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ORIGINAL ARTICLE

The effects of growth hormone therapy on the somatic development of a group of Polish children with Silver-Russell syndrome

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Abstract

OBJECTIVE: Silver-Russell Syndrome is both clinically and genetically a heterogeneous syndrome. Among the most important dysmorphic features of this condition are: a triangular shaped face with a small mandible, a prominent frontal eminence, a thin vermilion border with downward-pointing lip corners, clino- and brachydactyly of the 5th fingers as well as body asymmetry. The most well-known genetic mutations in this syndrome are: the 11p15 epimutation (20–60% patients) and the maternal uniparental chromosome 7 disomy present in 7% to 15% of patients. Children with SRS have severely impaired physical growth – intrauterine and after birth. This, together with the aforementioned dysmorphic features, forms the main diagnostic criteria.

MATERIAL AND METHODS: The study group consisted of 12 children treated with growth hormone, aged 2 to 17 (8.9±4.0 years), therein, all of whom met the phenotype diagnostic criteria by Wollmann and Price. The effects of growth hormone therapy on somatic development of these children are also presented.

RESULTS: Height and weight improved as a result of growth hormone treatment, but the effects were significantly worse than in children with IUGR. Children from the study group presented also a smaller an improvement in growth velocity than children from the control group, but the difference was statistically insignificant.

CONCLUSIONS: Growth hormone therapy accelerates the growth of children with SRS but to a smaller extent than the growth of children born with intrauterine growth retardation without dysmorphic features.

INTRODUCTION

Silver-Russell Syndrome is both clinically and genetically a heterogeneous syndrome. It presents a wide spectrum of clinical signs with a diverse manifestation of dysmorphic features, such as a triangular shaped face with a small mandible, a prominent frontal eminence, relative macrocephaly, ear lobe structure disorders, a thin vermilion zone with a long philtrum, downward-pointing lip corners and body asymmetry (Wollmann *et al.* 1995; Price *et al.* 1999). The most well-known genetic mutations in this syndrome are: the 11p15 epimutation found in 20% to 60% patients and the maternal uniparental chromosome 7 disomy (7–15%) (Netchine *et al.* 2007; Bruce *et al.* 2009; Bartholdi *et al.* 2009; Schönherr *et al.* 2006; Kotzot *et al.* 2008).

Silver-Russell Syndrome is related to an intrauterine growth retardation with a postnatal height deficit. Neonates with SRS are born on time and their birth weight is often below –2 SD. Later these children present with dwarfism and normal body proportions. Low, but consistent growth rate without catch-up growth constitutes to an intensification of growth retardation (Binder *et al.* 2011; Wakeling *et al.* 2011). Height deficit is amid the most serious impairments in children with SRS (Toumba *et al.* 2010). Such children do not reach their genetic growth potential and they are significantly shorter in adulthood (Cutfield *et al.* 2007). Contrary to most children born with IUGR, patients with SRS do not experience catch-up growth (Wollmann *et al.* 1995, Mascarenhas *et al.* 2012). Their growth rate is very low in postnatal and early childhood age (Cutfield *et al.* 2007).

As children with SRS have a negative growth prognosis, Tanner and Ham (Tanner *et al.* 1969) proposed early growth hormone treatment of these children. According to commonly accepted guidelines, short children born with intrauterine growth retardation should begin growth hormone therapy after reaching the age of 4 (Wakeling *et al.* 2011). Growth hormone treatment introduced during puberty improves final height, but is less effective than when started in childhood. Growth hormone therapy, when introduced in childhood, led to a normalization of final height – height standard deviation within the normal range and higher by 2.1SD compared to the height of children, who began the treatment in puberty (Cutfield *et al.* 2007). Most authors underline the high importance of the dosage prescribed. A correlation was shown between the dose and the growth rate, especially in the first year of treatment (Ranke *et al.* 2003; Boguszewski *et al.* 1998; Sas *et al.* 1999). It was concluded that 85% short kids born with intrauterine growth retardation achieve height within the population norms after 7–8 years of high dose growth hormone therapy (Cutfield *et al.* 2007).

The data regarding long-term growth hormone treatment of children with SRS are scarce. In a group of 33 children with SRS, a low dose of this medication led to an improvement in height by 1.8 SD (Cutfield *et al.* 2007; Azcona *et al.* 1999). Growth rate improvement of children with SRS is at least comparable to the growth rate of other children with IUGR treated with GH (Cutfield *et al.* 2007). However, despite growth hormone treatment, patients with SRS do not achieve normal adult height, even though their final height is far greater than the height of people not receiving such therapy (Azcona *et al.* 1999; Azcona *et al.* 1998). Newest study conducted by Toumba *et al.* in 2010 with 26 children with SRS treated with growth hormone for a longer period of time (average 9.8 years) showed a substantial improvement of height with a final height within population norms (–1.3 SD). Higher increase in height was observed in patients with lower height at the beginning of therapy (Wakeling *et al.* 2011; Mascarenhas *et al.* 2012).

Based on a number of studies, a high occurrence of growth hormone deficit (13–67%) was observed in short children with intrauterine growth retardation (De Zegher *et al.* 2000; De Zegher *et al.* 2005; Ong *et al.* 2005; De Zegher *et al.* 2002; Stanhope *et al.* 1989; Boguszewski *et al.* 1995). In children with SRS such a deficit is less frequent – 2%. It may point at a smaller biological activity of growth hormone in children with SRS or at a partial peripheral resistance to its effects (Lewandowska *et al.* 2002; Rakover *et al.* 1996).

Particularly underlined is the fact of beneficial effects of large doses of growth hormone on catch-up growth (De Zegher *et al.* 2000; Chatelain *et al.* 1993; Czernichow *et al.* 1997; Hokken-Koelega *et al.* 1999; De Zegher *et al.* 1999), as it is highly unlikely for children with SRS to achieve such a type of growth on their own (Toumba *et al.* 2010).

Earlier studies suggested that interrupting high dosage growth hormone therapy after two years in children with SRS in prepubertal age does not result in a deceleration of growth rate (Azcona *et al.* 1999; De Zegher *et al.* 1997). It may show that these children do not have to be treated until final height is reached, contrary to other short children with intrauterine growth retardation (Binder *et al.* 2011). Although there is not enough data on final effects of growth hormone therapy in children with SRS, it appears to be sensible and safe (Stanhope *et al.* 1991).

Study goal

The effect of growth hormone therapy on somatic development of group of Polish children with Silver Russell Syndrome.

MATERIAL AND METHODS:

The study included 12 children at the age of 2 to 17 years ($\bar{x}$ – 8.9±4.0 years) diagnosed with Silver-Russell syndrome based on phenotype features. To the study qualified were children who fulfilled the diagnostic criteria of SRS by Wollmann *et al.* (1995) and by Prince *et al.* (1999).

All the children were under care of Department of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology of Developmental Age, Pomeranian Medical University in Szczecin or other centres in Poland (30 children from Szczecin, 3 from Warsaw and 5 from Cracow).

Children were treated with growth hormone due to somatotroph pituitary insufficiency or short stature as a result of intrauterine growth retardation.

Each child was height and weight measured. The results were input on percentile population nets of Polish children by I. Palczewska and Z. Niedźwiecka (2001), considering age and gender. Standard deviations (SD) of height and weight were also calculated.

The control group consisted of 16 children treated with growth hormone in a standard dose, at the age of 2 to 17 years ($\bar{x}$ – 9.6±3.9 years), chosen randomly to match age and gender of children from the study group. These children were born with intrauterine growth retardation, that is a birth weight ≤–2 SD in relation to their gender and gestational age and without any dysmorphic features. They also have an afterbirth growth impairment, i.e. height ≤–2SD for their age and gender. An analysis of somatic development was performed in the control group, the same as in the study group. The control group was a comparison reference point to the study group in terms of somatic development.

RESULTS

In a studied group 12 children with Silver-Russell syndrome diagnosed using phenotype criteria, were treated with growth hormone. Three children began their therapy at the age of 6, four at the age of 7, one at the age of 8, one at the age of 10, two at the age of 11 and one at the age of 15. One child had begun the therapy at advanced bone age, therefore, the treatment period was shorter than one year. In one child the therapy was maintained for one year, in 2 children – 2,3 and 4 years and in one child – 5, 8, 9 and 10 years. Out of 12 children, 8 were treated for over 2 years.

In the control group 16 children received growth hormone. The therapy was introduced to 3 children at the age of 6, to 2 children at the age of 7, to one child at the age of 8, to three children and the age of 9, to two children at the age of 10, to one at the age of 11, 12 and 13. In the control group one child was treated for less than a year. In one the therapy was sustained for one year, two children were treated for 2 years, 2 children for 7 years, 3 children for 3 years, 3 children for 6 years and 4 children for 5 years. Out of 16 children treated with growth hormone, 12 were treated for over 2 years.

Figure 1 shows the effect of growth hormone treatment on the height of these children.

At the beginning of growth hormone therapy children from the study group had a larger height deficit expressed in SD compared to these children, who did not receive such treatment. During therapy a significant (p<0.05) improvement in height deficit (height SD) was seen from the age of 6 to 11. At the age of 17 only one patient from the study group continued growth hormone therapy. Therefore, despite seeing a significant difference of height expressed in standard deviation of 1.3SD between the treated child and the untreated children, the statistical significance of this difference was not calculated on account of the small number of children with this age.

Children from the control group treated with growth hormone at ages 6 to 8 and 11 to 17 were significantly (p<0.05) higher (height expressed in SD) than these, who did not receive such therapy, however, at ages 9 and 10 these differences were not significant.

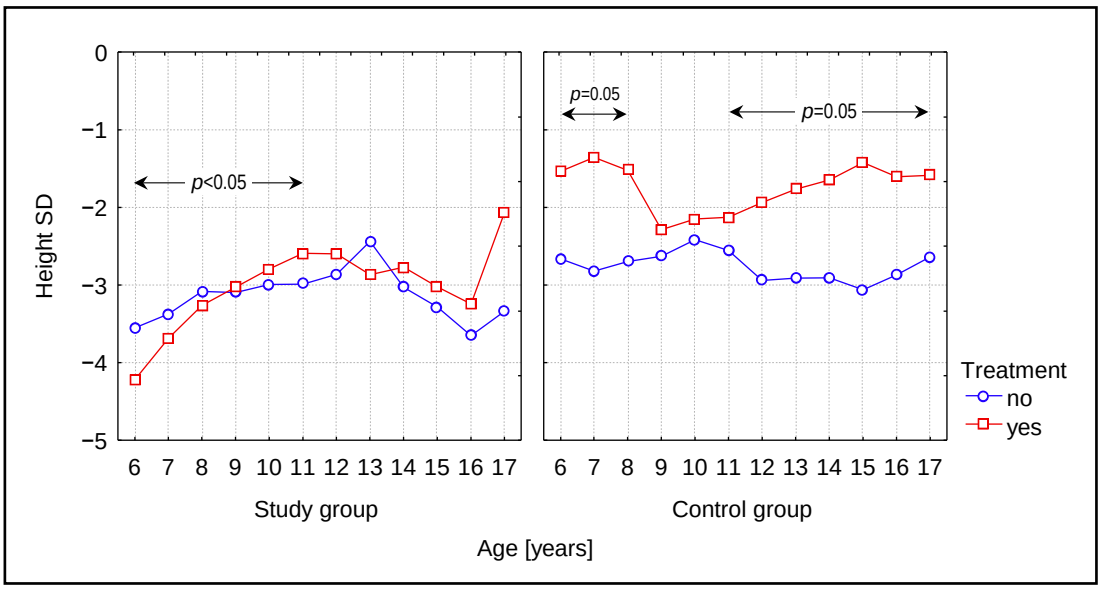

Fig. 1. Height SD of children treated with growth hormone from the study and the control groups (mean values).

At the end of observation period, no significant differences were observed between children from the study and control groups in reference to age and time of therapy. Mean therapy time (assuming only the children treated over 2 years) was, both in the study and the control group, slightly over 5 years.

Figure 2 compared the height SD of children from the study and the control group before introducing growth hormone treatment, after one and two years of therapy at the last year of observation.

Significantly larger growth deficit in height SD was spotted in subsequent years of GH therapy in children from the study group, compared to the control group. It is important to note, however, that the children from the study group began the therapy with significantly (p<0.003) smaller height than children from the control group. Growth hormone treatment significantly improved the height SD of children from the study group during the first and second years of therapy. In the following years no such improvement was seen.

Figure 3 compares the growth rate before beginning growth hormone therapy, one and two years after introducing such therapy and at the last year of observation.

As seen on Figure 3. children from both the control and the study group had similar height gains before beginning and during growth hormone therapy. However, during all years of therapy the growth rate of children from the study group was slightly slower than in the control group.

Figure 4 shows growth rate SD before introducing growth hormone treatment, one year and two years after introducing such treatment and at the last year of observation.

As seen on Figure 4 no significant difference was seen in growth rate SD between children from the study and the control group treated with growth hormone, both before, as during the first and second year of introducing such therapy, although a statistically significant (p=0.015) lower growth rate SD was seen in children from the study group above 2 years from beginning growth hormone therapy.

Figure 5 compares weight SD of children from the study and the control groups before beginning growth hormone treatment, one and two years after introducing such therapy and at the last year of observation.

Children from the study group began the treatment with significantly lower weight compared to the control group. However, under growth hormone therapy, the weight SD improved mainly in the study group, therefore at the last year of observation the weight SD differ-

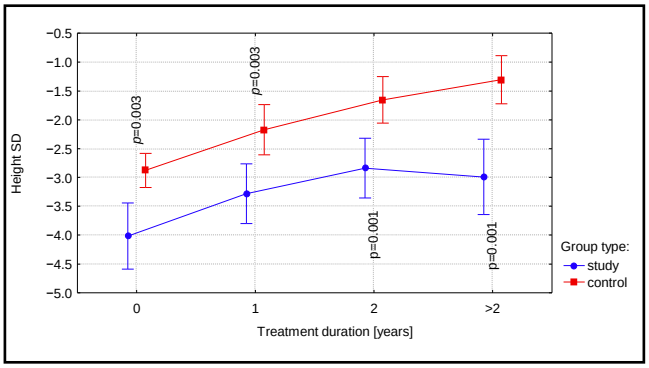

Fig. 2. Height SD of children from the study and the control group in subsequent years of growth hormone therapy (mean values with 95% confidence intervals).

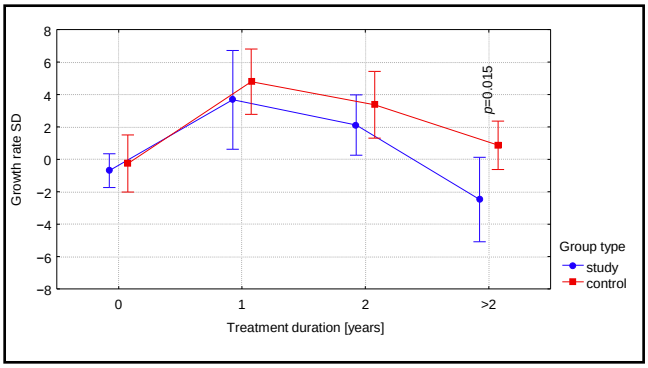

Fig. 4. Growth rate SD of children from the study and the control group in subsequent years of growth hormone therapy (mean values with 95% confidence intervals).

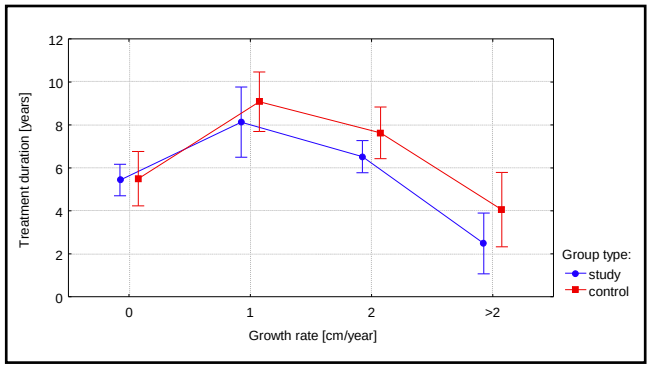

Fig. 3. Growth rate of children from the study and the control group in subsequent years of growth hormone therapy (mean values with 95% confidence intervals).

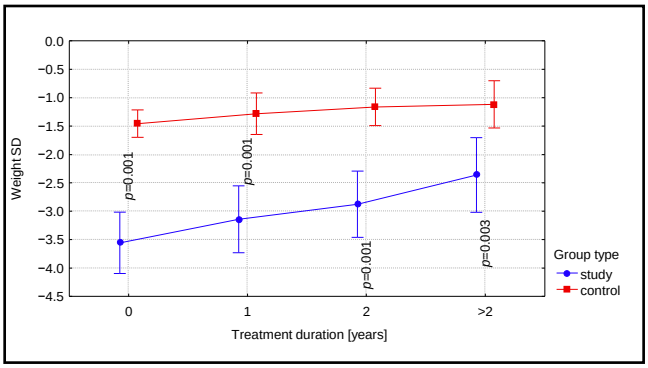

Fig. 5. Weight SD of children from the study and the control group in subsequent years of growth hormone therapy (mean values with 95% confidence intervals).

ence between children from the study and the control group decreased.

2 children with the genetic change (1 child with maternal uniparental disomy of chromosome 7 and 11p15 epimutation and 1 child with epimutation 11p15) were treated with recombinant human growth hormone.

The boy with maternal uniparental disomy of chromosome 7 began growth hormone therapy at the age of 10. After introducing recombinant human growth hormone treatment his growth rate improved noticeably, especially during the first year of therapy. His height SD before beginning therapy was only –3.75 and after two years of observation –2.02.

The girl with the 11p15 epimutation began treatment at the age of 8.

After one year of recombinant human growth hormone therapy her growth rate slightly improved. Before beginning therapy this child's height SD was –3.84 and after one year of treatment –3.46.

A comparison of growth parameters of two children with a genetic change (maternal uniparental disomy of chromosome 7 and 11p15 epimutation) after one year of growth hormone therapy showed that the boy with mUPD7 had a notably better response to treatment. His growth rate after one year of rhGH therapy improved from 5.9 cm/year to 13.5 cm/year, while the girl with 11p15 epimutation improved her growth rate from 5.2 cm/year to only 6.3 cm/year.

DISCUSSION

Growth hormone therapy has a positive effect on children with intrauterine growth retardation, including children with SRS (Rakover *et al.* 1996; Chatelain *et al.* 1993; Christofordis *et al.* 2005; Ranke *et al.* 1996; Chernausek *et al.* 1996; Stanhope *et al.* 1991). Several studies confirm beneficial effects of treating children with SRS (Lewandowska *et al.* 2002; Rakover *et al.* 1996; Christofordis *et al.* 2005; Ranke *et al.* 1996; Chernausek *et al.* 1996). It appears that early introduction of growth hormone therapy should positively affect growth and improve the quality of life of these patients. Introducing growth hormone therapy in later age also results in an improvement of height, although not as high, as if the treatment was begun in the prepubertal period (Cutfield *et al.* 2007; Mascarenhas *et al.* 2012).

Since 2015 growth hormone therapy for SRS patients in Poland is financed by the National Health Fund (NFZ), as part of short stature treatment for SGA children. Our observation is, however, a first description of treatment effects in 12 patients from before the treatment was refunded. Therefore, out of 38 children with phenotype features of SRS, only 12 were treated with growth hormone on the basis of somatotroph pituitary insufficiency or intrauterine growth retardation. Therapy introduction was also largely limited by the advanced age of patients at diagnosis. Thus, the age of patients at the beginning of therapy differed. Two youngest children were 6 years old and the oldest one – 15 years old. Numerous children did not receive growth hormone because of their age at the time of diagnosis. The observation of the effects of therapy was too short, since most patients did not complete their therapy. Growth hormone did not only increase height – from –4.02 SD to –2.99 SD, i.e. 1 SD, during the last year of observation, but also weight – from –3.56 SD to –2.36 SD. Height and weight gains were significantly bigger in a group of children with SRS, compared to the group with intrauterine growth retardation. Although at the end of the observation period higher weight and height was achieved by children with IUGR. It is, however, important to note, that children with SRS began the treatment with a substantially larger higher and weight deficit, much like the group observed by Ranke *et al.* in 2010. In our study, as in the study by Ranke *et al.* (2010), this difference was approximately 1 SD. The growth rate during the first two years of treatment was comparable between children with SRS and children with UIGR, albeit in the last year of observation, a significantly faster growth rate was seen in children with IUGR. It means, that children with SRS grow best during the first two years of therapy, unlike children with IUGR, who achieve good height gains also in later years of treatment. This result confirms the observation of other researchers (Cutfield *et al.* 2007).

Growth hormone therapy has a lot of positive effects on children with SRS. It leads not only to faster vertical growth, but is also beneficial for muscle mass growth, bone mineralization, and improves the quality of life and perception skills of these children (Cutfield *et al.* 2007). Despite the possible side effects, the advantages of growth hormone therapy outweigh the harmful effects.

During an approximately ten-year observation, Toumba *et al.* (2010) analysed the growth of 26 children with Silver-Russell Syndrome treated with growth hormone. The cited author reached similar conclusions, pointing at a positive effect of growth hormone therapy in that study. Median height at the beginning of therapy was –2.7 SD and it increased to –1.3 SD during the therapy. The control group consisting of children with IUGR reached a final height of approximately –1.0. Despite a noticeable final height improvement, no child reached the desired final height. In the group examined by this author the biggest height gains were observed at the beginning of puberty (Toumba *et al.* 2010).

It was commonly believed that pubertal growth spurt in children with SRS occurs a lot earlier than in normal population (Tanner *et al.* 1975). Toumba *et al.* (2010) observed, that growth hormone therapy may lead to a large growth rate acceleration, if introduced before puberty. This author states, however, that this data is not entirely reliable due to a small number of treated patients and a varied age of children at therapy introduction. Similar results were described earlier, although then, the observation period was shorter (Rakover *et al.* 1996; Chatelain *et al.* 1993; Ranke *et al.* 1996). Ranke *et al.*

(1996) suggests that despite discontinuing growth hormone therapy, children with SRS sustain good growth rate and perhaps, contrary to children with IUGR, a continuation of treatment until achieving final height would be, in case of children with SRS, unnecessary.

The views on growth hormone dosage vary. In the above studies, children were treated with 0.16–0.43 mg/kg/week. (average 0.25 mg/kg/week.).

It is commonly approved, that it is crucial to introduce treatment in an early period of life, to "maximize" the growth promoting effect. Some authors believe that to achieve the desired effect a much larger dose should be used than in the treatment of somatotroph pituitary insufficiency (Chatelain *et al.* 1993; Albanese *et al.* 1997; Chatelain *et al.* 1994). Other studies suggest, however, that despite applying different doses to all treated children, a significant growth rate acceleration was achieved (De Zegher *et al.* 2000; Chatelain *et al.* 1993; De Zegher *et al.* 1999).

The effectiveness of treating children with SRS with growth hormone is confirmed by data from the Australian OZGROW programme. In that study after 5 years of treatment the height deficit of children with SRS decreased from –3.2 SD to –2.0 SD. Increasing the dose did not further improve the growth rate of those patients, although a better growth response was seen in younger and shorter patients (Lewandowska *et al.* 2002; Rakover *et al.* 1996; Mascarenhas *et al.* 2012).

Similar data was presented by Ranke *et al.* in a study from 2010, where he describes the effects of growth hormone therapy on 161 children with IUGR, including 55 with SRS. Despite using a much higher growth hormone dose in patients with SRS, this author did not achieve significant differences in height gains during the first and subsequent years of therapy between children with SRS and IUGR.

In the study of Binder *et al.* (2013) the genotype was not a significant predictor of height gain in population children with SRS. There was however a trend toward a batter outcome in children with mUPD7 (Binder *et al.* 2013), but in our study, a comparison of growth parameters of two children with a genetic change (maternal uniparental disomy of chromosome 7 and 11p15 epimutation) after one year of growth hormone therapy showed clearly, that the boy with mUPD7 had a notably better response to treatment. His growth rate after one year of rhGH therapy improved from 5.9 cm/year to 13.5 cm/year, while the girl with 11p15 epimutation improved her growth rate from 5.2 cm/year to only 6.3 cm/year. However this observation needs to be confirmed in larger cohorts (Binder *et al.* 2013).

CONCLUSIONS

Recombinant human growth hormone therapy promotes somatic growth in children with Silver-Russell Syndrome, although to a smaller degree than in children with intrauterine growth retardation.

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