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Original Article

Growth response and genetic factors in SGA children: a study on rGH therapy and copy number variations

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ABSTRACT

Objective: Small for gestational age (SGA) is a heterogeneous condition influenced by fetal, placental, maternal, and genetic factors. While most SGA children experience catch-up growth within the first two years, up to 10-15% remain short-statured and may require growth hormone (GH) therapy. This study evaluated the clinical characteristics, genetic factors, and responses to recombinant GH (rGH) therapy in non-syndromic SGA children with persistent short stature.

Material and Methods: We retrospectively analyzed 36 non-syndromic short-statured children born SGA who were evaluated in a tertiary center. Genetic testing, including karyotyping and microarray analysis for copy number variations (CNVs), was performed. Growth response to rGH therapy was assessed in 19 patients over a three-year period.

Results: Among the 19 patients receiving rGH therapy, the mean height SDS improved from -3.04±0.58 at baseline to -2.07±0.67 after three years, with an average gain of 0.97 SDS. CNVs were identified in 6 patients (16.66%), with several pathogenic or likely pathogenic variants, including deletions and duplications in regions associated with growth and developmental disorders.

Conclusion: A significant proportion of non-syndromic SGA children with persistent short stature exhibit CNVs, underscoring the genetic complexity of this condition. rGH therapy effectively improves growth outcomes, but individual responses vary. These findings highlight the need for routine genetic screening and personalized treatment strategies to optimize care for SGA children.

Keywords: Copy number variations (CNVs), Small for gestational age, Short stature, Recombinant growth hormone (rGH)

INTRODUCTION

Small for gestational age (SGA) is defined as a condition in which the birth weight of a newborn falls below -2 standard deviation scores (SDS) relative to the reference population for the corresponding gestational age (1,2). The etiology of intrauterin growth restriction is heterogeneous, primarily associated with fetal-placental and maternal factors, with genetic factors also playing a significant role. Although there are various pathophysiological factors that can cause intrauterine growth restriction, being SGA does not necessarily indicate that a fetus is growth restricted. Some SGA fetuses may simply be constitutionally small, not necessarily growth restricted (3). While approximately 85-90% of children born SGA exhibit catch-up growth and reach the growth percentiles of their peers within the first two years of life, the remaining 10-15% experience persistent short stature (4,5). In diagnosing a child with short stature, clinicians should begin with a detailed medical history and physical examination. This is followed by targeted laboratory tests, imaging, and growth hormone (GH) evaluation. If a congenital syndrome is suspected, referral to a geneticist is often necessary. Chromosomal abnormalities, such as monosomies and trisomies, skeletal dysplasias, and malformation syndromes like Achondroplasia, as well as several single-gene syndromes, including Silver-Russell syndrome, Cornelia de Lange syndrome, 3M syndrome, and Mulibrey Nanism, are well-established causes associated with SGA and short stature (6,7). Karyotype analysis is typically the initial step in genetic testing. In cases where a genetic etiology is suspected, the choice of molecular diagnostic methods such as single-

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gene analysis, gene panels, or array-based analysis varies depending on the suspected underlying cause. Furthermore, children born SGA are at an increased risk of developing long-term metabolic and cardiovascular comorbidities (8). Identifying the probable genetic causes in this patient population may provide valuable insights into assessing potential long-term health risks. Recombinant growth hormone (rGH) therapy has been approved for treating short stature in children born small for gestational age (SGA). In most countries, treatment can begin at age four and typically continues until puberty is complete. Long-term GH therapy (beyond three years) has been shown to result in sustained height improvement. Initially, there is a significant boost in growth rate during the first year of the treatment, followed by a steady and consistent growth pattern over time (9,10). Demonstrating genetic etiologies in this patient group can serve to predict treatment response to rGH therapy, also. In this study, we aimed to evaluate the clinical characteristics and responses to rGH treatment and to identify the genetic causes underlying SGA in our patient cohort.

MATERIALS and METHODS

Patient selection and study design

This study was designed as a retrospective analysis of patients under 18 years of age with a history of SGA who presented to Ankara Bilkent City Hospital with complaints of short stature. The patients born SGA who, despite being over two years of age, exhibited pathological short stature included into study. Data from the hospital system, including clinical, laboratory, and molecular results, as well as detailed medical histories, were reviewed and systematically evaluated by a research team consisting of pediatric endocrinologists and geneticists. A retrospective evaluation was conducted over a retrospective evaluation was conducted between March 2021 to March 2023.. After excluding patients with syndromic features, the remaining 36 patients with non-syndromic short stature and unknown etiology were included in the study.

GH treatment was initiated at a dose of 35 µg/kg/day in accordance with European Medicines Agency (EMA) guidelines. In the United States, initiation doses can be as high as 70 µg/kg/day according to Food and Drug Administration (FDA) recommendations (1,11). Patients were monitored every three months through routine clinical assessments, including measurements of height, weight, body mass index (BMI), growth velocity, and serum IGF-1 levels. Treatment response was assessed individually due to the wide variability in outcomes among SGA patients, and GH doses were adjusted accordingly.

Genetic analysis

For patients in whom clinical evaluation does not identify a pathology explaining short stature, karyotype analysis is routinely performed as the initial genetic test to assess chromosomal number and structure. Genetic analyses were performed using the Illumina Infinium CytoSNP-850K v1.2 BeadChip platform (Illumina, San Diego, CA, USA). DNA samples were prepared according to the manufacturer's protocol and genotyped accordingly. The raw data were analyzed using the BlueFuse Multi software (Illumina, Cambridge, UK). Copy number variation (CNV) analysis was performed based on log R ratio and B-allele frequency values, using the GRCh37/hg19 human genome assembly as reference. Identified CNVs were interpreted with reference to international databases (DGV, DECIPHER, ClinGen, ClinVar) and classified according to the 2020 ACMG guidelines for CNV interpretation. In cases where further genetic testing is indicated based on phenotypic and clinical evaluation, access to advanced genetic techniques such as gene panels, whole exome sequencing (WES), and methylation analyses is limited. Consequently, third-line genetic testing could not be performed.

Statistical analysis

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences, version 25.0 (SPSS Inc., Armonk, NY, IBM Corp., USA. The data were expressed as mean and standard deviation or as median, minimum and maximum, categorical variables were presented as frequencies and percentages.

RESULTS

Patient characteristics: This study included 36 patients with non-syndromic short stature, a history of SGA, and unknown etiology. Eighteen patients (50%) were female. The mean age at presentation was 6.05±3.81 years. The cohort exhibited a mean birth weight SDS of -3.63±1.6 and a mean gestational age of 37.25±3.06 weeks. Thirteen patients (36%) had a history of preterm born. At the initial evaluation, the mean height SDS, weight SDS, and BMI SDS were -3.19±0.69, -2.87±1.10 and -1.08±1.19 respectively. The demographic and clinical characteristics of the study cohort at initial evaluation are summarized in Table I.

Table I: Patient characteristics at initial evaluation

	n	mean±SD	min-max
Gestational age, weeks	36	37.25±3.065	29-42
Birth weight, grams	36	1784.81±500.41	800-2480
Brith weight SDS	36	-3.63±1.60	-10.88-(-2.05)
Age, years	36	6.05±3.81	1.13-13.91
Heigth SDS	36	-3.19±0.69	-4.78-(-2.17)
Weigth SDS	36	-2.87±1.10	-5.91-(-.84)
BMI SDS	36	-1.08±1.19	-3.60-1.72
IGF-1 SDS	29	-1.04±1.74	-4.21-3.14
IGFBP-3 SDS	28	0.63±0.92	0-.87-2.90

Table II: The distribution of patients with CNVs.

Patient ID	Genetic Findings	Condition/Notes
1	1q24.3_1q25.2 5.3 Mb heterozygous deletion. (GRCh38) 1q24.3_ 1q25.2(172529076_1778005552)x1	Parental array normal. May be associated with 1q24.3 microdeletion syndrome which is a rare condition characterized with growth deficiency, varying intellectual disability, and skeletal abnormalities Due to the large size of the deletion, it is likely to have clinical significance.
2	2p14-16.1 7.4 Mb deletion. (GRCh38) 2p16.1-p14(57715943_65128610)x1	Parental array normal. May be associated with 2p15p16.1 microdeletion syndrome which is characterized by growth disorders, microcephaly, and intellectual disability.
3	4p16.3-p16.1; 7.2 Mb deletion (GRCh38) 16p13.11p12.3(14820784_16777698)	Associated with Wolf-Hirschhorn syndrome which is characterized by growth disorders,"Greek warrior helmet" facies, microcephaly, seizure disorder and intellectual disability .
4	16p13.11p12.3 1.8 Mb heterozygous deletion	The 16p13.11 microdeletion syndrome is reported with a wide spectrum of neurodevelopmental disorders, including schizophrenia, autism, intellectual disability, epilepsy, behavioral disorders, and mild microcephaly. However there are limited number of patients reported and it is not commonly associated with SGA. To determine its pathogenicity, parental analysis has been planned.
5	11p15; 742 kb heterozygous duplication (GRCh38) 11p15.5p15.4(2405754_3148158)x3	Associated with arrhythmia genes, patient has arrhythmia, mother also carries the same variant with arrhythmia and short stature; possibly significant.
6	5q13.1 771 kb heterozygous duplication	Possibly significant variation. Lack of parental analysis.

Table III: Outcomes of recombinant Growth Hormone treatment

	Start of r-GH treatment (n:19)	1st year of treatment (n:19)	2nd year of treatment (n:16)	3rd year of treatment (n:6)
Heigth SDS	-3.04±0.58	-2.53±0.66	-2.26±0.66	-2.07±0.67
ΔSDS of Heigth from the r-GH initiation	-	0.50±0.30	0.76±0.43	1.28±0.51
r-GH dosage, mcg/kg/day	34.72±9.11	34.50±7.15	34.75±8.55	40.08±10.66
IGF-1SDS		0.62±2.25	0.66±1.53	1.36±1.98

Genetic results: Microarray analysis revealed copy number variations (deletions/duplications) in six patients (16.66%). Microarray analysis did not reveal any CNVs in 23 patients (63.88%) with normal results. Genetic evaluation was incomplete in seven patients (19.44%) who did not undergo microarray analysis. The distribution of patients with CNVs is summarized in Table II.

Outcomes of recombinant growth hormone treatment: A total of 19 patients received recombinant growth hormone (rGH) therapy. The age at treatment initiation ranged from 3.29 to 14.03 years, with a mean of 8.34±3.20 years. At baseline, the mean height standard deviation score (SDS) was -3.04 ±0.58 (range: -4.05 to -2.14). The detailed outcomes of GH therapy, including growth response and related parameters, are presented in Table III. Additionally, height changes over the years in patients who initiated rGH treatment are illustrated by gender in Figure 1.

DISCUSSION

This study highlights the effectiveness of rGH therapy in promoting height gain among short statured children born SGA. Additionally, CNVs were identified in one-sixth of the cohort, a significantly higher frequency than in the general population emphasizing the heterogeneity of SGA-related short stature, the influence of genetic factors, and the need for further research to better understand the underlying mechanisms and optimize treatment approaches.

The efficacy of rGH therapy in our cohort aligns with previous reports and supports its role as a cornerstone treatment for SGA-related short stature. Among the 19 patients who received rGH, we observed a mean height gain of 0.50±0.30 SDS after the first year, increasing to 0.97 SDS by the third year. This response is comparable to meta-analyses, such as Maiorana et al.'s (12), which reported a mean height gain of 0.9–1.5 SDS in rGH-treated SGA children over 2–3 years, and to Arroyo-Ruiz et al. (13), who noted a dose-dependent height increase of 1.3 SDS after three years. The initial height SDS in our cohort (-3.04±0.58) improved to -2.07±0.67 by year-3, though patients remained below population norms, consistent with the persistent growth deficit often observed in SGA populations (1). Several factors may influence this response. The mean age at rGH initiation (8.34±3.20 years) was relatively late compared to optimal recommendations of 2–4 years, potentially limiting total height gain (14,15). Studies like de Bruin and Dauber (16) suggest that earlier intervention enhances outcomes, a trend supported by our observation of a negative correlation

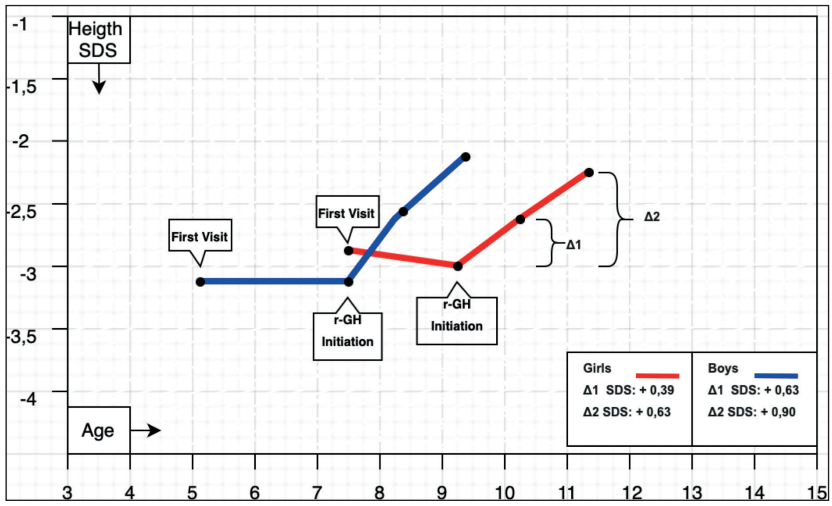

Figure 1: Height changes over the years in patients who started r-GH treatment are illustrated by gender.

between age at treatment start and height gain. Additionally, the mean rGH dose escalated from 34.72±9.11 µg/kg/day to 40.08±10.68 µg/kg/day by year-3, reflecting adjustments to maintain growth velocity, yet individual responses varied widely (e.g., IGF-1 SDS ranged from 0.62±2.25 to 1.36± 1.98). Particularly, GH therapy outcomes can be influenced by GH-IGF-1 resistance, which has been observed in some SGA children. This variability echoes findings by Jensen et al.(17), who noted heterogeneous IGF-1 responses despite consistent height gains, underscoring the need for personalized dosing strategies (13). Understanding the extent of GH-IGF-1 resistance in this population is crucial for optimizing treatment protocols and ensuring sustained growth benefits.

A key observation from this study is the notable prevalence of genetic abnormalities in our cohort. CNVs were identified in 16.66% (6/36) of patients who underwent microarray analysis, aligning with literature estimates of 10–25% prevalence of CNVs in SGA-related short stature (18-20). For instance, Homma et al. (21) identified CNVs in 14% (32/229) of patients with syndromic short stature of unknown etiology. When combined with data from other studies, the overall prevalence remains consistent at 13% (87/671). The specific CNVs identified in our cohort highlight their clinical significance. For example, Patient-1's 5.3 Mb deletion at 1q24.3-q25.2, potentially linked to 1q24.3 microdeletion syndrome, includes non-coding RNAs (DNM3OS, miR-214, and miR-199A2) implicated in skeletal development (22). Similarly, Patient-2's 7.4 Mb deletion at 2p15-p16.1, associated with 2p15p16.1 microdeletion syndrome, involves genes (USP34 and XPO1) tied to intrauterine growth restriction (IUGR). Although the exact mechanisms remain unclear, these genes are believed to influence cellular growth and development, with XPO1 potentially exerting a more dominant effect (23). Patient-3's 7.2 Mb deletion at 4p16.3-p16.1 aligns with Wolf-Hirschhorn syndrome, a well-documented cause of intrauterine growth retardation and growth failure (24). Patient-4's 1.8 Mb deletion on chromosome 16, associated with 16p13.11 microdeletion syndrome which is characterized by a wide spectrum of neurodevelopmental disorders, intellectual disability, and mild microcephaly. However, it is rarely associated with small for SGA or short stature. Only a limited number of cases have been reported in the literature (25). These findings highlight the diversity of genetic mechanisms underlying SGA and reinforce the importance of microarray analysis as a firsttier diagnostic tool in this population. However, 63.88% (23/36) of patients had normal microarray results, and 19.44% (7/36) lacked microarray and further data, suggesting that additional genetic or epigenetic factors remain undetected. This is consistent with the literature, where a significant proportion of SGA cases remain idiopathic despite standard genetic testing (7). Advanced techniques such as whole exome sequencing (WES) or methylation analysis could uncover underlying single gene mutations, imprinting defects, or polygenic contributions, as demonstrated in studies, where WES identified pathogenic variants in 25–47% of SGA patients with persistent short stature (26,27). Our findings thus advocate for a tiered genetic testing approach, progressing from karyotyping and microarray to WES when initial results are uninformative.

CONCLUSION

This study confirms the effectiveness of rGH therapy in increasing height in SGA-related short stature, with an average gain of 0.97 SDS over three years. Genetic factors played a significant role in one-sixth of cases, with CNVs emerging as a key cause, though most cases remain unexplained. This highlights the need for more advanced genetic testing. Given that chromosomal disorders are a major cause of SGA, it is essential to exclude chromosomal copy number variations, particularly before comprehensive gene panel testing or in settings where such testing is unavailable. These findings underscore the importance of targeted treatment in this diverse group while also supporting routine genetic screening for SGA patients with persistent short stature and personalized rGH treatments to account for individual differences.

Limitations

The small sample size (n=36, with only 19 on rGH) and retrospective design restrict statistical power and generalizability. The incomplete genetic evaluation in 19.44% (7/36) of patients highlights logistical challenges in comprehensive testing, while the lack of longterm follow-up to adult height precludes definitive conclusions on rGH efficacy. Additionally, the absence of epigenetic or WES data leaves potential etiologies unexplored, particularly in the 63.88% with normal microarray results. Future research should prioritize larger, prospective studies integrating WES and methylation analysis to fully elucidate SGA's genetic background.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the ethics committee of Ankara City Hospital (E2-21-283, 24.03.2021).

Contribution of the authors

Özer E: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar, Providing personnel, environment, financial support tools that are necessary for the study, Taking responsibility for biological materials and referred patients. ***Kılıç E:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Kocaay P:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Providing personnel, environment, financial support tools that are necessary for the study, Taking responsibility for biological materials and referred patients. ***Tepe D:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study. ***Altan M:*** Planning methodology to reach the conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Büyükyılmaz G:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Providing personnel, environment, financial support tools that are necessary for the study, Taking responsibility for biological materials and referred patients. ***Kılınç Uğurlu A:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Providing personnel, environment, financial support tools that are necessary for the study, Taking responsibility for biological materials and referred patients. ***Toksoy Adıgüzel K:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Providing personnel, environment, financial support tools that are necessary for the study, Taking responsibility for biological materials and referred patients. ***Boyraz M:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***Gürbüz F:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar, Providing personnel, environment, financial support tools that are necessary for the study, Taking responsibility for biological materials and referred patients.

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Conflict of interest

The authors declare that there is no conflict of interest.

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