Silver-Russell syndrome. Clinical and etiopathological aspects of a model genomic imprinting entity

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ABSTRACT
Silver-Russell syndrome is characterized by asymmetrical intrauterine growth retardation, with normal head circumference and small, pointed chin, which results in a triangular face. It can also include body asymmetry, among other characteristics. Its global incidence is estimated at 1 in 30 000-100 000 births, even though this figure may be underestimated. In approximately 60 % of cases, a molecular cause can be identified, and the main one is hypomethylation of the paternal allele at the imprinting control region 1 located at 11p15.5-p15.4. It is necessary to make the diagnosis of this entity, exclude differential diagnoses, and know (epi)genotype-phenotype correlations in order to ensure an adequate follow-up, provide available therapeutic options, and offer a timely family genetic counseling. The objective of this article is to describe the current status of the Silver-Russell syndrome, a model of genomic imprinting disorder.

Key words: *genomic imprinting, Silver-Russell syndrome, disease, genotype-phenotype correlation.*

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INTRODUCTION

Genomic imprinting is a type of transcription regulation which is almost exclusive to placental mammals.[1,2] This may occur due to deoxyribonucleic acid (DNA) methylation, when a methyl group is added to the cytosine nucleotide to reduce gene expression, impeding the binding of transcriptional proteins, which as a result are not able to play their role.[1] It is therefore a process of DNA epigenetic modifications that are acquired during gametogenesis,[1-3] affecting expression signals,[4] which allows a gene to be expressed in a monoallelic, parent-of-origin specific manner.[3,4]

Genomic imprinting disorders are a group of associated congenital entities, where four different types of molecular changes are described:[4]

1. Uniparental disomy (UPD) with a disturbance in the expression dosage of imprinted genes.[2,4]
2. Copy number variations.[4]
3. Epigenetic mutations, aberrant DNA methylation in imprinting control regions (ICRs) that regulate the specific allelic expression of imprinted genes.[2,4,5]
4. Less frequently, point mutations.[4]

ICRs are 2-4-kb long genomic sequences characterized by repressive and permissive epigenetic marks on the opposite parental allele. A large cluster of imprinted genes located on chromosome 11p15.5-p15.4 harbors two independent ICRs,[3] which will be then specified.

Silver-Russell syndrome (SRS, OMIM 180860) is part of these types of disorders, which are clinically characterized by growth alterations, body asymmetry, and metabolic, endocrinological, and neurological disorders,[2-3] among others. *Table 1* shows some of these entities.[1,2]

The objective of this article is to describe the current status of SRS, learn how to make a diagnosis based on clinical features, and rule out differential diagnoses. Given the various etiopathological causes, it is necessary to guide early medical surveillance protocols in order to minimize potential complications, ensure an adequate interdisciplinary follow-up, and include a timely family genetic counseling.

SILVER-RUSSELL SYNDROME

SRS is an example of congenital imprinting disorder. It is typically associated with intrauterine and postnatal growth retardation.[2,4,6-9] In 1953, Silver et al., first described the phenotype of two low birth weight children with marked congenital hemihypertrophy, growth failure, and elevated gonadotropin levels.[1,2,8,10] One year later, Russell described the cases of five patients born with severe intrauterine growth retardation,[1,2,10] with a very small infarcted placenta (4 cases out of 5), and specific craniofacial findings, such as a triangular face with a high, broad forehead, a pointed chin, and a wide mouth with thin lips.[1,8,10] Some of the cases had hemihypertrophy and insulin resistance.[10]

These were actually different characteristics of the same syndrome;[1] in 1961, Black et al., grouped these phenotypes and named it SRS.[10] Its global incidence is estimated to be 1 in 30 000-100 000 births.[1,8-10] This figure may be underestimated due to the lack of knowledge about the entity, the variety of clinical presentations, the severity of the disorder, and genetic alterations;[1,8,9] therefore, its exact incidence is still unknown.[8]

CLINICAL SIGNS AND SYMPTOMS

Its presentation encompasses a wide variety of signs that are easily recognizable in typical cases, but may be difficult to diagnose in less affected patients.[7,11] Asymmetrical intrauterine growth retardation is one of the main clinical characteristics, despite most pregnancies reaching term, with no history of obstetric complications. Such delay continues during the postnatal period[1,10-13] and is not due to growth hormone deficiency, even though its abnormal pulsatility is common in this entity.

Moreover, patients have a normal head circumference for age, which appears to be big, late closure of the anterior fontanelle, a prominent and wide forehead with a small, pointed chin, which results in the triangular face described by Russell (*Figure 1*).[1,11,12] These patients may have a convex and prominent nasal bridge, and a well-demarcated philtrum. Their mouth is wide, with thin lips, particularly the upper lip, with micrognathia, which may lead to dental crowding, especially in the lower dental arch, and posteriorly rotated ears.[1] These facial features tend to become less obvious with age, which may later on hinder diagnosis.[1,7]

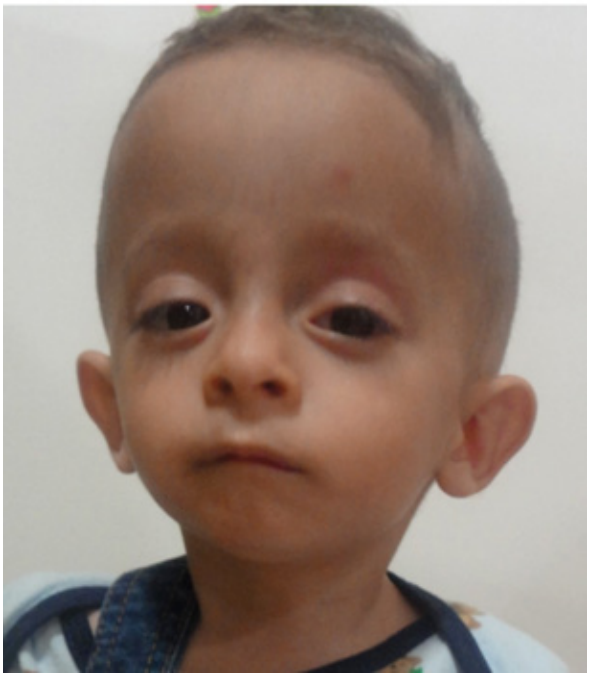
Body asymmetry is observed in almost a third of cases, as well as in the first years of life.[1,10-13] *Table 2* summarizes other findings.[1,8,10,12] Feeding difficulties are considered to be important characteristics, with a lack of interest in breastfeeding since birth, poor appetite, slow feeding, and oral-motor dysfunction.[1,11] Complications include gastroesophageal reflux and esophagitis.[2] In addition, cognitive delay is usually mild and entails language and learning difficulties.[11]

TABLE 1. *Imprinting disorders*[1,2]

Imprinting disorders	OMIM
Silver-Russell syndrome	180860
Beckwith-Wiedemann syndrome	130650
Angelman syndrome	105830
Prader-Willi syndrome	176270
Transient neonatal diabetes mellitus 1	601410
Pseudohypoparathyroidism type 1b	603233
Temple syndrome	616222
Kagami-Ogata syndrome	608149
Maternal UPD of chromosome 20	-
Precocious puberty syndrome	-

UPD: uniparental disomy.

FIGURE 1. *Wide forehead and pointed chin, resulting in a triangular face in a SRS patient with hypomethylation of the paternal allele at the imprinting control region 1 located at 11p15.5-p15.4*



ETIOPATHOLOGY

In almost 60 % of SRS cases an underlying molecular cause can be identified.[1,8] The main etiopathogenic mechanisms include the hypomethylation of the paternal allele at the ICR 1 in 50 % of cases, maternal UPD of chromosome 7 in 10 %, and submicroscopic chromosomal aberrations in 1 %. Thirty-nine percent of cases are considered to be idiopathic.[1-4,6-9,12,14-17] Therefore, a significant percentage of patients with potential phenotypes lack molecular confirmation, due to the genetic heterogeneity, which indicates that not all genetic causes have been identified.[4,7-9]

Familial cases with SRS clinical features and 12q14 microdeletion, including the *HMGA2* gene, which may cause growth retardation, have been reported.[13,18] Therefore, the haploinsufficiency of this gene should be investigated in patients without the main etiopathogenic causes.[13] Moreover, studies on 14q32 should be carried out in relation to Temple syndrome, SRS differential diagnosis; therefore, the use of molecular cytogenetic tests has been suggested as a subsequent step.[4]

It is important to consider that routine tests are done in lymphocytes, and almost all patients with ICR 1 hypomethylation have mosaicism. This means that a subgroup may not have a molecular diagnosis. If there is a solid SRS clinical suspicion, a second cellular system, such as oral epithelium, should be analyzed. However, given the heterogeneous etiology of the entity, the absence of a positive molecular test should not rule out the clinical diagnosis. This observed mosaicism is clinically reflected by the asymmetry present in this cases,[1] as well as in the variable phenotypic presentation.[11] Besides, the post-fertilization origin of epimutations may explain the high discrepancy rate between twins with SRS.[1]

Most cases are sporadic,[1,10,12] with no family history. However, cases with autosomal dominant, autosomal recessive or X-linked inheritance patterns linked to assisted reproductive techniques have been reported,[1,12] which will be analyzed later on.

For this reason, future research in patients with presently-unconfirmed genetic abnormalities may enable further SRS stratification and advance current efforts in association with prenatal testing.[9] Moreover, the identification of the molecular cause has raised questions regarding the management of patients according to molecular subtypes.[8]

DIAGNOSTIC CONSENSUS

Due to their clinical heterogeneity,[1,6] SRS clinical scoring systems are a precondition for the diagnostic protocol, which is relatively complex.[1,2,6] Even though many clinical trials have been conducted, identifying adequate patients for molecular testing still poses a challenge, given that many clinical features are mild or non-specific.[7]

TABLE 2. *Clinical characteristics observed in the Silver-Russell syndrome and their frequency*[1,8,10,12]

Clinical findings	Frequency (%)
Asymmetrical intrauterine growth retardation	100
Decreased muscle mass	56
Excessive sweating	54
Relative macrocephaly	-
Late closure of the anterior fontanelle	43
Protruding forehead	-
Broad forehead	-
Triangular face	94
Prominent nasal bridge	-
Convex nasal bridge	-
Well-demarcated philtrum	-
Thin (upper) lip	-
Downturned corners of the mouth	48
Wide mouth	-
Micrognathia	62
Dental crowding	37
Low-set/posteriorly rotated ears	49
Body asymmetry	-
Shoulder dimples	66
Kyphosis and/or scoliosis	9-36
Aplasia of the uterus	-
Hypoplastic vagina	-
Hypospadias	*
Cryptorchidism	*
Ambiguous genitalia	-
Precocious puberty	-
Camptodactyly	-
Clinodactyly of the fifth finger	75
Arthrogryposis of the distal interphalangeal joint	-
Syndactyly of second and third toes	30
Prominent heel	44
Feeding difficulties (breastfeeding)	-
Gastroesophageal reflux	55
Mild cognitive delay	-
Motor delay	37
Language difficulties	40
Squeaky voice	45
Learning difficulties	-
Metabolic disorders (hypoglycemia)	22-27

* Male genital anomalies in 40 %.
- Frequency is not available in the described bibliography.

The most recent, simple, and widely-accepted method for diagnosis suspicion is the Netchine-Harbison clinical scoring system, based on a prospective study. Probable clinical diagnosis is considered if a patient scores at least four of six from the described criteria (*Table 3*).[1,2,8-10] It has shown to be highly sensitive for identification of individuals most likely to test positive for one of the known molecular causes.[7]

A screening of 69 patients with the Netchine-Harbison system identified 98 % of SRS cases. In probable SRS cases with no ICR 1 hypomethylation or maternal UPD of chromosome 7, maternal UPD of chromosome 20 was observed in one patient, characterized by pre- and postnatal growth restriction, as well as feeding difficulties. Another patient had hypomethylation at *DLK1/MEG3* intergenic DMR (*IG-DMR*), which was a characteristic of Temple syndrome.[2,7]

Therefore, the clinical diagnosis is not completely accurate. It depends on the clinician's experience and the recognition of the wide spectrum of features that SRS may have.[1] A review conducted by Fokstuen and Kotzot pointed out that none of the systems included bone-age retardation, even though this feature was observed in most patients with maternal UPD of chromosome 7.[2,19]

DIFFERENTIAL DIAGNOSIS

In children with short stature of prenatal onset, the differential diagnosis should include chromosomal rearrangements and syndromic diagnosis (*Table 4*).[4,8] Some of the most common typical SRS characteristics overlap with other entities with intrauterine growth retardation, such as 3-M syndrome (OMIM 273750, 612921, 614205).[7] Disproportionate short stature is suggestive of skeletal dysplasias. Photosensitive or recurrent skin rash and bronchopulmonary infections should prompt the investigation for chromosome breakage disorders. As SRS tends to be sporadic, a family history of growth failure and/or consanguinity might indicate an alternative underlying diagnosis,[8] which would mainly suggest an autosomal recessive inheritance pattern.

A correct diagnosis can have extremely important implications for management with growth hormone treatment, which varies depending on the diagnosis. For instance, this is contraindicated in patients with chromosome breakage disorders, such as Bloom syndrome (OMIM 210900), due to the associated risk of malignancy. Also, in patients with SHORT syndrome (short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly, and teething delay) (OMIM 269880), it may precipitate insulin resistance and, subsequently, type 2 diabetes mellitus.[8]

TREATMENT

Treatment is symptomatic, and the main therapeutic goals for the first 2 years of life are nutritional support, prevention of hypoglycemia, and recovery of length/height deficit with the initiation of recombinant

TABLE 3. *Netchine-Harbison clinical scoring system*[1,2,8-10]

Clinical criteria	Definition
Small for gestational age based on birth weight and length	≤−2 Z-score for gestational age.
Postnatal growth failure	Height at 24 ± 1 months ≤−2 Z-score or height ≤−2 Z-score below mean mid-parental height.
Relative macrocephaly at birth	Head circumference at birth ≥1.5 Z-score above birth weight and length.
Protruding forehead	Forehead projecting beyond the facial plane on a side view as a toddler (1-3 years).
Body asymmetry	LLD of ≥0.5 cm or arm asymmetry or LLD <0.5 cm with at least two other asymmetrical body parts (one non-face).
Feeding difficulties and/or low BMI	BMI ≤−2 Z-score at 24 months or current use of a feeding tube or cyproheptadine for appetite stimulation.

LLD: leg length discrepancy; BMI: body mass index.
Probable clinical diagnosis is considered if a patient scores at least four of six from these criteria. If all molecular tests are normal and differential diagnoses have been ruled out, prominent forehead and relative macrocephaly should be included in the diagnosis.

growth hormone therapy suggested at 2-4 years of age.[8] Hypoglycemia is initially managed through feeding and monitoring.[1,9] Intravenous administration of 40 % glucose or dextrose may be used to avoid brain injury and neurodevelopmental disorders.[1] Recurrent hypoglycemia can be determined through strict monitoring of urine ketone levels. Night-time hypoglycemia can be prevented by adding high molecular weight glucose polymers (for infants younger than 10 months)[1,8,9] or uncooked corn starch (for older children) to the last evening feed. Dental hygiene is important since complex carbohydrates can promote cavities.[8]

Its prognosis is favorable. The mean height reached is 153.5 cm among males and 147 cm among females. However, these figures may be improved with the use of recombinant growth hormone therapy during an extended period.[1,9] This is supported by the theory that appetite and food intake may be related to growth.[1,8] A greater increase in height was observed among patients with a shorter stature at treatment initiation.[1] Subcutaneous administration was used, and the dose has been increased from twice or thrice a week to a daily dose, since it has been shown that it results in a better final height,[1,9] regardless of the etiology, even in cases with no hormone deficiency.

Motor delay may be present, mainly due to relative macrocephaly and muscle mass decrease. The average age for walking is 20 months in almost 50 % of cases. There might be an association with cognitive delay and learning difficulties, which is why some children require language therapy. Moreover, recurrent ear infections have been documented; it is therefore important to consider performing hearing tests to identify a potential hearing involvement.[1]

Considering the aforementioned characteristics and other disorders which may occur, an interdisciplinary team should guide, educate, and support parents and other family members.[1] Follow-up should be early and specific, and interventions are required for optimal management. This team should be made up of different pediatric subspecialities, such as neuropediatrics, psychology, language therapy, speech therapy, dentistry, otolaryngology, endocrinology, gastroenterology, pediatric surgery, nutrition, orthopedics, and medical genetics.[2,8]

(EPI) GENOTYPE-PHENOTYPE CORRELATION

Consensuses have been reached through expert collaboration regarding clinical implications, which may serve as a framework for future diagnostic guidelines. Recommendations are aimed at allowing physicians to provide optimal care based on SRS etiology.[9]

Loss of methylation at 11p15.5 has been associated with lower birth weight and length,[8] with postnatal catch-up growth,[1] body asymmetry,[1,8] relative macrocephaly, dental alterations, gothic palate, downturned corners of the mouth, brachydactyly, clinodactyly of the fifth finger, syndactyly,[1] as well as early puberty onset and growth plate fusion.[9] Congenital malformations have also been frequently

TABLE 4. *Differential diagnosis of Silver-Russell syndrome*[4,8]

Relative normocephaly or macrocephaly	Relative microcephaly
3-M syndrome	Bloom syndrome
Mulibrey nanism	Nijmegen breakage syndrome
SHORT syndrome	MOPD II
Floating-Harbour syndrome	Meier-Gorlin syndrome
IMAGe syndrome	IGF1R mutation or deletion
Osteogenesis imperfecta	*IGF1* mutation
Neurofibromatosis type 1	KBG syndrome
Temple syndrome	-

3-M: Its name is derived from the initials of the three researchers who first identified it (Miller, McKusick, and Malvaux).
SHORT: Short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly, and teething delay.
IMAGe: Intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita, and male genitourinary anomalies.
MOPD II: Microcephalic osteodysplastic primordial dwarfism, type II.
IGF1R: Insulin-like growth factor 1 receptor.
IGF1: Gene that codes the insulin-like growth factor 1.
KBG: Its name derives from the first three patients described with this condition.

observed, including heart disease, kidney[10] and genital disorders, such as cryptorchidism,[1,10] hypospadias, and Mayer-Rokitansky-Küster-Hauser syndrome.[10]

Moreover, patients with maternal UPD of chromosome 7 have a generalized developmental disorder,[10] neurocognitive disorders,[8] language delay, squeaky voice, feeding difficulties, excessive sweating, low-set ears, and postnatal growth deficiency.[1]

GENETIC COUNSELING

Genetic counseling depends on the underlying molecular cause. Loss of methylation at 11p15 generally does not entail a recurrence risk, and the offspring risk among individuals with SRS is also low. In the bibliography, only three sibships are reported with this etiology, with an unknown underlying mechanism. Likewise, recurrence in maternal UPD of chromosome 7 is not common. Rare familial cases of SRS have been reported with underlying mechanisms, including maternally inherited 11p15 duplication, maternally inherited *CDKN1C* gain-of-function mutations, and paternally inherited *IGF2* loss-of-function mutations; and in these cases, the risk of recurrence might be as high as 50 %.[8-10]

RELATION WITH ASSISTED REPRODUCTIVE TECHNIQUES

The use of this type of technology may have resulted in the observed SRS increase.[1] Most published studies have suggested that products derived from these techniques show a higher risk for imprinting disorders.[1,5] Nevertheless, our reports did not find such relation, which is therefore still unclear.[5]

Many studies have suggested that procedures such as ovarian stimulation, culture media used for gametes and embryos, *in vitro* fertilization and intracytoplasmic sperm injection manipulations,[1,5] the freezing and thawing of embryos, may prevent the proper establishment and maintenance of genomic imprinting.[5] For instance, the use of a mixture of growth factors in culture media may have an impact on methylation not only on domains responsible for imprinting disorders, but also on additional multiple imprinted loci, at a time when genomic footprints are most vulnerable. Nevertheless, these are not the only procedures that cause this type of defect.[1]

In 2005, the first two SRS cases were reported after an intracytoplasmic sperm injection. In 2006, another case was reported associated with hypomethylation of the *H19* promoter; and one year later, a fourth case was described in a twin girl conceived via *in vitro* fertilization. Nevertheless, the association between an intracytoplasmic sperm injection and a higher incidence of SRS is inconclusive.[1]

Based on these data, pediatricians should consider the different clinical features SRS may have, taking into account the Netchine-Harbison clinical scoring system, as well as inquiring about family history, if there are similar cases within the family, prenatal information, such as intrauterine growth retardation, and even if assisted reproductive technologies were used. Once the diagnostic impression is done, the etiological cause confirming diagnosis should be established, and available therapeutic options and family genetic counseling should be provided. ■

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