

Introduction

Russell-Silver Syndrome [RSS] (or Silver-Russell Syndrome) is a rare genetic disorder characterized by delayed growth in-utero (IUGR) that spares head growth (meaning the newborn has a head size that is large for his body) and ongoing postnatal growth failure. This disorder also includes feeding difficulties and/or low BMI, dysmorphic features including a protruding forehead, and frequently body asymmetry (hemihypotrophy). The true incidence is unknown but is estimated at 1 per every 35,000 – 100,000 live births.

It was back in 1953 and 1954 that Dr. Silver and Dr. Russell independently described groups of small-for-gestational-age (SGA) children whose pregnancies had been complicated by IUGR (one group with body asymmetry and one without). These two groups of patients are now considered to have had variations of the same disorder that we now call RSS in North America and SRS in Europe.

One interesting and important aspect of the Russell-Silver syndrome is its variation in phenotype. In this context, a phenotype is all the physical characteristics and abnormalities found in an individual patient that are attributed specifically to RSS. Some individuals with RSS have many traits, thus a severe phenotype, while others have very few traits, thus a mild phenotype.

When first described, RSS was NOT thought to be a genetic disorder because it recurred within families rarely, and when it did recur, its pattern of transmission failed to follow a consistent genetic mode of inheritance. More recent understandings of genetic mechanisms have led scientists to conclude that RSS is genetic, but its genetics are not simple. Scientists now believe that the RSS phenotype is associated with more than one genotype.

A genotype is the status of a specific gene at a specific location on a specific chromosome. Therefore, an abnormal genotype means there has been a specific alteration, such as a deletion, duplication, insertion, substitution or imprinting error within the code of a specific gene located at a specific site in an individual's genetic code.

Since our genotype is responsible for our phenotype, abnormal genotypes result in abnormal phenotypes. If we assume several genotypes for RSS, then we should not be surprised at a variety of phenotypes. We view this as one reason for the marked variability within the group

of patients considered to have RSS. But deciding which child should be considered to have RSS is not always easy.

How is RSS Diagnosed?

A child with Russell-Silver syndrome can be diagnosed either by a clinical diagnosis or molecular/genetic testing, but negative genetic testing does *not* rule out a clinical diagnosis. Currently there are two specific chromosomes known to be involved in causing Russell-Silver syndrome – chromosomes 7 and 11.

Maternal uniparental disomy of chromosome 7 (matUPD7) is the cause of RSS in about 10% of cases. Genetic testing should rule out both heterodisomy (rare) or isodisomy (more common) forms of matUPD7 – the latter requires a blood sample from one parent.

Chromosome 11 at band 11p15 is involved in multiple different RSS mechanisms. The most common, found in 40-55% of RSS cases, is 11p15 loss of methylation, which requires special methylation testing. Chromosome duplications, deletions or mutations within 11p15 are very rare causes of RSS (less than 5% of cases) and are typically familial – meaning RSS or short stature may be found in other siblings or prior generations. SNP microarray testing will usually catch these abnormalities.

However, genetic testing can currently only confirm known epigenetic causes of RSS for approximately 60-70% of RSS cases. The remaining cases (who test negative for known causes) would be considered “idiopathic RSS” (meaning the cause is unknown) if the physician makes a clinical diagnosis of RSS. It can be easy to diagnose the “textbook” RSS phenotype but other cases are more difficult to classify. The published International RSS Consensus Statement provides details on the recommended RSS clinical diagnosis requirements, which uses the Netchine-Harbison RSS clinical scoring system. This scoring system found that a combination of six characteristics could statistically differentiate children who tested positive for RSS from children who were SGA and had growth failure but did not have RSS (see below for details).

MAGIC's RSS/SGA Research & Education Fund offers a free RSS screening using this scoring system. Interested families can email rss@magicfoundation.org and request screening information.

What is the Typical RSS Phenotype?

Statistically, the Netchine-Harbison RSS scoring system found that children who have 4 or more of the following six characteristics are more likely to have RSS, and especially when the last two factors are present:

- Born small-for-gestational-age
- Low BMI [< 14.4 (boys)/ 14.0 (girls)] or on feeding tube in first 2 years
- Poor catch-up growth in first 2 years
- Body asymmetry -LARGE side is "normal" side
- Large head size for body size AT BIRTH
- Prominent forehead that protrudes from face

The RSS phenotype also includes a number of physical and developmental characteristics that are common to many children who had IUGR or were born SGA. Some occur more frequently in RSS than other SGA/IUGR children and others occur equally as often.

Characteristics of SGA/IUGR Children that Occur More Frequently in RSS Children:

- lack of interest in eating
- lack of muscle mass and/or poor muscle tone
- clinodactyly (inward curving) of the 5th finger
- syndactyly (webbing) of the 2nd and 3rd toes
- hypoplastic (underdeveloped) chin & midface
- downturned corners of mouth
- thin upper lip
- high-arched palate
- small, crowded teeth
- low-set, posteriorly rotated and/or prominent ears
- unusually, high-pitched voice in early years
- café-au-lait (coffee-with-milk) birth marks
- dimples in the posterior shoulders and hips
- narrow, flat feet
- scoliosis - curved spine, associated with spinal asymmetry and accentuated by a short leg
- prominent heels (mUPD7 primarily)

Characteristics Commonly Found in SGA/IUGR and/or RSS Patients:

- fasting hypoglycemia & mild metabolic acidosis
- generalized intestinal movement abnormalities:
 - a. esophageal reflux resulting in movement of food up from stomach into food tube
 - b. delayed stomach emptying resulting in vomiting or frequent spitting up
 - c. slow movement of the small intestine &/or large intestine (constipation)
- blue sclera (bluish tinge in white of eye)

- hypospadias - abnormal opening of the penis
- cryptorchidism - undescended testicles
- late closure of the anterior fontanel (soft spot)
- frequent ear infections or chronic fluid in ears
- congenital absence of the second premolars
- delay of gross and fine motor development
- delay of speech and oral motor development
- kidney abnormalities
- delayed bone age early, later fast advancement
- early pubic hair and underarm odor (adrenarche)
- early puberty or rarely true precocious puberty
- classical or neurosecretory growth hormone deficiency
- ADD and specific learning disabilities

What Should I Do If I Think My Child Has RSS?

- Have your child's diagnosis confirmed by a doctor who is familiar with RSS-SGA patients. If you would like to request a free RSS screening from MAGIC, simply email rss@magicfoundation.org.
- Make sure your child is measured carefully & frequently. KEEP YOUR OWN RECORDS. Find an endocrinologist who knows how to treat SGA children's growth failure and discuss the options.
- Find a pediatrician who is willing to learn from experts about RSS-SGA children, and will coordinate care and opinions with consulting specialists.
- Get adequate calories into your child. Insufficient nutrition & low blood sugar damage the developing brain and compound the growth failure.
- Take necessary measures to prevent hypoglycemia in young RSS children. Pay special attention to the night when everyone is asleep, anytime your child is ill or not eating normally, and when your child is unusually active or stressed.
- Know clues that hypoglycemia is occurring:
 - a. waking to feed at night past early infancy
 - b. excessive sweating
 - c. extreme crankiness improved by feeding
 - d. difficulty waking up in the morning
 - e. ketones in the urine
- Prevent hypoglycemia by:
 - a. feeding frequently during the day & night
 - b. keeping snacks with you at all time
 - c. feeding through gastrostomy tube
 - d. adding glucose polymer in infant's, & cornstarch in child's, bed- & night-time feeding
 - e. keeping glucose gel with you at all times

- f. making prior arrangements with your doctor and local ER to start IV glucose if feeding is impossible
- g. having urine ketone sticks at home
- h. Download RSS-SGA emergency medical instructions from the MAGIC website if your child is unable to eat for more than 4 hours and/or is spilling ketones in urine.
- Treat your child his age not his size. Arrange safe, age-appropriate activities; buy age-appropriate clothes; and expect age-appropriate behavior and responsibility.
- Watch your child's psychosocial and motor development. All states have developmental evaluation & intervention services for children younger than age 3. These programs are based on the child's needs not parental income. For children over 3 years old, the school district becomes responsible for providing these services. Take advantage of this; intervention can make a world of difference for your child!
- Seek appropriate consultation for recurrent otitis, hypospadias, undescended testicles, leg length discrepancies, etc. But remember:
 - a. Only emergency surgery should be done until the child is gaining weight well.
 - b. A young SGA child should NEVER be fasted or kept NPO for more than 4 hours for ANY reason without glucose-running IV
 - c. For surgery, IV glucose should be given during the procedure and continued in the recovery room.

What Can I Expect Regarding My Child's Cognitive Abilities?

An infant with RSS is generally born with normal intelligence. Learning disabilities and Attention Deficit Disorder (ADD) appear to be increased in incidence in RSS-SGA for unknown reasons. Autism and similar disorders like pervasive developmental disorder (PDD) may also be increased, especially in RSS caused by matUPD7. It is unclear whether these problems just appear to be increased in RSS, are innate to RSS, or are acquired through early malnutrition and hypoglycemia, both of which are preventable.

Where Can I Meet Other RSS Families?

Coping with time-consuming special attention and services necessary to care for an RSS-SGA child can be overwhelming, especially if you try to face it alone. Good physicians often have no experience with routine

needs of RSS-SGA children. Day-to-day challenges such as feeding, formulas, fitting clothes, school issues and peer pressures can be less stressful if you are in contact with other families who "have been there and done that." Making connections between families with similar issues and facilitating sharing of information and experience is a major goal of the MAGIC Foundation's RSS Division. We can put you in touch with other people who have had, and have solved, problems similar to yours.

What Treatments Are Available for RSS?

The treatment of RSS children's medical problems should be approached in a systematic and timely fashion. The major problems that require intervention in the various age periods are all different, but most all these problems can be solved or dealt with successfully if you get the help you need. Due to space, it is beyond the scope of this brochure to go into treatment protocols on every possible medical issue. However, comprehensive information in a question-and-answer format is available on our RSS pages at www.magicfoundation.org.

It is, however, imperative that the RSS child's physician be aware of the recommendations for keeping the SGA child as lean as possible (typically with a BMI between 12-14.5 depending on the child's muscle mass and body asymmetry) due to the increased risks for health issues associated with metabolic syndrome. Research has found that these risks increase with rapid weight gain catch-up, or even with small amounts of extra subcutaneous body fat, for an SGA child. On the other hand, short SGA children cannot grow on air – meaning their length/height can be diminished if they do not consume enough calories. It is a balancing act and not an easy one.

Can My RSS Child's Height Be Improved?

Yes, the height of an RSS child can be improved above the 3rd percentile and closer to where he should be for his parents through the use of recombinant growth hormone therapy (rGHT). In 2001, the U.S. FDA approved the use of rGHT as long-term treatment of growth failure in children who were born small-for-gestational-age and do not achieve catch-up growth by age 2. And in 2003, the European Agency for the Evaluation of Medicinal Products (EMEA) made the same approval for SGA children who had not achieved catch-up growth by age 3. In addition, almost universally, research in the last two decades have found that growth hormone therapy increases childhood height for RSS/SGA children to a percentile in the "normal" range, and that rGHT also

increases and normalizes final adult height. And possible more important, rGHT has been found to result in many other improvements in health for RSS/SGA children.

The choice of whether or not to increase the RSS child's significantly shorter stature is a personal decision that must be made by each family, and balanced with the other health improvements that can come with using rGHT. Each child's parents and endocrinologist should discuss the benefits and risks of rGHT, and discuss the various factors that impact the success of rGHT, as they relate to their specific child.

RSS-SGA Guidebook Available

MAGIC offers an RSS-SGA Guidebook free to any new member. This Guidebook is 330 pages long and includes comprehensive information on caring for an RSS-SGA child, along with many personal stories and photos.

Written by:

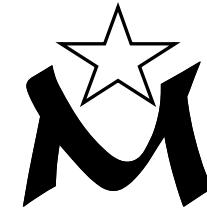
Madeleine D. Harbison, M.D.
 Assistant Professor of Pediatrics
 Adrenal & Steroid Disorders
 Pediatric Endocrinology
 Mt. Sinai School of Medicine of
 NY University
 New York, New York 10029

Jennifer Salem
 RSS/SGA Research & Education Fund
 MAGIC Foundation

This brochure is for informational purposes only. Neither The MAGIC Foundation nor the contributing physician assumes any liability for its content. Consult your physician for diagnosis and treatment.

Revised 2.2017

Russell-Silver Syndrome



The MAGIC Foundation®
For Children's Growth

“Children have a short time to grow and a lifetime to live with the results”®

Not an illusion or magical,
 But the caring for children
 and their families

* * * *

Dedicated to the growth
 and overall development
 of children

4200 Cantera Dr.
 Suite 106
 Warrenville, IL 60555
 630-836-8200
 630-836-8181 fax
 800-3MAGIC3
www.magicfoundation.org