Pediatric Endocrinology Diabetes and Metabolism
Endokrynologia, Diabetologia i Choroby Przemiany Materii Wieku Rozwojowego

Praca poglądowa | Review Articles

Pediatr Endocrinol Diabetes Metab 2015;21,3:132-142
DOI: 10.18544/PEDM-21.03.0035

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Silver-Russell syndrome. Part II

Zespół Silvera-Rusella. Część II

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Abstract

Features of the Silver-Russell syndrome (SRS) may overlap with other entities characterized by intrauterine growth restriction, making clinical diagnosis often ambiguous. Numerous scoring systems have been continuously modified, based on anthropometric parameters, dysmorphic features and health issues, including growth and gastrointestinal disturbances. Clinical criteria serve for screening patients for further genetic tests. The latter include tests for analyzing DNA methylation of 11p15 loci and multilocus methylation/imprinting defects (MLMD/MLID). Other techniques useful for SRS diagnosis include analysis for maternal uniparental disomy (UPD(7)mat) and molecular karyotypying if submicroscopic imbalances are suspected. The recurrence risk of SRS within a family is generally estimated low; rare familial cases depend on influence of additional genetic mechanisms. Children with SRS should be under multidisciplinary care. Failure to thrive or gastroesophageal reflux require careful estimation of caloric intake and composition of foods by a gastroenterologist and a nutritionist. Growth and puberty should be followed by an endocrinologist, and treatment with recombinant or biosimilar growth hormone is available for children with SRS. Speech and physiotherapists, psychologists and neurologists are involved in management of psychomotor development. Studies in genetically confirmed cohorts of children with SRS are necessary to evaluate long-term developmental outcome and metabolic sequelae, particularly carbohydrate disturbances in this group of patients.

Key words

Silver-Russell syndrome, clinical scoring system, methylation analysis, uniparental disomy, failure to thrive, growth hormone treatment

Acknowledgements:
The manuscript was prepared within the scientific grant, subsidized by the National Science Centre, no. NN 407 285339.
KCH is a member of the COST Action BM1208.
Authors declare no conflict of interest

Streszczenie

Niektóre cechy zespołu Silvera-Russella (SRS) mogą być wspólne z innymi jednostkami odznaczającymi się wewnątrzmacicznym ograniczeniem wzrastania, stąd kliniczne rozpoznanie tego zespołu jest często niejednoznaczne. Liczne skale punktowe, stale modyfikowane, oparte są na pomiarach antropometrycznych, cechach dysmorfii i na występowaniu objawów chorobowych związanych m.in. z zaburzeniami żołądkowo-jelitowymi i nieprawidłowym wzrastaniem. Na podstawie obrazu klinicznego pacjenci są kwalifikowani do badań genetycznych. Obejmują one analizę metylacji loci 11p15 jak również zaburzeń metylacji/piętnowania wielu loci (ang. *multilocus methylation/imprinting defects*; MLMD/MLID). W diagnostyce SRS wykorzystywane są także techniki analizy jednorodzicielskiej matczynej disomii chromosomu 7 (UPD(7)mat) i metody cytogenetyki molekularnej w przypadku podejrzenia rearanżacji submikroskopowych. Ryzyko powtórzenia się SRS w rodzinie jest małe; znane rzadkie przypadki rodzinne uwarunkowane są dodatkowymi mechanizmami genetycznymi. Dzieci z SRS powinny pozostawać pod wielospecjalistyczną opieką. Słaby przyrost masy ciała czy refluks żołądkowo-przełykowy wymagają dokładnej oceny przez gastroenterologa i dietetyka pod kątem zapotrzebowania kalorycznego i składu pokarmów. Wzrost i dojrzewanie powinny być monitorowane przez endokrynologa.

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Received: 2015-12-14.
Accepted: 2016-02-15.
Conflict of interests: none dedared.

Pediatr Endocrinol Diabetes Metab 2015;21,3:132-142

Dostępne jest również leczenie rekombinowanym lub biopodobnym hormonem wzrostu. Natomiast rozwój psychoruchowy dzieci z SRS powinien być nadzorowany przez zespół składający się z logopedy, rehabilitanta, psychologa i neurologa. Nadal potrzebne są badania w grupach z potwierdzonym genetycznie SRS w celu długofalowej oceny rozwoju i możliwych następstw metabolicznych, w szczególności zaburzeń gospodarki węglowodanowej w tej grupie pacjentów.

Słowa kluczowe
zespół Silvera i Russella, kliniczne skale punktowe, analiza metylacji, disomia jednorodzicielska, słaby przyrost masy ciała, leczenie hormonem wzrostu

Praca powstała w ramach grantu, finansowanego przez Narodowe Centrum Nauki, grant nr NN 407 285339.KCH jest członkiem projektu COST Action BM1208
Autorzy nie zgłaszają żadnego konfliktu interesów związanego z przygotowaniem niniejszego manuskryptu.

Introduction

Literature reports on the natural course, phenotype-genotype correlations, as well as outcomes of the management in subjects with Silver-Russell syndrome (SRS), are diverse. These discrepancies result from the fact that the syndrome clinically and genetically is heterogeneous, as it has been presented in the first part of our review on SRS. Besides, reported cohorts often include small numbers of patients, whereas larger groups are based on clinical diagnosis, and many cases have not been genotyped. Clinical features often overlap with other syndromes of intrauterine growth restriction (IUGR). The common denominator is small birth weight and/or length in relation to the gestational age. However, the definition of a child born small for gestational age (SGA) is not straightforward itself. The cut-off values tend to be arbitrary, set at the 10th, 3rd centile or less than -2 standard deviations (SD) from the mean. Endocrine Societies recommend that SGA should be defined as the birth weight and/or length less than -2 SD in relation to the gestational age, as this value identifies subjects requiring growth assessment and who will most probably be candidates for recombinant growth hormone (rGH) therapy [1]. On the other hand, the cut-off value preferably used by neonatologists and obstetricians is the birth weight below the 10th centile, as it identifies those at risk of perinatal morbidity and mortality [2].

In this part of the review we shall also present genetic methods confirming clinical diagnosis. We believe that accuracy in diagnosis will contribute to critical assessment of the somatic development of children with SRS, as well as it will help in genetic counselling.

Diagnosis and diagnostic criteria

Wide spectrum of clinical features of SRS makes the diagnosis difficult in everyday practice. Usually classical phenotypes are reported, whereas severe cases are rarely presented, and patients with mild phenotypes may be overlooked and not selected for molecular testing. Diagnostic criteria proposed by different authors include at least one subjective parameter, thus the assessment depends on the experience of a clinician [3–6; Table I]. The scoring system comprising only measurable variables has been recently developed by the Birmingham team [7; Table I]. However, it is rather disputable if one can rely on anthropometric measurements exclusively, since knowledge of certain clinical and dysmorphic features not only targets patients for genetic testing, but also contribute to differential diagnosis. Moreover, SGA is no longer an obligate criterion according to another new scoring system by Netchine and Harbison [6], adapted from the original system by Netchine [4]. These systems also include both birth weight and length in contrast to other algorithms based only on birth weight.

Genetic assays

Currently the most popular technique for methylation analysis of the 11p15 loci is methylation-specific multiplex ligation probe-dependent analysis (MS-MLPA) which is easy to handle and commercially available. Great advantage of MS-MLPA is that except aberrant methylation defects at both imprinting control regions (ICR1 and ICR2), it can also detect copy number variation (CNV) as well as uniparental disomy (UPD) of this region.

Other quick and easy to handle methods include methylation specific PCR-based techniques such as MS-PCR analysis or methylation-sensitive high-resolution melting assay (MS-HRM) which require small amount of DNA input. When quantitative data on individual CpG sites is required MS, pyrosequencing seems to be the first choice option [8, 9].

Most of the above mentioned methods are semi-quantitative and can detect aberrant methylation only in one locus. Diagnostic strategy for multilocus methylation defects (MLMD) had to include identification of epimutations at different loci in a single assay. Lately established multilocus methylation-specific single nucleotide primer extension (MS-SNuPE) technology allows rapid screening of aberrant methylation of several differentially methylated regions. This method has been proven to be the most effective in the MLMDs diagnostics [10, 11].

For UPD(7)mat screening microsatellite analysis of chromosome 7 can be applied or locus-specific methylation-specific polymerase chain reaction (MS-PCR) approaches for GRB10 (7p12) and MEST (7q32), respectively. Detection of UPD detection by microsatellite analysis is possible by the comparison of the alleles of the patient and his parents, so except patient's DNA also DNA from parents is needed [11, 12].

Table I. Summary of published scoring systems for diagnosis of SRS
Tabela I. *Podsumowanie skali punktowych wykorzystywanych w rozpoznawaniu SRS*

Scoring system	*Price et al.* 1999 [3]	*Netchine et al.* 2007 [4] *Azzi et al*. 2015 [6] (Netchine-Harbisson)	*Bartholdi et al.* 2009 [5]	*Dias et al.* 2013 [7] (Birmingham)
Common – objective parameters	Low BW<-2SD	*SGA, mandatory [4], not mandatory [6]	BW / BL £10 c	Low BW<-2SD
	PNGR at any age	PNGR or height below MPTH at age of 24 months, BMI<-2SD at 24 month [4,6]	PNGR	PNGR at any age after 2 years
	Relative macrocephaly	**Relative macrocephaly at birth [4, 6]	Normal HC	Relative macrocephaly**
	Asymmetry	Asymmetry [4, 6]	Asymmetry	Asymmetry
Distinctive-subjective parameters	Facial features	Prominent forehead (under age of 3 years)	Facial features	
		Feeding difficulties [4]	Normal cognitive development	
			Other***	
Minimum score for clinical diagnosis	³3 of 5	SGA mandatory and ³4 of 5 [4], SGA not mandatory and ³4 of 6 [6]	³8 of 15	³3 of 4

BL (birth length), BW (birth weight), HC (head circumference), PNGR (postnatal growth restriction; height <-2 SD), MPTH (mid-parental target height)
*SGA – BW and/or BL <-2 SD
**Relative macrocephaly (HC >1.5 SD than height SD) [4, 7]
*** 5th finger clinodactyly, genital abnormalities, other congenital defects, pigmentary lesions

Chromosomal imbalances like maternal duplication of the ICR2 domain or both ICRs have been described, thus application of aCGH analysis in familial SRS cases is justified. For family studies fluorescence in situ hybridization (FISH) analysis is suggested to verify array results, as well as for detecting additional balanced rearrangements not identified by aCGH [13–16]. As chromosomal imbalances may result from transmission of a familial translocation routine G-banded chromosome analysis of cultured peripheral blood lymphocytes is necessary to verify such possibility.

In patients suspected for SRS, but negative for hypomethylation in ICR1 and UPD(7)mat, and/or presenting atypical features (e.g. severe developmental delay / intellectual deficiency) molecular karyotyping by using aCGH for detecting pathogenic submicroscopic chromosomal imbalances is also recommended [6, 15, 17]

Progress in molecular diagnostics of SRS and other imprinted disorders foresees that currently available tests will be replaced by new highly sensitive techniques, such as bisulfite conversion with next-generation sequencing, allowing detection of changes at DNA level as well as epimutations [18]. Application of high-resolution SNP array will facilitate wide detection of unbalanced rearrangements as well as the presence of isodisomy [12].

Differential diagnosis

Prenatal growth disturbances are observed in numerous genetic syndromes. They may also be caused by maternal, environmental and placental factors such as inborn infections, mother's diseases, medications, toxins, placental insufficiency.

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Children born SGA whose body mass and/or length is below 10th centile or -2SD, depending on assumed criteria, should be assessed for SRS and SRS-like entities. These include among the others: Mulibrey nanism, 3-M syndrome, SHORT syndrome, IMAG-e syndrome, Temple syndrome, microdeletion/microduplication syndromes (eg. microdeletions in 12q14, 15q26, 22q11, Yq deletions) [15; Table II], but also familial constitutional short stature and isolated hemihipotrophy. Disorders

Table II. Genetic IUGR syndromes differentiated with SRS
Tabela II. *Genetycznie uwarunkowane zespoły IUGR, z którymi należy różnicować SRS*

Syndrome name [OMIM number] (mode of inheritance, *defected gene*)	Common features	Distinctive features
Mulibrey nanism [#253250] (AR; *TRIM37*)	Pre- and postnatal growth retardation, relative macrocephaly, triangular face, prominent forehead, crowded teeth, high-pitched voice; feeding difficulties, lack of catch-up growth	Cardiovascular involvement (globular shaped heart on X-ray, myocardial fibrosis, pericardial constriction), hepatomegaly, eye anomalies (decreased retinal pigmentation, choroid hypoplasia, yellowish dots in eye fundi), large cerebral ventricles and cisternae, fibrous dysplasia (long bones), normal bone age
3-M syndrome [#273750] (AR; *CUL7*)	Pre- and postnatal growth retardation, relative macrocephaly, triangular face, hypoplastic midface, prominent forehead	Pointed, prominent chin, full lips and eyebrows, upturned nose, X-ray abnormalities (slender long bones, thin ribs, tall vertebral bodies, spina bifida occulta, small pelvis, small iliac wings), joint hypermobility, prominent heels
SHORT syndrome [269880] (AD; *PIK3R1*)	Pre and post-natal growth retardation, prominent forehead, triangular face, speech delay	Hearing loss, sensorineural, eye anomalies (deep-set eyes, myopia, megacornea, Rieger anomaly, glaucoma, cataracts), hypodontia, joint laxity, lipoatrophy (dimples in chin, buttocks), glucose intolerance (hyperglycemia)
IMAGe [#614732] (maternal transmission of *CDKN1C* mutation)	Severe pre- and postnatal growth retardation, relative macrocephaly in some patients, prominent forehead, micrognathia, genitourinary abnormalities (males)	Normal head circumference, epiphyseal/ metaphyseal dysplasia, congenital adrenal hypoplasia; hypercalcemia, hypercalciuria
Temple syndrome (UPD(14)mat) [19]	Pre and post-natal growth retardation, relative macrocephaly (in some), prominent forehead, micrognathia, genitourinary abnormalities (males) feeding difficulties (in infancy), early puberty, scoliosis; speech delay	Overweight after infancy, small feet and hands, hypotonia, joint hypermobility, learning difficulties/ intellectual disability
12q14 microdeletion syndrome (involving *HMGA2* gene) [17]	Pre and post-natal growth retardation, relative macrocephaly (rare), feeding difficulties micrognathia, early puberty; speech delay (severe)	Microcephaly, cardiac anomalies, osteopoikilosis, congenital anomalies of kidneys, liver, intestines, learning difficulties / intellectual disability
15q26 microdeletion syndrome (involving *IGF1R* gene) [15]	Pre and post-natal growth retardation, triangular face; speech delay	Anomalies of heart, diaphragm, lungs, kidneys, limbs; hearing loss; variable neurobehavioral problems (learning difficulties / intellectual disability, ADHD, autism)

SRS – Silver-Russell syndrome, IUGR – intrauterine growth restriction, AR – autosomal recessive, AD – autosomal dominant, ADHD – attention deficit hyperactivity disorder

of DNA repair, including Bloom syndrome, Fanconi anemia and Nijmegen breakage syndrome are frequently associated with IUGR, failure to thrive and short stature. Similar features are also found in children with foetal alcohol syndrome (FAS). However, in these conditions, additional clinical characteristics, including microcephaly, are usually evident.

Genetic counselling

Genetic counselling depends on the molecular mechanism involved. Silver-Russell syndrome is a well known genetically heterogenous congenital imprinting disorder. Epimutations in two different chromosomes, i.e. a hypomethylation of the ICR1 on 11p15 and a maternal uniparental disomy of chromosome 7 (UPD(7)mat) cause a similar clinical phenotype. The recurrence risk is estimated to be low in both cases (<1%), as they generally occur sporadically [20].

However, in literature there are reports on familial cases indicating a contribution of different genetic mechanisms [5, 13, 14, 16, 21–24]

Genomic imbalances (CNV), particularly duplications including ICR1 and/or ICR2 region, when transmitted maternally result in SRS [14–16, 20]. These microaberrations may result from balanced familial reciprocal translocations involving 11p15, however, many cryptic chromosomal imbalances remain undetected by conventional cytogenetics in SRS [15,16].

Exceptionally, familial reciprocal translocation with involvement of chromosome 7 can result not only in unbalanced karyotype, but also in UPD(7)mat [25].

Recent studies identified that maternally inherited gain-of-function *CDKN1C* mutation and paternally derived loss-of-function *IGF2* mutation can be responsible for familial SRS [22, 23]. Therefore in patients with familial history of SRS, negative for hypomethylation in ICR1 and UPD(7)mat, molecular testing for mutations in *CDKN1C* and *IGF2* genes should be considered, along with the other possible causes of this syndrome, such as maternal-of-origin 11p15 duplications [12, 22].

Increased recurrence risk is also expected in MLMD/MLID patients due to likely familial mutations in trans-acting factors. Consequently sequencing analysis of candidate genes including *ZFP57, NLRP2 and NLRP7,* as well in *NLRP5* is recommended in MLMDs cases [11, 26].

Prenatal testing can be offered for families at risk of maternal transmission of identified rearrangements (translocations) or CNV involving chromosomes carrying imprinted genes (i.e. chromosome 7 or 11), as well as a mutation in *CDKN1C and IGF2* genes located in 11p15 region. In some countries prenatal testing for known epigenetic causes of SRS, i.e. loss of paternal methylation of ICR1 and UPD(7)mat is justified in case of IUGR identified by foetal ultrasonography. Early diagnosis of SRS may prevent complications of delivery and neonatal period, and refer a child to specific monitoring of psychomotor development [9].

Treatment and management

No specific therapy is available for SRS. The management is supportive and symptomatic, aimed for reduction of psychosomatic deficits. A general practitioner should be in close co-operation with a gastroenterologist, a nutritionist and an endocrinologist in monitoring nutrition, growth and puberty, as well with a neurologist, a speech therapist, and a psychologist in supervising intellectual and social achievements. Follow-up of children with SRS involves multidisciplinary approach, including other specialists, depending on the spectrum of congenital defects, described in the previous part of this review. A suggested expertise for SRS patients is presented in the table III.

Feeding

In early stages of life, failure to thrive is the most conspicuous problem, affecting even 70% children with SRS [27]. Recommended feeding strategies usually concentrate on preterm and/or IUGR children, who constitute a high-risk group for necrotizing enterocolitis (NEC). However there is no clear consensus regarding the optimum feeding method. It is suggested that delayed and careful introduction of enteral feeding, preferably with human breast milk for its antimicrobial and anti-inflammatory characteristics, prevents NEC. On the other hand early enteral feeding is advantageous, stimulating hormone secretion and gastrointestinal motility, hence improving the functional adaptation of the gastrointestinal tract. It also diminishes complications connected with invasive character of parenteral nutrition, such as catheter related sepsis, cholestasis, cardiac tamponade, osteopenia and other metabolic disturbances. An alternative approach to delaying feeding is the minimal enteral feeding (MEF), increasing the feed volumes during the first week of life [28].

Children with SRS are characterized by feeding aversion, poor sucking, constipation, and often gastroesophageal reflux disease (GERD), largely related to hypotonia [27]. These symptoms contribute to a vicious circle of undernutrition, incidents of hypoglycaemia and fatigue. Children with SRS tend to avoid solid foods, having problems with swallowing. They often display selective and queer appetite, preferring either sweet or, on contrary, salty and spicy foods. Hence diet should be carefully balanced in order to provide appropriate caloric intake, diminish hypoglycaemic incidents and facilitate satisfactory growth. Counselling includes frequent feeding, use of complex carbohydrates, availability of snacks, particularly in kindergarten or school settings. On the other hand, the use of nutrient-enriched formulas, excessive and rapid weight gain in infancy and childhood may lead to development of obesity and its metabolic consequences [2]. It is recommended to maintain ratio of weight/ expected weight to height at 80–85% [27].

Composition and consistency of food and modes of feeding are also closely related to mouth and tongue movements. Hence eating habits should be supervised not only by a dietician, but also by a speech therapist [www.childgrowthfoundation.org].

Table III. Specialists involved in SRS management and follow-up.
Tabela III. *Specjaliści zaangażowani w leczeniu i monitorowaniu dzieci z SRS*

Specialist	Assessment
Paediatrician	General assessment of body composition, growth and puberty
Pediatrician/pediatric endocrinologist/pediatric gastroenterologist/ auxologist	Assessment of body proportions, measuring weight/ length, height/ head circumference/ BMI/ height velocity in the reference to auxologic charts (1st year of life – every 3 months; later – every 6 months)
Clinical geneticist	Assessment of the phenotype and referral to genetic testing, genetic counselling
Paediatric endocrinologist	Assessment of stature, height velocity, pubertal development, lipid and carbohydrate metabolism; evaluation of hormonal status, management of rGH therapy and GnRHa therapy
Paediatric gastroenterologist	Assessment of weight gain and feeding needs; diagnosis and management of GERD
Nutritionist/dietician	Balanced diet, directed at appropriate weight gain, avoiding hypoglycaemia, but also preventing obesity
Paediatric neurologist	Assessment of neurodevelopment
Physiotherapist	Assessment of hypotonia and muscular asymmetry; early physiotherapy
Speech therapist	Mouth and tongue movements in infants, supervising speech and language skills
Psychologist	Neuropsychological testing, identifying school difficulties, peer and social interactions
Craniofacial surgical team/Orthodontist/Dentist	Management of micrognathia, cleft palate, dental crowding; dental hygiene
Orthopaedist	Assessment of limb asymmetry length, scoliosis and other spinal curves, possible hip dysplasia and other deformities of skeletal system; shoe lifts, corsets; referral to surgical intervention.
Urologist/Surgeon	Assessment of genitourinary defects; surgical intervention
Cardiologist	Assessment of possible congenital heart defects
Ophthalmologist	Assessment of visual acuity, and eye fundus
Other	Depending on the spectrum of congenital defects

BMI – body mass index, rGH – recombinant growth hormone, GnRHa – gonadotrophin releasing hormone agonist, GERD – gastroesophageal reflux disease

In case conservative methods are not sufficient, more aggressive ways of feeding have to be considered. They include tube feeding, and in the most severe cases of failure to thrive, percutaneous endoscopic gastrostomy (PEG) may be needed [4].

Gastroesophageal reflux disease, which may be accompanied by oesophagitis, diagnosed on the basis of clinical symptoms and confirmed by radiological studies, endoscopy and esophageal pH monitoring, should include antireflux regimen with appropriate positioning and thickened foods, along with use of acid-blocking medications. In more severe cases surgical management with fundoplication may be necessary [4, 27]. It is also noteworthy, according to observational studies by the French, that most feeding difficulties tend to diminish after the age of 3 years [27].

Growth

Most data concerning growth and puberty in SRS are based on observations of broad cohorts of children born SGA. However, it is justified to precise these observations and separate a SRS group for its distinctive genetic background. Due to rarity (or underdiagnosing) of this syndrome, reports on the development of SRS patients usually include heterogeneous cohorts of patients with clinical diagnosis [29, 30]. Groups with genetic diagnosis of SRS are of less relevant size, and somatic development may differ depending on the epi(genotype) [31].

Body proportions and sexual development in SGA, including SRS children should be assessed regularly. The recommendation of International Societies for Paediatric Endocrinology is to monitor anthropometry of SGA children every 3 months in the first year of life and then every 6 months [1]. Children born SGA at term who remain short by 2 years of age, and by 4 years of age for the preterm, have poor prognosis of further catch-up growth [1]. They should be managed in the endocrine setting. It would be preferable to monitor growth of SRS children, plotting anthropometric measurements against disorder-specific growth charts. However these are still lacking, particularly for children with genetically confirmed diagnosis. European charts have been developed for children with clinical diagnosis of SRS by Wollmann et al. in 1995 [32]. Growth charts are also available for North American children with SRS, provided by the MAGIC Foundation [see: *resources*]. In the course of preparation there are Polish SRS-specific growth charts, based on anthropometric assessment of over 70 patients with genetically confirmed diagnosis of SRS, followed-up in the Department of Medical Genetics in the Children's Memorial Health Institute in Warsaw, Poland.

Growth disturbances are the hallmark of the development in children with SRS, with adult height deficit reaching more than 4 SD below the normal mean in both sexes, causing significant handicap in adulthood [32]. Hence reducing these differences is the main target of the treatment. In 2001 Food and Drug Administration (FDA) has approved growth hormone therapy in short SGA children, including SRS, followed by the European Agency for the Evaluation of Medicinal Products (EMEA) in 2003. Following European pharmaceutical indications, the national programme of reimbursement of the biosimilar or recombinant GH (rGH) in SGA children has also been initiated in Poland this year [www.mz.gov.pl/leki/refundacja/programy-lekowe].

Growth hormone is administered in SGA children regardless their GH secretion. However it is still argued if SGA and SRS children should be tested for GH deficiency and if the hormonal status would condition the outcome of the rGH treatment. Azcona et al. [33] compared two groups of prepubertal IUGR patients, including SRS children, with and without GH deficiency, diagnosed on the basis of stimulation tests. Height deficit was comparable and significant in both groups (-3.7 SD), but GH deficient group was characterized by slower height velocity prior to rGH therapy. After GH administration in both groups there was significant height acceleration, again comparable in GH-deficient and GH non-deficient groups, improving height to -1.4 and -1.7 SD respectively. The authors concluded that the decision to treat a short IUGR child with rGH should not be based upon GH response to a provocative test [33]. The same authors report causes of hypoglycaemia in young children with SRS. None of 24 patients included in their study presented cortisol insufficiency, but 7 children were GH-deficient. The authors indicate poor feeding and/or GH insufficiency contributing to hypoglycaemic incidents in children with SRS [34]. Considering heterogeneity of SGA patients, typical diagnostic procedures assessing hypothalamic-pituitary function may constitute one of the stages in differential diagnosis of growth disorders, particularly in cases of slowing down height velocity. It should also be attempted to find a background of pre- and postnatal growth retardation, as it may condition safety of rGH treatment in other IUGR syndromes associated with neoplasm risk, eg. in DNA-repair disorders [35].

There is no uniform agreement in regard to the age and degree of height deficit at the initiation of rGH therapy or the optimal dose of rGH in SGA patients. It is suggested to start rGH therapy in SGA children with height deficit of -2.5 SD or shorter. Another option is to treat SGA children over 4 years of age with height below -2.0 or -2.5 SDS, in favour of the first cut-off value [1]. In the Polish programme, children born SGA, including some SRS patients, who do not show catch-up growth and whose height deficit at the age of 4 years remains below -2SDS will undergo diagnostic procedures qualifying for the reimbursed rGH therapy [www.mz.gov.pl/leki/refundacja/programy-lekowe].

So far, rGH treatment of short SGA children has been demonstrated to be generally effective and well-tolerated, with most children reaching a normal adult height [36]. However reports on its efficacy in SRS patients have been discrepant, depending on the type of cohort included in the analysis, the dosage of rGH used for the treatment and the time of observation. One of the largest report comes from the International KIGS Survey including 3164 SGA children of whom 501 (15.8%) were classified as SRS [29]. This high percentage of SRS within the whole group of SGA children may discredit the syndrome diagnosis. Similarly, the US American National Cooperative Growth Study did not separate SRS children from those with "primordial short

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stature" [37]. Results coming from KIGS database, show that diagnosis of SRS is one of negative predictive factors for the response to rGH as compared with other SGA children. On contrary, Mehls et al. [38] did not show any significant differences in growth, regardless SRS diagnosis, presence of congenital heart defects or nicotine abuse by mothers during pregnancy, based on retrospective analysis of 135 SGA children treated with rGH.

Although SRS children may not reach target height, in long-term observations they show significant height improvement [39, 40]. Binder et al. [40] compared adult height in SRS treated and untreated with rGH. Epigenetic alternations were proven in approximately half of patients. It was shown that normal height within population norms was achieved in half of male patients but only in quarter of girls. Overall mean height gain during rGH therapy was +1.22 SD, whereas in untreated group spontaneous growth resulted only in +0.21 SD height gain. It must be underlined however, that the study included also children treated with gonadotropin-releasing hormone analogs (GnRHa) due to short stature at the onset of puberty, which will be discussed later in this review. Factors which may be predictive of best therapeutic outcome are the height at the start of the rGH treatment (inversely correlated) and the height gain at the onset of puberty (positively correlated) [39].

Interesting data comes from Binder et al. [31], showing endocrine phenotype-genotype correlations, depending on the presence of 11p15 hypomethylation or UPD(7)mat. In the first part of the review anthropometric differences between these two groups were discussed. Deficient in vitro expression of IGF2 has been reported in the presence of ICR1 hypomethylation [41]. A convincing hypothesis explaining the growth failure for UPD(7)mat has not been put forward yet. Moreover, higher serum concentrations of IGF-1 and IGFBP-3 were found in SRS patients with 11p15 hypomethylation as compared with non-syndromic SGA children or SRS subjects with UPD(7)mat [31]. It was speculated this finding might reflect a mild form of IGF-1 insensitivity. Besides, a trend toward better response to rGH therapy was noticed in children with UPD(7)mat, however this observation should be verified in larger cohorts [31, 40].

Another aspect related to rGH therapy in SGA children, apart from decreasing height deficit, is also improving their body proportions. Arends et al. [42] analysed body proportions of SGA children during 3-year period of rGH treatment, showing normalization of anthropometric measurements, including head circumference, in contrast to untreated SGA control subjects. In studies narrowed down to SRS patients, it was observed that their sitting or spinal height increases, similarly to weight and BMI [39]. Another study did not show any significant changes of limb asymmetry in SRS during rGH therapy [43].

As it was mentioned previously, risk factors for the development of metabolic syndrome, including type 2 diabetes mellitus and cardiovascular disease are already present during childhood in children born SGA [44]. Treatment with rGH therapy in SGA children, and possibly in subjects with SRS, include beneficial effects on serum lipid profiles and blood pressure, as well as bone mineral density [36, 44]. On the other hand rGH therapy, particularly higher doses, may increase fasting and glucose-stimulated insulin levels, however rather in the initial period of treatment, returning to normal after termination of rGH therapy [36].

Doses of GH used in most published studies on SGA and SRS children are higher than recommended by the registration label (*eg.* 0.05 mg/kg/day *vs* 0.035 mg/kg/day or 2 mg/m^2/day *vs* 1 mg/m^2/day). Higher doses of rGH may result in better height velocity. However they also cause elevation of IGF-1 levels, consequences of which are still unknown. Hence most authors recommend monitoring IGF-1 concentrations during rGH therapy, aiming for values not exceeding 2 SDS [36].

Another, rather ultimate, controversial method of improving final height is invasive limb lengthening. Goldman et al. [45] reported on efficacy of such surgical intervention in SRS children, showing mean length gain of 3.3 cm, but faster healing process in the SRS group as compared to other aetiologies of short stature. The authors speculate it may also be influenced by GH treatment.

Puberty

Children born SGA show tendency for early pubertal development [46]. It is suggested that the age at the onset, the progression and duration of puberty are not influenced by GH therapy [47]. On the other hand, postponing puberty by using GnRHa delays epiphyseal fusion, but it also may reduce growth velocity [48]. Binder et al. [40] showed GnRHa therapy as a negative predictor for adult height and overall height gain. At present, there is no convincing evidence that inhibiting pubertal progression by of gonadotrophin releasing hormone agonists (GnRHa) in the absence of precocious puberty is associated with additional height gain [1, 49]. Combination of rGH therapy and GnRHa can be more effective. However, some authors claim the modest height gain along with the cost and burden of such treatment regimen, as well as possible adverse effects on bone mineralization, do not justify it as routine therapy for short SGA children [50]. On contrary, another Dutch group studied adult height in 121 SGA children treated with GH in two doses (1 and 2 mg/m^2/day) and additionally GnRHa, concluding that when SGA children are short at the start of puberty, they can benefit from such combined treatment [51]. It was found that adolescents can still have significant catch-up growth, even when they already entered puberty at the start of treatment. It was demonstrated that adolescents treated with combined GH/GnRHa regimen grew on average 34.5 cm (boys) and 24.2 cm (girls) until adult height. Authors recommend high GH dosing during puberty only when assumed period of growing is short, or in combination with GnRHa, monitoring IGF-1 levels. Continuation of GH treatment until adult height is essential to achieve maximum height gain. Again, narrowing SGA subjects to SRS children may change the outcome of the analysis. The authors however admit that their results may be caused by selection bias [51]. It remains to be shown whether genetic testing of SRS patients will improve the interpretation of study results on growth and puberty.

Neurodevelopment and psychological support

Due to hypotonia, children with SRS require physical therapy starting from infancy. Speech therapist should also be involved from the very early stages of life to guide mouth and tongue movements and supervise feeding aids, and later development of speech skills. Neuropsychological testing should be performed to identify possible deficits and foresee school difficulties. When such are present, appropriate educational plan and psychological assistance should be elaborated individually [52].

Disproportionate body composition may cause low self-esteem, resulting in social isolation. However, in case of children with SRS, it is speculated that possible developmental impairments do not result from the short stature. Lower performance is rather connected with additional congenital defects, as well as with family and socioeconomic background [52].

Prognosis

Long-term prognosis is good. Growth can be improved with GH treatment, however usually SRS children are short or the height of the GH-treated is in lower norm ranges. Some patients may have a learning disability.Hemihypotrophy **is not** associated with an increased tumoral risk.

Key points

Diagnosis

- Clinical diagnosis of SRS is facilitated by scoring systems including small birth weight and length (SGA), postnatal growth retardation, relative macrocephaly body asymmetry, and feeding difficulties (and/or low BMI).
- Genetic assays include, in the order of incidence of genetic abnormalities: MS-MLPA for hypomethylation of 11p15, microsatellite analysis for UPD(7)mat, analysis of peripheral blood lymphocytes for karyotype, and molecular karyotyping for submicroscopic imbalances

Management

- SRS children require multidisciplinary team including gastroenterologist, endocrinologist, speech therapist, psychologist, neurologist and other specialists depending on congenital defects
- Feeding problems such as poor sucking, GERD or queer appetite affect most children with SRS and require assessment of caloric intake, composition of food and sometimes application of feeding aids.
- Dietary counselling aims for avoidance of hypoglycaemic incidents, but also rapid weight gain, as it is considered to be a risk factor for metabolic syndrome in adolescence and adulthood
- Recombinant or biosimilar growth hormone is available for SGA children who do not catch-up growth in early childhood and SRS children may also qualify for such a treatment
- Early puberty observed in children with SRS may influence growth, however delaying puberty with GnRH analogues remains disputable
- Neuropsychological testing should be used to identify possible deficits and indicate appropriate stimulation of psychomotor development

Genetic counselling

- Family recurrence risk/offspring risk is generally low (<1%) (if classic and/or molecular karyotype is normal) in case of:
  - Loss of methylation (LOM) at 11p15
  - UPD(7)mat
- Family recurrence risk/offspring risk is supposed to be increased when LOM at ICR1 is associated with MLMD/MLID (precise figure not possible to estimate yet)
- Family recurrence risk/offspring risk is elevated (up to 50%) when:
  - 11p15 duplication is maternally transmitted,
  - Gain-of-function mutation in *CDKN1C* is maternally transmitted,
  - Loss-of-function mutation in *IGF2* is paternally transmitted.

Resources

MAGIC Foundation. Russell Silver syndrome
6645 West North Avenue, Oak Park IL 60302; USA
Phone: 708-383-0808;Fax: 708-383-0899;Email: mary@magicfoundation.org

- Silver-Russell Support Group; c/o Child Growth Foundation
  2 Mayfield Avenue; Chiswick WA 1PW; United Kingdom
  Phone: 020 8995 0257; 020 8994 7625; Fax: 020 8995 9075
- Stowarzyszenie Chorych na Zespół Silvera-Russella
  Żabieniec, ul. Graniczna 36, 05-500 Piaseczno
  kontakt@silver-russell.org.pl
  WWW.silver-russell.org.pl
  WWW.facebook.com/silverrussellpolska

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