ORIGINAL PAPER

Submitted: 05.12.2022
Accepted: 11.03.2023
Early publication date: 12.06.2023

Endokrynologia Polska
DOI: 10.5603/EP.a2023.0042
ISSN 0423–104X, e-ISSN 2299–8306

The effects of 3-year growth hormone treatment and body composition in Polish patients with Silver-Russell syndrome

Anna Świąder-Leśniak[1], Dorota Jurkiewicz[2], Honorata Kołodziejczyk[1], Agata Kozłowska[3], Alicja Korpysz[3], Mieczysław Szalecki[4, 5], Krystyna Chrzanowska[2]

[1]*Laboratory of Anthropology, The Children's Memorial Health Institute, Warsaw, Poland*
[2]*Department of Medical Genetics, The Children's Memorial Health Institute, Warsaw, Poland*
[3]*Department of Endocrinology and Diabetology, The Children's Memorial Health Institute, Warsaw, Poland*
[4]*Department of Endocrinology and Diabetology, The Children's Memorial Health Institute, Warsaw, Poland*
[5]*Collegium Medicum, Jan Kochanowski University of Kielce, Kielce, Poland*

Abstract

Introduction: Silver-Russell syndrome (SRS) is characterized by clinical and genetic heterogeneity. SRS is the only disease entity associated with (epi)genetic abnormalities of 2 different chromosomes: 7 and 11. In SRS, the 2 most frequent molecular abnormalities are hypomethylation (loss of methylation) of region *H19/IGF2*:IG-DMR on chromosome 11p15.5 (11p15 LOM) and maternal uniparental disomy of chromosome 7 (upd(7)mat). Therapy with recombinant human growth hormone (rhGH) is implemented to increase body height in children with SRS. The effect of the administered rhGH on height, weight, body mass index (BMI), body composition, and height velocity in patients with SRS during 3 years of rhGH therapy was analysed.

Material and methods: 31 SRS patients (23 with 11p15 LOM, 8 with upd(7)mat) and 16 patients small for gestational age (SGA) as a control group were diagnosed and followed up in The Children's Memorial Health Institute. Patients were eligible for the 2 Polish rhGH treatment programmes [for patients with SGA or with growth hormone deficiency (GHD)]. Anthropometric parameters were collected in all patients. Body composition using bioelectrical impedance was measured in 13 SRS and 14 SGA patients.

Results: Height, weight, and weight for height (SDS) at baseline of rhGH therapy were lower in SRS patients than in the SGA control group: –3.3 ± 1.2 *vs*. -2.6 ± 06 ($p = 0.012$), –2.5 *vs*. -1.9 ($p = 0.037$), –1.7 *vs*. –1.1 ($p = 0.038$), respectively. Height SDS was increased from –3.3 ± 1.2 to –1.8 ± 1.0 and from –2.6 ± 0.6 to –1.3 ± 0.7 in the SRS and SGA groups, respectively. Patients with 11p15 LOM and upd(7)mat achieved similar height, 127.0 ± 15.7 *vs*. 128.9 ± 21.6 cm, and –2.0 ± 1.3 *vs*. –1.7 ± 1.0 SDS, respectively. Fat mass percentage decreased in SRS patients from 4.2% to 3.0% ($p < 0.05$) and in SGA patients from 7.6% to 6.6% ($p < 0.05$).

Conclusions: Growth hormone therapy has a positive influence on the growth of SRS patients. Regardless of molecular abnormality type (11p15 LOM *vs*. upd(7)mat), height velocity was similar in SRS patients during 3 years of rhGH therapy.

Key words: *Silver-Russell syndrome; genomic imprinting; uniparental disomy; growth hormone; body composition*

Introduction

Silver-Russell syndrome (SRS, OMIM #180860) is a rare congenital imprinting disorder associated with the loss of methylation in H19/IGF2:IG-DMR at chromosome 11p15.5 (11p15 LOM) or maternal uniparental disomy of chromosome 7 (upd(7)mat) found in 30–60% and in 5–10% of patients, respectively [1–4]. The molecular aetiology remains unknown in about 40% of patients with clinical symptoms of SRS [5]. In 2017, the first international consensus about the diagnosis and management of Silver-Russell syndrome was published [4]. Patients with SRS are characterized by intrauterine and postnatal growth retardation — their growth rate is slow, without catch-up [2, 4, 6, 7]. Children with SRS show a wide spectrum of minor dysmorphic and clinical features: triangular face, small mandible, irregular and crowded teeth, down-turned mouth, low-set and/or posteriorly rotated ears, clinodactyly of the fifth finger and/or syndactyly of 2 to 3 toes, delayed closure of the frontal fontanel, low muscle mass, excessive sweating in early childhood, or spinal deformity [2, 3, 8–13].

In many countries, the treatment of children with SRS using recombinant human growth hormone (rhGH) has been used for many years [14-16]. In Poland, rhGH is assigned for SRS patients within the framework of 2 national programs: for children with growth hormone deficiency (GHD), or for children born small for gestational age (SGA). The latter has

Anna Świąder-Leśniak, Laboratory of Anthropology, The Children's Memorial Health Institute, Warsaw, Poland;
e-mail: a.swiader-lesniak@ipczd.pl

been available since 2015. The effectiveness of rhGH therapy for increasing height (SDS) is well documented, i.e. in children with isolated growth hormone deficiency, idiopathic short stature, SGA, or patients with Noonan syndrome, Turner syndrome, and Prader-Willi syndrome [17-19].

Growth hormone treatment has several metabolic effects in children born SGA, such as a decrease in fat mass and an increase in lean body mass [20]. Similar effects were observed in patients with GHD and in patients born SGA [21, 22].

This study aimed to analyse the effect of the administered rhGH on anthropometric parameters and body composition, especially with respect to molecular abnormalities and, additionally, considering gender and rhGH treatment programs, in patients with SRS during 3 years of rhGH therapy.

Material and methods

Patients

Thirty-one patients with SRS: 18 (58.1%) boys and 13 (41.9%) girls were included in this study. All the patients had the following genetically confirmed abnormalities: 11p15 LOM in 23 (74.2%) cases, and upd(7)mat in 8 (25.8%) cases. The patients were diagnosed and followed up in one hospital, and all of them were treated with rhGH. The control group consisted of 16 patients with SGA: 9 (56.3%) boys (SRS excluded). For all patients, birth parameters were obtained from patients' medical records and were standardized according to gender and gestational age [23]. Relative macrocephaly at birth was defined as a head circumference at birth ≥ 1.5 standard deviation score (SDS) above birth length and/or weight [4], SGA was defined as a birth body weight ≤ –2 SDS [24], and premature birth was defined as birth before 37 weeks of pregnancy. Birth parameters of patients with SRS were compared with the SGA control group, and within the SRS group, according to molecular abnormality. Anthropometric measurements were performed in all SRS and SGA patients at the beginning and during 3 years of rhGH therapy at one-year intervals. Body composition was evaluated in 13 SRS patients, 9 boys and 4 girls (10 with 11p15 LOM and 3 with upd(7)mat), and in 14 SGA patients (7 boys). Only patients who had complete BIA measurements at baseline and after 3 years of rhGH treatment were analysed. The study was performed in accordance with the Helsinki Declaration and approved by the Bioethics Committee of The Children's Memorial Health Institute. All the subjects (patients' parents) gave informed consent to participate in the research.

Measurements

Height was measured using the SECA 264 stadiometer; the result was the mean of 3 independent measurements (in the case of body asymmetry, equalization was applied for the shorter limb). Weight was measured using a medical scale (Radwag WPT 100/200 O). Age- and sex-specific height, weight, weight for height, and body mass index (BMI) SDS were calculated using the Polish growth references [25]. Anthropometric parameters (SDS) at baseline and after 3 years of rhGH treatment were compared between the SRS study group and the SGA control group, and also within the SRS group (11p15 LOM *vs*. upd(7)mat).

Height velocity (Hv) (cm/year and SDS/year) was compared between the SRS group and the SGA control group and, additionally, in SRS subgroups according to molecular abnormality rhGH therapy program and gender.

Growth hormone therapy

Growth hormone therapy for children with SRS is available under 2 national programs for children with SGA, and with GHD. The inclusion criteria for both programs are described in detail in Appendix 1. The recommended doses of rhGH for children with SGA and GHD are 0.48–1.29 IU/kg/week (optimal 0.75 IU/kg/week) and 0.3–1.0 IU/kg/week, respectively [26]. The mean dose in 3 years of rhGH treatment was calculated. The median dose of rhGH in the entire SRS group was 0.63 IU/kg/week. The normal level of growth hormone in the SRS group was measured in 12 patients (10 with 11p15 LOM, 2 with upd(7)mat) who were treated under the program for children with SGA (median of mean dose 0.70 IU/kg/week). Reduced "bursts" of GH in 2 independent tests were indicated in 19 patients (13 with 11p15 LOM, 6 with upd(7)mat) who followed the GHD program. In the SGA control group, the median of the mean dose was 0.97 IU/kg/week. The mean age of all patients with SRS at the beginning of rhGH treatment was 6.6 ± 2.7 years, and in the SGA control group it was 7.6 ± 1.5 years. All SRS and SGA patients were in prepubertal stage at the beginning of the therapy.

Body composition

Body composition was measured at one-year intervals using a non-invasive and safe testing method: bioelectrical impedance (BIA). BIA was performed using a Jawon Medical Contact 357S analyser based on the tetra-polar electrode method with 8 touch electrodes and multi-frequency: 5, 50, 250, and 550 kHz. Lean body mass (LBM), skeletal muscle mass (SMM), total body water (TBW), intracellular body water (ICW), extracellular body water (ECW), and fat mass (FM) (in kg and %) was analysed. BIA was performed in the morning, on an empty stomach, or at least 3 hours after a meal. Inclusion criteria were as follows: ability to maintain a stable standing position for 30 seconds and a minimum bodyweight of 10 kg. For children, Jawon Medical software uses standard FM (%) depending on age range. References used in the software are the standard range of FM (%), which is 15–20% of standard bodyweight for men and 20–30% of standard bodyweight for women.

Molecular analysis

Blood samples were collected from the patients, and genomic DNA was extracted from peripheral blood leukocytes using standard procedures. Methylation-sensitive multiplex ligation-dependent probe amplification (MS-MLPA) with the use of a SALSA MLPA KIT ME030BWS/SRS (MRC-Holland, Amsterdam, Netherlands) was performed according to the instructions of the manufacturer. Raw data were analysed using the GeneMarker software v.1.8 (Soft Genetics LLC, State College, PA, USA). Microsatellite analysis was conducted using markers for chromosome 7: D7S507 (7p21), D7S460 (7p14), D7S663 (7q11), and D7S820 (7q21). Informed consent was obtained from the patients' parents.

Statistical analysis

To describe the baseline characteristics, descriptive analyses were performed. The Shapiro-Wilk test was used to analyse data normality. The homogeneity of variance was checked using Levene's test and the Brown-Forsythe test. Differences between the examined groups were analysed using Student's t-test or the Mann-Whitney U test. The chi-square test was used to compare the number of patients in groups and the frequency of comparison characteristics. The analysis of variance (ANOVA, Kruskal-Wallis test) was performed to compare birth parameters between the 11p15 LOM, upd(7)mat, and SGA groups. Differences in height, weight, weight for height, BMI, and Hv during a period of 3 years of rhGH treatment were analysed using the ANOVA Friedman test. Changes in FM between the beginning and the third year of rhGH treatment were assessed using the Wilcoxon test. p-values < 0.05 were considered to be statistically significant. Statistical analysis was carried out using Statistica 13.3 software.

Results

Birth parameters: SRS vs. SGA

The birth parameters of the study group are presented in Table 1. Prematurely born patients were identified: 7 (22.6%) in the SRS group (including 6 children with body weight ≤ –2 SDS) and 7 (43.8%) in the SGA group. SRS patients presented RM at birth more often than patients with SGA: 23 (74.2%) *vs*. 5 (33.3%); p = 0.008. Gestational age was higher in the SRS group: 39 *vs*. 37 weeks of pregnancy, respectively (p = 0.031). Head circumference at birth was higher in children with SRS: –1.0 *vs*. –1.8 SDS, respectively (p <0.001). The difference between head and chest circumference at birth was higher in the SRS group: 5.0 *vs*. 3.0 cm, respectively (p = 0.018). Weight and length at birth were lower in SRS patients, but not statistically significantly (ns)

Birth parameters in the SRS group: 11p15 LOM vs. upd(7)mat

Within the SRS group, 23 (100%) patients with 11p15 LOM and 6 (75%) with upd(7)mat were born SGA. The number of prematurely born children was lower in the 11p15 LOM group than in the upd(7)mat group: 3 (13%) *vs*. 4 (50%), respectively, p = 0.053. The average birth weight SDS was significantly lower in patients with 11p15 LOM than in those with upd(7)mat: –4.2 ± 1.5 SDS *vs*. –2.7 ± 1.5SDS, respectively (p = 0.034). Birth length (SDS) was lower in the 11p15 LOM group: -1.9 ± 1.4 *vs*. –1.4 ± 1.2 SDS, respectively (ns). The median of head circumference was –1.0 SDS in both groups. RM at birth was revealed in 17 (73.9%) patients with 11p15 LOM and in 6 (75%) patients with upd(7)mat.

Netchine-Harbison clinical scoring system

Patients with SRS were scored using the Netchine-Harbison clinical scoring system (NH-CSS) proposed in the consensus [4]. Twenty-two patients with 11p15 LOM and 4 patients with upd(7)mat met at least 4 of the NH-CSS criteria, including both RM and protruding forehead (p = 0.01). Body asymmetry was identified significantly more often in the group with 11p15 LOM than in the group with upd(7)mat: (18 [78.3%] *vs*. 1 [12.5%]; p = 0.002). No statistically significant differences were found between the analysed groups with regard to the features: RM (17 [73.9%] *vs*. 6 [75%]), SGA (23 [100%] *vs*. 6 [75%]), postnatal growth failure (23 [100%] *vs*. 8 [100%]), feeding difficulties and/or low BMI (19 [82.6%] *vs*. 6 [75%]), and protruding forehead (22 [95.7%] *vs*. 6 [85.7%]).

Table 1. *Clinical characteristics and birth parameters*

	Total group	Control group	p*	SRS		p**	p***
	SRS (n = 31)	SGA (n = 16)		11p15 LOM (n = 23)	upd(7)mat (n = 8)		
Boys/Girls (%)	18/13 (58.1/41.9)	9/7 (56.2/43.8)	0.906	13/10 (56.5/43.5)	5/3 (62.5/37.5)	1.00	0.952
Premature (%)	7 (22.6)	7 (43.8)	0.243	3 (13.0)	4 (50.0)	0.053	0.049
SGA at birth (%)	29 (93.5)	16 (100)	0.783	23 (100)	6 (75.0)	0.060	0.007
RM[a] (%)	23 (74.2)	5 (33.3)	0.008	17 (73.9)	6 (75.0)	1.00	0.031
Gestational age [wk]	39.0 (37.0/40.0)	37.0 (33.5/38.0)	0.031	39.0 (38.0/40.0)	36.5 (33.5/38.5)	0.035	0.008
Birth weight [g]	1980.2 ± 572.7	1665.2 ± 659.7	0.117	2033.7 ± 526.9	1826.3 ± 704.6	0.387	0.181
Birth length [cm]	45.7 ± 4.1	44.1 ± 6.0	0.384	46.3 ± 3.7	43.7 ± 5.0	0.153	0.289
Birth HC[b] [cm]	33.0 (32.0/34.0)	31.0 (27.0/32.0)	0.001	33.0 (32.0/34.0)	31.5 (29.5/32.5)	0.038	< 0.001
Birth ChC[c] [cm]	27.2 ± 3.3	26.3 ± 3.8	0.455	28.0 ± 3.0	24.9 ± 3.3	0.028	0.084
CH-ChC[d] [cm]	5.0 (4.0/7.0)	3.0 (1.0/4.0)	0.018	5.0 (4.0/7.0)	4.0 (4.0/6.0)	0.650	0.032
Birth weight (SDS)	–3.8 ± 1.6	–3.5 ± 1.7	0.583	–4.2 ± 1.5	–2.7 ± 1.5	0.034	0.072
Birth length (SDS)	–1.7 ± 1.4	–1.5 ± 2.1	0.710	–1.9 ± 1.4	–1.4 ± 1.2	0.354	0.701
Birth HC[b] (SDS)	–1.0 (–1.6/–0.7)	–1.8 (–3.1/–1.1)	<0.001	–1.0 (–1.5/–0,5)	–1.0 (–2.0/–0.8)	0.572	0.003

[a]Relative macrocephaly (SRS n = 30, SGA n = 15, 11p15 LOM n = 23, upd(7)mat n = 7); [b]Birth head circumference; [c]Birth chest circumference; [d]difference between head circumference and chest circumference at birth in children born in term ≥ 37 gestational age (SRS n = 22, SGA n = 9, 11p15 LOM n = 19, upd(7)mat n = 3). Values were expressed as mean ± SD for normal distribution and as median (Q1/Q3) for skewed distribution

*p of SRS *vs*. SGA (Student's t-test for normal distribution and Mann-Whitney U test for skewed distribution); **p of 11p15 LOM *vs* upd(7)mat (Student's t-test for normal distribution and Mann-Whitney U test for skewed distribution); ***p of 11p15 LOM *vs*. upd(7)mat *vs*. SGA (ANOVA for normal distribution and Kruskal-Wallis test for skewed distribution)

SRS — Silver-Russell syndrome; SGA — small for gestational age; 11p15 LOM — loss of methylation at chromosome 11p15.5; upd(7)mat — maternal uniparental disomy of chromosome 7; SDS — standard deviation score

Table 2. *Anthropometric parameters at baseline and after 3 years of recombinant human growth hormone (rhGH) treatment*

	Total group	Control group	p*	11p15 LOM (n = 23)	upd(7)mat (n = 8)	p**
	SRS (n = 31)	SGA (n = 16)				
At rhGH-baseline						
Age [y]	6.6 ± 2.7	7.6 ± 1.5	0.105	6.4 ± 2.5	7.0 ± 0.1	0.689
Age for height [y]	4.1 ± 2.2	5.2 ± 1.3	0.041	4.1 ± 2.0	4.2 ± 3.3	0.947
Height [cm]	103.6 ± 16.8	112.4 ± 9.4	0.026	103.7 ± 15.6	103.3 ± 2.9	0.960
Weight [kg]	13.9 (10.0/17.9)	16.1 (15.1/19.1)	0.035	13.9 (10.0/17.9)	13.5 (10.4/19.6)	0.982
BMI [kg/m^2]	12.9 (11.7/14.1)	13.3 (12.2/14.0)	0.452	12.4 (11.6/13.7)	13.8 (12.9/14.1)	0.142
Height (SDS)	–3.3 ± 1.2	–2.6 ± 0.6	0.012	–3.1 ± 1.0	–3.7 ± 0.4	0.394
Weight (SDS)	–2.5 (–3.2/–1.8)	–1.9 (–2.2/–1.7)	0.037	–2.5 (–3.2/–1.8)	–2.4 (–3.1/–1.8)	0.928
Weight for height (SDS)	–1.7 (–2.1/–0.9)	–1.1 (–1.6/–0.8)	0.038	–1.7 (–2.1/–0.8)	–1.7 (–2.1/–0.9)	0.982
BMI (SDS)	–1.9 (–2.3/–1.0)	–1.4 (–1.8–/1.0)	0.121	–2.1 (–2.4/–1.0)	–1.4 (–1.7/–1.1)	0.289
At 3 y rhGH						
Age [y]	9.5 ± 2.7	10.6 ± 1.6	0.108	9.4 ± 2.5	9.9 ± 3.3	0.681
Height [cm]	127.5 ± 17.0	135.9 ± 9.4	0.035	127.0 ± 15.7	128.9 ± 21.6	0.823
Weight [kg]	22.1 (17.4/27.0)	26.8 (23.7/29.9)	0.045	21.4 (17.4/27.0)	22.4 (17.4/31.8)	0.981
BMI [kg/m^2]	13.3 (12.5/15.6)	14.7 (13.0/15.9)	0.154	12.9 (12.1/15.6)	14.2 (12.9/15.4)	0.379
Height (SDS)	–1.8 ± 1.0	–1.3 ± 0.7	0.107	–1.7 ± 1.0	–2.0 ± 1.3	0.621
Weight (SDS)	–1.8 (–2.1/–1.1)	–1.5 (–1.7/–0.6)	0.080	–1.9 (–2.1–/1.2)	–1.5 (–2.1/–1.0)	0.635
Weight for height (SDS)	–1.1 (–1.5/–0.5)	–0.7 (–1.0/–0.2)	0.078	–1.1 (–1.5/–0.3)	–0.9 (–1.5/–0.7)	0.928
BMI (SDS)	–1.4 (–2.0/–1.0)	–1.2 (–1.5/–0.5)	0.106	–1.6 (–2.0/–0.9)	–1.4 (–1.7/–1.1)	0.512

Values were expressed as mean ± standard deviation (SD) for normal distribution and as median (Q1/Q3) for skewed distribution. * Represents p of SRS *vs*. SGA; ** Represents p of 11p15 LOM *vs*. upd(7)mat. SGA — small for gestational age; SRS — Silver-Russell syndrome; 11p15 LOM — loss of methylation at chromosome 11p15.5; upd(7)mat — maternal uniparental disomy of chromosome 7; SDS — standard deviation score

Anthropometric parameters

The mean age at the beginning of rhGH treatment was 6.6 ± 2.7 years in the SRS group and 7.6 ± 1.5 years in the SGA group. Age for height, defined as the age at which a patient's body height corresponds with the 50th percentile, was lower in the SRS group: 4.1 ± 2.2 *vs*. 5.2 ± 1.3 years, respectively (p = 0.041). At baseline of rhGH therapy, SRS patients had lower height, weight, and weight for height (SDS) than patients in the SGA control group: –3.3 ± 1.2 *vs*. –2.6 ± 06 SDS (p = 0.012), –2.5 *vs*. –1.9 SDS (p = 0.037), and –1.7 *vs*. –1.1 (p = 0.038), respectively. BMI (SDS) was also lower in the SRS group (non significant — ns). No such differences were identified between patients with 11p15 LOM and upd(7)mat. After 3 years of rhGH therapy, SRS patients had still lower height, weight, weight for height, and BMI (SDS) than patients from the SGA control group (ns) (Tab. 2).

All analysed parameters (SDS) significantly increased after a 3-year rhGH treatment, except BMI SDS in patients with upd(7)mat. Figure 1 shows the evolution of anthropometric parameters (SDS) in the entire SRS group, in the SRS subgroups: 11p15 LOM and upd(7)mat), and in the SGA control group.

Height velocity

The highest increase in Hv (cm/year and SDS/year) was observed in the first year of treatment in all examined groups. In the first year of rhGH treatment, patients with SRS had significantly higher Hv than patients with SGA: 8.8 ± 1.7 *vs*. 8.0 ± 0.9 cm/year (p = 0.041) and 0.7 ± 0.4 *vs*. 0.5 ± 0.2 SDS/year (p = 0.033), respectively. In the second and third year of rhGH therapy, these differences were not statistically significant. In the third year of therapy, Hv (SDS/year) was the lowest in both examined groups (Tab. 3). Hv in patients with SRS significantly decreased between the first and third year of rhGH treatment, from 8.8 ± 1.7 to 7.4 ± 1.5 cm/year (p = 0.03) and from 0.7 ± 0.4 to 0.3 ± 0.3 SDS/year (p < 0.0001), respectively. In patients in the SGA control group, Hv also decreased, but not statistically significantly (Fig. 2).

Patients with upd(7)mat had higher Hv than patients with 11p15 LOM in all the analysed periods, but the difference was statistically significant only in the second year of rhGH treatment. Hv in patients treated under the GHD program was shown to be slightly higher than in patients treated under the SGA program, in all analysed periods. Taking into account

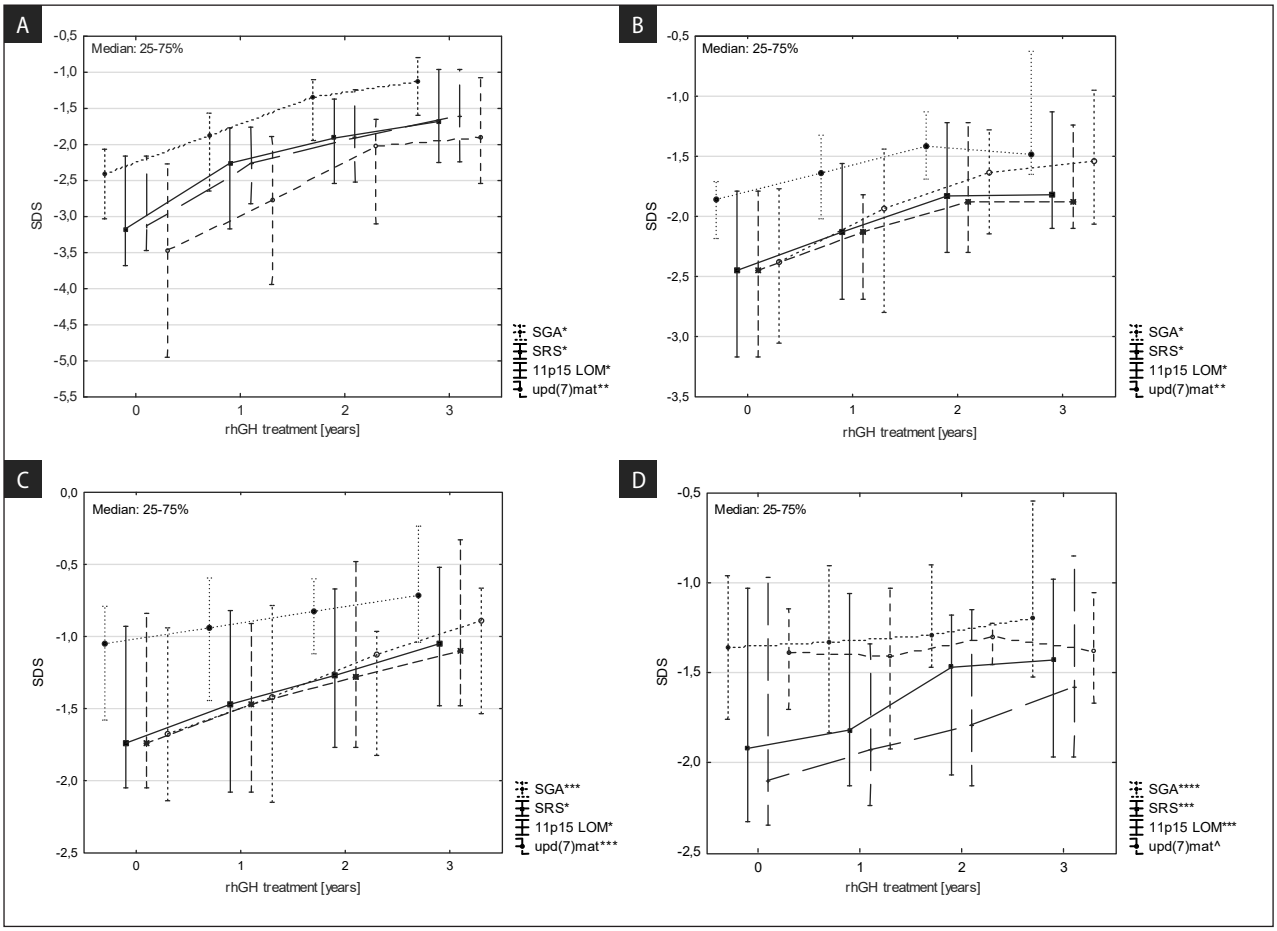

Figure 1. A. *Height standard deviation score (SDS);* **B.** *Weight SDS;* **C.** *Weight for height SDS;* **D.** *Body mas index (BMI) SDS; Changes during recombinant human growth hormone (rhGH) treatment in total Silver-Russell syndrome (SRS) group and according to molecular abnormality (loss of methylation at chromosome 11p15.5 [11p15 LOM] and maternal uniparental disomy of chromosome 7 [upd(7)mat]) and in the small for gestational age (SGA) control group. ANOVA Friedman test: ^ns (not significant); *p < 0.00001; **p < 0.001; ***p < 0.01; ****p < 0.5*

the division by gender, Hv was similar in boys and girls. Patients with SRS received a significantly lower mean dose of rhGH than patients with SGA: 0.63 *vs*. 0.97 IU/kg/week, respectively ($p < 0.001$). In all patients with SRS, the mean dose was similar, regardless of the subgroup (Table 3).

Body composition

The mean age at baseline of rhGH treatment was 7.4 ± 3.0 and 7.6 ± 1.4 for patients with SRS and SGA, respectively. At baseline and after 3 years of rhGH treatment, no statistically significant differences were identified between the examined groups within the following parameters: weight, LBM, SMM, TBW, ICW, ECW, FM (kg), and FM (%) (Tab. 4). Individual parameters of body composition expressed in kilograms significantly increased during the 3 years of rhGH therapy in both groups, in relation to the increase in whole body weight (kg), but the percentage of FM decreased significantly in patients with SRS, from 4.2% to 3.0% ($p = 0.033$), and in patients with SGA, from 7.6% to 6.6% ($p = 0.046$).

Discussion

Silver-Russell syndrome is known to be associated mainly with epigenetic changes in 2 chromosomes: 11p15 LOM and upd(7)mat. In the remaining individuals, diagnosis is based on clinical manifestations and is therefore more probabilistic. The authors have chosen a confirmed epigenetic status as an inclusion criterion for this study.

In analyses of birth parameters, it was indicated that SDS of birth weight and length were lower in patients with SRS than in the SGA control group. Birth weight and length were also lower in the 11p15 group than in the upd(7)mat patients, which is consistent with research studies by other authors [11, 16, 27, 28]. Head circumference was close to the 3rd percentile for SGA children, but for SRS patients it was in the scope of

Table 3. *Height velocity (Hv; cm/year) and standard deviation score (SDS)/year after 1, 2, and 3 years of recombinant human growth hormone (rhGH) treatment: a comparison between Silver-Russell syndrome (SRS; total group) and small for gestational age (SGA; control group) and in SRS subgroups: loss of methylation at chromosome 11p15.5 (11p15 LOM) vs. maternal uniparental disomy of chromosome 7 (upd(7)mat); growth hormone deficiency (GHD) recombinant human growth hormone (rhGH) program vs. SGA rhGH program; boys vs. girls*

	Total group	Control group		SRS group			SRS group			SRS group		
	SRS (n = 31)	SGA (n = 16)	p	11p15 LOM (n = 23)	upd(7)mat (n = 8)	p	GHD rhGH program (n = 19)	SGA rhGH program (n = 12)	p	Boys (n = 18)	Girls (n = 13)	p
Mean dose [UI/kg/week] median	0.63	0.97	< 0.001	0.68	0.62	0.362	0.63	0.70	0.093	0.63	0.96	0.332
Hv [cm/year]												
1 y.	8.8 ± 1.7	8.0 ± 0.9	0.041	8.7 ± 1.7	9.3 ± 1.9	0.373	9.1 ± 1.5	8.5 ± 2.1	0.353	8.7 ± 1.8	9.1 ± 1.7	0.515
2 y.	7.7 ± 1.4	7.7 ± 0.9	0.916	7.4 ± 1.1	8.7 ± 1.5	0.013	7.8 ± 1.2	7.7 ± 1.6	0.940	7.9 ± 1.5	7.5 ± 1.1	0.339
3 y.	7.4 ± 1.5	7.8 ± 1.3	0.330	7.3 ± 1.5	7.5 ± 1.4	0.705	7.7 ± 0.9	6.8 ± 2.0	0.078	7.3 ± 1.6	7.4 ± 1.4	0.781
Hv (SDS/year)												
1 y.	0.7 ± 0.4	0.5 ± 0.2	0.033	0.7 ± 0.3	0.8 ± 0.5	0.608	0.7 ± 0.4	0.7 ± 0.4	0.939	0.7 ± 0.3	0.8 ± 0.4	0.781
2 y.	0.4 ± 0.3	0.5 ± 0.2	0.980	0.4 ± 0.3	0.6 ± 0.4	0.277	0.5 ± 0.4	0.4 ± 0.3	0.807	0.5 ± 0.3	0.4 ± 0.4	0.781
3 y.	0.3 ± 0.3	0.3 ± 0.3	0.831	0.3 ± 0.3	0.3 ± 0.4	0.770	0.4 ± 0.3	0.2 ± 0.3	0.054	0.3 ± 0.3	0.3 ± 0.3	0.759

the standard range. Within the SRS group, median of birth head circumference was the same in both groups, regardless of the type of molecular abnormality, which is similar to results obtained in another study [27]. In the presented study, we indicated that birth chest circumference was significantly lower than birth head circumference in the SRS group than in the SGA control group: 5 cm *vs*. 3 cm (p=0.018). This feature was not considered in other published studies, so the results cannot be compared, but it seems reasonable to suggest that this feature may be important in screening patients suspected of SRS syndrome.

Numerous studies have shown that treatment with rhGH has a positive effect on patients with intrauterine and postnatal growth retardation, including children with SRS [14–16, 27, 29–33]. However, in the majority of studies, SRS diagnosis was based on clinical assessment [14, 15, 31, 33]. Only a few reports on GH therapy include patients with identified (epi)mutations [16, 27, 34]. The most important factors influencing the final height are growth deficiency, time of treatment commencement, parental height, birth weight and length, bone age, the dose of rhGH, puberty, and the height at the beginning of and during rhGH treatment (earlier commencement and longer duration of therapy give better outcomes). Response to rhGH treatment proved to be best during the first year of the therapy, which was expressed as significantly higher Hv after the first year of rhGH therapy in all examined subgroups. Our result is similar to the result of the KIGS study [30], which suggested that a better height achievement depends particularly on the response to therapy during the first year of GH application. Unfortunately, the number of molecularly confirmed SRS patients in the KIGS study is unknown; all SRS patients were classified based on clinical criteria.

In our study, we indicated that during 3 years of rhGH therapy, height SDS decreased in both SRS patients and the SGA control group. After 3 years of rhGH therapy, patients with SGA had higher height SDS than patients with SRS, but attention must be drawn to the fact that patients in the SGA control group also had higher height SDS at baseline. Finally, the increase in height was similar in both described groups: 1.5 SDS/23.9 cm for SRS patients and 1.3 SDS/23.5 cm for the SGA control group during 3 years. It was observed that after 3 years of rhGH therapy, height SDS was almost the same in the SRS subgroups analysed with respect to molecular abnormality, gender, and therapy program. Although patients with upd(7)mat had lower height SDS at the beginning of rhGH therapy than patients with 11p15 LOM, patients from both groups achieved similar height SDS after 3 years of rhGH treatment. A similar observation was published by Smeets

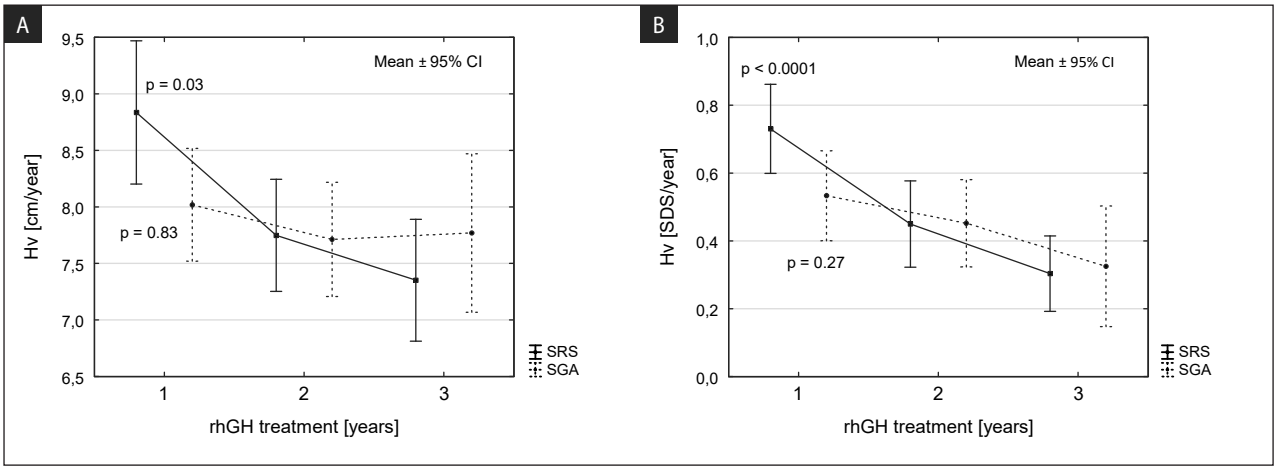

Figure 2. *Height velocity (Hv; in cm/year) (***A***) and standard deviation score (SDS)/year (***B***) during recombinant human growth hormone (rhGH) therapy in patients with Silver-Russell syndrome (SRS) and small for gestational age (SGA)*

Table 4. ***Body composition in Silver-Russell syndrome (SRS) patients and in small for gestational age (SGA) control group patients at baseline and after 3 years of recombinant human growth hormone (rhGH) treatment***

Body composition	Group SRS (n = 13, 9 boys/4 girls)	Control Group SGA (n = 14, 7 boys/7 girls)	p
At rhGH-baseline			
Age [y]	7.4 ± 3.0*	7.6 ± 1.4*	0.891
Weight [kg]	17.0 ± 6.2*	17.5 ± 4.6*	0.802
LBM [kg]	15.7 ± 6.0*	15.7 ± 3.9*	0.999
SMM [kg]	8.8 ± 3.4*	8.8 ± 2.2*	0.997
TBW [kg]	11.3 ± 4.3*	11.3 ± 3.0*	0.975
ICW [kg]	7.1 ± 2.7*	7.0 ± 1.8*	0.898
ECW [kg]	4.1 ± 1.7*	4.3 ± 1.1*	0.779
FM [kg]	0.8 (0.4/1.4) ^	1.2 (0.6/2.5)**	0.382
FM (%)	4.2 (3.0/12.9)**	7.6 (3.1/17.9)**	0.357
At 3 y rhGH			
Age [y]	10.3 ± 2.9*	10.5 ± 1.5*	0.766
Weight [kg]	26.4 ± 9.01*	28.6 ± 7.3*	0.502
LBM [kg]	25.0 ± 8.7*	26.0 ± 5.7*	0.713
SMM [kg]	14.0 ± 5.0*	14.5 ± 3.2*	0.731
TBW [kg]	18.0 ± 6.3*	18.7 ± 4.1*	0.708
ICW [kg]	11.1 ± 3.9*	11.5 ± 2.5*	0.767
ECW [kg]	6.9 ± 2.4*	7.3 ± .1.6*	0.620
FM [kg]	1.2 (0.7/1.6) ^	1.6 (0.7/3.6)**	0.286
FM (%)	3.0 (3.0/7.0)**	6.6 (3.0/13.5)**	0.275

p comparison between Group SRS and Control Group SGA; *p < 0.00001; **p < 0.05; ^ not significant: comparison between rhGH-baseline and after 3 years of rhGH treatment: t-test for paired samples (normal distribution) or Wilcoxon singled-rank test for paired samples (skewed distributions)

SDS — standard deviation score; LBM — lean body mass; SMM — skeletal muscle mass; TBW — total body water; ICW — intracellular body water; ECW — extracellular body water; FM — fat mass

[35], who suggested that there was a trend towards a greater height gain in the groups with upd(7)mat and idiopathic SRS compared to patients with 11p15 LOM, which was also in line with the observation of Binder [36], who reported that during approximately 5 years of rhGH treatment, the epigenetic mutation was not a significant predictor of the height SDS. We observed that weight, weight for height, and BMI also increased during rhGH therapy in SRS patients, which corresponds with other studies [15, 35].

The group analysed in this study was heterogeneous regarding the concentration of GH: GHD was diagnosed in 19 patients. We observed that height increased by 0.7 SDS after the first year of rhGH treatment in both the SGA and the GHD rhGH program group. After 3 years of treatment, an increase in height SDS was slightly higher in the GHD group than in the SGA group (1.6 *vs*. 1.3 SDS/year), which corresponds to another outcome [37]. The better response to rhGH treatment of GHD patients probably results from the fact that this is a substitution therapy in cases of insufficient growth hormone excretion. Conversely, in the case of SRS patients with SGA but without GHD, growth is stimulated in individuals with an epigenetically disturbed growth process.

GH therapy can favourably influence body composition [38]. In the presented study, the authors used BIA to analyse body composition because this is a safe, reliable [coefficient of variation (CV) 3.5–4%], effective, relatively cheap, and non-invasive method for children, with a short time of examination. In the presented study it was noticed that during 3 years of rhGH treatment, all analysed parameters, such as LBM, SMM, TBW, ICW, ECW, and FM (kg), increased, which is related to increased whole-body mass. To estimate changes in body composition, the percentage of FM was calculated. It was indicated that FM% decreased during rhGH therapy in both SRS and SGA group, which is probably related to the catabolic effect of growth hormone on adipose tissue. Similar scores were published by Willemsen et al. [20]. In 2001, a study indicating that patients with SRS had less body fat (%) than patients from a intrauterine growth retardation (IUGR) group (11.68 ± 7.67 *vs*. 18.21 ± 8.33%, respectively) was published [39]. Its authors also used the BIA method, but patients with SRS were classified based on clinical criteria, which is why it may be a heterogeneous group. Smeets et al. [35] analysed body composition using DXA and noticed that during GH treatment, LBM seemed to be stable whereas body fat (%) increased in both SRS and non-SRS children.

Recently, outcomes of fat percentage in older patients with SRS, mainly adults, were published. In Lokulo-Sodipe's [28] and Patti's [40] studies the age range was from 13.32 to 67.71 years and from 18 to 46 years, respectively. Both studies indicated a trend that the percentage of FM in elder SRS patients increased during ontogenesis, and the fat percentage exceeded standard levels. To our knowledge, no other studies evaluated body composition exclusively in SRS children. In our study, related to younger children, we observed a decrease of FM (%) during 3 years of rhGH therapy. However, regarding reported outcomes in older patients, we see the need for continuous monitoring of fat percentage during all stages of development in SRS patients.

There are several limitations to this study. First, the study presented a relatively short time of observation, which follows from the fact that patients with SRS without GHD gained the opportunity of GH treatment in 2015, and it takes several months to classify patients for therapy. Second, our group was younger than others described in the literature. Third, BIA was performed in 13 patients, but we decided to include only complete data (at baseline and after 3 years of rhGH treatment). On the other hand, we described a relatively large group of SRS patients, from one country, and treated rhGH in a single hospital according to 2 national programs. Because our group is relatively young, we have the opportunity for long-term observation and enlargement of our group in the future.

Conclusion

The authors indicated a positive effect of rhGH therapy for growth of SRS patients. It was demonstrated that height, weight, and BMI (SDS) increased and FM (%) decreased significantly. However, longer-term observation and a larger study group are necessary to draw stronger conclusions, especially on body composition.

References

1. Kotzot D, Schmitt S, Bernasconi F, et al. Uniparental disomy 7 in Silver-Russell syndrome and primordial growth retardation. Hum Mol Genet. 1995; 4(4): 583–587, doi: 10.1093/hmg/4.4.583, indexed in Pubmed: 7633407.
2. Netchine I, Rossignol S, Dufourg MN, et al. 11p15 imprinting center region 1 loss of methylation is a common and specific cause of typical Russell-Silver syndrome: clinical scoring system and epigenetic-phenotypic correlations. J Clin Endocrinol Metab. 2007; 92(8): 3148–3154, doi: 10.1210/jc.2007-0354, indexed in Pubmed: 17504900.
3. Bruce S, Hannula-Jouppi K, Peltonen J, et al. Clinically distinct epigenetic subgroups in Silver-Russell syndrome: the degree of H19 hypomethylation associates with phenotype severity and genital and skeletal anomalies. J Clin Endocrinol Metab. 2009; 94(2): 579–587, doi: 10.1210/jc.2008-1805, indexed in Pubmed: 19017756.
4. Wakeling EL, Brioude F, Lokulo-Sodipe O, et al. Diagnosis and management of Silver-Russell syndrome: first international consensus statement. Nat Rev Endocrinol. 2017; 13(2): 105–124, doi: 10.1038/nrendo.2016.138, indexed in Pubmed: 27585961.
5. Abu-Amero S, Monk D, Frost J, et al. The search for the gene for Silver-Russell syndrome. Acta Paediatr Suppl. 1999; 88(433): 42–48, doi: 10.1111/j.1651-2227.1999.tb14402.x, indexed in Pubmed: 10626544.
6. Wollmann HA, Kirchner T, Enders H, et al. Growth and symptoms in Silver-Russell syndrome: review on the basis of 386 patients. Eur J Pediatr. 1995; 154(12): 958–968, doi: 10.1007/BF01958638, indexed in Pubmed: 8801103.
7. Price SM, Stanhope R, Garrett C, et al. The spectrum of Silver-Russell syndrome: a clinical and molecular genetic study and new diagnostic criteria. J Med Genet. 1999; 36(11): 837–842, indexed in Pubmed: 10544228.
8. Abraham E, Altiok H, Lubicky JP. Musculoskeletal manifestations of Russell-Silver syndrome. J Pediatr Orthop. 2004; 24(5): 552–564, doi: 10.1097/00004694-200409000-00017, indexed in Pubmed: 15308907.
9. Bliek J, Terhal P, van den Bogaard MJ, et al. Hypomethylation of the H19 gene causes not only Silver-Russell syndrome (SRS) but also isolated asymmetry or an SRS-like phenotype. Am J Hum Genet. 2006; 78(4): 604–614, doi: 10.1086/502981, indexed in Pubmed: 16532391.

10. Wakeling EL, Amero SA, Alders M, et al. Epigenotype-phenotype correlations in Silver-Russell syndrome. J Med Genet. 2010; 47(11): 760–768, doi: 10.1136/jmg.2010.079111, indexed in Pubmed: 20685669.
11. Fuke T, Mizuno S, Nagai T, et al. Molecular and clinical studies in 138 Japanese patients with Silver-Russell syndrome. PLoS One. 2013; 8(3): e60105, doi: 10.1371/journal.pone.0060105, indexed in Pubmed: 23533668.
12. Azzi S, Salem J, Thibaud N, et al. A prospective study validating a clinical scoring system and demonstrating phenotypical-genotypical correlations in Silver-Russell syndrome. J Med Genet. 2015; 52(7): 446–453, doi: 10.1136/jmedgenet-2014-102979, indexed in Pubmed: 25951829.
13. Yamaguchi KT, Salem JB, Myung KS, et al. Spinal Deformity in Russell-Silver Syndrome. Spine Deform. 2015; 3(1): 95–97, doi: 10.1016/j.jspd.2014.06.003, indexed in Pubmed: 27927458.
14. Rakover Y, Dietsch S, Ambler GR, et al. Growth hormone therapy in Silver Russell syndrome: 5 years experience of the Australian and New Zealand Growth database (OZGROW). Eur J Pediatr. 1996; 155(10): 851–857, doi: 10.1007/BF02282833, indexed in Pubmed: 8891553.
15. Toumba M, Albanese A, Azcona C, et al. Effect of long-term growth hormone treatment on final height of children with Russell-Silver syndrome. Horm Res Paediatr. 2010; 74(3): 212–217, doi: 10.1159/000295924, indexed in Pubmed: 20424422.
16. Smeets CCJ, Zandwijken GRJ, Renes JS, et al. Long-Term Results of GH Treatment in Silver-Russell Syndrome (SRS): Do They Benefit the Same as Non-SRS Short-SGA? J Clin Endocrinol Metab. 2016; 101(5): 2105–2112, doi: 10.1210/jc.2015-4273, indexed in Pubmed: 27007691.
17. Lee PA, Sävendahl L, Oliver I, et al. Comparison of response to 2-years' growth hormone treatment in children with isolated growth hormone deficiency, born small for gestational age, idiopathic short stature, or multiple pituitary hormone deficiency: combined results from two large observational studies. Int J Pediatr Endocrinol. 2012; 2012(1): 22, doi: 10.1186/1687-9856-2012-22, indexed in Pubmed: 22788856.
18. Lee PA, Ross JL, Pedersen BT, et al. Noonan syndrome and Turner syndrome patients respond similarly to 4 years' growth-hormone therapy: longitudinal analysis of growth-hormone-naïve patients enrolled in the NordiNet® International Outcome Study and the ANSWER Program. Int J Pediatr Endocrinol. 2015; 2015(1): 17, doi: 10.1186/s13633-015-0015-1, indexed in Pubmed: 26351466.
19. Angulo M, Abuzzahab MJ, Pietropoli A, et al. Outcomes in children treated with growth hormone for Prader-Willi syndrome: data from the ANSWER Program® and NordiNet® International Outcome Study. Int J Pediatr Endocrinol. 2020; 2020(1): 20, doi: 10.1186/s13633-020-00090-6, indexed in Pubmed: 33292530.
20. Willemsen RH, Arends NJT, Bakker-van Waarde WM, et al. Long-term effects of growth hormone (GH) treatment on body composition and bone mineral density in short children born small-for-gestational-age: six-year follow-up of a randomized controlled GH trial. Clin Endocrinol (Oxf). 2007; 67(4): 485–492, doi: 10.1111/j.1365-2265.2007.02913.x, indexed in Pubmed: 17561977.
21. Roemmich JN, Huerta MG, Sundaresan SM, et al. Alterations in body composition and fat distribution in growth hormone-deficient prepubertal children during growth hormone therapy. Metabolism. 2001; 50(5): 537–547, doi: 10.1053/meta.2001.22510, indexed in Pubmed: 11319714.
22. Esen I, Demirel F, Tepe D, et al. The association between growth response to growth hormone and baseline body composition of children with growth hormone deficiency. Growth Horm IGF Res. 2013; 23(5): 196–199, doi: 10.1016/j.ghir.2013.07.001, indexed in Pubmed: 23890535.
23. Niklasson A, Albertsson-Wikland K. Continuous growth reference from 24th week of gestation to 24 months by gender. BMC Pediatr. 2008; 8: 8, doi: 10.1186/1471-2431-8-8, indexed in Pubmed: 18307822.
24. Clayton PE, Cianfarani S, Czernichow P, et al. Management of the child born small for gestational age through to adulthood: a consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. J Clin Endocrinol Metab. 2007; 92(3): 804–810, doi: 10.1210/jc.2006-2017, indexed in Pubmed: 17200164.
25. Palczewska I, Niedźwiecka Z. Wskaźniki rozwoju somatycznego dzieci i młodzieży warszawskiej. Dev Period Med. 2001; 5(2): 17–118.
26. Walczak M. Leczenie hormonem wzrostu oraz insulinopodobnym czynnikiem wzrostu u dzieci. In: Pyrżak B, Walczak M. ed. Endokrynologia Wieku Rozwojowego. PZWL, Warszawa 2018: 211–231.
27. Binder G, Seidel AK, Martin DD, et al. The endocrine phenotype in silver-russell syndrome is defined by the underlying epigenetic alteration. J Clin Endocrinol Metab. 2008; 93(4): 1402–1407, doi: 10.1210/jc.2007-1897, indexed in Pubmed: 18230663.
28. Lokulo-Sodipe O, Ballard L, Child J, et al. Phenotype of genetically confirmed Silver-Russell syndrome beyond childhood. J Med Genet. 2020; 57(10): 683–691, doi: 10.1136/jmedgenet-2019-106561, indexed in Pubmed: 32054688.
29. Ranke MB, Lindberg A. Growth hormone treatment of short children born small for gestational age or with Silver–Russell syndrome: results from KIGS (Kabi International Growth Study), including the first report on final height. Acta Paediatr. 1996; 85(s417): 18–26, doi: 10.1111/j.1651-2227.1996.tb14288.x, indexed in Pubmed: 9055904.
30. Ranke MB, Lindberg A. KIGS International Board. Height at start, first-year growth response and cause of shortness at birth are major determinants of adult height outcomes of short children born small for gestational age and Silver-Russell syndrome treated with growth hormone: analysis of data from KIGS. Horm Res Paediatr. 2010; 74(4): 259–266, doi: 10.1159/000289570, indexed in Pubmed: 20431273.
31. Stanhope R, Albanese A, Azcona C, et al. Growth hormone treatment in growth hormone-sufficient and -insufficient children with intrauterine growth retardation/Russell-Silver syndrome. Horm Res. 1998; 50(1): 22–27, doi: 10.1159/000023196, indexed in Pubmed: 9691209.
32. Van Pareren Y, Mulder P, Houdijk M, et al. Adult height after long-term, continuous growth hormone (GH) treatment in short children born small for gestational age: results of a randomized, double-blind, dose-response GH trial. J Clin Endocrinol Metab. 2003; 88(8): 3584–3590, doi: 10.1210/jc.2002-021172, indexed in Pubmed: 12915640.
33. Sienko M, Petriczko E, Zajaczek S, et al. The effects of growth hormone therapy on the somatic development of a group of Polish children with Silver-Russell syndrome. Neuro Endocrinol Lett. 2017; 38(6): 415–421, indexed in Pubmed: 29298282.
34. Lokulo-Sodipe O, Giabicani E, Canton APM, et al. Height and body mass index in molecularly confirmed Silver-Russell syndrome and the long-term effects of growth hormone treatment. Clin Endocrinol (Oxf). 2022; 97(3): 284–292, doi: 10.1111/cen.14715, indexed in Pubmed: 35261046.
35. Smeets CCJ, Renes JS, van der Steen M, et al. Metabolic Health and Long-Term Safety of Growth Hormone Treatment in Silver-Russell Syndrome. J Clin Endocrinol Metab. 2017; 102(3): 983–991, doi: 10.1210/jc.2016-3388, indexed in Pubmed: 28001454.
36. Binder G, Liebl M, Woelfle J, et al. Adult height and epigenotype in children with Silver-Russell syndrome treated with GH. Horm Res Paediatr. 2013; 80(3): 193–200, doi: 10.1159/000354658, indexed in Pubmed: 24051620.
37. Rapaport R, Lee P, Ross J, et al. Growth hormone therapy in children born small for gestational age: results from the ANSWER program. Endocr Connect. 2018 [Epub ahead of print]; 7(10): 1096–1104, doi: 10.1530/EC-18-0286, indexed in Pubmed: 30139820.
38. Binder G, Donner J, Becker B, et al. Changes in body composition in male adolescents with childhood-onset GH deficiency during transition. Clin Endocrinol (Oxf). 2019; 91(3): 432–439, doi: 10.1111/cen.14041, indexed in Pubmed: 31116442.
39. Blissett J, Harris G, Kirk J. Feeding problems in Silver-Russell syndrome. Dev Med Child Neurol. 2001; 43(1): 39–44, doi: 10.1017/s0012162201000068, indexed in Pubmed: 11201421.
40. Patti G, Giaccardi M, Capra V, et al. Clinical Manifestations and Metabolic Outcomes of Seven Adults With Silver-Russell Syndrome. J Clin Endocrinol Metab. 2018; 103(6): 2225–2233, doi: 10.1210/jc.2017-02589, indexed in Pubmed: 29546330.