies need to be done with longer follow up to assess the long term benefits of growth hormone in Indian children with RSS and SGA.

## Conclusion

In our conclusion, our study conforms to the results of others studies, indicating benefit of growth hormone therapy in short stature in children with RSS and SGA.

This is the first Indian study of children with RSS and SGA with statistically significant height benefits with growth hormone therapy resulting in improvement in predicted adult height. Further studies need to be directed to evaluate the whole spectrum of growth hormone effects on final adult height and establishing the safety profile.

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