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Clinical Study

IGF-I and IGF Binding Protein-3 Generation Tests and Response to Growth Hormone in Children with Silver-Russell Syndrome

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Objectives. To evaluate, in children with Silver-Russell Syndrome, the response to the IGF-I and IGFBP-3 generation test and compare results to the growth response after 6 months of rhGH. *Methods*. Eight children (6 males), with a mean age of 5.71 ± 2.48 years and height SDS of −3.88 ± 1.28 received rhGH for 6 months. IGF-I and IGFBP-3 were analyzed before and after 4 doses of rhGH. *Results*. The mean growth velocity (GV) before treatment was 5.28 ± 1.9 cm/year. GV increased after rhGH in five children to a mean GV of 10.3 ± 3.64 cm/year. Six children had normal basal IGF-I levels and two low levels. After 4 doses of rhGH, the IGF-I levels were normal in seven. There was no correlation between the growth response and the IGF-I generation test. *Conclusions*. Children with SRS have normal IGF-I generation test. There is no correlation between the generation test and the growth velocity after 6 months of rhGH.

1. Introduction

Silver-Russell syndrome (SRS) was first described in 1953 by Silver et al. [1]and in 1954 by Russell [2]. Ten percent of the cases are due to maternal chromosome 7 disomy (mUPD7) suggesting a genomic "imprinting" [3, 4]. In 2005 Gicquel et al. [5] identified an epimutation (loss of methylation) of the central telomeric imprinting center region 1 (ICR1) on chromosome 11p15 in various patients with typical SRS clinical characteristics. Other authors subsequently confirmed the presence of these mutations with a high frequency (20–63.8%) in patients with SRS [6]. This region is associated with the regulation of many genes, such as tumor suppressor genes (H19) and the IGF-2 gene. Hypermethylation in this region is associated with Beckwith-Wiedemann syndrome characterized by excessive growth and/or asymmetry. Hypomethylation in the H19/IGF2 region could lead to asymmetry and fetal growth retardation as seen in SRS [7]. SRS and Beckwith-Wiedemann syndrome are currently considered two diseases caused by opposite epigenetic alteration in the same chromosomal region (11p15) thus leading to different growth disorders [8–10]. This epigenetic defect can be involved in syndromic intrauterine growth retardation [5, 11]. The diagnosis is clinical and requires at least 3 of the following criteria: (1) birth weight 2 SDS or more below the mean for gestational age (GA), (2) short stature (height more than 2 SDS below the mean for children of the same age and gender) at the time of the diagnosis, (3) characteristic appearance (triangular face, small mandible, low ear implantation, down turned corners of the mouth, proeminent forehead), (4) clinodactyly of the 5th finger, and (5) body asymmetry [12]. The incidence of SRS is 1 in 50.000 to 100.000 newborns [13], and it can be as high as 1 : 3000 with a male predominance [14]. SRS diagnosis

although easily recognizable in extreme cases can be difficult in more subtle situations, especially in the absence of body asymmetry. In their review of the published data, Netchine et al. [10] recently proposed a clinical scoring system for diagnosis in those cases where the patient was born SGA. They suggested that the patient must also have at least three of the five following criteria: postnatal growth retardation, relative macrocephaly, body asymmetry, prominent forehead, and feeding difficulties, with a body mass index (BMI) < -2SD during infancy and early childhood. The latter criterion was included because it is particularly severe and frequent in these children. They also stated that the scoring system is highly predictive of a molecular defect in the diagnosis as 63.8% of patients here classified as SRS under this scoring present 11p15 ICR1 epimutation (loss of methylation).

Many of these children do not present a postnatal catch-up growth and show persistent short stature. The growth in the first three years of life is slow, and from this point on it remains parallel to the curve but below the third percentile [15]. Puberty may occur earlier than normal, and the growth spurt can be smaller [16, 17]. The cumulative result of this growth deficiency is short stature with an average adult height of 151.2 ± 7.8 cm for males and 139.9 ± 9.0 cm for females, between –3.6 and –4.0 SD [15, 18].

GH treatment was approved in the United States in 2001 to be used in children with intrauterine growth retardation (IUGR) (including SRS) who did not present a catch-up growth until 2-3 years of age [19] and in Europe in 2003 after the age of 4 years. The initial age, the dose used, and the height deficit related to the parents height at the beginning of the treatment are predictor factors of the growth response [20–24]. These results were independent of the GH status [23, 25–30]. Boguszewisk et al. [31] described abnormalities in the 24-hour spontaneous GH secretion and lower levels of IGF-I and IGFBP-3 demonstrating that although these children do not present classical GH deficiency (GHD), their growth hormone secretion is frequently abnormal. Even though the majority of these children achieve a normal adult height when treatment is initiated early and is long lasting, the response to rhGH therapy is heterogeneous.

Previous studies suggest that the IGF generation test can be useful in the diagnosis of GH insensitivity syndrome and in predicting their response to rhGH therapy. We raise the question if in some cases of SRS the growth hormone insensitivity could be influencing adult height and response to rhGH.

The objectives of our study were to compare the growth response after six months of rhGH to the response to the IGF-I and IGFBP-3 generation test.

2. Methods

All SRS patients followed at the Instituto de Puericultura e Pediatria Martagão Gesteira, the pediatric hospital of the Universidade Federal do Rio de Janeiro, were evaluated. The inclusion criteria were children clinically diagnosed with SRS, older than 2 years, prepubertal, with a height more than 2 SD below the mean, bone age (BA) below 10 years, with a minimum of 6 months of follow-up to calculate growth velocity (GV), and never treated with rhGH. Children with poor compliance with the regular visits or showing other conditions that could affect growth, like hypothyroidism, were excluded.

This study was approved by the ethics committee of the Universidade Federal do Rio de Janeiro. Informed consent and child assent were obtained from parents or legal guardians and from the patients.

The diagnosis of SRS was established by an expert geneticist based on the presence of at least 3 of the following clinical criteria: (1) short stature; (2) weight and/or height at birth below –2 SDS for gestational age [32]; (3) characteristic facial features; [4] clinodactyly of the fifth digit; (5) body asymmetry.

In order to exclude the presence of other possible conditions that could affect growth or the IGF-I and IGFBP-3 generation, a set of laboratories tests were performed in all patients—complete blood count, erythrocyte sedimentation rate, electrolytes, liver and kidney function tests, lipid profile, urine analysis, free thyroxine, and thyroid-stimulating hormone. Magnetic resonance imaging (MRI) scan or computed tomography (CT) of the brain and of the pituitary gland and abdominal ultrasound were performed in all children. All female patients had a karyotype to exclude Turner syndrome.

Serum samples were collected before the initiation of rhGH and after 4 doses (in the morning of the fifth day). Immediately after collection, samples were centrifuged, divided, and frozen at -20°C. The IGF-I and IGFBP-3 analyses were performed at the same time. Serum levels of IGF-I were analyzed by an IRMA assay (DSL, Webster, TX) with an intra-assay coefficient of variation of 3.4% and interassay coefficient of variation of 8.2%. The limit of detection is 0,8 ng/dL in a dilution of 1 : 30. Serum levels of IGFBP-3 were analyzed by an IRMA assay (DSL, Webster, TX) with an intra- and interassay coefficient of variation of 1.8% and 8.9%, respectively. The limit of detection is 0.0005 mg/L.

Following the protocol described by Blum et al. [33], a basal blood sample was collected, and all children received subcutaneous rhGH (0.05 mg/kg/day) daily for 4 doses. In the morning of the fifth day, another blood sample was collected. An increment of 15 ng/mL for IGF-I (IGF-I Δ) and of 0.4 mg/L for IGFBP-3 (IGFBP-3 Δ) was considered a positive response to the generation test. After the generation test, all patients continue to receive rhGH (same dose) for 6 months. Anthropometrical data collected at the beginning of the generation tests and after 6 months of rhGH therapy were used to calculate the growth velocity.

Pre-and posttreatment bone age (BA) radiograph was done and evaluated by Greulich-Pyle [34] method.

3. Results

3.1. Patients. Ten children (8 males) with age range from 2.08 to 8.67 (5.71 ± 2.48) years old entered the study. Two boys left the protocol after the first month and were excluded from the study. The clinical characteristics of the eight remaining

patients are described on Table 1. Three children (patients **3**, **4,** and **8**) showed body asymmetry. Two of them (**3** and **4**) showed the left leg longer than the right. Patient **3** asymmetry was the more obvious one with the left leg 2 cm longer than the right one and the left foot 1 cm longer than the right one.

3.2. Gestational and Delivery History. The gestational age varied from 36 to 40 weeks with a mean ± SD of 38.25 ± 1.75. Just two children were born at less than 37 weeks of gestation. The mean birth weight (±SD) was 1953.8 g (±464.1). Six of the patients were born with a weight more than 2 SD below the mean. The mean birth length (±SD) was 41.88 cm (±3.27), and all of them had the birth length more than 2 SD below the mean for gestational age. There was no uniform history of teratogenic conditions.

3.3. Target Height. The fathers' heights ranged from 165 to 189 cm (–1.72 to 1.85 SDS) with a mean height of 178.3 ± 9.8 cm and a mean height SDS of 0.23 ± 1.46. The mothers' heights ranged from 156 cm to 171 cm, and the range of maternal heights SDS was –1.29 to 0.55 with a mean height SDS of −0.46 ± 0.96. One of the patients was adopted, and no family information was available.

3.4. Growth Velocity (GV), Height SD Score and Bone Age Pre- and Posttreatment. All 8 children were short with heights SDS ranging from –6.53 to –2.5 (−3.88 ± 1.28). The mean (±SD) bone age was 3.78 ± 2.85 years. All participants were prepubertal throughout the study. The average growth velocity (GV1) before treatment was 5.28 ± 1.9 cm/year Figure 1. Only two children had their growth velocity pretreatment more than 2 SD below the mean.

After 6 months of treatment with rhGH, four patients had a delta GH below 3 cm/year Figure 1. The other 4 patients doubled their GV. Considering the height SDS, it improved for at least 0.5 SD in half of the patients while the other half had no change. The mean posttreatment growth velocity (GV2) was 10.3 ± 3.64 cm/year, and the mean height SDS after 6 months of treatment was −3.35 ± 0.89.

3.5. IGF-I. Two children had basal serum levels of IGF-I more than 2 SDS below the mean, and 6 had normal basal levels. On the 5th day, serum IGF-I levels were normal in 7 children and remained low in one child. The IGF-I generation test was normal (delta >15 ng/dl) in all children. Figure 2 demonstrates the comparison between serum IGF-I levels before and after 4 days of rhGH.

The greatest Δ IGF-I was observed in patient 1, and this did not reflect the change in growth velocity as his growth velocity remained unaltered with rhGH therapy.

Figure 3 demonstrates the correlation between the IGF-I generation test and the change in growth velocity when comparing the growth velocity before and after 6 months of rhGH. Not only there was no correlation but the child with the highest delta in IGF-I had the lowest change in growth velocity and the one with the second highest change in growth velocity had one of the lowest delta in serum IGF-I.

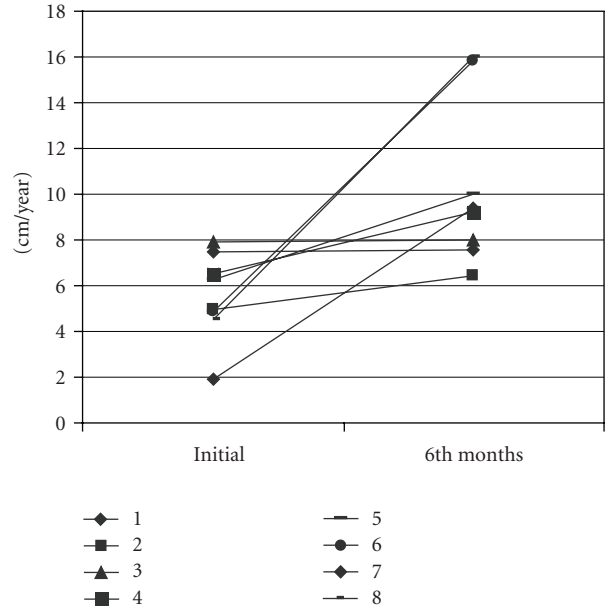

Figure 1: growth velocities before and after 6 months of treatment.

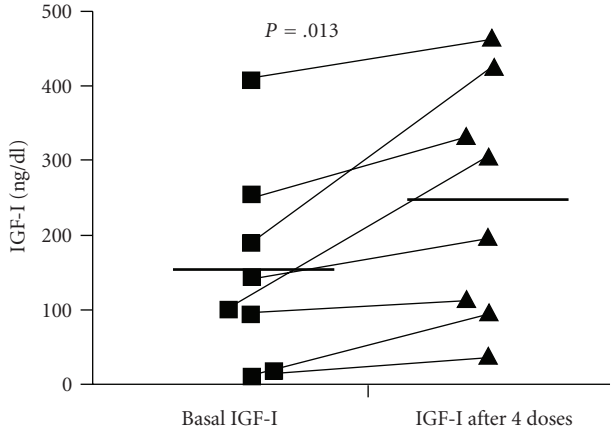

Figure 2: IGF-I values before and after 4 doses of rhGH.

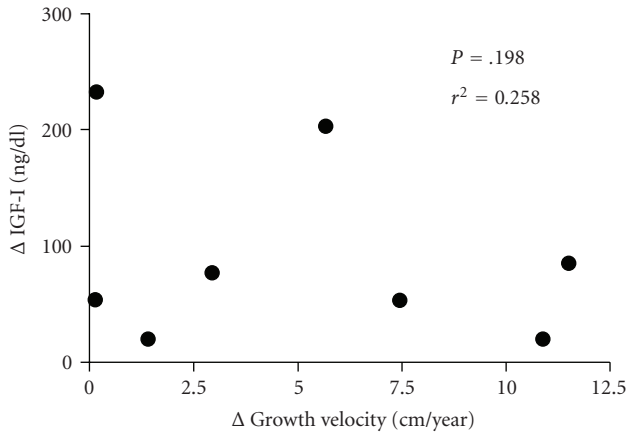

Figure 3: Correlation between the IGF-I generation test and the change in growth velocity.

Table 1: Clinical characteristics.

Patient	Gender	Age (year)	Height (SDS)	Gestational Age (weeks)	Birth Weight (g)	Birth Length (cm)	Characteristic Facial features	Asymmetry	Clinodactyly
1	Male	3.75	−3.44	40	2050	43	+	−	+
2	Male	2.08	−2.5	40	2100	45	+	−	+
3	Female	4.42	−3.38	39	1370	38	+	+	+
4	Male	6.42	−2.7	40	2390	45	+	+	+
5	Male	7.83	−4.71	36	1300	36	+	−	+
6	Male	4.00	−4.08	36	1650	42	+	−	+
7	Male	8.50	−3.67	37	2220	42	+	−	+
8	Female	8.67	−6.53	38	2550	44	+	+	+

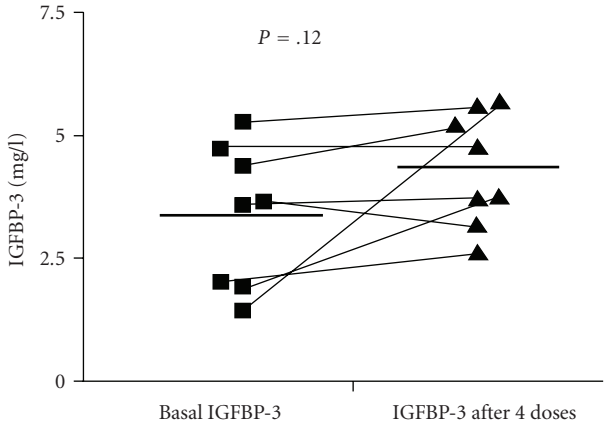

Figure 4: IGFBP-3 values before and after 4 doses of rhGH.

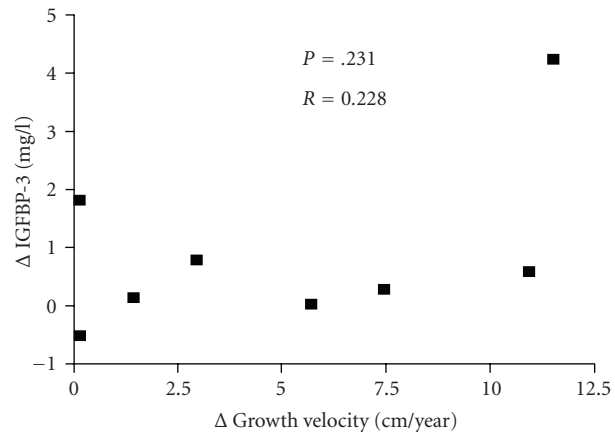

Figure 5: Correlation between the IGFBP-3 generation test and the change in growth velocity.

3.6. IGFBP-3. One child had low basal serum levels of IGFBP-3, two had normal serum levels, and 5 had basal serum IGFBP-3 levels more than 2 SD above the mean. After 5 days of rhGH therapy, three children had normal serum levels of IGFBP-3 and 5 had values more than 2 SD above the mean. Four children had a positive IGFBP-3 generation test (delta >0.4 mg/L), and 4 had a negative test. Figure 4 demonstrates the comparison between serum IGFBP-3 levels before and after 4 days of rhGH. There was no correlation between the IGFBP-3 generation test and the change in growth velocity. Even though the greatest change in IGFBP-3 was seen in the patient with the largest change in the growth velocity (Figure 5), the second highest change in IGFBP-3 had one of the lowest changes in growth velocity.

3.7. Laboratories Parameters and Adverse Events. There were no adverse events during rhGH therapy. Lower limb asymmetry did not change during treatment.

4. Discussion

The number of patients in this study reflects the low incidence of SRS (3).

The male gender is predominant in this study (6 boys) as in the literature [35, 36] probably reflecting the predominance of males in the referral to Pediatric Endocrinologists due to short stature.

Among the facial characteristics, the small triangular face with small mandible and prominent forehead (relative macrocephaly) was evident in all children. Wollmann et al. [18] analyzed data of 386 published patients and reported that the small triangular facies is the most common characteristic, present in 79% of patients.

Corporal asymmetry was detected in 1/3 of the patients. The literature shows that body asymmetry has a frequency between 33% to 51% [12, 15, 18]. This range can be partially justified by the difficulty in detecting and quantifying the asymmetry, especially in children with less manifested phenotypes [35].

All patients had clinodactyly of the 5th finger similarly to the published data (68%). One child had café au lait spots. The published prevalence is around 19% [18].

Concerning birth data, 6 children were born with low weight and all of them with their length more than 2SD below the mean, similarly to published data [18].

Not all children with SRS respond well to rhGH therapy. At the moment, most centers will administer rhGH and evaluate the change in growth velocity after 6–12 months to decide whether to continue or discontinue treatment. In this study, we investigated if the short term (4 doses-5 days) IGF-I and IGFBP-3 generation tests could predict the growth response to 6 months of treatment with rhGH.

In this study the basal serum IGF-I was low in two children (25%) while normal for the others (75%). Most studies evaluating the growth response to rhGH in children with SRS include them in studies investigating children with intrauterine growth retardation (IUGR). Our data are in contrast to Boguszewski's et al. [20], who had shown IGF-I and IGFBP-3 low levels in prepubertal children with IUGR. In the studies by Thieriot-Prevost et al. [37] and Boguszewski et al. [38], serum IGF-I levels increased in children who had catch-up growth during the first year of life, but not in children without this catch-up growth. This statement is not confirmed in the findings here since serum levels of IGF-I increased in all children, independently of the change in growth velocity.

The used rhGH dose for the generation test was based on the one used for children born SGA, since the SRS is the extreme of IUGR. Buckway et al. [39] used 0.025 and 0.05 mg/kg/day dose and observed little advantage of larger rhGH dose. Blair et al. [40] did test in idiopathic short stature (ISS) children using a standard dose (0.033 mg/kg/day) and low dose (0.011 mg/kg/day) observing a better result with the higher dose. From Stanhope et al. [41] and Albertsson-Wikland et al. [42] studies was selected the use of a dose of 0.05 mg/kg/day as they postulated that the presence of some resistance to GH action by children with SRS. The test duration time was based in the literature, where the majority was carried through in 4 days. Buckway et al. [43] and Jorge et al. [44] found no advantage in more than 4-day test, as there is no significant difference in the increment and no evidence that children with GHD or GHIS would show a normal reply on more prolonged test.

In the present study serum levels of IGF-I increased more than 15 ng/mL in all children after rhGH, demonstrating a non-GH resistant response. Regarding serum levels of IGFBP-3, half of the patients did not increase serum levels by more than 0.4 mg/L, "failing" the generation test. When we correlated the growth response to the generation tests results, there were no correlations, indicating that we cannot use the short-term biochemical response to rhGH therapy to predict the 6-month growth response.

One interesting patient to discuss is patient 8: she had the lowest prestudy serum levels of IGF-I and IGFBP-3 (10 ng/mL and 1.44 mg/L, resp.) and the second lowest prestudy growth velocity (4.5 cm/year). When we look at her response to 4 days of rhGH, her serum levels of IGF-I went to 96 ng/mL, and serum levels of IGFBP-3 went to 5.7 mg/L. After 6 months of rhGH, she had the highest annualized growth velocity (16 cm/year). These results suggest that she could have GHD. The generation test was carried through with no previous evaluation of GH deficiency since SGA born children can show normal response to GH stimulation tests even when they produce less GH than children with a birth weight adequate for gestational age (AGA) or with short stature [45–47].

Based on the results of our study, where not only there was no correlation between the generation tests and the growth response to rhGH therapy but also some of the more robust responses to one of the tests were associated with some of the poorer responses to the other test, and vice versa, we do not believe that increasing the number of patients or increasing the length of follow-up would increase the predictability of the test.

References

[1] H. K. Silver, W. Kiyasu, J. George, and W. C. Deamer, "Syndrome of congenital hemihypertrophy, shortness of stature, and elevated urinary gonadotropins," *Pediatrics*, vol. 12, pp. 368–376, 1953.

[2] A. Russell, "A syndrome of intra-uterine dwarfism recognizable at birth with cranio-facial dysostosis, disproportionately short arms, and other anomalies (5 examples)," *Proceedings of the Royal Society of Medicine*, vol. 47, no. 12, pp. 1040–1044, 1954.

[3] D. Kotzot, D. Balmer, A. Baumer et al., "Maternal uniparental disomy 7—review and further delineation of the phenotype," *European Journal of Pediatrics*, vol. 159, no. 4, pp. 247–256, 2000.

[4] H. Yoshihashi, K. Maeyama, R. Kosaki et al., "Imprinting of human GRB10 and its mutations in two patients with Russell-Silver syndrome," *American Journal of Human Genetics*, vol. 67, no. 2, pp. 476–482, 2000.

[5] C. Gicquel, S. Rossignol, S. Cabrol et al., "Epimutation of the telomeric imprinting center region on chromosome 11p15 in Silver-Russell syndrome," *Nature Genetics*, vol. 37, no. 9, pp. 1003–1007, 2005.

[6] N. Schönherr, E. Meyer, K. Eggermann, M. B. Ranke, H. A. Wollmann, and T. Eggermann, "(Epi)mutations in 11p15 significantly contribute to Silver-Russell syndrome: but are they generally involved in growth retardation?" *European Journal of Medical Genetics*, vol. 49, no. 5, pp. 414–418, 2006.

[7] J. Bliek, P. Terhal, M.-J. Van Den Bogaard et al., "Hypomethylation of the H19 gene causes not only silver-russell syndrome (SRS) but also isolated asymmetry or an SRS-like phenotype," *American Journal of Human Genetics*, vol. 78, no. 4, pp. 604–614, 2006.

[8] T. Eggermann, N. Schönherr, E. Meyer et al., "Epigenetic mutations in 11p15 in Silver-Russell syndrome are restricted to the telomeric imprinting domain," *Journal of Medical Genetics*, vol. 43, no. 7, pp. 615–616, 2006.

[9] N. Schönherr, E. Meyer, A. Roos, A. Schmidt, H. A. Wollmann, and T. Eggermann, "The centromeric 11p15 imprinting centre is also involved in Silver-Russell syndrome," *Journal of Medical Genetics*, vol. 44, no. 1, pp. 59–63, 2007.

[10] I. Netchine, S. Rossignol, M.-N. Dufourg et al., "Brief report: 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," *Journal of Clinical Endocrinology and Metabolism*, vol. 92, no. 8, pp. 3148–3154, 2007.

[11] G. Binder, A.-K. Seidel, K. Weber et al., "IGF-II serum levels are normal in children with Silver-Russell syndrome who frequently carry epimutations at the IGF2 locus," *Journal of*

Clinical Endocrinology and Metabolism, vol. 91, no. 11, pp. 4709–4712, 2006.

[12] S. M. Price, R. Stanhope, C. Garrett, M. A. Preece, and R. C. Trembath, "The spectrum of Silver-Russell syndrome: a clinical and molecular genetic study and new diagnostic criteria," *Journal of Medical Genetics*, vol. 36, no. 11, pp. 837–842, 1999.

[13] R. Stanhope, A. Albanese, and C. Azcona, "Growth hormone treatment of Russell-Silver syndrome," *Hormone Research*, vol. 49, supplement 2, pp. 37–40, 1998.

[14] G. E. Moore, S. Abu-Amero, E. Wakeling et al., "The search for the gene for Silver-Russell syndrome," *Acta Paediatrica*, vol. 88, no. 433, supplement, pp. 42–48, 1999.

[15] J. M. Tanner, H. Lejarraga, and N. Cameron, "The natural history of the Silver Russell syndrome: a longitudinal study of thirty nine cases," *Pediatric Research*, vol. 9, no. 8, pp. 611–623, 1975.

[16] P. S. W. Davies, R. Valley, and M. A. Preece, "Adolescent growth and pubertal progression in the Silver-Russell syndrome," *Archives of Disease in Childhood*, vol. 63, no. 2, pp. 130–135, 1988.

[17] L. Ibáñez, A. Ferrer, M. V. Marcos, F. R. Hierro, and F. de Zegher, "Early puberty: rapid progression and reduced final height in girls with low birth weight," *Pediatrics*, vol. 106, no. 5, p. E72, 2000.

[18] H. A. Wollmann, T. Kirchner, H. Enders, M. A. Preece, and M. B. Ranke, "Growth and symptoms in Silver-Russell syndrome: review on the basis of 386 patients," *European Journal of Pediatrics*, vol. 154, no. 12, pp. 958–968, 1995.

[19] P. A. Lee, S. D. Chernausek, A. C. S. Hokken-Koelega, and P. Czernichow, "International small for gestational age advisory board consensus development conference statement: management of short children born small for gestational age, April 24-October 1, 2001," *Pediatrics*, vol. 111, no. 6, pp. 1253–1261, 2003.

[20] M. Boguszewski, K. Albertsson-Wikland, S. Aronsson et al., "Growth hormone treatment of short children born small-for-gestational-age: the Nordic Multicentre Trial," *Acta Paediatrica*, vol. 87, no. 3, pp. 257–263, 1998.

[21] M. Boguszewisk, C. Jansson, S. Rosberg, and K. Albertsson-Wikland, "Changes in serum insulin-like growth factor I (IGF-I) and IGF-binding protein-3 levels during growth hormone treatment in prepubertal short children born small for gestational age," *Journal of Clinical Endocrinology and Metabolism*, vol. 81, no. 11, pp. 3902–3908, 1996.

[22] A. Fjellestad-Paulsen, P. Czernichow, R. Brauner et al., "Three-year data from a comparative study with recombinant human growth hormone in the treatment of short stature in young children with intrauterine growth retardation," *Acta Paediatrica*, vol. 87, no. 5, pp. 511–517, 1998.

[23] F. De Zegher, K. Albertsson-Wikland, H. A. Wollmann et al., "Growth hormone treatment of short children born small for gestational age: growth responses with continuous and discontinuous regimens over 6 years," *Journal of Clinical Endocrinology and Metabolism*, vol. 85, no. 8, pp. 2816–2821, 2000.

[24] T. C. J. Sas, W.-J. M. Gerver, R. De Bruin et al., "Body proportions during 6 years of GH treatment in children with short stature born small for gestational age participating in a randomised, double-blind, dose-response trial," *Clinical Endocrinology*, vol. 53, no. 6, pp. 675–681, 2000.

[25] A. Albanese and R. Stanhope, "GH treatment induces sustained catch-up growth in children with intrauterine growth retardation: 7-year results," *Hormone Research*, vol. 48, no. 4, pp. 173–177, 1997.

[26] C. Azcona, A. Albanese, P. Bareille, and R. Stanhope, "Growth hormone treatment in growth hormone-sufficient and -insufficient children with intrauterine growth retardation/ Russell-Silver Syndrome," *Hormone Research*, vol. 50, no. 1, pp. 22–27, 1998.

[27] C. Azcona and R. Stanhope, "Absence of catch-down growth in Russell-Silver syndrome after short-term growth hormone treatment," *Hormone Research*, vol. 51, no. 1, pp. 47–49, 1999.

[28] P. G. Chatelain, "Auxology and response to growth hormone treatment of patients with intrauterine growth retardation or Silver-Russell syndrome: analysis of data from the Kabi Pharmacia International Growth Study," *Acta Paediatrica*, vol. 391, supplement, pp. 79–81, 1993.

[29] Y. Rakover, S. Dietsch, G. R. Ambler, C. Chock, M. Thomsett, and C. T. Cowell, "Growth hormone therapy in Silver Russell syndrome: 5 years experience of the Australian and New Zealand growth database (OZGROW)," *European Journal of Pediatrics*, vol. 155, no. 10, pp. 851–857, 1996.

[30] M. B. Ranke and A. Lindberg, "Growth hormone treatment of short children born small for gestation-al age or with Sliver-Russell syndrome: results from KIGS (Kabi Pharmacia International Growth Study), including the first report on final height," *Acta Paediatrica*, supplement 417, pp. 18–26, 1996.

[31] M. Boguszewski, S. Rosberg, and K. Albertsson-Wikland, "Spontaneous 24-hour growth hormone profiles in prepubertal small for gestational age children," *Journal of Clinical Endocrinology and Metabolism*, vol. 80, no. 9, pp. 2599–2606, 1995.

[32] R. Usher and F. McLean, "Intrauterine growth of live-born Caucasian infants at sea level: standards obtained from measurements in 7 dimensions of infants born between 25 and 44 weeks of gestation," *The Journal of Pediatrics*, vol. 74, no. 6, pp. 901–910, 1969.

[33] W. F. Blum, A. M. Cotterill, M. C. Postel-Vinay et al., "Improvement of diagnostic criteria in growth hormone insensitivity syndrome: solutions and pitfalls," *Acta Paediatrica*, vol. 83, supplement 399, pp. 117–124, 1994.

[34] W. W. Greulich and S. I. Pyle, *Radiographic Atlas Ok Skeletal Development of the Hand and Wrist*, Stanford University Press, Stanford, Calif, USA, 1st edition, 1950.

[35] H. M. Saal, R. A. Pagon, and M. G. Pepin, "Reevaluation of Russell-Silver syndrome," *Journal of Pediatrics*, vol. 107, no. 5, pp. 733–737, 1985.

[36] L. J. Marks and P. S. Bergeson, "The Silver Russell syndrome," *American Journal of Diseases of Children*, vol. 131, no. 4, pp. 447–451, 1977.

[37] G. Thieriot-Prevost, J. F. Boccara, C. Francoual, J. Badoual, and J. C. Job, "Serum insulin-like growth factor 1 and serum growth-promoting activity during the first postnatal year in infants with intrauterine growth retardation," *Pediatric Research*, vol. 24, no. 3, pp. 380–383, 1988.

[38] M. Boguszewski, C. Jansson, S. Rosberg, and K. Albertsson-Wikland, "Changes in serum insulin-like growth factor I (IGF-I) and IGF-binding protein-3 levels during growth hormone treatment in prepubertal short children born small for gestational age," *Journal of Clinical Endocrinology and Metabolism*, vol. 81, no. 11, pp. 3902–3908, 1996.

[39] C. K. Buckway, J. Guevara-Aguirre, K. L. Pratt, C. P. Burren, and R. G. Rosenfeld, "The IGF-I generation test revisited: a marker of GH sensitivity," *Journal of Clinical Endocrinology and Metabolism*, vol. 86, no. 11, pp. 5176–5183, 2001.

[40] J. C. Blair, C. Camacho-Hübner, F. Miraki Moud et al., "Standard and low-dose IGF-I generation tests and spontaneous

growth hormone secretion in children with idiopathic short stature," *Clinical Endocrinology*, vol. 60, no. 2, pp. 163–168, 2004.

[41] R. Stanhope, F. Ackland, G. Hamill, J. Clayton, J. Jones, and M. A. Preece, "Physiological growth hormone secretion and response to growth hormone treatment in children with short stature and intrauterine growth retardation," *Acta Paediatrica Scandinavica*, vol. 78, no. 349, supplement, pp. 47–52, 1989.

[42] K. Albertsson-Wikland, M. Boguszewski, and J. Karlberg, "Children born small-for-gestational age: postnatal growth and hormonal status," *Hormone Research*, vol. 49, supplement 2, pp. 7–13, 1998.

[43] C. K. Buckway, K. A. Selva, K. L. Pratt, E. Tjoeng, J. Guevara-Aguirre, and R. G. Rosenfeld, "Insulin-like growth factor binding protein-3 generation as a measure of GH sensitivity," *Journal of Clinical Endocrinology and Metabolism*, vol. 87, no. 10, pp. 4754–4765, 2002.

[44] A. A. Jorge, S. C. Souza, I. J. Arnhold, and B. B. Mendonca, "Poor reproducibility of IGF-I and IGF binding protein-3 generation test in children with short stature and normal coding region of the GH receptor gene," *Journal of Clinical Endocrinology and Metabolism*, vol. 87, no. 2, pp. 469–472, 2002.

[45] W. J. de Waal, A. C. S. Hokken-Koelega, T. Stijnen, S. M. P. F. de Muinck Keizer-Schrama, and S. L. S. Drop, "Endogenous and stimulated GH secretion, urinary GH excretion, and plasma IGF-I and IGF-II levels in prepubertal children with short stature after intrauterine growth retardation," *Clinical Endocrinology*, vol. 41, no. 5, pp. 621–630, 1994.

[46] F. De Zegher, I. Francois, M. Van Helvoirt, and G. Van Den Berghe, "Small as fetus and short as child: from endogenous to exogenous growth hormone," *Journal of Clinical Endocrinology and Metabolism*, vol. 82, no. 7, pp. 2021–2026, 1997.

[47] W. S. Cutfield, P. L. Hofman, M. Vickers, B. Breier, W. F. Blum, and E. M. Robinson, "IGFs and binding proteins in short children with intrauterine growth retardation," *Journal of Clinical Endocrinology and Metabolism*, vol. 87, no. 1, pp. 235–239, 2002.