ORIGINAL ARTICLE

A ten-year observation of somatic development of a first group of Polish children with Silver-Russell syndrome

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Abstract

OBJECTIVE: Silver-Russell syndrome is heterogeneous both clinically and genetically. The best known genetic aberrations existing in this syndrome are an 11p15 epimutation, present in 20–60% patients, and a maternal uniparental chromosome 7 disomy (7–15%) (upd(7)mat). Children with SRS suffer from physical growth impairments – intrauterine and after birth. **MATERIAL AND METHODS:** The study group consisted of 38 children aged 2 to 17 ($\bar{x}$=8.9±4.0 years). These children had undergone a genetic analysis in search for the 11p15 epimutation and the upd(7) mat. Somatic growth was also analysed in terms of birth parameters and postnatal BMI, weight and height. The aforementioned parameters were compared in a subgroup of children with the genetic aberrations and with a control group of children born with IUGR. **RESULTS:** In the study group a mean weight SD on birth was –3.41±1.22, the birth height was –1.25±2.08 SD and a head circumference of –3.56±1.93 SD. No significant differences were noted between the SRS study group and the control group in reference to weight and head circumference (p>0.05). Such difference was, however, seen in birth height. Children with 11p15 epimutation had significantly lower weight and height at birth, but a significantly larger head circumference than children without this genetic aberration. When analysing further development of children with SRS, a significantly smaller height SD, body mass and BMI was observed, compared with children from the control group. **CONCLUSIONS:** Children with SRS present impaired somatic development compared to children with IUGR, and these with a genetic aberration develop worse.

INTRODUCTION

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

Silver-Russell Syndrome is characterised by an intrauterine growth retardation with a postnatal height deficit. Neonates with SRS are born on time and their birth weight is usually under –2 SD. After birth these children present with dwarfism with normal body proportions. Growth rate is constant, but low gains in height without catch-up growth constitute to an intensification of growth retardation (Wollmann *et al.* 1995; Price *et al.* 1999; Netchine *et al.* 2007; Bruce *et al.* 2009; Bartholdi *et al.* 2009; Schönherr *et al.* 2006).

Height deficit is among the most serious impairments in children with SRS (Toumba *et al.* 2010). Such children do not achieve their genetic growth potential and in adult age they are significantly shorter (Cutfield *et al.* 2007). In contrast with most children born with IUGR, patients with SRS do not present catch-up growth (Wollmann *et al.* 1995; Mascarenhas *et al.* 2012). Their growth rate is very low in postnatal and early childhood periods (Cutfield *et al.* 2007). At the age of 4 they have a standard deviation of height of –3.5 to –4.4 (Wollmann *et al.* 1995; Cutfield *et al.* 2007; Binder *et al.* 2011) and their growth spurt occurs around the age of 10, constituting to early puberty and a reduction of final height (Wakeling, 2011).

Height deficit deteriorates during the whole childhood period, leading to a final height of –3.6 to –2.9 SD (Wollmann *et al.* 1995; Toumba *et al.* 2010; Tanner *et al.* 1975; Davies *et al.* 1988). Tanner *et al.* (Tanner *et al.* 1975) described a natural growth history of children with SRS untreated with growth hormone. They described the maximal height of women as 147cm and the maximal height of men as 153.5cm. Twenty years later, a long-term observation was conducted by Wollmann (Wollmann *et al.* 1995) on a group of 386 patients. He estimated the mean height of an adult man to 151.2cm and of an adult women to 139.9 cm.

STUDY GOAL

The goal of this study was an assessment of somatic growth in a selected group of Polish children with SRS.

MATERIAL AND METHODS:

The study included 38 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, 18 (47.4%) girls and 20 (52.6%) boys therein. To the study qualified were children who fulfilled the diagnostic criteria of SRS by Wollmann *et al.* (1995) from 1995 and by Prince *et al.* from 1999.

All the children were under observation/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).

These children had a DNA analysis in search of a maternal uniparental disomy of chromosome 7 (mUPD7) and a 11p15 epimutaion. These tests were done in the Cytogenetics Unit, Department of Pathology, Pomeranian Medical University in Szczecin.

To diagnose mUPD7 the microsatellite polymorphism phenomenon was used, that is an analysis of selected microsatellite markers from the child and from its parents. Confirming mUPD7 was based on a family analysis of the existence of a polymorphism of six microsatellite markers located in regions critical for the Silver-Russell syndrome: a region including the GRB10 gene on the p arm of chromosome 7 and a region including the IGFBP-1 and IGFBP-3 genes on the q arm of that chromosome. Six polymorphic STRP markers were amplified in a polymerase chain reaction (PCR) with specifically 5'-fluorescent marked primers. The amplification products had undergone electrophoresis on polyacrylamide gel, on 3130 ABI Prism (Applied Biosystems, USA) and analysed using the Gene Mapper ID-X 1.1 programme. With this method the size of given loci and their heterozygosity was determined in parents and in their child. In 6 (15.8%) cases it was not possible to acquire full genetic material, i.e. DNA from the parents, inter alia because of lack of contact or the death of one of the parents. Therefore mUPD7 analysis was done in 32 children. MS-MLPA technique (Methylation Specific Multiplex Ligation – dependant probe amplification) utilizing a dedicated SALSA MLPA, ME030 BWS/RSS kit made by MRC-Holland b.y. and used according to the manufacturers guidelines was used to assess the methylation anomalies in the 15.5 region of chromosome 11. A kit includes 26 probes specific for the 11p15 region. 11 of them gave information on possible methylation dysfunctions of that region. Results were read and analysed using the GeneMarker 1.7 programme. For this test only isolated genetic material from the child was needed. Therefore, such an analysis was performed in the entire study group, that is in 38 children.

Each child was weighed, measured and had a BMI calculated. Based on available medical history, in each of the study group child anthropometric parameters

(weight, length, head circumference) were assessed at birth and in later periods of life. The data from birth (weight, length, head circumference) were corrected with the length of pregnancy and the child's gender, compared with tables and input on percentile population nets of Polish children by I. Palczewska and Z. Niedźwiecka from 2001 (Palczewska *et al.* 2001).

On each visit taking place every 6 months height, weight, head circumference and BMI measurements were taken. The results were input on percentile population nets of Polish children by I. Palczewska and Z. Niedźwiecka from 2001 (Palczewska *et al.* 2001), considering age and gender. Children born premature were classified based on the percentile population nets of Polish children by I. Palczewska and Z. Niedźwiecka from 1995 (Palczewska *et al.* 1995) for pre-term children (i.e. born before a gestational age of 37 complete weeks). Standard deviations (SD) of height, weight and head circumference were also calculated. In the study group, 12 children were treated with growth hormone due to somatotroph pituitary insufficiency or IUGR. In the study group, sub-groups of children with and without a genetic aberration were created and both sub-groups were then compared in terms of somatic development.

The control group consisted of 32 children at the age of 2 to 17 years ($\bar{x}$=9.6±3.9 years) – 17 (53.1%) girls and 15 (46.9%) boys therein, chosen randomly to match age and gender of children from the study group. These children were born with intrauterine growth retardation, that is with a birth weight ≤–2 SD in relation to gestational age and gender without dysmorphic features. They also presented with afterbirth growth retardation, i.e. height ≤–2 SD for their age and gender. In the control group an analysis of somatic development was performed, the same as in the study group. The control group was a reference point in a comparison of the somatic development of the study group. 16 children from the control group were treated with growth hormone in a standard dose because of somatotroph pituitary insufficiency or dwarfism as a result of intrauterine growth retardation.

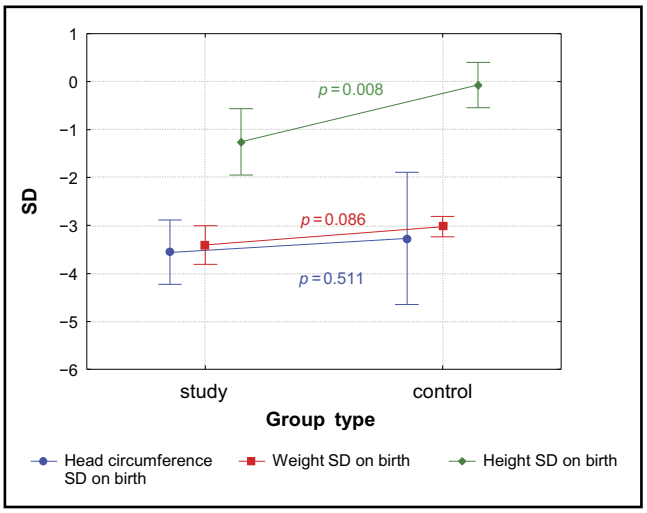

Fig. 1. A comparison of birth length, weight and head circumference SD of children from the study and control groups (mean values with 95% confidence intervals).

RESULTS

Genetic analysis

Out of 38 examined children, genetic aberrations specific for SRS were confirmed in 9 (23.7%). Only in one (3.1%) child the maternal uniparental disomy of chromosome 7 (mUPD7) was confirmed. In 8 (21.1%) children an 11p15 epimutation was confirmed.

Somatic development of children with SRS – birth data

Children from the study group were born between the 31st and 42nd week of gestation ($\bar{x}$=38.56±2.46). Only 8 (21.1%) of them were born preterm (gestational age <37 weeks)

In the control group the length of pregnancy varied from 32 to 41 weeks ($\bar{x}$=38.56±1.81). As in the study group, in case of 8 children (25%), the pregnancy ended pre-term.

The status of children from the study group, expressed by Apgar Score in the 5th minute after birth ranged from 5 to 10 points ($\bar{x}$=8.62±1.30). 32 (83.8%) children were born in a good condition, i.e. 8–10 points in the Apgar Score, while 6 (16.2%) in a fair condition with 4–7 points.

In the control group 27 (84.4%) children were born in a good condition and 5 (15.6%) in a fair condition.

On Figure 1 compared are the birth data (length, weight and head circumference) of children from the control and study groups.

The average weight on birth of children from the study group was 2 010 g, birth weight SD was –3.41. Birth length was 46.89 cm average, –1.25 SD under mean values. Average head circumference was 31.59 cm, which is –3.56 SD.

Between the study and the control groups no significant differences were noted in weight on birth, however, children from the study group were significantly shorter.

The boy diagnosed with maternal uniparental disomy of chromosome 7 was born after 39 weeks through a caesarean section due to breech presentation and irregular heart rate. Birth weight was 1 660 g, i.e. –4.96 standard deviation; birth length was 43 cm (–4.0 SD); head circumference was 31 cm (–4.24 SD). The boy scored 3/6/8 points on Apgar score.

Children with the 11p15 epimutation were born after 36 to 41 weeks ($\bar{x}$=38.8±1.64) and their Apgar score at the 5th minute after birth was 6 to 10 points ($\bar{x}$=8.25±1.16).

Anthropometric parameters of children with the 11p15 epimutation measured at birth are presented on Figures 2–4.

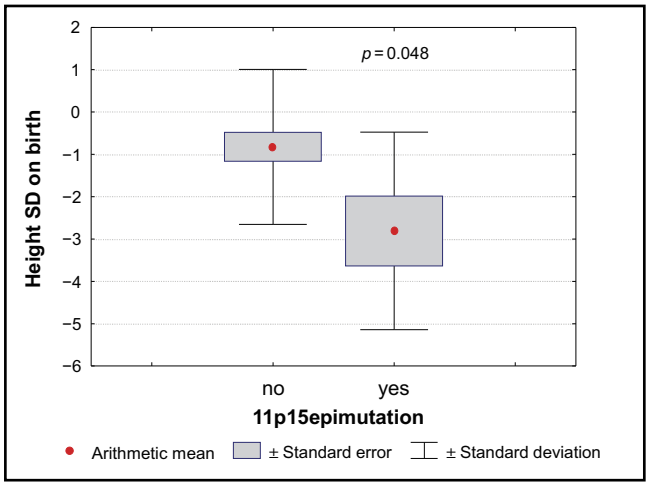

Fig. 2. Birth length SD of children with 11p15 epimutation.

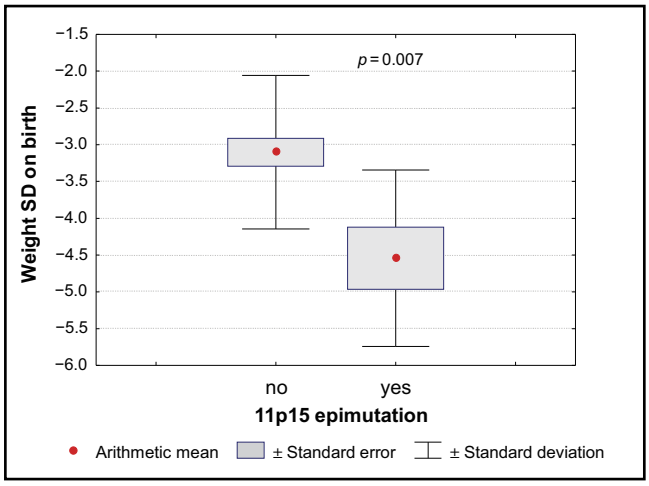

Fig. 3. Birth weight SD of children with the 11p15 epimutation.

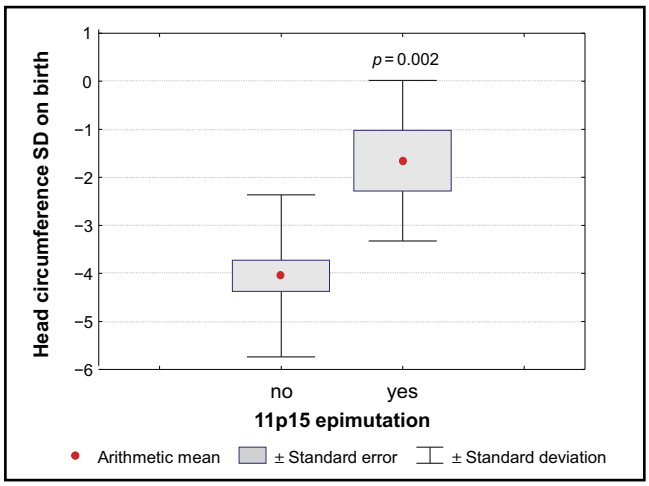

Fig. 4. Head circumference SD of children with the 11p15 epimutation.

Birth length SD ($\bar{x}$=−2.81±2.33) in children with the 11p15 epimutation was also significantly lower (p=0.048), compared to the children without this genetic disorder ($\bar{x}$=−0.82±1.83).

Children with the 11p15 epimutation had a standard deviation of birth weight also significantly lower (p=0.007) ($\bar{x}$=−4.54±1.20) than children without this genetic disorder ($\bar{x}$=−3.10±1.04).

Unlike the height and weight standard deviations, the standard deviation of head circumference of children with the 11p15 epimutation was significantly larger (p=0.002) ($\bar{x}$=−1.65 SD±1.67), compared to children without this genetic aberration ($\bar{x}$=−4.05±1.69).

As seen on figures 2 and 3, children with the 11p15 epimutation were significantly smaller and lighter than children without this mutation. Moreover, children with the 11p15 epimutation had a larger, although not significantly, head circumference (Figure 4.).

Children with a genetically confirmed 11p15 epimutation had a significantly (p=0.048) smaller height after birth. Birth height SD in these children ranged from −6.05 to 0.67 ($\bar{x}$=−2.81±2.33). Children without the 11p15 epimutation had a birth height SD between −5.25 and 2.75 ($\bar{x}$=−0.82±1.83).

A significant (p=0.007) difference between the birth weight expressed in SD in children with the 11p15 epimutation and children without this genetic aberration was shown. Children with the 11p15 epimutation had a birth weight SD of −6.03 to −2.88 ($\bar{x}$=−4.54±1.20), while birth weight SD of children without this genetic aberration ranged from −4.96 to −1 ($\bar{x}$=−3.10±1.04).

Further somatic development

The data regarding age, height, weight and BMI of the control and study groups are shown on figure 5. The age of children from the study group was between 2 and 17 years ($\bar{x}$=8.91±4.02 years) and in the control group between 2 and 18 years ($\bar{x}$=9.63±3.93).

A statistically significant height, weight and BMI deficit (expressed in SD) was seen in children from the study group, compared to the control group.

Table 1 shows a profile of children from the study group, based on their genetic aberrations. 9 children had a genetically confirmed mutation; 11p15 epimutation in 8 and a maternal uniparental disomy of chromosome 7 in 1 case.

A significant difference in height SD of children with a genetic change was seen, compared to children who only had phenotype features of the Silver-Russell Syndrome. Mean height expressed in SD of children with a genetic change was notably lower.

Children with Silver-Russell Syndrome had a significantly (p<0.001) continuously increasing height deficit. Mean height deficit SD deteriorated from −1.25 after birth to −3.48 at the age of two.

Figure 6 compares the height of children from the study and control groups in subsequent years.

Statistically significant lower values of height SD in the study group, compared to the control group, were also seen in age groups of 5–10 and at the age of 16. Predicted final height was also significantly lower in the study group than in the control group.

Tab. 1. Study group profile based on the existence on mUPD7 or 11p15 epimutation.

Examined parameter	Negative genetic analysis result n=29			Positive genetic analysis result n=9			*p*-value
	$\bar{x}$ (min.–maks.)	SD	Median	$\bar{x}$ (min.–max.)	SD	Median	
Age [years]	9.04 (2.00–17.00)	4.05	8.80	8.43 (2.40–16.20)	4.12	7.75	0.579
Height [cm]	118.61 (78.90–159.70)	22.02	117.10	108.71 (64.60–158.50)	27.61	111.15	0.371
Height [SD]	−2.98 (−5.93–−1.17)	1.11	−2.87	−4.81 (−9.71–−1.86)	2.55	−4.21	0.038
Weight [kg]	20.78 (7.70–42.30)	9.56	18.25	16.61 (5.84–36.30)	9.83	14.35	0.267
Weight SD	−3.04 (−5.43–−1.35)	1.01	−2.93	−4.02 (−5.97–−1.56)	1.59	−3.95	0.082
BMI	13.95 (11.11–20.43)	2.09	13.13	12.99 (10.29–17.05)	2.13	12.51	0.163
BMI SD	−1.35 (−2.88–0.39)	0.85	−1.38	−1.76 (−3.47–0.40)	1.15	−1.87	0.267

N - group size, $\bar{x}$ - arithmetic mean; SD - standard deviation; *p* - statistical significance

Children with a phenotypically diagnosed SRS had a significantly lower weight than in the control group (p=0.001).

Standard deviation weight gains were compared in the study group at the 12th and 18th month after birth. No statistically significant weight deficit deterioration was seen in the 12th and 18th month after birth. Body mass standard deviation in the study group did not differ significantly in that period either. Weight measurements acquired in the control group at 12th and 18th months after birth were insufficient to conduct statistical analysis.

Figure 7 shows a comparison on weight of children from the control and study groups in subsequent years.

After birth no significant differences were seen between the weight of children from the control and study groups.

Body mass expressed in standard deviation in children from the study group, compared to the control group, was statistically significant at ages from 2 to 10, at 16 and at 17.

While analysing the development process of the child with maternal uniparental disomy of chromosome 7, an improvement of both weight and height deficits was observed, especially after introducing recombinant human growth hormone therapy at the age of 10. The boy responded well to growth hormone treatment and achieved a height of −2 SD (approximately 3rd percentile) at the age of 12.

In subsequent years of observation the differences in height between the group of children with the 11p15 epimutation and the group without this change were not significant. However, between the age of 11 and 17 a statistically significant (p=0.003) higher height SD

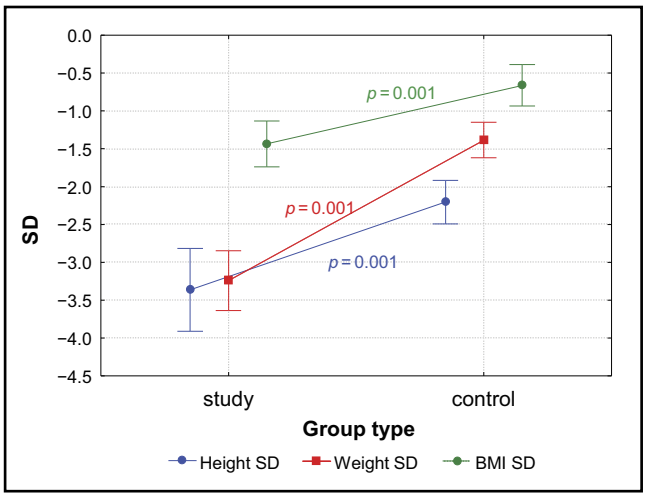

Fig. 5. Standard deviation (SD) of height, weight and BMI in children from the study and control groups (mean values with 95% confidence intervals).

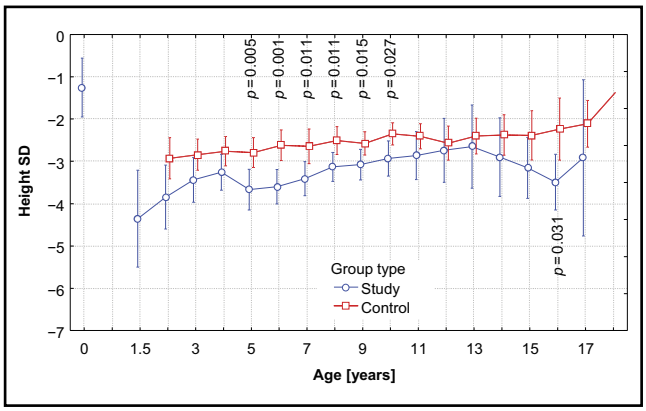

Fig. 6. Height SD of children from the study and control groups in subsequent years (mean values with 95% confidence intervals).

was observed in the group of children with 11p15 epimutation compared to children without it.

Figure 8 compares height standard deviation between children with the 11p15 epimutation and children without this genetic aberration.

The group of children with the 11p15 epimutation had a statistically significant smaller weight SD compared to children without this genetic change. From birth until the age of 6 this difference was also significant ($p<0.02$) for mean weight SD=–4.64 for children with the 11p15 epimutation and –3.35 for children without this epimutation. At the age of 6 and 7 a smaller deficit of weight expressed in SD was observed in the group without the genetic mutation, but this difference was not significant statistically. In subsequent years the difference in weight SD between both groups did not differ significantly.

Figure 9 compares weight SD of children with and without the 11p15 epimutation.

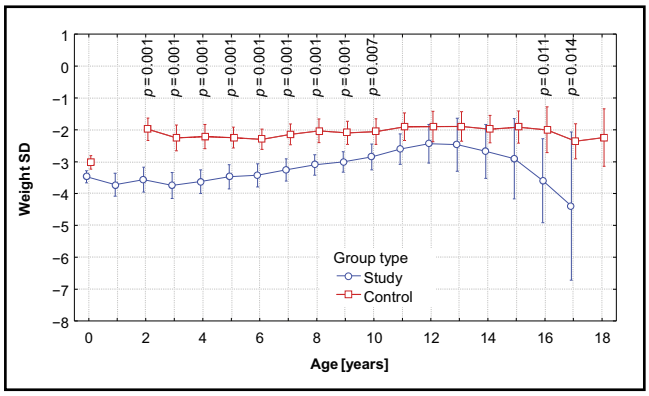

Fig. 7. Weight SD of children from the study and control groups in subsequent years (mean values with 95% confidence intervals).

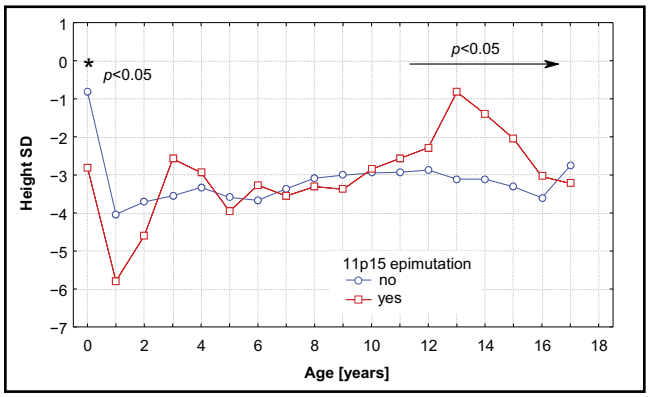

Fig. 8. Height standard deviation of children with the 11p15 epimutation and children without this genetic aberration in subsequent years (mean values).

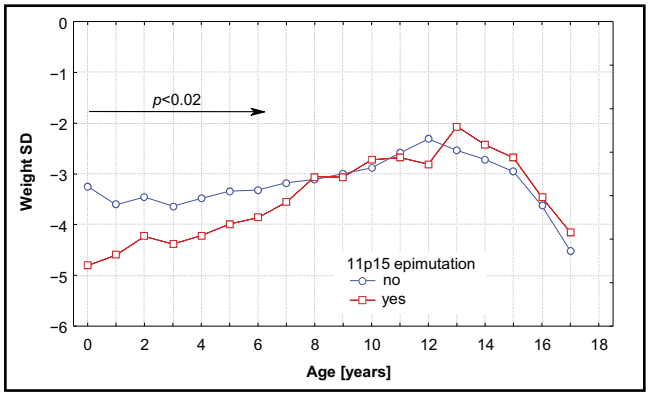

Fig. 9. Weight SD of children with and without the 11p15 epimutation in subsequent years (mean values).

DISCUSSION

Until lately the diagnostic of SRS relied exclusively on phenotype features. The advancement in many fields of medicine, most importantly genetics, allowed introducing molecular testing to diagnose this condition.

Genetic diagnostic of the Silver Russell Syndrome is based mainly on identifying the two main genetic changes, namely the maternal uniparental disomy of chromosome 7, occurring in 7–10% cases (Binder *et al.* 2011; Kotzot *et al.* 2000; Eggermann *et al.* 2009; Moore *et al.* 1999; Schönherr *et al.* 2007; Bernard *et al.* 1999; Kim *et al.* 2005) and the 11p15 epimutation, seen in 20–65% children (Netchine *et al.* 2007; Gicquel *et al.* 2005; Bliek *et al.* 2006; Eggermann *et al.* 2008).

In the above study the maternal uniparental disomy of chromosome 7 was observed in only one child (3.1% of children with phenotype SRS features), while the 11p15 epimutation was confirmed in 8 (21%) children. Eggermann showed a similar incidence of mUPD7 – 2.3% (Eggermann *et al.* 2009), but achieved worse results with 11p15 epimutation – 14.9% (Eggermann *et al.* 2008).

In the studied group of children with a phenotype diagnosis of SRS, birth weight SD was on average –3.42±1.22, similar to the study group of Netchine (Netchine *et al.* 2007) ($\bar{x}$=–3.1±1.2 SD) and Binder (Binder *et al.* 2008) ($\bar{x}$=–3.12±1.11 SD). Four children with a birth weight of over –2 SD and a phenotype typical for SRS were also qualified to the study. Price (Price *et al.* 1999) had also included 6 children with the typical phenotype for SRS and a birth weight over –2 SD to his study. Out of these children, 3 presented with body asymmetry and one of them was diagnosed with maternal uniparental disomy of chromosome 7. These children were born with substantially lower birth weight than their siblings and their birth parameters were also inadequate to the height and weight of their parents (Price *et al.* 1999). In the study group, the SD of height at birth was on average –1.25. This score differed from data provided by Netchine (Netchine *et al.* 2007) and Binder (Binder *et al.* 2008) ($\bar{x}$=–4.1±1.5 and $\bar{x}$=–3.06±1.52; respectfully). In these two studies, an 11p15 epimutation was confirmed in two children with a birth length of over –2 SD (respectfully +0.33 SD and +0.67 SD).

Mean head circumference SD was –3.36. This result differs substantially from data provided by Netchine

(Netchine *et al.* 2007) and Binder (Binder *et al.* 2008) (–1.5 SD±1.1 and –0.96 SD±1.29; respectfully). In our study, the boy with maternal uniparental disomy of chromosome 7 did not present with a relative macrocephaly on birth (birth weight SD of –4.96; birth length SD of –4.0; head circumference SD on birth of –4.24). A head circumference large in relation to body height was also not seen in 4 children with 11p15 epimutation, moreover, one girl from this group had an opposite situation (birth height SD of +0.67; head circumference SD of –2.11). Similar results on "relative' macrocephaly after birth in children with phenotype features of SRS were also recorded by Eggermann *et al.* (2009) and Wakeling *et al. (*2010).

The differences in birth parameters of children with SRS phenotype features resulted probably from distinct measurement methodology of height and head circumference used in many hospitals. In some cases systematic error cannot be excluded. Moreover, a part of researches adopted very strict diagnostic criteria for low birth height and head circumference (Netchine *et al.* 2007; Binder *et al.* 2008).

The aforementioned results and literature data prove that with age the height deficit deteriorates, especially in children with a maternal uniparental disomy of chromosome 7 and a relative macrocephaly develops (Binder *et al.* 2008). This disorder in most evident in first year after birth. Similar observations were made in many other publications (Netchine *et al.* 2007; Binder *et al.* 2008; Kotzot, 2008). It is commonly known, that severe somatic development disorders in children with SRS are seen prenatal and after birth the deterioration of weight and height growth rate continues.

In a group of 386 patients with SRS phenotype Wollmann *et al.* (1995) conducted an analysis of somatic development parameters. He observed that the growth of these children can be divided into four distinctive phases: intrauterine, neonate-infant and toddler (early childhood), childhood and adolescent. Worse intrauterine development was, according to this author, a result of a progressing placenta insufficiency – small size and calcifications of this organ were observed in 1/3 of mothers. After birth these children presented with severe somatic growth retardation, both in weight with mean SD of –4.0 and in height. Contrary to other parameters, head circumference of these children was on the lower border of the normal range. During early childhood, up to the age of 3, children with SRS did not experience catch-up growth. Height SD was –4.6 on average. Between the ages of 3 and 11 the growth curve of these children shifted to higher values with a mean height SD of –3.9. No pubertal growth spurt occurred. The height of an adult man with SRS was approximately –3.7 SD, the height of an adult woman –4.2 SD. Weight deficit was not as severe as the height deficit. From birth to the age of 3, the weight of these children remained on a stable level of approximately –4 SD. During childhood (age 4–12) weight gains were substantially higher, –3 SD averagely. In those studies the height deficit was, therefore, larger than the deficit of weight.

Similar results were also observed in this study. Moreover, the somatic development was also compared between children with a phenotype diagnosis of SRS and children with IUGR without dysmorphic features. This comparison showed a noticeably smaller weight and height of children with SRS.

Children with 11p15 epimutation had a significantly smaller height up to the age of 2, compared to children without this genetic mutation. In a later period of life, children with 11p15 epimutation developed "better" and achieved a significantly higher height at 11 to 17 years. Children with 11p15 epimutation did not, however, achieve a greater height at the age of 17. Neither children with 11p15 epimutation, nor these without this genetic mutation achieved expected height at the age of 17. The differences between expected and achieved height at the age of 17 were statistically significant in these groups.

The weight of children with 11p15 epimutation was significantly smaller until the age of 5, compared to the group of children without this genetic mutation. In further years no significant difference between weight was observed between these groups. Height deficit is the most severe anomaly in children with SRS. Progressing during the entire childhood period, it leads to an adult height of –3.6 SD (Bliek *et al.* 2006).

Tanner *et al.* (1975) presented a natural history of the growth of children with SRS. These studies show that final height of these children is approximately –2.9 SD. Studies conducted by Wollmann *et al.* (1995) confirmed earlier observations. They include information on final height of children with SRS, which turned out to be smaller than expected.

CONCLUSIONS

Children with SRS have a considerable somatic development impairment with a lack of catch-up growth after birth. Therefore, children with SRS were significantly shorter compared to children with intrauterine growth retardation without dysmorphic features. Moreover, children with 11p15 epimutation grew slower than children without this genetic change.

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