ORIGINAL ARTICLE



A retrospective analysis of growth hormone therapy in children with Schaaf-Yang syndrome

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Abstract

Short stature is a common phenotype in children with Schaaf-Yang syndrome (SYS). Prader-Willi syndrome (PWS) and SYS share several phenotypic features including short stature, muscular hypotonia and developmental delay/intellectual disability. Evidence exists that similar to PWS, growth hormone (GH) deficiency may also be a feature of SYS. Recombinant human GH (rhGH) therapy has been approved for PWS, but the effects of rhGH therapy in individuals with SYS have not yet been documented. This retrospective, questionnaire-based study analyzes the prevalence of rhGH therapy in children with SYS, the effects of rhGH therapy on anthropometric measures, and parental perception of the treatment. Twenty-six individuals with SYS were sent a clinical questionnaire and a request for growth charts. We found a significant increase in height z-score ($p^* = 0.04$) as well as a significant decrease in body mass index 6 months after rhGH therapy initiation ($p^* = 0.04$). Furthermore, height z-scores of the treated group (mean z-score = -1.00) were significantly higher than those of the untreated group (mean z-score = -3.36, p = 0.01) at time of enrollment. All parents reported an increase in muscle strength and endurance, and several families noted beneficial effects such as improved cognition and motor development.

KEYWORDS

clinical genetics, neurodevelopmental disorder, pediatric endocrinology, rare disease

1 INTRODUCTION

Schaaf-Yang syndrome (SYS, OMIM # 615547) is a rare autosomal-dominant, imprinted genetic disorder, caused by truncating variants of the MAGEL2 gene. MAGEL2 is located within the Prader-Willi critical region on chromosome 15. While Prader-Willi syndrome (PWS, OMIM #176270, PWS) is typically caused by the deletion of paternal chromosome 15q11-q13 or maternal uniparental disomy of chromosome 15, SYS is caused by truncating point mutations of the paternal copy of MAGEL2, one of the protein-coding genes within the PWS critical region.

SYS was initially termed "Prader-Willi like syndrome" due to an overlap in the phenotype between SYS and PWS.¹ This phenotypic overlap includes hypotonia, developmental delay (DD)/intellectual disability (ID) and short stature. However, as the cohort of SYS increased, it became more apparent that the phenotypes of the two syndromes were clinically distinct: The prevalence of autism spectrum disorder (ASD) and joint contractures is significantly higher in SYS in comparison to PWS.²⁻⁵ Furthermore, profound hyperphagia and morbid obesity appear to be less prevalent in $SYS^{5,6}$ or may manifest later in life.7

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The MAGEL2 gene encodes for a regulator protein of E3 ubiquitin ligase and affects retromer endosomal protein recycling.⁸ It is highly expressed in the central nervous system, especially within the hypothalamus.^{9,10} This has led to endocrinological assessments of individuals with SYS, indicating that similarly to PWS, growth hormone (GH) deficiency is a feature of SYS.¹¹

For PWS, recombinant-human growth hormone (rhGH) therapy has been FDA-approved since 2000. It has been shown that in PWS, rhGH therapy not only significantly increases body height, but also improves body composition by decreasing fat mass and increasing lean body mass.¹²⁻¹⁶ More recent studies have shown benefits regarding mental and motor development,^{17,18} as well as an improvement in overall cognition.¹⁹ Adverse events reported during rhGH therapy in PWS include worsening of sleep apnea, respiratory tract infections and peripheral oedema.^{15,20,21} rhGH therapy is contraindicated in patients with PWS who are "severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment."22

The strong positive effect of rhGH therapy in individuals with PWS poses the question whether rhGH therapy may be a suitable treatment for individuals with SYS. Apart from one case study,²³ rhGH therapy in SYS has not yet been reported in the literature.

Here, we present the effects of rhGH therapy in 14 individuals with SYS and compare them to 12 untreated individuals. Our study provides evidence of a positive effect of rhGH therapy in SYS regarding body height and body composition, as well as subjective improvements of motor ability and cognition.

2 SUBJECTS AND METHODS

2.1 Subjects

To this date, 136 individuals with nonsense and frameshift mutations in MAGEL2 have been included in our SYS registry. From this cohort, all eligible patients were contacted by the research coordinator via email to inform them of the study. Additionally, the research study was announced in the closed Facebook group for SYS (https://www. facebook.com/groups/SchaafYangFamilyGroup/). Inclusion criterion was a previously identified truncating variant in MAGEL2. There were no exclusion criteria. Families were sent a consent form, a clinical questionnaire (MAGEL2 Growth Hormone Fillable Questionnaire, Supporting Information), and were asked for growth charts of the affected patients. The study was approved by the Institutional Review Board at Baylor College of Medicine.

2.2 Methods

Information on muscle strength, endurance and satisfaction was measured on a 5-level Likert scale. Height and body mass index (BMI) z-scores (defined as the SD from average height or BMI compared to children of the same sex and age) were calculated using WHO/CDC data and the PedZ calculator (https://www.pedz.de/en/ bmi.html).

Since height, weight, and BMI were collected at various time points within the treated group, we estimated the values at 90 and 180 days after treatment start. These values were calculated using linear interpolation within the R zoo package v1.8-8. The predictor was defined as 0, 90, or 180 days following treatment (categorical).

Data were approximately normally distributed for change in height and BMI z-scores. Therefore, to detect a difference in height or BMI z-scores based on the time since treatment start, we conducted a repeated measures analysis of variance (ANOVA) with a Greenhouse-Geisser correction. We then performed post-hoc paired t tests with a Bonferroni correction to assess pairwise statistical differences.

Anthropometric measures at birth were compared to the general population using the one-sample Wilcoxon test. In order to compare anthropometric measurements as well as sex and age distribution between the treated and untreated groups, we performed Mann-Whitney U tests. Effect size of Mann-Whitney U tests were calculated using the R rcompanion package v2.3.27 and reported according to Fritz et al.²⁴

Statistical significance was determined as p < 0.05. All statistical analyses were carried out using R v4.0.4.

RESULTS 3

Prevalence of GH Therapy 3.1

In this sample, 14 of 26 individuals with SYS (54%) were on rhGH therapy. There were no significant differences between the two groups regarding age and sex distribution (Figure 1A,B). However, males were overrepresented in the treatment group (64%, 9 out of 14) and underrepresented in the untreated group (33%, 4 out of 12). The clinical phenotype between the two groups was also similar (Figure 1C). Detailed growth charts were available for 16 of the children (11 treated, 5 untreated, Figures 2 and S1).

The average age of rhGH therapy initiation was 2.72 years (range 0.42-8.0 years) and the average treatment duration was 3.07 years (range 0.38-15.78 years). No patient had to interrupt or discontinue rhGH therapy. The average dose administered was 0.23 mg rhGH/kg bodyweight/week (SD 0.09), similar to the recommended dose for PWS which is 0.24 mg rhGH/kg bodyweight/week.²²

3.2 Pre-treatment assessment

We were able to collect information from 16 patients (13 treated, 3 untreated) on endocrinological assessments prior to treatment (Table 1).

IGF-1 level measurement is the most common test (75%) prior to treatment in our sample, followed by IGF-BP3 level measurement in 44% of all individuals. Stimulation tests (either with clonidine [STH] or arginine) were performed in only 25% of all kids. Bone mineral density



FIGURE 1 Comparison of the treated and untreated group. (A) Age in years of the untreated group and the treated group. (B) Composition of the untreated and the treated group by sex. (C) Prevalence of conditions associated with Schaaf-Yang syndrome (SYS) phenotype in the treated and untreated group [Colour figure can be viewed at wileyonlinelibrary.com]



FIGURE 2 Growth progression of individuals with Schaaf-Yang syndrome: All available growth charts, plotted with variable x axes for better readability [Colour figure can be viewed at wileyonlinelibrary.com]

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	Patients																	
	rhGH tr	satment												w/o trea	atment			
Diagnostic tests	111	112	114	115	116	117	118	119	120	121	122	123	124	211	214	216	N/n	%
IGF-1	×	×	×	×	×	×	×		×	×		×		×	×		12/16	75
IGF3-BP	×						×		×			×		×	×	×	7/16	44
Stimulation test	×	×						×						×			4/16	25
Bone mineral density		×					×						×				3/16	19
ALS							×										1/16	9
No test											×						1/16	9
Note: Stimulation test perfo Abbreviations: ALS, acid-lab	rmed eith. ile subuni	er with cloi test; rhGł	H, recombi	H) or argin inant hum	iine. an GH.													

Diagnostic tests run prior to rhGH treatment initiation

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TABI

measurements and acid-labile subunit tests are also less common. Only one patient has reported not to have had a pre-treatment assessment. rhGH therapy was justified with his short stature alone.

3.3 Growth progression of individuals with SYS

In this sample, the children with SYS were born within the normal height, weight and BMI range (one-sample Wilcoxon tests; p = 0.87, p = 0.06, p = 0.08 respectively). There were no significant differences in height z-score between the treated and untreated group in this study at birth (p = 0.71, Figure 3A). Only 4 (2 in the untreated group and 2 in the treated group) out of 26 individuals in total had a height z-score below -2 at birth, meeting the CDC criterion for short stature (15%).

At an age of 6 months, 8 of the 16 individuals with detailed growth charts (50%) had already had a height z-score below -2. At an age of 3 years, all 16 individuals (100%) had a height z-score below -2 (Figure S2).

Similarly, at time of enrollment in this study, only 2 out of the 12 untreated individuals had a height z-score above -2. The other 10 untreated children (83%) met the CDC criterion for short stature.

3.4 Effects of rhGH therapy on height

Comparing height z-scores of all treated individuals to all untreated individuals at time of enrollment in this study, there was a significant difference in height z-scores (Mann-Whitney U test, p = 0.01) (Figure 3B and Table 2). The effect size r was 0.51, indicating that rhGH treatment had a large effect on height z-score.

Eight of the 14 patients on rhGH treatment had sufficient data for a more detailed analysis of the effect of rhGH on height z-score during the first 6 months of treatment. The mean height z-score at the start of treatment initiation was -2.6 and increased to -2.1 and -1.7 after three and 6 months of treatment respectively. A repeated measures ANOVA with Greenhouse-Geisser correction determined that height z-score differences between time points were statistically significant (F = 9.97, p = 0.02). Post-hoc paired t tests with a Bonferroni correction further confirmed the significant increase in height z-score over the timespan of 6 months ($p^* = 0.04$) as well as a significant increase from month 3 to month 6 ($p^* = 0.02$). The increase in height z-score from treatment start to 3 months was not significant $(p^* = 0.10)$ (Figure 3C,D).

3.5 Effects of rhGH therapy on body composition

BMI z-scores were used as a surrogate parameter of body composition. Seven of the 14 individuals on rhGH treatment had sufficient data for a more detailed analysis of the effect of rhGH on BMI z-score during the first 6 months of treatment. The mean BMI z-score at the start of treatment initiation was 1.3 and decreased to 0.9 and 0.7 after

FIGURE 3 Height z-scores of the treated and untreated group. (A) Height z-scores of both groups at birth. (B) Height z-scores of both groups at time of enrollment in this study. (C) Absolute height zscore values of the treated group at treatment start, after 3 months of treatment and after 6 months of treatment. (D) Change in height z-scores of the treated group 3 and 6 months after treatment start [Colour figure can be viewed at wileyonlinelibrary.com]



TABLE 2 Anthropometric measures of the treated and untreated group

	Start of treatment	After 3 months	After 6 months	Birth (untreated)	Birth (treated)	Time of enrollment (untreated)	Time of enrollment (treated)
Height z-score	-2.6 (1.0) ^a	-2.1 (0.1) ^a	-1.7 (1.0) ^a	-0.3 (1.9) ^b	-0.4 (1.7) ^c	-3.4 (1.8) ^d	-1.0 (2.1) ^c
Weight z-score	-0.6 (1.1) ^e	-0.7 (1.2) ^e	-0.6 (1.4) ^e	-1.0 (1.4) ^d	-0.5 (1.9) ^c	-1.4 (1.1) ^d	-0.4 (1.9) ^c
BMI z-score	1.3 (0.9) ^e	0.9 (1.0) ^e	0.7 (1.1) ^e	-1.9 (1.5) ^b	-0.6 (2.2) ^c	1.0 (2.1) ^d	-0.5 (1.5) ^c

Note: Values presented are mean and SD. ^a8 out of 14 patients with sufficient data.

^b8 out of 12 patients with sufficient data. ^c14 out of 14 patients with sufficient data.

^d12 out of 12 patients with sufficient data.

^e7 out of 14 patients with sufficient data.

three and 6 months of treatment respectively. The statistical analysis was identical to the analysis performed for height z-score. Here, BMI z-score change was also significant (repeated measures ANOVA with Greenhouse–Geisser correction: F = 10.71, p = 0.01). Post-hoc paired t tests were only significant for the full observation period of

6 months ($p^* = 0.04$) (Figure 4C,D). Likewise, weight for stature (WFS) z-scores decreased from 1.0 to 0.6 and 0.2 after three and 6 months of treatment respectively (Figure S3).

However, there were no significant differences in BMI zscores between the treated and untreated group neither at birth



FIGURE 4 Body mass index (BMI) z-scores of the treated and untreated group. (A): BMI z-scores of both groups at birth. (B): BMI z-scores of both groups at time of enrollment in this study. (C): Absolute BMI z-scores of the treated group at treatment start, after 3 months of treatment and after 6 months of treatment. (D): Change in BMI z-scores of the treated group 3 and 6 months after treatment start [Colour figure can be viewed at wileyonlinelibrary.com]

nor at time of enrollment (Figure 4A,B). Furthermore, there was no significant difference in weight z-score change of the treated group between time points (repeated measures ANOVA with Greenhouse–Geisser correction: F = 0.13, p = 0.73, Figure S4).

3.6 | Subjective effects of rhGH therapy

Parental perception of changes after the onset of treatment was unanimously positive: All families noted either an increase (seven patients) or strong increase (six patients) in muscle strength. For endurance, feedback was exactly the same. Overall, general satisfaction with the treatment was high, with eight families stating they were very satisfied, three families stating they were satisfied and two families being neutral (Figure 5). Additional reported benefits were improved cognitive and social skills (six patients) and improved motor development (five patients).

3.7 | Adverse events of rhGH therapy

During the time-span of rhGH treatment, worsening of sleep apnoea in one individual and worsening of scoliosis/kyphosis in further two individuals was reported. These events did not require any intervention or alteration of rhGH treatment. In both cases of scoliosis, treatment start coincided with local *Covid19* restrictions, and physical therapy and new back braces were no longer accessible for both patients.

4 | DISCUSSION

4.1 | GH deficiency is the likely cause for short stature in children with SYS

In this population of individuals with SYS, children were born within normal height z-score range, which is, in fact, unsurprising, because



FIGURE 5 Perception of families. (A) Answers to the question "How has your child's muscle strength changed after Growth Hormone Therapy?" (B) Answers to the question "How has your child's stamina/endurance changed after Growth Hormone Therapy?" (C) Answers to the question "How satisfied are you with the Growth Hormone Treatment?"

fetal growth is considered to be independent of pituitary GH secretion.²⁵ However, the onset of growth retardation after birth was rapid and severe: At 6 months of age, 50% of the infants with detailed growth charts had already had a height z-score below -2. This is similar to observations made in infants with congenital GH deficiency, who have a decrease in height z-score by -1.6 in the first 6 months of life²⁶ and further strengthens the assumption that GH deficiency is responsible for the short stature in children with SYS.

4.2 rhGH treatment significantly improves Height

In our sample, height z-score increased on average by 0.47 after the first 3 months and by 0.85 after the first 6 months of rhGH therapy. This effect is in line with studies on PWS noting an increase in height

z-score of 0.8 after 6 months of treatment,¹² and an increase in height z-score of $+1.1^{20}$ or +1.5 after 1 year of treatment.

4.3 rhGH treatment may improve body composition

We also found that BMI z-score decreased on average by 0.43 after the first 3 months and by 0.64 after the first 6 months of rhGH therapy. This is similar to previous studies in PWS, which have shown that rhGH therapy decreases the BMI z-score, decreases body fat percentage, and increases lean body mass.^{12–16,27} In our sample, this decrease in BMI is partially due to the increase in height. To further investigate if the BMI decrease can also be partially attributed to change in body composition, we investigated WFS z-scores: Here, we were also able

to show a decrease by 0.4 after the first 3 months and by 0.8 after the first 6 months of rhGH therapy. The observed decrease in BMI z-score with a similar decrease in WFS z-scores and additional individual parental reports suggest that rhGH therapy has a comparable effect on body composition in children with SYS. On the other hand, the effect may not be very pronounced, because we could not find statistical differences in BMI z-score between the treated and the untreated group.

In the future, lean body mass should be evaluated directly using dual-energy X-ray absorptiometry scans. This will give a more accurate insight into the changes of body composition than the surrogate parameter BMI.

4.4 | Adverse events and beneficial side effects

In our sample, adverse events were not severe enough for rhGH treatment to be interrupted or discontinued. Furthermore, sleep apnea and scoliosis/kyphosis are both common features of SYS.^{3,7} Our study was not designed and does not have the power to attribute these events to the rhGh treatment. Worsening of sleep apnea has also been reported in the context of rhGH treatment for PWS,^{20,21,28} which may indicate that the same precautions as for PWS should be taken when prescribing rhGH to SYS patients.

Beneficial side effects reported by parents in our study were improved motor development and improved social skills. The impact of rhGH therapy on ASD phenotypic severity and developmental milestones should be assessed more systematically in the future.

4.5 | Time of treatment start

For PWS, recommendations are to start rhGH therapy as early as between 6 and 12 months of age,²⁹ and definitely before the onset of obesity, which often begins at 2 years of age.³⁰ As rhGH has been shown to improve motor developmental and cognitive skills¹⁷⁻¹⁹ and these benefits have also been noted by parents of children with SYS, there are indications that an early treatment start may not only stop growth retardation, but may also be beneficial for the child's development.

4.6 | Limitations and strengths

Our study must be considered in the light of some limitations. First, this study is a retrospective, questionnaire-based analysis. However, we were able to demonstrate that there were no significant differences regarding age and sex distribution between the treated and the untreated group and that the phenotypic severity was similar, which suggests that selection bias due to demographic characteristics was not likely to play an important role. Furthermore, differences in anthropomorphic measurements at birth were non-significant. However, the proportion of individuals with short stature reported here (100% of individuals at 3 years of age) is significantly larger than the 56% previously reported.¹¹ We expect a recruitment bias favoring those families whose children have been diagnosed with short stature, as this study may appear to be more relevant to them, which might explain the discrepancy. Likewise, while we contacted all families of children with SYS in our registry, we also expect a recruitment bias favoring those families whose children received rhGH for much the same reason.

Furthermore, rhGH therapy is an invasive and time-consuming treatment requiring daily subcutaneous injections. Therefore, it is possible that parents who follow through with this treatment are convinced of its beneficial effects and have a high outcome expectation. Thus, placebo effects may be more pronounced and could exaggerate the effect of rhGH therapy. Finally, as this was a retrospective study, recall biases might also enhance effects of rhGH. However, the anthropometric measurements have been taken before enrollment in this study and should remain unaffected by recall or observer biases.

Strengths of this study include the similar distribution of the treated and untreated group, which allows for a direct comparison, the large study population size, and the detailed growth information we are able to present.

5 | CONCLUSION

Our findings suggest that rhGH therapy should be considered as a treatment for SYS. In this cohort, it led to an increase of body height and parental reports suggested an improvement of endurance and muscle strength. Furthermore, several families also noted additional beneficial side effects such as improved cognition and motor development. These data pave the way for a prospective clinical trial of rhGH therapy for individuals with SYS.

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CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

Nils R. Hebach and Pilar Caro: Performed the study and analyzed the data. Nils R. Hebach: Designed the questionnaires, generated figures and wrote the initial version of the manuscript. Pilar Caro: Coordinated the study and participated in designing the questionnaires. Bailey A. Martin-Giacalone: Performed the statistical analyses and gave feedback on study endpoints. Philip J. Lupo: Oversaw the statistical analyses. Felix Marbach: Gave feedback on overall study design and participated in the questionnaire design. Daniela Choukair: Gave

feedback on the questionnaire design. **Christian Patrick Schaaf:** Conceived the study, supervised the study and acquired funding. All authors reviewed, edited and approve of the manuscript.

PROVENANCE AND PEER REVIEW

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data are available upon reasonable request. Detailed data from clinical questionnaires as well as growth charts analysed during the current study are available from the corresponding author.

ETHICS STATEMENT

This study was approved by the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals, H-34578. Informed consent was obtained from all individuals and their guardians.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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