Metabolic Health and Long-Term Safety of Growth Hormone Treatment in Silver-Russell Syndrome

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Context: Children with Silver-Russell syndrome (SRS) are born small for gestational age (SGA) and remain short. Growth hormone (GH) treatment improves height in short SGA children, including those with SRS. Data on metabolic health and long-term safety of GH treatment in SRS are lacking.

Objective: To investigate metabolic health in SRS patients during and until 2 years after discontinuation of GH treatment.

Design: Metabolic health was assessed longitudinally at GH-start, GH-stop, 6 months, and 2 years thereafter.

Patients: Twenty-nine SRS patients vs 171 non-SRS subjects born SGA.

Main Outcome Measures: Lean body mass (LBM), fat mass percentage (FM%), insulin sensitivity (Si), β-cell function, blood pressure, and serum lipids.

Results: At GH-start [mean age (standard deviation) 5.4 (2.1) years in SRS and 6.7 (2.0) years in non-SRS (P = 0.003)], blood pressure, serum lipids, glucose, and insulin levels were similar and within normal ranges in SRS and non-SRS. LBM standard deviation score (SDS) and FM% SDS were lower than average in both groups. During treatment, LBM SDS remained stable whereas FM% SDS increased in both groups. During the 2 years after GH-stop, LBM decreased and FM% increased, whereas Si and β-cell function improved. At 2 years after GH-stop (mean age 18 years), all parameters were similar and within normal ranges in SRS and non-SRS. None of the SRS patients developed metabolic syndrome, diabetes mellitus type 2, or adverse events.

Conclusion: GH-treated SRS patients have a similar metabolic health and safety profile as non-SRS subjects born SGA, both during and until 2 years after GH-stop. (***J Clin Endocrinol Metab*** **102: 983–991, 2017)**

Silver-Russell syndrome (SRS) is characterized by small for gestational age (SGA) birth, postnatal growth retardation, feeding difficulties, and several dysmorphic features (1–3). Approximately 60% of cases are caused by an aberration in the imprinting control region of the 11p15 region (4) and 5% to 10% by a maternal uniparental disomy of chromosome 7 (mUPD7) (5). In 30% to 40%, the genetic cause is unknown, which is referred to as clinical SRS (6).

Children born with a low birth weight are at increased risk to develop adult-onset disorders such as diabetes

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Abbreviations: AH, adult height; AIR, acute insulin response; AIRg, acute insulin response to glucose; ATP-III, adult treatment panel III; BL, birth length; BP, blood pressure; BW, birth weight; DBP, diastolic blood pressure; DI, disposition index; DM2, diabetes mellitus type 2; FM, fat mass; FM%, fat mass percentage; FSIGT, frequently sampled intravenous glucose tolerance; GFR, glomerular filtration rate; GH, growth hormone; HDLc, high-density lipoprotein cholesterol; IGF, insulin-like growth factor; IGFBP3, insulin-like growth factor binding protein 3; LBM, lean body mass; LDLc, low-density lipoprotein cholesterol; mUPD7, maternal uniparental disomy of chromosome 7; SBP, systolic blood pressure; SD, standard deviation; SDS, standard deviation score; Sg, glucose effectiveness; SGA, small for gestational age; Si, insulin sensitivity; SRS, Silver-Russell syndrome; TC, total cholesterol; Tg, triglyceride.

mellitus type 2 (DM2), hypertension, and hyperlipidemia at a relatively young age (7). Epigenetic changes could be one of the underlying mechanisms behind this increased risk (8), but the risk for adult-onset disorders has not been investigated in SRS. Overall, adult follow-up data in SRS are lacking, which was also emphasized by the recently published consensus statement on diagnosis and management of SRS (6).

Growth hormone (GH) treatment is a registered growth-promoting therapy for short children born SGA (9), including children with SRS. It has been shown that GH treatment is effective at increasing adult height (AH) in SRS (10, 11). GH treatment has also several metabolic effects in children born SGA, namely an increase in lean body mass (LBM), a decline in fat mass (FM), a decrease in blood pressure (BP), and a more favorable lipid profile, but also a lower insulin sensitivity (Si) (12–14). Data on whether these effects also occur in GH-treated SRS patients are lacking.

In the present study, we assessed longitudinal changes in metabolic health (*i.e.*, BP, fasting lipid levels, body composition, Si, and occurrence of DM2 and metabolic syndrome) in patients with SRS, from start of GH treatment until 2 years after discontinuation of GH due to AH attainment. We compared these data with GH-treated non-SRS subjects born SGA, hypothesizing that SRS patients have a less favorable metabolic health profile due to their epigenetic changes but that the metabolic changes during and after GH treatment are similar in SRS and non-SRS subjects.

Methods

Subjects

The study group comprised 29 SRS and 171 non-SRS subjects who participated in a large, multicenter GH trial (13–15) and had attained AH. All subjects were born SGA [birth length (BL) and/or birth weight (BW) ≤ -2 standard deviation score (SDS) for gestational age (16)] and received biosynthetic GH at a dose of 1 mg/m^2/d ($\sim$0.035 mg/kg/d) because of short stature (height ≤ -2.5 SDS) (17), until they attained AH (*i.e.*, height velocity <0.5 cm in 6 months and bone age ≥ 15 years for girls and ≥ 16.5 years for boys). Excluded were subjects with chromosomal abnormalities or signs of a syndrome except SRS.

From start of GH until 2 years after discontinuation of treatment, parameters of vascular and metabolic health were investigated at 4 time points: 1) at GH-start, 2) when subjects reached AH (*i.e.*, GH-stop), 3) at 6 months after GH-stop, and 4) at 2 years after GH-stop. Owing to the time-consuming aspect of the study and the fact that not all patients had already discontinued GH for 2 years, data were available for 18 SRS patients and 165 non-SRS subjects at 6 months after GH-stop and 13 SRS patients and 109 non-SRS subjects at 2 years after GH-stop.

Subjects were diagnosed with SRS based on the Netchine–Harbison clinical scoring system (18), which includes the following 6 factors: (1) prenatal growth retardation (BL and/or BW ≤ -2 SDS for gestational age); (2) postnatal growth retardation (height SDS <-2.0 according to national reference) (17); (3) relative macrocephaly at birth (head circumference at birth ≥ 1.5 SDS above BL and/or BW SDS according to Usher and McLean (16); (4) prominent forehead; (5) body asymmetry [leg length discrepancy of ≥ 0.5 cm or arm asymmetry or leg length discrepancy of <0.5 cm with ≥ 2 other asymmetrical body parts (one being a nonface part)]; and (6) feeding difficulties during early childhood. Patients were classified as SRS if at least 4 factors were present. SRS patients were tested for methylation aberrations of the 11p15 region and mUPD7, and when negative, also for CDKN1C and insulin-like growth factor (IGF)2 mutations. Patients with SRS based on the Netchine–Harbison clinical scoring system but without a known genetic aberration were classified as clinical SRS.

This study was performed according to the Helsinki Declaration and approved by the Medical Ethics Committees of all participating centers. Written informed consent was obtained from all participants and/or their parents.

Measurements

Birth data were obtained from records of hospitals and primary health care centers. Anthropometric measurements were performed twice according to standardized methods, after which the mean was calculated. Height was measured to the nearest 0.1 cm (Harpenden stadiometer), weight to the nearest 0.1 kg (Servo Balance KA-20-150S). Waist circumference was measured midway between the lower margin of the lowest rib and the upper margin of the iliac crest at the end of a normal expiration.

Diastolic BP (DBP) and systolic BP (SBP) were measured after 10 minutes of rest, in sitting position, using the nondominant arm, with an automatic device (Accutorr Plus; Datascope, Montvale NJ) at every 5 minutes for 1 hour; the mean value was taken to reflect resting BP.

LBM and FM were measured on a dual-energy X-ray absorptiometry machine (Lunar Prodigy; GE Healthcare, Chalfont St. Giles, UK). FM was measured as a percentage of total body weight (FM%). Quality control was performed daily.

Glucose homeostasis was assessed at GH-stop and 6 months and 2 years thereafter by frequently sampled intravenous glucose tolerance (FSIGT) tests with tolbutamide after an overnight fast (19). Si, glucose effectiveness (Sg), acute insulin response (AIRg), and disposition index (DI) were calculated using R. N. Bergman's minimal model software (MINMOD 6.01). Si quantifies the capacity of insulin to promote glucose disposal, and Sg reflects the capacity of glucose to mediate its own disposal. AIRg is an estimate of insulin secretory capacity and was measured as the area under the curve from 0 to 10 minutes corrected for baseline insulin levels. DI equals AIRg times Si (DI = AIRg $\times$ Si) and indicates the β-cell function.

Revised criteria of the National Cholesterol Education Program [adult treatment panel III (ATP-III)] were used to determine components of metabolic syndrome (20). Metabolic syndrome was defined as having ≥ 3 of the following risk factors: (1) waist circumference in men >102 cm, and in women >88 cm; (2) triglycerides (Tg) >1.7 mmol/L; (3) high-density lipoprotein cholesterol (HDLc) in men <1.03, in women <1.3 mmol/L; (4) BP $\geq$ 130/$\geq$85 mm Hg; (5) fasting glucose >5.6 mmol/L.

Behavioral problems were defined as attention deficit hyperactivity disorder, pervasive developmental disorder, or autism spectrum disorder, diagnosed by an experienced psychologist.

Laboratory measurements

After centrifugation, all samples were kept frozen until assayed (−80°C). Fasting levels of total cholesterol (TC), Tg, and HDLc were measured using the CHOD-PAP and the GPO-PAP reagent kits (Roche Diagnostics, Mannheim, Germany) (TC and Tg), and using a homogeneous enzymatic colorimetric assay (Roche Diagnostics) (HDLc). Low-density lipoprotein cholesterol (LDLc) was calculated using the Friedewald formula: LDLc (mmol/L) = TC − HDLc − 0.45 × level of Tg. Fasting glucose levels were determined on an Architect ci8200 system (Abbott Laboratories, Abbott Park, IL). Fasting insulin levels were measured by immunoradiometric assay (Medgenix, Biosource Europe, Nivelles, Belgium). Calculated glomerular filtration rate (GFR) was calculated using the Schwartz equation: GFR (mL/min/1.73 m^2) = [0.41 × height (cm)]/serum creatinine (mg/dL) (21).

DNA analyses

DNA methylation testing of the 11p15 region [ICR1 (H19) and ICR2 (KCNQ1OT1)] and mUPD7 was performed using methylation-specific multiplex ligation-mediated probe amplification, as previously described (11). To identify CDKN1C mutations [c.836G>T (pArg279Leu)] (22) or IGF2 mutations [IGF2c.191C>A (p.Ser64Ter)] (23), genomic DNA extracted from peripheral blood leukocytes was diluted to a concentration of 5 ng/μL and target regions of CDKN1C and IGF2 were amplified by PCR using primers. The IGF2 region containing the mutation was amplified using the IGF2exR3 forward primer 5′-CTCGGCATTATGACCTGTGT-′3 and IGF2ex3R reverse primer 5′-AGGCGTGTGATGGGAAAG-′3, as well as the CKDN1C target region containing the mutation using the primers described previously (22).

Calculations and statistics

SD scores for BL and BW were calculated to correct for gestational age and sex (16), SD scores for height, serum IGF-I, and IGF binding protein 3 (IGFBP3) to correct for sex and age (17, 24), and SD scores for weight and BP to correct for height and sex (25). SD scores for BL, BW, height, and weight were calculated using the Growth Analyser software (http://www.growthanalyser.org). FM% SDS was calculated according to age- and sex-matched Dutch reference values (26). Because LBM is strongly related to height, LBM was expressed as SDS for height and sex (26).

Distribution of variables was determined by Shapiro–Wilk tests and normal Q-Q-plots. Because of a skewed distribution, Si, Sg, AIR, and DI were log transformed. Differences between SRS and non-SRS were analyzed using independent-sample *t* tests. To analyze differences in longitudinal changes during GH treatment between SRS and non-SRS, linear mixed modeling for repeated measurements was used with SRS and time as factors. An unstructured repeated covariance type was used, adjusting for missing values. A *P* value of <0.05 was considered statistically significant. Analyses were performed with SPSS version 21.0.

Results

Clinical characteristics

Clinical characteristics of the SRS and non-SRS subjects are listed in Table 1. Fourteen SRS patients had an 11p15 aberration and 6 patients an mUPD7. There were no patients with an IGF2 or CDKN1C mutation. Nine SRS patients tested negative for all known aberrations causing SRS and were assigned to the clinical SRS group. SRS patients had a lower BL and BW SDS than did the non-SRS subjects ($P = 0.005$ and $P = 0.04$, respectively). Head circumference SDS was similar in SRS and non-SRS ($P = 0.56$), but the discrepancy between head circumference and BL was larger in SRS ($P = 0.009$).

At GH-start, SRS patients were significantly younger than non-SRS subjects [mean age (SD), 5.4 (2.1) years vs 6.7 (2.0) years, respectively; $P = 0.003$] and had a lower height SDS ($P < 0.001$) and weight for height SDS ($P < 0.001$). SRS patients attained AH at a younger age [15.7 (1.5) years vs 16.4 (1.3) years, respectively; $P = 0.01$]. Mean AH SDS (SD) was −1.63 (0.8) in SRS and −1.43 (0.8) in non-SRS ($P = 0.26$). SRS patients had a lower weight for height SDS at AH ($P < 0.001$). At 2 years after GH-stop, age was similar in the 2 groups ($P = 0.72$).

BP and fasting lipid levels

At GH-start, SRS patients had a lower mean SBP SDS than did non-SRS subjects ($P = 0.04$), whereas DBP SDS was similar in both groups (Table 2). At the end of treatment, SBP and DBP SDS had remained similar in SRS whereas they had decreased in non-SRS ($P < 0.001$). At GH-stop, SRS patients had a similar SBP and DBP SDS as did non-SRS ($P = 0.44$ and $P = 0.07$, respectively). In the 2 years after GH-stop, SBP and DBP SDS remained stable in SRS, whereas DBP and SBP SDS increased in the 6 months after GH-stop in non-SRS and decreased again in the 18 months thereafter. At 2 years after GH-stop, SBP and DBP SDS were similar and within normal ranges in SRS and non-SRS.

At GH-start, fasting serum levels of TC, LDLc, HDLc, and Tg were similar in SRS and non-SRS (Table 2). During treatment, serum lipids remained similar and within normal ranges in SRS. In non-SRS, there was a significant decrease of TC and LDLc during treatment, followed by an increase in the 2 years after GH-stop, whereas HDLc and Tg remained similar during and after GH-stop.

Body composition

Figure 1 shows the longitudinal changes in LBM and FM% during GH and after GH-stop in SRS and non-SRS. At GH-start, estimated mean (SE) LBM SDS was −1.63 (0.9) in SRS vs −0.53 (0.3) in non-SRS ($P = 0.12$). During treatment, LBM remained similar in both groups, and SRS patients had a lower LBM at GH-stop ($P = 0.007$). In the 6 months after GH-stop, LBM SDS deteriorated in both groups, but remained stable in the 18 months thereafter. At 2 years after GH-stop, there was still a trend toward a lower LBM in SRS than in non-SRS ($P = 0.10$).

Table 1. Clinical Characteristics

	SRS (n = 29)	Non-SRS (n = 171)	*P*
Male/female	13/16	82/89	0.76
11p15/mUPD7/clinical	14/6/9	N/A	N/A
Gestational age, wk	37.6 (2.8)	35.7 (3.9)	**0.003**
Birth length SDS	−4.26 (1.6)	−3.02 (1.5)	**0.005**
Birth weight SDS	−2.76 (1.4)	−2.21 (1.2)	**0.04**
Birth head circumference SDS	−1.73 (1.5)	−2.02 (1.1)	0.56
Target height SDS	−0.09 (0.7)	−0.48 (0.8)	**0.02**
At GH-start			
Age, y	5.4 (2.1)	6.7 (2.0)	**0.003**
Height SDS	−3.60 (0.8)	−2.96 (0.5)	**<0.001**
Weight/height SDS	−2.76 (1.1)	−1.26 (1.2)	**<0.001**
Head circumference SDS	−0.64 (1.1)	−1.23 (0.9)	**0.003**
IGF-I SDS	−0.33 (1.4)	−0.55 (1.2)	0.49
IGFBP3 SDS	−1.51 (1.2)	−1.38 (1.2)	0.69
At AH (GH-stop)			
Age, y	15.7 (1.5)	16.4 (1.3)	**0.01**
Height SDS	−1.63 (0.8)	−1.43 (0.8)	0.26
Weight/height SDS	−0.30 (1.1)	0.48 (1.0)	**<0.001**
Head circumference SDS	−0.47 (1.0)	−0.82 (0.9)	0.24
IGF-I SDS	1.27 (0.9)	1.25 (0.8)	0.95
IGFBP3 SDS	−0.12 (0.5)	−0.32 (0.6)	0.35
At 2 y after GH-stop			
Age, y	18.3 (1.6)	18.4 (1.3)	0.72

Values are expressed as mean (SD). Boldface *P* values are <0.05.

Abbreviation: N/A, not applicable.

At GH-start, FM% SDS was similar in both groups [estimated mean (SE), −0.51 (0.3) in SRS vs −0.65 (0.2) in non-SRS; $P = 0.72$). During GH treatment, FM% SDS increased in both groups. During the 6 months after GH-stop, FM% SDS increased further in SRS, but remained stable in the 18 months thereafter. In non-SRS, FM% SDS increased persistently until 2 years after GH-stop. At 2 years after GH-stop, FM% SDS was similar in SRS and non-SRS ($P = 0.97$).

Table 2. Metabolic Parameters in SRS and Non-SRS at GH-Start, GH-Stop, and 6 Months and 2 Years After GH-Stop

	GH-Start			GH-Stop			6 Months After GH-Stop			2 Years After GH-Stop		
	SRS	Non-SRS	*P*	SRS	Non-SRS	*P*	SRS	Non-SRS	*P*	SRS	Non-SRS	*P*
BP												
SBP SDS	0.37 (1.1)	0.83 (1.0)	**0.04**	0.19 (1.0)	0.04 (0.9)[a]	0.44	0.21 (0.8)	0.43 (1.0)[a]	0.41	0.11 (0.7)	−0.00 (0.8)[a]	0.65
DBP SDS	0.45 (1.1)	0.28 (1.0)	0.44	0.21 (0.6)	−0.04 (0.5)[a]	0.07	0.44 (0.6)	0.36 (0.7)[a]	0.68	0.10 (0.5)	0.00 (0.5)[a]	0.54
Lipid levels												
TC, mmol/L	4.1 (0.4)	4.2 (0.7)	0.15	4.0 (0.9)	4.0 (0.8)[a]	0.85	4.1 (0.9)	4.0 (0.9)	0.73	4.4 (1.0)[a]	4.3 (0.9)[a]	0.31
LDLc, mmol/L	2.3 (0.6)	2.4 (0.7)	0.56	2.2 (0.7)	2.3 (0.7)[a]	0.71	2.4 (0.6)	2.3 (0.7)	0.61	2.7 (0.8)[a]	2.5 (0.8)[a]	0.22
HDLc, mmol/L	1.3 (0.4)	1.4 (0.4)	0.09	1.4 (0.3)	1.5 (0.4)	0.31	1.4 (0.3)	1.5 (0.4)	0.38	1.4 (0.4)	1.5 (0.4)	0.64
Tg, mmol/L	1.1 (0.5)	1.0 (0.5)	0.45	1.3 (0.9)	1.0 (0.5)	0.053	1.1 (0.5)	0.9 (0.6)	0.10	1.1 (0.4)	0.9 (0.4)	0.14
Glucose and insulin												
Fasting glucose, mmol/L	4.0 (0.7)	4.4 (0.7)	**0.047**	4.9 (0.5)[a]	5.0 (0.5)[a]	0.69	4.9 (0.5)	4.7 (0.5)[a]	0.21	5.0 (0.3)	4.7 (0.4)	0.12
Fasting insulin, mU/L	13.8 (14.6)	15.0 (14.0)	0.81	15.0 (6.6)	15.1 (7.0)	0.95	8.0 (4.2)[a]	10.9 (4.6)[a]	0.07	9.4 (4.4)	9.9 (4.0)	0.78
ATP-III score[b]												
0	9	85		13	95		9	92		9	70	
1	8	29	0.14	8	34	0.19	4	45	0.57	4	29	0.67
2	2	7		3	5		2	9		0	5	
3	0	0		0	2		0	0		0	0	
Renal function												
Creatinine, μmol/L	28.5 (13.1)	35.6 (12.7)	**0.02**	62.3 (13.0)[a]	68.3 (12.4)[a]	**0.04**	70.1 (11.2)[a]	70.6 (13.1)[a]	0.89	70.9 (14.0)	72.0 (12.6)[a]	0.60
Calculated GFR, mL/min/1.73 m^2	148.9 (59.7)	119.0 (44.1)	**0.02**	95.5 (20.1)[a]	86.3 (22.8)[a]	0.14	86.6 (11.4)[a]	84.7 (35.1)	0.84	89.6 (15.1)[a]	84.8 (15.8)	0.34

Values are expressed as mean (SD) unless stated otherwise. Boldface *P* values are <0.05.

[a] $P < 0.05$ with respect to previous time point.

[b] Expressed as number of patients.

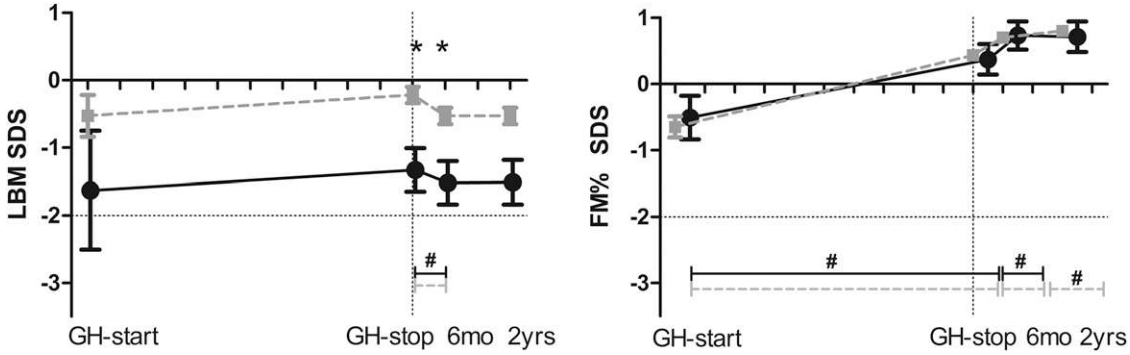

Figure 1. Longitudinal changes in body composition at GH-start, GH-stop, and 6 months and 2 years thereafter in SRS (black lines) and non-SRS (gray dotted lines). Data are expressed as estimated marginal means ± standard error of the mean. $^{*}P < 0.05$ SRS vs non-SRS; $^{\#}P < 0.05$ compared with previous time point (in black for SRS and gray for non-SRS).

Insulin sensitivity and β-cell function

At GH-start, fasting glucose levels were lower in SRS than in non-SRS ($P = 0.047$), whereas fasting insulin levels were similar in the 2 groups (Table 2). During treatment, fasting glucose levels increased, whereas insulin levels remained stable in both groups. After GH-stop, glucose levels remained stable in SRS, whereas they decreased in the 6 months after GH-stop in non-SRS. Insulin levels decreased in the 6 months after GH-stop and remained stable in the 18 months thereafter in both groups.

Figure 2 shows the longitudinal changes in Si, Sg, AIR, and DI from GH-stop until 2 years thereafter. At GH-stop, Si, Sg, AIR, and DI were similar in SRS and non-SRS. During the 6 months after GH-stop, Si and DI increased significantly in both groups and remained stable in the 18 months thereafter. Sg only increased in non-SRS in the 6 months after GH-stop and remained stable in both groups in the 18 months thereafter. At 2 years after GH-stop, SRS patients had a lower AIR than did non-SRS subjects ($P = 0.009$), whereas Si, Sg, and DI were similar in both groups. Until 2 years after GH-stop, none of the SRS and non-SRS patients had developed DM2.

Metabolic syndrome

ATP-III score was similar and overall low in SRS and non-SRS at GH-start, GH-stop, and 6 months and 2 years thereafter (Table 2). There were no SRS patients with an ATP-III score ≥ 3 at any time point. One girl of 15.4 years and 1 boy of 15.9 years in the non-SRS group had an ATP-III score of 3, and thus met the criteria for metabolic syndrome. Two SRS patients had an ATP-III score of 2 at

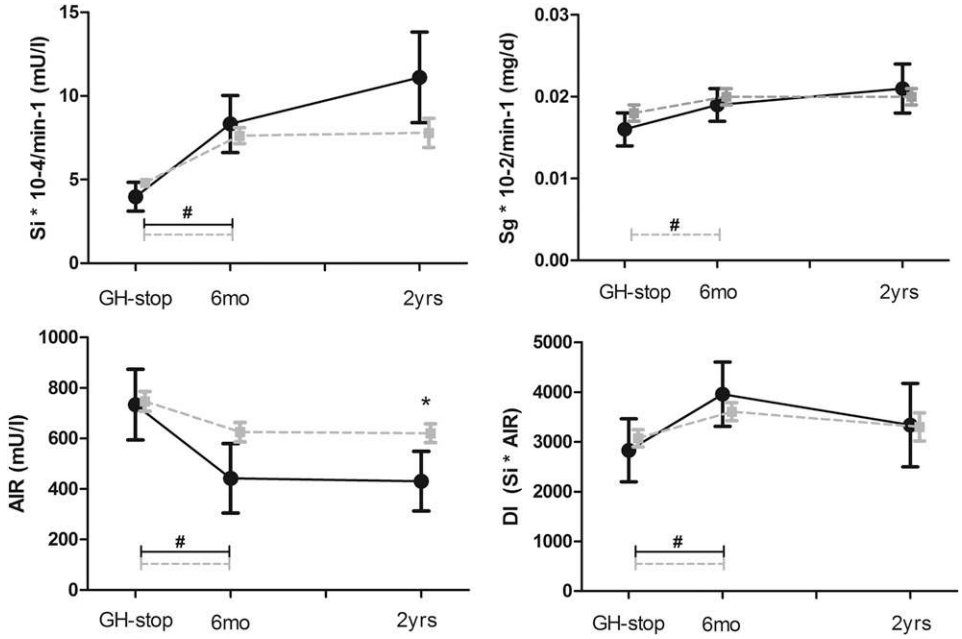

Figure 2. Longitudinal changes in FSIGT results at GH-stop and 6 months and 2 years thereafter in SRS (black lines) and non-SRS (gray dotted lines). Data are expressed as estimated marginal means ± standard error of the mean. $^{*}P < 0.05$ SRS vs non-SRS; $^{\#}P < 0.05$ compared with previous time point (in black for SRS and gray for non-SRS).

GH-start due to an adverse lipid profile. In both patients, this improved during treatment, resulting in an ATP-III score of 1 and 0 at GH-stop. Three other SRS patients, all girls, had an ATP-III score of 2 at GH-stop due to adverse lipid levels and high BP. At 2 years after GH-stop, the lipid levels of 1 girl had improved, probably due to dietary changes, resulting in an ATP-III score of 1. Of the other 2 girls, there were no follow-up data available.

Renal function

At GH-start, mean (SD) serum creatinine was significantly lower in SRS than in non-SRS ($P = 0.02$), probably due to the younger age and the trend toward a lower LBM in SRS patients at GH-start (Table 2). Consequently, calculated GFR was higher in SRS than in non-SRS at GH-start. At GH-stop, serum creatinine was lower in SRS ($P = 0.04$), whereas calculated GFR was similar in the 2 groups. There were no differences in serum creatinine and calculated GFR 6 months and 2 years after GH-stop. Serum creatinine and calculated GFR fell within the normal ranges for age at all time points.

Follow-up of congenital malformations in SRS

Table 3 shows the congenital malformations, anomalies, and developmental problems in the total group of SRS patients and per subgroup based on the underlying epigenetic alteration. Multiple patients had craniofacial and musculoskeletal anomalies such as micrognathia and retrognathia, as well as asymmetry of face or limbs. A congenital heart defect was seen in 1 patient with an 11p15 aberration and in 1 patient with clinical SRS. Genital anomalies were only seen in SRS males, of which 1 patient with an 11p15 aberration had a hypospadias, and 2 patients (1 with an 11p15 aberration and 1 with clinical SRS) had cryptorchidism. Developmental impairments were seen in 33.3% of the mUPD7 patients and in 14.3% of the 11p15 patients, but not in the clinical SRS patients. Behavioral problems were present in half of the mUPD7 patients, vs in <15% of the 11p15 and clinical SRS patients. Besides these known malformations and developmental problems, there were also patients with various other anomalies, such as hearing loss (in 1 patient with mUPD7), strabismus (in 1 patient with an 11p15 aberration), and epilepsy (in 1 patient with clinical SRS).

Safety of GH treatment

At GH-start, SRS and non-SRS subjects had similar mean (SD) serum IGF-I SDS [−0.33 (1.4) in SRS and −0.55 (1.2) in non-SRS; $P = 0.49$] (Table 1). At GH-stop, IGF-I SDS had significantly increased in both groups, but was still similar and within normal ranges in SRS and non-SRS [1.27 (0.9) in SRS and 1.25 (0.8) in non-SRS; $P = 0.95$].

Two female SRS patients with an 11p15 aberration were diagnosed with a slipped capital femoral epiphysis

Table 3. Congenital Malformations, Anomalies, and Developmental Problems in the Total Group of SRS Patients and per Subgroup

	Anomaly	Total SRS (n = 29)	11p15 (n = 14)	mUPD7 (n = 6)	Clinical (n = 9)
Craniofacial	Micrognathia/retrognathia	4 (13.8)	2 (14.3)	2 (33.3)	—
	Face asymmetry	3 (10.3)	3 (21.4)	—	—
Musculoskeletal	Limb asymmetry	7 (24.1)	6 (42.9)	1 (16.7)	1 (11.1)
	Scoliosis	2 (6.9)	1 (7.1)	1 (16.7)	—
	Bilateral club feet	1 (3.5)	1 (7.1)	—	—
	Hip dysplasia	1 (3.5)	1 (7.1)	—	—
	Slipped femoral epiphysis	2 (6.9)	2 (14.3)	—	—
	Joint contractures	1 (3.5)	1 (7.1)	—	—
	Inguinal hernia	1 (3.5)	—	—	1 (11.1)
	Exostosis	1 (3.5)	—	—	1 (11.1)
Heart	Atrial septal defect	1 (3.5)	1 (7.1)	—	—
	Ventricular septal defect	1 (3.5)	—	—	1 (11.1)
Genital	Hypospadias	1 (3.5)	1 (7.1)	—	—
	Cryptorchidism	2 (6.9)	1 (7.1)	—	1 (11.1)
Development	Mild impairment	2 (6.9)	—	2 (33.3)	—
	Speech delay	1 (3.5)	1 (7.1)	—	—
	Delayed motor milestones	2 (6.9)	1 (7.1)	1 (16.7)	—
	Behavioral problems	4 (13.8)	1 (7.1)	3 (50.0)	1 (11.1)
Other	Hearing loss	1 (3.3)	—	1 (16.7)	—
	Strabismus	1 (3.5)	1 (7.1)	—	—
	Thrombocytopenia	1 (3.5)	—	1 (16.7)	—
	Lung hypoplasia	1 (3.5)	1 (7.1)	—	—
	Hashimoto thyroiditis	1 (3.5)	—	—	1 (11.1)
	Epilepsy	1 (3.5)	—	—	1 (11.1)

Values are n (%).

—, no anomaly.

during GH treatment at the ages of 10 and 11 years after 6 and 7 years, respectively, of GH treatment. Both girls were simultaneously treated with a gonadotropin-releasing hormone analog for 1 month and 1 year, respectively, when their capital femoral epiphyses slipped. Both girls underwent surgical fixation of the hip joint. After this, GH treatment was continued and they both attained an AH around −1 SDS (−0.95 SDS and −1.04 SDS).

Discussion

This study shows long-term data on metabolic health, safety of GH treatment, and phenotype in SRS patients compared with non-SRS short SGA subjects treated with GH. We found that SRS and non-SRS patients have a very similar metabolic health profile at the start of treatment, and that, apart from minor variations, the metabolic profile of SRS and non-SRS patients responds similarly to GH treatment. At the age of 18 years, there is no difference in risk for metabolic syndrome between SRS and non-SRS.

This longitudinal study describes extensive metabolic health data in a cohort of GH-treated SRS patients that was followed from childhood into early adulthood. We used gold standard tests such as dual-energy X-ray absorptiometry to measure body composition, and FSIGT tests with tolbutamide to assess Si and β-cell function, making our data unique (27). All major determinants of cardiovascular disease risk were similar in SRS and non-SRS at the start of treatment, and SBP and fasting glucose levels were even lower in SRS than in non-SRS. LBM was low in both groups, especially in SRS patients, but this difference did not reach statistical significance. We found some differences between the 2 groups regarding the response to GH treatment. In SRS, BP and lipid levels did not change during treatment, although the lack of difference could be caused by the relatively small number of patients in the SRS group. BP, TC, and LDLc significantly decreased in non-SRS, but the actual differences were small, and thus most likely not clinically relevant. Both groups responded similarly to GH with respect to the changes in body composition, but LBM remained lower in SRS patients. During the 2 years after GH-stop, we found several changes related to the loss of pharmacologic effects of GH in SRS patients, such as a decrease in LBM and an increase in FM%, but this was similar as in non-SRS patients. Si and β-cell function improved after GH-stop. Most importantly, at 2 years after GH-stop, at a mean age of ~18 years, there were no significant differences between the groups, and none of the SRS patients had developed DM2 or metabolic syndrome.

To our knowledge, there are only 2 case reports addressing metabolic health in SRS. The first described 3 SRS patients (all with an 11p15 aberration, 2 having received GH treatment for several years during childhood) who developed adult diseases such as obesity, hypertension, and DM2 in their early 20s (28). The second described the oldest SRS patient known so far, who has DM2, osteopenia, and hypercholesterolemia at the age of 69 years (29). However, these studies were very small and did not compare the data of SRS patients with those of non-SRS subjects who were similarly treated with GH.

We found multiple malformations, anomalies, and developmental problems in the SRS patients, with differences between the 11p15, mUPD7, and clinical patients. In particular, behavioral problems and mild developmental impairments were very common in the mUPD7 patients. However, most SRS patients went to a normal school and had a similar educational level as did their non-SRS peers born SGA. These findings are in contrast with a previous study that found an impairment of cognitive abilities in half of the SRS patients (30). That study was, however, conducted before genetic testing for SRS was available and patients were compared with healthy controls, instead of short children born SGA. In our cohort of SRS patients, there were 2 patients with a congenital heart defect: one 11p15 patient with an atrial septal defect, and 1 clinical SRS patient with a ventricular septal defect. Previous literature showed that the prevalence of congenital heart defects is increased to 5.5% in SRS patients with an 11p15 aberration, compared with 1% in the general population (31). We also found malformations that have not been described in association with SRS, such as hearing loss and epilepsy. Renal anomalies in SRS have been described (32, 33), but they were not present in our study group, and kidney function was similar in SRS and non-SRS. Future studies are needed to decide whether there is an increased risk for these anomalies in SRS. Overall, although we did not perform statistical tests due to the low number of patients in the subgroups, our findings seem in concordance with the study of Wakeling *et al.* (34), who found that 11p15 aberrations are associated with more typical SRS features and congenital defects, and mUPD7 with an increased prevalence of developmental delay.

Considering that SRS is a rare disorder, our study cohort comprises a relatively large group. However, to be able to draw definitive conclusions, larger cohorts are needed. Unfortunately, due to the heterogeneous phenotype and the fact that ~40% of the patients remain even nowadays without a genetically confirmed diagnosis, underdiagnosis is still a problem. Therefore, developments in finding new (epi)genetic causes of SRS (4, 22, 23, 35), advanced molecular testing, and guidelines on how to diagnose SRS (6, 18, 36) are valuable to improve awareness and identification of SRS patients.

In conclusion, we showed that there are no metabolic differences between SRS and non-SRS subjects born SGA, before, during, and after GH treatment. However, a longer follow-up of SGA born adults, and SRS patients specifically, is needed to see whether this will be maintained over the years when patients reach their 30s and 40s.

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