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Silver-Russell Syndrome – Part I: Clinical Characteristics and Genetic Background

Zespół Silver-Russela cz. 1 charakterystyka kliniczna i podstawy genetyczne

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Abstract
Silver-Russell syndrome (SRS) is a rare, clinically and genetically heterogeneous entity, caused by (epi)genetic alternations. It is characterized by prenatal and postnatal growth retardation, relative macrocephaly, the triangular face and body asymmetry. About 40-60% of cases are caused by hypomethylation of 11p.15.5 Imprinting Centre Region 1 (ICR1) on the paternal chromosome, and maternal uniparental disomy for chromosome 7 (UPD(7)mat) is found in 5-10% of cases. There are suggested correlations between genotype and the phenotype. Psychomotor development may be delayed, usually mildly, with school difficulties and speech delay more common in patients with UPD(7)mat. Children with 11p15 hypomethylation are shorter and lighter at birth in comparison to children with UPD(7)mat, however further deceleration tends to be more apparent in the latter group. The onset of puberty tends to occur early, with acceleration of bone age, resulting in less apparent growth spurt. Failure to thrive and feeding problems are characteristic for the infant period, and further development of a child may be conditioned by additional congenital defects.
Key words:
Silver-Russell syndrome, epigenetics, intrauterine growth restriction, 11p15 epimutation, UPD(7)mat, genomic imprinting

Streszczenie
Zespół Silvera i Russella jest rzadką jednostką, zróżnicowaną klinicznie i genetycznie, u której podłoża leżą zmiany (epi)genetyczne. Charakteryzuje się zaburzeniami wzrastania w okresie płodowym i postnatalnym, względną makrocefalią, trójkątnym kształtem twarzy i asymetrią ciała. Około 40–60% przypadków spowodowanych jest hipometalacją centrum piętnowania ICR1 w regionie 11p.15.5 chromosomu pochodzenia ojcowskiego, a u 5–10% pacjentów stwierdza się matczyną disomię chromosomu 7 (UPD(7) mat). W literaturze opisywane są korelacje fenotypowo-genotypowe. Rozwój psychomotoryczny może być opóźniony, zwykle w łagodnym stopniu, a zaburzenia mowy i trudności szkolne częściej występują w przypadku pacjentów z UPD(7)mat. Dzieci z hipometylacją 11p15 są mniejsze przy urodzeniu w porównaniu z dziećmi z UPD(7)mat, jednak postnatalne zwolnienie wzrastania jest bardziej wyrażone w grupie UPD(7)mat. Początek dojrzewania występuje stosunkowo wcześnie, z akceleracją wieku kostnego i słabiej wyrażonym skokiem pokwitaniowym. Okres niemowlęcy charakteryzuje się słabym przyrostem masy ciała i trudnościami w żywieniu, a dalszy rozwój dziecka warunkowany jest w znacznym stopniu współwystępującymi wadami wrodzonymi
Słowa kluczowe:
zespół Silvera i Russella, zmiany epigenetyczne, wewnątrzmaciczne opóźnienie wzrastania, epimutacja regionu 11p15, UPD(7)mat, piętnowanie rodzicielskie

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Introduction

The aim of this two-part review is presentation of Silver-Russell syndrome, an exemplary disorder of intrauterine growth retardation (IUGR). It may be connected with long-term sequelae, thus requiring multidisciplinary approach, including endocrine monitoring of the somatic development. Its clinical presentation and genetic background are provided in the first part of the review, followed by the diagnostic algorithm and management in part two.

Definition

Silver-Russell syndrome (SRS; *Russell-Silver syndrome*, RSS; *Silver-Russell dwarfism*; OMIM#180860) is a rare, clinically and genetically heterogeneous entity, basis of which is formed by epigenetic alternations. It is characterized by prenatal and postnatal growth retardation, relative macrocephaly, the triangular face and body asymmetry.

Historical notes

The first description of the syndrome was provided by Silver et al. in 1953, who presented two unrelated children with low birth weight, short stature, body hemihypertrophy and elevated urinary concentrations of gonadotropins [1]. Shortly after the first report, in 1954, Russell et al. independently presented clinical data of five unrelated patients with intrauterine hypotrophy, triangular facial gestalt, micrognathia and wide mouth with narrow lips. Besides, body asymmetry was found in two of those children [2].

Not until four decades after the first clinical descriptions, was it shown that genetic factors were involved in the pathomechanism of SRS. Identification of uniparental maternal disomy of chromosome 7 (UPD(7)mat) in a child with IUGR contributed to systematic and comparative examinations in patients with SRS and in children with IUGR [3]. It was shown that the mechanism of UPD(7)mat was responsible for about 4-10% of SRS cases [4] Further research focused on the p15 region of chromosome 11, containing genes connected with foetal growth. Interesting findings pertained to the duplication of the region p15 on the maternal chromosome 11 in a child with IUGR [4]. Duplications of the same region on the paternal chromosome were found in some cases of Beckwith-Wiedemann syndrome, which, by contrast, is characterised by excessive growth. Subsequent findings of hypomethylation of the ICR (*imprinting control region*) of p15 on the maternal copy of the chromosome 11, contributed to the statement that alternations in 11p15 region should be taken into account in patients with growth disorders, even without apparent dysmorphic features [5, 6].

Epidemiology

Silver-Russell syndrome is a rare entity, and its prevalence is estimated as high as 1-30-50/100 000 population [7]. Most cases are sporadic, with equal gender distribution. Until now there have been several hundred cases described in the literature, comprising all racial groups. The number of reports is still increasing, mainly due to multicentre investigations, focusing on genetic factors confirming clinical diagnosis of SRS.

Clinical description

Prenatal and postnatal growth retardation along with craniofacial dysmorphy and body asymmetry are the major features constituting the clinical presentation of SRS. It should be emphasized that the phenotype, which is described below, changes with age, particularly on the face and the characteristic features are maintained until the age of 3 years [8-10]. The shape

Table I. Craniofacial features of children with SRS
Tabela I. *Cechy twarzoczaszki u dzieci z SRS*

Part of the head	Characteristic
Forehead	high, frontal bossing
Fontanels and sutures	wide, late closure
Eyes	wide palpebral fissures, dense eyelashes, bluish sclera
Ears	occipital rotation
Nose	prominent nasal bridge, round tip
Chin	micrognathia
Mouth	wide, downturned corners, narrow lips
Oral cavity and teeth	high palate, narrow dental arches with crowding of teeth, abnormal size and shape of teeth, premolar hypodontia

of the face tends to get rounder in females and the jaw enlarges in males [8]. Thus photographs from the early childhood may be helpful in diagnosing the syndrome in older children. Besides, long follow-up of children with SRS proved the need of interdisciplinary care due to health problems appearing in different periods of life, related to various systems and organs.

The head

The face has a characteristic appearance [8,11–13] [table 1]. It is generally small, with triangular shape, hypoplasia of the mid-part, and variable asymmetry in a proportion of children are observed [fig. 1A, 1B].

Head circumference is within the centile norm for the age and gender, most often below the population mean. However it exceeds the number of standard deviations (SD) for the length or height of the body. Along with the characteristic shape of the skull, it results in the relative macrocephaly [8,11,14,15].

Growth and body proportions

Most children with SRS are full term babies, however their auxologic parameters at birth, apart from the head circumference, are significantly smaller in relation to the healthy population, and also as compared to other children born small for gestational age (SGA) without SRS [8-10, 15,]. According to data provided by Binder et al., mean standard deviation score (SDS) for the mass and length at birth is -3 SDS [16]. Essential information about further course of spontaneous growth was provided by Wollmann et al. [11] Observation comprising over 380 patients with clinical diagnosis of SRS showed increasing height deficit during the first 3 years of life. Then, between 4 and 10 years of age, height velocity was stable, parallel to the 3rd centile, with the mean height SD equal to -4.3 SDS. Mean final height was 151.2 cm ± 7.8 cm for men and 139.9 ± 9.0 cm for women.

Weight changes are parallel to height. Failure to thrive is often a striking feature in infancy, requiring feeding aids. Children with SRS present poorly developed subcutaneous tissue and usually are underweight, with body mass index (BMI) rarely exceeding 25th centile in adolescence [9].

It should be emphasized that mean values of weight and height deficits, as well as growth dynamics may differ depending on the epi(genotype). It is observed that SRS children with 11p15 hypomethylation are shorter and lighter at birth in comparison to children with UPD(7)mat. However height deficit is sustained at the same level in the first group, whereas deceleration is observed more often in children with UPD(7)mat. Initial length deficit in the latter group is not as significant as in children with 11p15 hypomethylation. Thus, in the UPD(7)mat group relative macrocephaly at birth may not be as apparent [15].

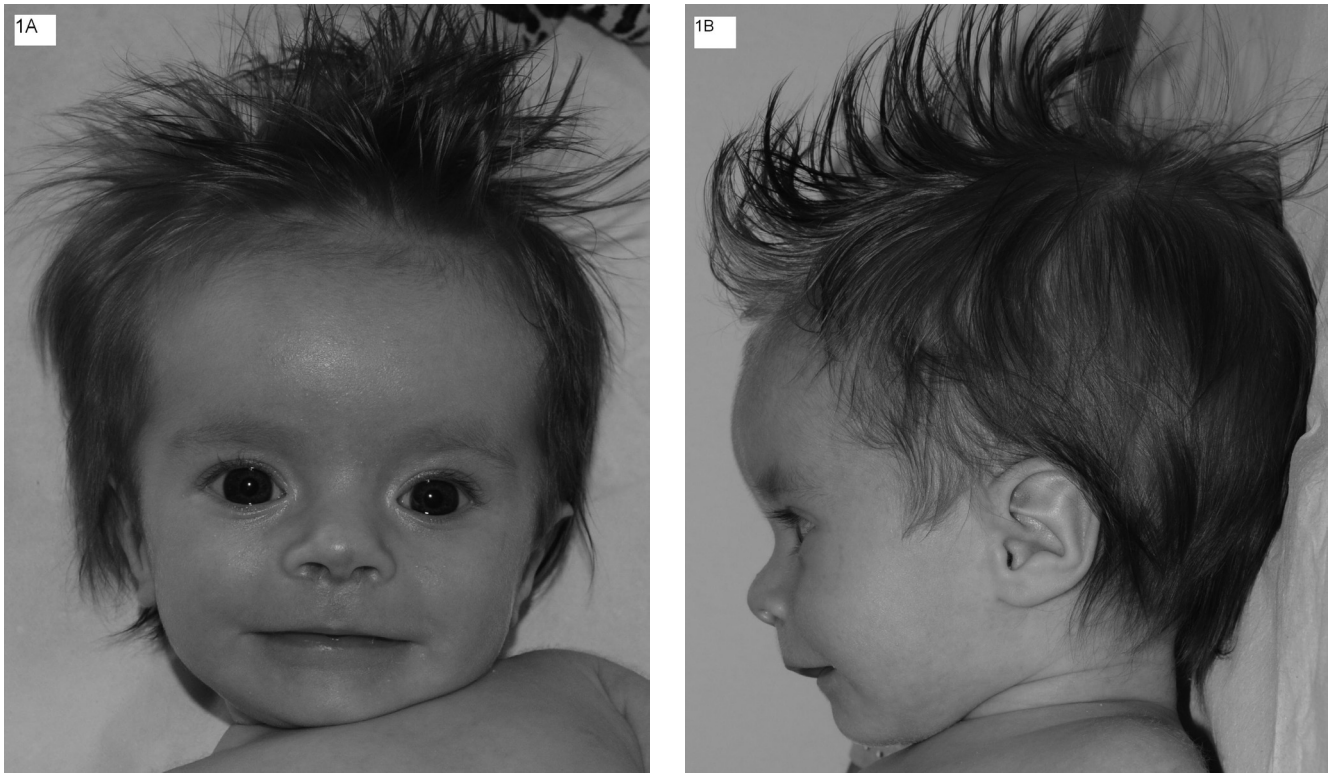

Fig. 1. The head of a 3-month old infant with Silver-Russell syndrome (SRS) caused by 11p15.5 hypomethylation; en face (1A) and the profile (2B)
Ryc. 1. *Głowa 3 miesięcznego niemowlęcia z zespołem Silver-Russella spowodowana hypometylacją 11p15,5 1a twarz 2 profil*

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Body proportions are also disturbed by asymmetry of the trunk, head and limbs, observed in about one third of patients with SRS. It is related more often to the 11p15 hypomethylation, possibly resulting from the mosaicism of the hypomethylation level in different tissues [8, 10, 17, 18]. Asymmetry can be apparent not only as differences of the length, but also of the circumference of extremities. The difference of the limbs length may reach 2.5 cm, causing significant scoliosis later in life, increasing body disproportions [8].

Puberty

Data on sexual development in SRS children are based on general trend of puberty in SGA children. Pubic hair appear earlier (*pubarche praecox*), and other pubertal signs, including menarche, may also occur relatively early but not necessarily precociously, progressing quickly [16,19]. However there are also case reports of delayed puberty, primary amenorrhea and congenital defects of the genitourinary system [17] [table 2]. In children with SRS, bone age is delayed in the first years of life and then it advances parallel to growth [11]. Generally, in children with SGA, including SRS, acceleration of the bone age and height velocity takes place in earlier stages of sexual development, resulting in shorter period of puberty and less apparent growth spurt [11,19]. It is also suggested that occurrence of visceral adiposity with insulin resistance already in the childhood, may influence the onset of puberty in SGA children [19].

Table II. Congenital defects and clinical features in patients with SRS
Tabela II. *Wady wrodzone i objawy klinicznie zespołu Silver-Russela*

Systemic involvement [reference]	Clinical features
Skeletal [8, 12, 16]	Limb asymmetry Scoliosis Lumbar hypolordosis Hip dysplasia 5th finger clinodactyly 2/3 toe syndactyly Brachydactyly Camptodactyly Arthrogryposis
Gastrointestinal [9, 10 22]	Failure to thrive, poor sucking, food aversion in infancy Gastro-oesphageal reflux Esophagitis
Genitourinary [8, 10, 16]	Renal anomalies Defects of the posterior urethral valve Hypospadias Cryptorchidism, Anorchia, Inguinal hernia Absent/hypoplastic vagina, Hypoplastic/bicornuate uterus
Cardiovascular [10, 23]	Congenital heart defects – ASD, VSD, PDA Total anomalous pulmonary venous return, Triatriatum sinistrum
Ophthalmological [24]	Refractive errors Visual acuity disturbances Strabismus Small optic discs Increased tortuosity of retinal vessels Strabismus
Dental [13, 11]	Malocclusion Crowded teeth Hypodontia
Other [8-10]	Hypoglycemia Excessive sweating Café-au-lait patches Delayed closure of fontanels Otitis media Metabolic syndrome

Psychomotor development

Psychomotor delay, observed even in half of the SRS patients, is usually mild [8, 10, 14]. It has been reported that in UPD(7)mat group, school difficulties and speech problems occur more often [17]. Lai et al. assessed full scale IQ, using Wechsler test, in 25 children with clinical diagnosis of SRS at the mean age of 8.8 years. Impairment of cognitive abilities was found in approximately half of the subjects, with the reading rate age 2 years behind the chronological age [14]. Similar investigations were also conducted in Poland, finding normal IQ in nearly 40% of cases, whereas in about 20% of subjects the value of full scale IQ was lower than 69, indicating intellectual disability in some children with SRS [20]. Noekler and Wollmann carried out comparative analysis of cognitive abilities In children with SRS and their health siblings, showing higher IQ scores by 8 points in the control group. Intellectual development was not influenced by additional parameters like birth weight and length, intensity of phenotypic features or growth hormone therapy [21].

Delay of the motor development is connected probably with decreased muscular tone and relative macrocephaly in the neonatal period, and the mean age of walking is 20 months according to Wakeling et al [10].

Congenital defects

It is suggested that congenital abnormalities are more common in patients with ICR1 hypomethylation. Diversity as well intensity of defects depend on the degree of ICR methylation in different tissues [10, 17] [table 2].

Aetiopathogenesis

Silver-Russell syndrome is an imprinting disorder caused by the epigenetic abnormalities at chromosome 11p15.5. Imprinted genes, expression of which is determined by their parental origin, are involved in various aspects of human growth. They tend to cluster, thus the imprinting control is not usually limited to a single gene at an imprinted locus. Chromosome 11p15.5 contains a cluster of imprinted genes that play a vital role in the control of foetal growth. The cluster consists of two neighbouring imprinted domains, the *IGF2*/*H19* domain in the telomeric region and the *KCNQ1OT1*/*CDKN1C* domain in the centromeric region, each under control of its own imprinting centre, ICR1 and ICR2, respectively. ICR1 is methylated on the paternal allele and that methylation protects from binding CTCF protein which allows the enhancer downstream of *H19* gene access to the *IGF2* promoter. On the maternal allele the ICR1 is unmethylated and CTCF binds to it. CTCF acts as an insulator and prevents the activation of IGF2 promoter by enhancer, at the same time it induces activation of the *H19* promoter (encoding a noncoding RNA). Methylated on the maternal allele ICR2 allows expression of *CDKN1C* and *KCNQ1* genes. On the unmethylated paternal allele expression of *KCNQ1OT1* (long noncoding RNA) regulates the imprinting of the domain [25][fig. 2A].

About 38–64% of SRS patients display hypomethylation at the imprinting center region 1 (ICR1) on 11p15.5.This epigenetic defect leads to the downregulation of paternally expressed *IGF2* which encodes major foetal growth factor and the biallelic expression of *H19* [25, 26] [fig. 2B].

Most of the SRS patients with imprinting aberrations show mosaic distribution of the epimutation what makes the molecular diagnosis challenging. Uneven distribution of epimutation in different tissues can result in false-negatives when almost normal methylation level is presented in lymphocytes [27].

About 7–10% of patients with SRS phenotype carry maternal uniparental disomy of chromosome 7 (UPD(7)mat). Interestingly, maternal UPD of chromosome 11 (UPD(11)mat) have been reported only once [6, 28]. Chromosomal duplications of 7p11.2-p13 and deletion of the paternal allele 7q32 region have also been confirmed in patients with Silver-Russell syndrome features [29, 30].Furthermore, chromosomal imbalances i.e., duplications of maternal 11p15.5 region [Fig. 2C], structural aberrations of chromosome 7, rearrangements of other chromosomes and point mutations are associated with an increased recurrence risk and the need of identifying carriers in the family [28].

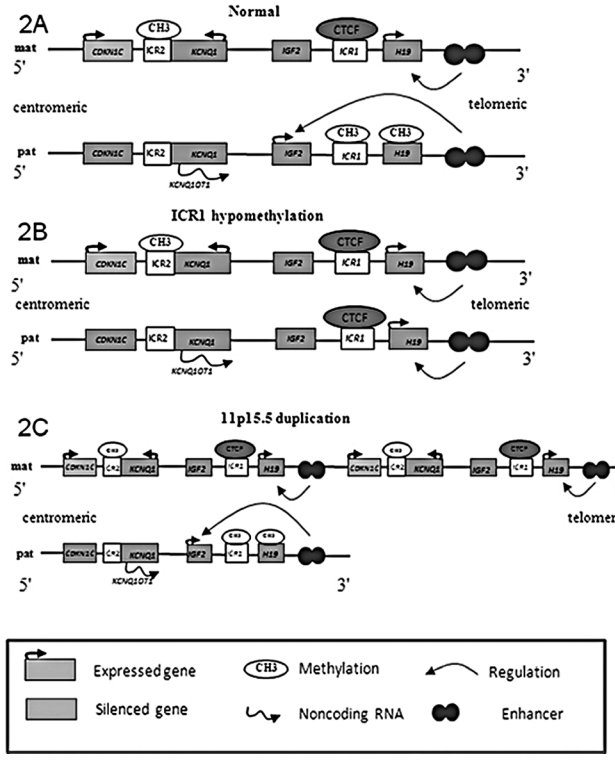

Fig. 2. Scheme of epigenetic regulation of 11p15.5 region (2A) and possible (epi)mutations detectable in SRS. Hypomethylation of the 11p15.5 region (2B) which leads to the downregulation of paternally expressed *IGF2* gene. Imbalance of *IGF2* expression is also caused by maternal duplication of that region (2C).

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Recently Brioude et al. reported one family with maternally transmitted dominant *CDKN1C* mutation. The author has proved that gain-of-function mutations in *CDKN1C* can lead to severe prenatal and postnatal growth retardation [31]. Also overexpression of the *CDKN1C* gene due to maternal duplication of the ICR2 domain is causally associated with SRS and it has been described in a three generation family associated with SRS [32].

The aetiology of almost half of SRS cases is so far unknown. Numerous (sub)-microscopic chromosome imbalances with SRS phenotype have been published recently. In 1-2% of SRS cases maternal duplications of the whole 11p15 chromosomal region have been reported. It has been shown that up to 19% of patients with short stature and features reminiscent to SRS carry relevant pathogenic chromosome aberrations, among which the most common were deletions in 1q21, 12q14 15q26, 17p13, and 22q11 [6, 26]

In the last few years a notable number of SRS patients have been reported with aberrant methylation at disease specific 11p15.5 locus as well as with methylation abnormalities at other chromosomal sites. In the group of patient with ICR1 hypomethylation about 7.1% of them had affected other loci. This observation defined new subgroup of patients known to be predisposed to multilocus methylation defects (MLMDs). In order to specify the frequency and distribution of molecular changes, in patients clinically diagnosed as SRS, the molecular test should combine assays with broad range of detection of mutations, epimutations, translocations and multilocus methylation defects [28].

Key points

Clinical presentation

- The clinical hallmark of SRS is prenatal and postnatal growth retardation
- Characteristic phenotype includes triangular face with relative macrocephaly, body asymmetry, 5th finger clinodactyly; the spectrum of congenital defects may be wide
- Feeding problems in infancy result in failure to thrive
- Children with 11p15 hypomethylation are shorter and lighter at birth in comparison to children with UPD(7)mat, however further deceleration tends to be more apparent in the latter group.
- Puberty may occur early, with acceleration of the bone age and height velocity in earlier stages of sexual development, resulting in less apparent growth spurt
- Psychomotor development may be delayed, including speech delay, depending on the genotype and severity of the phenotype

Genetic defects

- 40-60% of SRS cases are caused by hypomethylation at the ICR1 in 11p15 (loss of paternal methylation) which occur in mosaic state in the affected tissues of the body
- Maternal UPD7 has been implicated in 5%-10% of SRS.
- Up to 19% of SRS-like patients carry structural chromosomal aberrations.
- Some patients with ICR1 hypomethylation also display multilocus methylation defects (MLMDs).
- In patients with family history of SRS-like phenotypes CDKN1C point mutation or microduplication of the ICR2 domain should be taken into account.

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