

For Affected Individuals, Families and Caregivers

HIGHLIGHTS and SUMMARY
of
**“Diagnosis and Management of Silver–Russell Syndrome:
First International Consensus Statement”**

Condensed by Jennifer B. Salem, Emma L. Wakeling, Deborah J.G. Mackay, Thomas Eggermann and Irène Netchine

Original Consensus: Diagnosis and Management of Silver-Russell Syndrome: First International Consensus Statement. *Nature Reviews/Endocrinology*, 13, 105-124 (2017). Published online 02 September 2016. Authors: Emma L Wakeling, Frédéric Brioude, Oluwakemi Lokulo-Sodipe, Susan Mary O’Connell, Jennifer Salem, Jet Bliiek, Ana Pinheiro Machado Canton, Krystyna Halina Chrzanowska, Justin Huw Davies, Renuka P Dias, Béatrice Dubern, Miriam Elbracht, Eloise Giabicani, Adda Grimberg, Karen Grønskov, Anita Charlotte Suzanna Hokken-Koelega, Alexander Augusto Jorge, Masayo Kagami, Agnes Linglart, Mohamad Maghnie, Klaus Mohnike, David Monk, Gudrun Elisabeth Moore, Philip G Murray, Tsutomu Ogata, Isabelle Oliver Petit, Silvia Russo, Edith Said, Meropi Toumba, Zeynep Tümer, Gerhard Binder, Thomas Eggermann, Madeleine D Harbison, I Karen Temple, Deborah JG Mackay, Irène Netchine

This document is an abbreviated version of the first International SRS Consensus Statement, and does not include research citations or references. The SRS Consensus Statement, written by 36 international SRS specialists, voted on at a meeting in October 2015 and published in October 2016, provides recommendations for the clinical diagnosis, molecular investigation and care management of patients with Silver–Russell syndrome (SRS). The original SRS Consensus Statement with all cited references can be found at the following link: <http://www.nature.com/.../ncurrent/full/nrendo.2016.138.html>

Introduction

Silver–Russell syndrome (SRS), also known as Russell–Silver syndrome (RSS), is a growth restriction condition affecting 1 in 30,000 to 100,000 children. Characteristic features include being born small for gestational age (SGA), continued growth failure after birth (postnatal growth failure), large head size for body at birth (relative macrocephaly at birth), a forehead that protrudes from the plane of the face (prominent forehead, most visible at 12-36 months), body asymmetry and feeding difficulties/low BMI. A genetic cause can be identified in about 60% of patients clinically diagnosed with SRS: most commonly, loss of methylation on chromosome 11p15 (11p15 LOM; 30–60% of patients) and maternal uniparental disomy for chromosome 7 (matUPD7; 5–10% of patients). This summary of the clinical consensus statement will provide highlights of the guidelines for the diagnosis and management of SRS.

Definitions

Small for gestational age (SGA)

Diagnosis made when the birth weight and/or length is less than -2SDS for gestational age [approximately the 3rd percentile].

Intrauterine growth restriction (IUGR)

Prenatal diagnosis based on at least two ultrasound measurements of the fetus showing a slowing of growth, below the 10th percentile. IUGR may or may not result in a baby born SGA.

Clinical Diagnosis

SRS is first and foremost a clinical diagnosis, based on a combination of characteristic features. Molecular genetic testing may confirm the clinical diagnosis, and positive SRS genetic test results can help guide the health care of the SRS patient. In those individuals with negative test results, a clinical diagnosis will help provide access to patient support groups and appropriate treatment.

Physical characteristics among individuals with SRS vary widely and many features are also common to other growth disorders. This consensus therefore recommends the use of the Netchine-Harbison SRS clinical scoring system (NH-CSS; see Table 1) both for determining when SRS genetic testing should be run and when a clinical diagnosis of SRS should be given. The NH-CSS has six factors that have been found to be statistically strong at identifying those patients who will turn out *not* to have SRS (those scoring 3 or less out of 6 factors), and also at identifying which patients might have SRS and would therefore benefit from having SRS molecular testing (those scoring 4 or more of 6 factors). These six factors are easily scored by a physician, and the scoring system is flexible enough to use even with missing data.

If all molecular testing is normal (i.e. no genetic cause is found) (see Molecular Testing section), a

clinical diagnosis of SRS should be given *only* to patients scoring 4 or more of the 6 NH-CSS factors *and* where the 4+ criteria include *both* protruding forehead and relative macrocephaly at birth. It is important to note that it is relative macrocephaly **at birth** that is a distinguishing characteristic of SRS. Although large head size-for-body is present in almost all toddlers and children with SRS, it is also common to children with other growth disorders and as such, cannot solely be used to diagnose SRS. Lastly, the clinical diagnosis of SRS can be difficult to make in adolescence or adulthood because facial features change and early measurement data may be missing. To make a diagnosis in older children, it is important to obtain photographs at 1-3 years of age, from both front and side views of the face, as well as measurements at birth and in the first 2 years.

In addition to the six clinical features in the NH-CSS, a number of other characteristics are common in SRS individuals *but are not exclusive to SRS* (Table 2, pg. 3). Most of these characteristics may be present in children born SGA who do not have SRS, as well as in other syndromes. However, some of these characteristics occur far more often in children with SRS than in children with non-SRS SGA; these characteristics are marked in Table 2 with an asterisk (*).

Table 1: Netchine-Harbison Clinical Scoring System

Clinical criteria	Definition
SGA (birth weight and/or birth length)	≤ -2 SDS for gestational age
Postnatal growth failure	Height at 24±1 months ≤ -2 SDS or height ≤ -2 SDS below mid-parental target height
Relative macrocephaly at birth	Head circumference at birth ≥ 1.5 SDS above birth weight and/or length SDS
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 SDS at 24 months or current use of a feeding tube or cyproheptadine for appetite stimulation

Clinical diagnosis is suspected if patient scores at least four out of six from these criteria. If all molecular test are normal and differential diagnoses have been ruled out, patients scoring at least four of six criteria, including both prominent forehead and relative macrocephaly, can be diagnosed as clinical SRS. Abbreviations: LLD, leg length discrepancy; SDS, SD score; SGA, small for gestational age.

Acronyms list and descriptions can be found on page 9

Molecular Diagnosis

Figure 1 (pg. 4) provides the recommendations for the molecular testing and diagnosis of SRS. Molecular testing for SRS is recommended for patients scoring 4 or more of the 6 NH-CSS factors. In rare cases scoring 3 out of 6, especially when the patient is an infant and/or a factor is “almost” a yes (e.g., maybe the head size just misses the cut-off for relative macrocephaly), a physician may consider ordering SRS testing. But in general, molecular testing for the known SRS causes is not recommended for patients scoring “yes” on 3 or fewer factors. Instead, testing for other syndromes is recommended in these circumstances. ***It is important to remember that a positive SRS molecular test result confirms a SRS clinical diagnosis, but a negative test result does not exclude a clinical diagnosis.*** However, knowing the molecular cause of an individual’s SRS can be helpful in guiding the physician in the care of the child, because 11p15 LOM and matUPD7, for example, are each known to be associated with specific health issues.

Currently, testing is routinely run for known causes of SRS involving two chromosomes – chromosome 7 and chromosome 11. Maternal uniparental disomy of chromosome 7 (matUPD7) affects approximately 10% of SRS cases.

Chromosome 11, region p15 (11p15), is involved in at least five different causes of SRS, representing around 45-60% of all SRS cases:

- A) loss of methylation of the paternal imprinting control region 1 (ICR1) due to an imprinting error (40-55% of cases);
- B) duplication of ICR1 and ICR2;
- C) deletion or duplication affecting ICR or ICR2;
- D) mutation of *CDKN1C* gene;
- E) mutation of *IGF2* gene.

Molecular causes B and C are known as copy number variations (CNVs) and can be inherited. This means that if a patient is found to have an 11p15 CNV, there is a risk that their current or future siblings and/or their future children may inherit the same CNV and have SRS or in some cases, Beckwith-Wiedemann syndrome. The effect of a CNV depends on the parent from whom it is inherited, and therefore both parents should be offered testing and the results discussed with a geneticist. *CDKN1C* mutations causing SRS may be inherited via the mother, and *IGF2* mutations via the

father. Testing should be offered to parents of children with these mutations, and the results discussed with a geneticist.

If a patient is suspected to have SRS by the N-H CSS (scoring 4+ out of 6 factors), and testing of both chromosomes 7 and 11p15 are negative, then additional molecular testing can be considered (see Figure 1). First, there are several chromosomal abnormalities that share some similar physical characteristics with SRS, including matUPD16, matUPD20, and chromosome 14q32 abnormalities [Temple Syndrome]. For now, we do not know if these are part of SRS, though they have similar treatment plans.

Some patients score 4+ out of 6 factors on the N-H CSS but have features which are unusual for SRS: for example, more severe developmental delay, intellectual disability and/or relative *microcephaly* (when the head circumference is below the 3rd percentile and is lower on the growth curves than the height and/or weight curves). In these cases,

Table 2: Additional clinical features of SRS

Clinical Feature	Frequency % (total no. patients)
Triangular face	94% (164)
5th finger clinodactyly*	75% (319)
Shoulder dimples	66% (61)
Micrognathia*	62% (115)
Low muscle mass*	56% (103)
Excessive sweating*	54% (106)
Low-set and/or posteriorly rotated ears	49% (266)
Down-turned mouth corners*	48% (176)
High pitched or squeaky voice	45% (26)
Prominent heels	44% (61)
Delayed closure of fontanelle	43% (47)
Male genital abnormalities	40% (85)
Speech delay	40% (189)
Irregular or crowded teeth*	37% (195)
Motor delay	37% (254)
Syndactyly of toes	30% (264)
Hypoglycaemia	22% (103)
Scoliosis and/or kyphosis	18% (227)

* These characteristics have been found to occur more often in individuals with SRS than those SGA-non SRS individuals

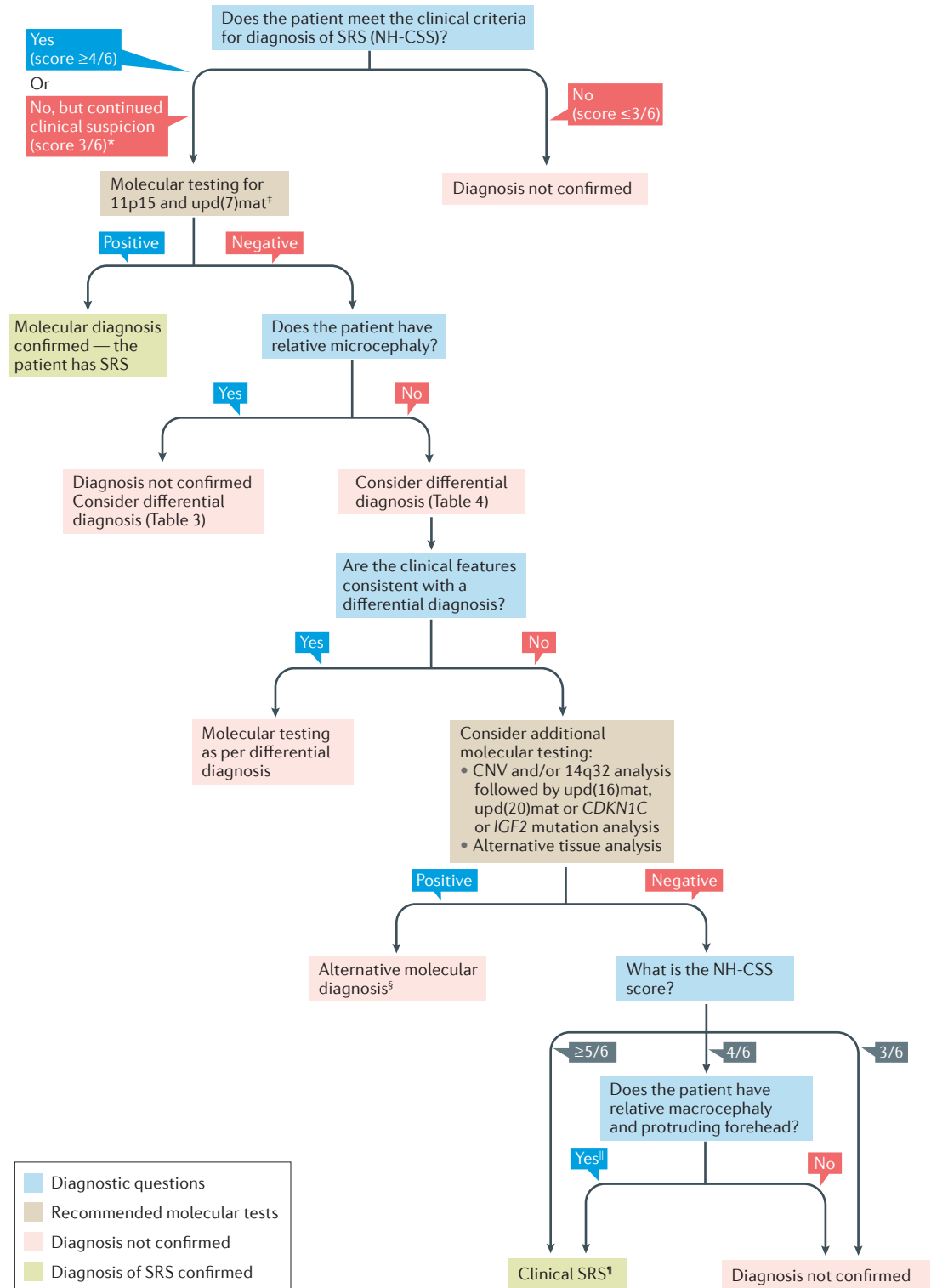


Figure 1 | **Flow chart for investigation and diagnosis of SRS.** Diagnostic questions are in blue boxes; recommended molecular tests are in beige boxes. Pink boxes: diagnosis not confirmed; green boxes: diagnosis of SRS confirmed. *Studies have excluded 11p15 LOM and upd(7)mat in patients with intrauterine growth retardation and postnatal growth retardation alone; some patients, particularly those with upd(7)mat or children under 2 years, score 3/6 (see text for details). †Arrange CNV analysis before other investigations if patient has notable unexplained global developmental delay and/or intellectual disability and/or relative microcephaly. §Insufficient evidence at present to determine relationship to SRS, with the exception of tissue mosaicism for 11p15 LOM. ||Unless evidence of catch-up growth by 2 years. ¶Previously known as idiopathic SRS. CNV, copy number variant; LOM, loss of methylation; NH-CSS, Netchine-Harbitson clinical scoring system; SRS, Silver–Russell syndrome.

microarray testing would be recommended. If a CNV is found in a region other than 11p15, even if the child has some features typical of SRS, the diagnosis should be the CNV and *not* a clinical diagnosis of SRS. This will allow for more specific care management of the child.

Lastly, Figure 1 refers to “differential diagnoses” – other possible causes of ongoing growth issues and physical characteristics in a child born SGA. Some of these potential causes can have important implications for the child’s care management (and in some cases, indicate that a child should not undergo growth hormone [GH] treatment). Physicians should consider these differential diagnoses, especially if the patient has relative *microcephaly*, notable global developmental delay and/or intellectual disability, absence of severe feeding difficulties, additional congenital anomalies, or other features atypical for SRS. Please refer to Tables 3 and 4 in the full-length Consensus Statement which detail the most important and/or likely differential diagnoses.

(Epi)Genotype-Phenotype Correlations

An SRS *phenotype* is all of the physical characteristics found in an individual that are thought to be due to SRS, and a *genotype* is the genetic make-up of that individual. Since we know that SRS can be caused by different genotypes, we should not be surprised that, even though there are many characteristics common to all SRS phenotypes, there are also some unique differences. We call these differences “genotype/phenotype correlations”.

There are a number of known SRS genotype/phenotype correlations. Patients with 11p15 LOM tend to have lower birth length and weight (over 99% are born IUGR/SGA), more frequent body asymmetry and more congenital anomalies than both matUPD7 and clinical SRS. Some patients with matUPD7 are not born SGA but have immediate fall-off in both their weight and length curves after birth. In addition, matUPD7 patients have more frequent neurocognitive problems (including autism spectrum disorder and speech delays) than other SRS patients. Supplementary Table 1 of the original full-length SRS Consensus Statement details individual physical characteristics for the different SRS

genotype subgroups, compared to non-SRS SGA patients.

Management Recommendations

SRS can involve a wide variety of medical problems, and follow-up with different specialists and early interventions are necessary for the ideal management of this group of patients. Almost 60 different care management recommendations were passed by the authors of the SRS Consensus Statement. Management recommendations are divided based on topic, and a summary of each section is included below, with a detailed list of all care management recommendations provided at the end of this document. Please refer to the original Consensus Statement for greater detail and references.

Early feeding and nutritional support

During pregnancy, the typical SRS baby experiences greater in-utero growth restriction of his length than of his weight, and, as a newborn, has a birth length lower on the percentile curves than his birth weight. After birth, however, the baby’s weight curve begins to drop and soon falls to a percentile curve below the length curve. Over time, as the SRS baby’s weight curve continues to pull further below the 3rd percentile (often termed “failure to thrive”), the child’s length curve may also begin to fall farther away from the 3rd percentile, as a result of “calorie-related length deficit” – meaning the child’s ability to grow in length is being negatively affected by not getting enough calories.

Failure to thrive in children with SRS is due to a combination of factors, including feeding difficulties and gastrointestinal problems. Feeding difficulties can include poor appetite as well as oromotor issues, which involve difficulty in using the lips, tongue and jaw. Gastrointestinal problems include gastroesophageal reflux (often with no visible symptoms in children), delayed gastric emptying, and constipation (which is more common after 2 years of age). The antihistamine cyproheptadine, used as an appetite stimulant, has been shown to improve weight gain in other paediatric conditions; specific studies are needed before it can be officially recommended for SRS patients.

The main therapeutic goals for infants with SRS are nutritional support, prevention of hypoglycaemia

(low blood sugar levels), and recovery of any calorie-related length or height deficit, which should be addressed before starting GH therapy. However, careful monitoring is needed, especially if the child is being fed by gastrostomy tube feeding. Rapid weight-gain (when the weight curve climbs up too fast and the BMI rises) is associated with an increased risk of metabolic and cardiovascular disease in later life.

Children with SRS have abnormally low muscle mass and are typically light for their length/height. It can be difficult to determine an appropriate weight-for-height or BMI, and the target depends greatly on individual muscle mass. In SRS children, even slight over-feeding can rapidly increase their relative fat mass. At the same time, if a SRS child's weight/BMI is too low, he may not be able to grow well in length/height and his response to growth hormone therapy may also be negatively affected. It is therefore extremely important to closely monitor a SRS child's weight/BMI. Please see the Consensus for specific recommended weight-for-height targets, but in general a BMI between 12–14 kg/m², or a weight 75-85% of the 50th percentile weight for length or height, is recommended. For children older than 4 years, the optimal target BMI will depend on their muscle mass (muscle weighs more than fat, so more muscle can mean a higher BMI). Two groups of patients are exceptions to this recommended BMI range: in 11p15 LOM patients who have very low muscle mass and body asymmetry, a lower BMI may be adequate (11–12 kg/m²), and in patients with matUPD7 and near-normal muscle mass a higher BMI may be adequate (14–15 kg/m²).

Prevention of hypoglycaemia

Children with SRS, particularly those under five years old, have a disproportionately large brain-for-body size, low muscle and liver mass, and feeding difficulties, all of which increase their risk of fasting hypoglycaemia and its potential neurocognitive consequences. Hypoglycaemia often occurs at night while the child is sleeping, with no visible symptoms.

In these children, the presence of ketones in the urine typically occurs prior to hypoglycaemia resulting from fasting, activity or illness. As such, the monitoring of ketone levels in the urine using Ketostix can be effective in pre-empting such hypoglycaemia, and can be used to determine the

'safe fasting time'. The 'safe fasting time' is essentially the number of hours a child can go without eating or drinking milk/formula without showing evidence of urinary ketones. This is particularly important at night, when a child may go for an extended period of time without eating/drinking. If urinary ketones are present, then hypoglycaemia may soon occur and intervention is needed. Night-time hypoglycaemia can be prevented by adding either glucose polymer (for infants under 10 months) or uncooked corn starch (for older infants and children particularly at risk) to the last evening feed (milk or formula but not gastrostomy tube feedings). Teeth brushing (or rinsing the mouth with water) is essential as complex carbohydrates can promote cavities.

A child with SRS may need to be given intravenous glucose (10% dextrose through an intravenous (IV) drip) during illnesses involving fever or non-eating, or during fasting before surgeries or medical testing. After illnesses that involve vomiting, children with SRS might need periods of gut rest before feeding again because of their gastrointestinal issues. Before being discharged from the hospital, it is important to make sure that the child can manage at least 12 hours of feeding, without IV support, and without ketones in the urine. When hypoglycaemia remains a problem, early GH therapy should be considered as it can help control recurring hypoglycaemia.

Surgery and anaesthesia

Surgeries should be carefully planned. Patients are usually required to fast in the hours before surgery, which increases the risk of fasting hypoglycaemia. IV glucose infusion may be needed. Young patients with SRS are also at risk of hypothermia, and wounds may heal slowly due to poor nutrition. Abnormal tooth distribution or small jaw size may affect airway management. Families should request a meeting with the anaesthesiologist before any surgery to ensure that the anaesthesiologist is aware of these risks.

Growth hormone treatment

SRS is associated with significantly short adult height – studies report approximately 151-154 cm for untreated males and 139-147cm for untreated females. Most children with SRS would qualify for

GH treatment under the SGA registered licences of the U.S. FDA and the European Medicines Agency. GH deficiency is not common in SRS and GH stimulation testing can have risks as it requires fasting. In addition, children who are SGA and not growth hormone deficient respond similarly to GH treatment as those who are SGA and growth hormone deficient. As such, GH stimulation testing should be avoided for most SRS children.

Clinical trials of GH treatment in SGA patients (including SRS) have shown an increase in predicted adult height of 7-11cm. Additional benefits of GH treatment include increased appetite, lean body mass and muscle power which can result in improved mobility and reduction of hypoglycaemia. Most negative side effects of GH treatment are transient (meaning they go away after stopping GH), occur rarely, and do not appear to be more frequent in SRS than SGA non-SRS.

Children with SRS, especially those with 11p15 LOM, often have relatively high levels of IGF1 before starting GH, suggesting some level of IGF1 resistance. When comparing these children's IGF1 levels to the normal range for their age, they tend to be in the high end of normal. Their IGFBP3 levels also tend to be on the higher side. On standard doses of GH, IGF1 levels might rise significantly above the normal reference range. Further studies are needed to understand how best to use these levels to monitor GH doses in children with SRS and IGF1 resistance.

Bone age advancement and puberty

The bone age is initially delayed in the typical patient with SRS (meaning the bone age is younger than the child's chronological age), then rapidly advances so that the child's bone age becomes older than his chronological age. This bone age advancement results in a loss of growing time and a final adult height that is shorter than originally predicted. Usually children with SRS experience bone age advancement around 8-9 years of age. This advancement can occur much earlier, particularly in children with higher BMIs. In SRS children, particularly those with 11p15 LOM, adrenarche (i.e. pre-puberty signs such as body odor, underarm hair, elevated DHEA or DHEA-S levels) can begin early and progress more rapidly in comparison with non-SRS SGA children. Children with SRS usually start

puberty within the normal age range (8 to 13 years in girls and 9 to 14 years in boys) but at the younger end of the spectrum. Early physical signs of puberty include breast bud development in girls and increase in testicular volume in boys (although some SRS boys go into puberty without testicular enlargement).

Our experience is that patients with SRS who go through early adrenarche often begin puberty sooner and their puberty progresses faster than expected. This early puberty accelerates the bone age advancement even faster than before, which then decreases the growth spurt that occurs during puberty. As a result, final adult height is shorter than originally predicted. A rapid increase in BMI can trigger the onset of adrenarche and puberty, even in young children.

Early adrenarche and puberty may shorten the period of time that a child can effectively be treated with GH. SRS patients appear to start puberty earlier than non-SRS SGA children and, without intervention, will experience a decline in their pubertal growth spurt contributing to a shorter final adult height than predicted before puberty. Studies of gonadotropin-releasing hormone analogues (GnRHa), which are used to suppress pubertal hormones, have looked at the effects on final adult height in SGA patients, including a group of children with SRS. The results suggested that the combination of GnRHa, started at the beginning of puberty and continued for at least 2 years, along with GH treatment, improves final adult height in these patients. More studies with GnRHa are needed to look at its effect on final height in larger groups of SRS patients.

In patients with adrenarche and advancing bone age, but who have not yet started puberty, third-generation aromatase inhibitors (such as anastrozole) might be helpful in preventing further rapid bone age advancement, but they are not currently licensed for growth disorders. Clinical research trials are necessary.

Long-term metabolic complications

Individuals born SGA or with a low birth weight are at increased risk of adult health problems including coronary heart disease, hypertension, dyslipidaemia (such as high cholesterol levels), insulin resistance and obesity. (These are all components of metabolic syndrome.) Studies of children born SGA also show

that those who have rapid or disproportionate weight gain catch-up are at particularly high risk of developing these health problems in adulthood.

Overall, GH therapy seems to have positive metabolic effects in children born SGA, including increased lean body mass, reduced fat mass, decreased blood pressure and improvement in their lipid profile. These benefits may last even after GH is discontinued.

Compared to children who have SRS due to matUPD7 as well as other children born SGA, children with SRS due to 11p15 LOM seem to face higher metabolic health risks due to their low muscle mass and higher IGF1 levels. Further research is required into the long-term effects of GH therapy on body composition and metabolic parameters in SRS.

Neurocognitive problems

Motor and speech delays are common in children with SRS (Table 2) and early intervention therapies (such as speech and physiotherapy) are essential. Motor delay may be related to their reduced muscle mass and relatively large head size. Some children with SRS, particularly those with matUPD7, experience verbal dyspraxia and global developmental delay or mild learning difficulties. Autism spectrum disorder has also been reported more frequently in the matUPD7 subgroup, and myoclonus-dystonia may also be an increased risk.

Orthopaedic problems

Orthopaedic problems associated with SRS include asymmetry, scoliosis, hip dysplasia and minor hand and/or foot anomalies (see Table 2). For SRS children with asymmetric limb lengths, limb lengthening surgery to make the two limbs equal length has shown positive results, when needed. Scoliosis has been reported in 9-36% of individuals with SRS. Research in non-SRS patient groups has found that GH therapy does not alter the start or progression of scoliosis; research in patients with SRS is needed.

Maxillofacial abnormalities

SRS is characterized by a triangular-shaped face and protruding forehead, and micrognathia (small, often recessed, lower jaw) is quite frequent. Children with SRS also often have a small, pointed chin and an overbite because their lower jaw tends

to grow slower than non-SRS children. Crowding of the teeth is common, especially in the lower jaw, and SRS children may get their teeth later than their peers. Orthodontic techniques have been used successfully to treat these problems. Orthodontic treatment also seems to improve the ear infections that young children with SRS frequently have. Patients with 11p15 LOM SRS also commonly have velopharyngeal insufficiency (i.e., the inability to temporarily close the passageway between the nasal cavity and mouth when talking or swallowing) with or without a cleft palate. This can result in the patient's voice having a nasal tone. Lastly, many patients with SRS report excessive daytime fatigue, snoring and/or disrupted sleep. One study identified mild sleep disordered breathing (SDB) in 74% of patients. Of note, GH therapy did not worsen the SDB.

Other congenital anomalies

Congenital anomalies have been reported in some patients with SRS, particularly those with 11p15 LOM (see Supplementary Table 1 of the Consensus Paper). Genital abnormalities, including undescended testicle(s) and hypospadias, occur frequently in SRS males, and also in males born SGA without SRS. A small number of female 11p15 LOM patients are born with Mayer–Rokitansky–Kuster–Hauser syndrome, which is characterised by an underdeveloped or absent uterus and upper part of the vagina. Structural kidney anomalies and congenital heart defects have also been reported in some SRS patients.

Adulthood

Very little research has been published about the long-term health of adults with SRS. The majority of adult individuals with SRS are not routinely followed up, and the small number of adults reported have had very few medical problems. However, it is well recognised that being SGA at birth with accelerated gain in weight for length, particularly during early life, increases the risk of metabolic problems in adulthood.

Genetic counselling

Accurate genetic counselling depends on the underlying molecular cause of SRS. The risk of most parents of a child with matUPD7, 11p15 LOM or

clinical SRS having another child with SRS appears to be very low. Similarly, the risk of one of these individuals having a child with SRS also is very low. In rare cases, primarily with 11p15 CNVs (duplications, deletions), the risk of recurrence may be as high as 50%. Genetic testing is therefore essential before giving advice about familial risk for SRS.

Conclusions

Children with SRS and their families face challenges from birth to adulthood, including severe postnatal growth failure with no catch-up, substantial feeding difficulties, ongoing hypoglycaemia, premature adrenarche, early and rapid puberty, insulin resistance, body asymmetry, orthodontic issues, sleep disordered breathing and other congenital anomalies. These consensus recommendations for diagnosis and management apply to all patients clinically diagnosed with SRS, with or without a molecularly confirmed diagnosis. However, identification of the underlying molecular subtype can guide treatment with regards to specific risk factors. Management should include a multi-disciplinary approach, working closely with parents and affected individuals.

Acronym	Description
SRS or RSS	Silver-Russell Syndrome OR Russell-Silver Syndrome
11p15 LOM	Loss of methylation on chromosome 11p15
BMI	Body mass index
CNV	Chromosomal copy number variation (e.g., duplication or deletion)
GER	Gastroesophageal reflux
GH	Growth hormone
GI	Gastrointestinal
GnRHa	Gonadotrophin-releasing hormone analogues
GT	Gastrostomy tube
ICR	Imprinting control region
IGF1	Insulin-like growth factor 1
IGFBP3	Insulin-like growth factor-binding protein 3
LLD	Leg length discrepancy
matUPD7	Maternal uniparental disomy for chromosome 7
MRKH	Mayer-Rokitansky-Kuster-Hauser syndrome
N-H CSS	Netchine-Harbisson SRS clinical scoring system
PCOS	Polycystic ovarian syndrome
SDB	Sleep disordered breathing
SDS	Standard deviation score

Author Addresses

Jennifer B. Salem, The MAGIC Foundation, RSS/SGA Research & Education, 4200 Cantera Dr., Warrenville, IL 60555, USA.

Emma L. Wakeling, North West Thames Regional Genetics Service, London North West Healthcare NHS Trust, Watford Road, Harrow HA1 3UJ, UK.

Deborah J.G. Mackay, Human Development and Health, Faculty of Medicine, University of Southampton, Southampton SO17 1BJ, UK.

Thomas Eggemann, Institute of Human Genetics, Technical University of Aachen, Pauwelsstr. 30, D-52074 Aachen, Germany.

Irène Netchine, AP-HP, Hôpitaux Universitaires Paris Est (AP-HP) Hôpital des Enfants Armand Trousseau, Service d'Explorations Fonctionnelles Endocriniennes, 26 avenue du Dr Arnold Netter, 75012 Paris, France.

SRS PATIENT CARE MANAGEMENT RECOMMENDATIONS from FIRST INTERNATIONAL SRS CONSENSUS STATEMENT*

CARE MANAGEMENT

- 4.1 Patients with SRS should receive multidisciplinary care in a centre of expertise in SRS in coordination with their local centre. The multidisciplinary team should be composed of paediatric subspecialists such as an endocrinologist (coordinator), gastroenterologist, dietician, clinical geneticist, craniofacial team, orthopaedic surgeon, neurologist, speech and language therapist and psychologist.

EARLY FEEDING & NUTRITIONAL SUPPORT

- 5.1 For nutritional goals in the first years of life, we recommend nutritional repletion* with awareness of possible hazards of rapid postnatal catch-up leading to subsequent increased metabolic risk.
*Note: Low muscle mass makes typical BMI targets excessive in this population.
- 5.2 Ask for and/or screen early for gut dysmotility (gastroesophageal reflux, delayed gastric emptying and constipation) in all children.
- 5.3 Diagnose and treat any oromotor and/or sensory issues that affect oral intake of food.
- 5.4 In patients with severe feeding failure who are unresponsive to standard care, anatomical or functional disorders of the GI tract, such as malrotation, should be excluded.
- 5.5 Avoid enteral feeding by nasogastric or gastrostomy tube in a child capable of eating where there is adequate nutritional repletion.
- 5.6 In cases of extreme feeding difficulties or GER, consider enteral feeding by GT (with or without a fundoplication) or low-profile transgastric jejunostomy as a last resort to protect against hypoglycaemia and/or malnutrition.
- 5.7 In the case of enteral feeding, prevent excessive weight gain in both volitionally and non-volitionally fed children.

PREVENTION OF HYPOGLYCAEMIA

- 6.1 Monitoring for ketonuria at home is useful to determine which children need intervention for impending hypoglycaemia. [Note: Children with a history of hypoglycaemia who do not have an appropriate ketone response will require formal fasting studies.]
- 6.2 Develop a plan with the child's local paediatrician and emergency room for rapid admission and intravenous dextrose treatment when the child is ill.
- 6.3 Admit children with SRS to the hospital early in the course of an illness associated with ketonuria or hypoglycaemia and do not discharge them until they are metabolically stable and can be adequately fed.
- 6.4 Glucagon is not recommended to correct hypoglycaemia, because of poor glycogen stores and limited ability for gluconeogenesis.
- 6.5 Provide parents with an emergency guidance plan for illnesses.
- 6.6 Teach parents how to recognize signs of hypoglycaemia, measure ketones, determine the 'safe fasting time' for their child, prevent hypoglycaemia using complex carbohydrates and avoid fasting outside a controlled environment.
- 6.7 In severe cases of fasting hypoglycaemia, where other causes have been excluded and if other alternatives are ineffective, consider:
- Early start of GH therapy to support glucose sources (increase in muscle mass and gluconeogenesis)
 - Placement of a gastrostomy tube or jejunostomy tube.

SURGERY and ANAESTHESIA

- 7.1 Review issues related to SRS with the anesthesiologist and surgeon in advance.
- 7.2 Consider admission the night before surgery for early administration of intravenous dextrose before surgery to avoid ketonuria and hypoglycaemia.
- 7.3 Schedule first on the surgical list where possible.

SURGERY and ANAESTHESIA, con't.

- 7.4 Monitor blood glucose and administer intravenous dextrose during and after surgery. Do not discharge until ketonuria is absent and the child can sustain themselves on oral or enteral feeding.
- 7.5 Follow the intraoperative temperature maintenance protocol appropriate for the patient's size, not age.
- 7.6 Delay elective surgery until the child is adequately nourished.
- 7.7 Be aware of the high risk of malnutrition after surgery and follow appropriate guidelines.

GROWTH HORMONE TREATMENT

- 8.1 Defer GH treatment until caloric deficits are addressed.
- 8.2 Avoid GH stimulation testing.
- 8.3 Goals of GH treatment are to improve body composition (especially lean body mass), psychomotor development and appetite, to reduce the risk of hypoglycaemia, and to optimise linear growth.
- 8.4 Treat with GH as soon as possible; starting at age 2-4 years is adequate for the majority of patients; however, due consideration should be given to the exceptions listed below*.
- 8.5 Start GH at a dose approximately 35 µg/kg per day. Use the lowest dose that results in catch-up growth.
- 8.6 Terminate GH therapy when height velocity is <2cm per year over a 6-month period and bone age is >14 years (female patients) or >17 years (male patients).
- 8.7 If response to GH is poor, re-evaluate the underlying diagnosis, GH dose, IGF1 response, adherence to therapy and other confounding systemic problems.
- 8.8 Monitor circulating levels of IGF1 and IGFBP3 at least yearly during GH treatment.

*Note: GH treatment does not have a specific indication for SRS and is prescribed under the SGA indication (height SDS -2.5; age >2-4 years; dose 35-70 µg/kg per day). Exemptions from the current SGA licensed indication used in some centres include starting GH therapy below the age of 2 years in case of: severe fasting hypoglycaemia; severe malnutrition, despite nutritional support, which will lead to gastrostomy if no improvement is seen; and severe muscular hypotonia.

BONE AGE ADVANCEMENT and PUBERTY

- 9.1 Monitor for signs of premature adrenarche, fairly early and accelerated central puberty, and insulin resistance.
- 9.2 Monitor and anticipate acceleration of bone age especially from mid childhood.
- 9.3 Consider personalized treatment with GnRHa for at least 2 years in children with evidence of central puberty (starting no later than age 12 years in girls and age 13 years in boys) to preserve adult height potential.

LONG-TERM METABOLIC COMPLICATIONS

- 10.1 Avoid excessive or rapid weight gain to prevent increased insulin resistance, which is associated with early and rapidly advancing adrenarche, early central puberty, and, in girls, a future risk of developing polycystic ovary syndrome.
- 10.2 Raise awareness among gastroenterologists, dietitians, neonatologists, paediatricians and primary health-care providers of the importance of not overfeeding this group of children.
- 10.3 Advise parents, grandparents and care-givers about the risk of insulin resistance associated with intrauterine growth retardation and overfeeding.
- 10.4 Screen for physical and biochemical indicators of insulin resistance during GH treatment, especially in children with low muscle mass and high baseline levels of IGF1.
- 10.5 In patients with clinical signs of insulin resistance, consider formal assessment of insulin sensitivity with a 2-hour oral glucose tolerance test including measurement of insulin and C-peptide levels.
- 10.6 Advocate a healthy diet and lifestyle in older children and young adults with particular emphasis on protein calorie balance and regular exercise to avoid disproportionate weight gain, particularly after discontinuation of GH treatment.

NEUROCOGNITIVE PROBLEMS

- 11.1 Refer infants and children with SRS for a developmental assessment when necessary to ensure appropriate intervention as early as possible.
- 11.2 In patients with upd(7)mat, check for symptoms of myoclonus dystonia at each clinical appointment and refer early to a paediatric neurologist if required.
- 11.3 Monitor children with upd(7)mat for signs of verbal or oromotor dyspraxia and/or signs of autistic spectrum disorders.
- 11.4 Inform parents about increased risk of speech, oromotor and learning disabilities (especially in those with upd(7)mat).
- 11.5 Follow up school-age children for any learning difficulties, psychosocial challenges and/or cognitive delay, to enable appropriate intervention.

ORTHOPAEDIC PROBLEMS

- 12.1 Where necessary, refer to a paediatric orthopaedic surgeon for collaborative management of body asymmetry, limb length discrepancy and scoliosis.
- 12.2 Routinely examine all patients with SRS for scoliosis.
- 12.3 Before initiation of GH therapy, refer patients with scoliosis to the orthopaedic team and monitor while receiving GH.
- 12.4 Evaluate leg length asymmetry regularly and consider orthopaedic management if necessary.

MAXILLOFACIAL ABNORMALITIES

- 13.1 Develop a referral relationship with a maxillofacial team or orthodontist who has experience caring for patients with SRS.
- 13.2 Refer patients to the maxillofacial team for assessment after eruption of primary dentition when necessary.
- 13.3 Encourage early orthodontic intervention and compliance with follow-up.
- 13.4 Screen for symptoms of sleep disordered breathing (such as snoring, apneas, excessive daytime fatigue, disrupted sleep and agitation).
- 13.5 Refer patients with suspected sleep disordered breathing to the appropriate specialist for evaluation of obstructive sleep apnea.

OTHER CONGENITAL ANOMALIES

- 14.1 Investigate genital abnormalities in boys.
- 14.2 Investigate girls with primary amenorrhoea for Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome.

ADULTHOOD

- 15.1 Consider medical follow-up of adolescents and young adult patients with SRS or develop collaboration with a general or internal medicine team for follow-up.
- 15.2 Avoid losing contact with adult patients with SRS, to facilitate their participation in, and potential benefit from, future clinical research.

GENETIC COUNSELING

- 16.1 Genetic counselling should be performed by a health professional experienced in the field of imprinting disorders. As the recurrence risk associated with CNVs is dependent on their size, location and parental origin, these should be taken into consideration during counselling for the family.