**Diagnosis and management of Silver-Russell syndrome:**

**First international consensus statement**

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**ABSTRACT**

This Consensus Statement summarises recommendations for clinical diagnosis, investigation and management of Silver-Russell syndrome (SRS), an imprinting disorder causing pre- and postnatal growth retardation. There is considerable overlap between the care of individuals born small for gestational age and with SRS. However, many specific management issues exist and evidence from controlled trials remains limited. SRS is primarily a clinical diagnosis, though molecular testing allows confirmation and defines subtype. Normal molecular test results do not exclude the diagnosis of SRS. Management of children with SRS requires an experienced, multidisciplinary approach. Specific issues include growth failure, severe feeding difficulties, gastrointestinal problems, hypoglycaemia, body asymmetry, scoliosis, motor and speech delay and psychosocial challenges. Early emphasis on adequate nutritional status is important, with awareness that rapid postnatal weight gain may lead to later metabolic risk. Benefits of growth hormone treatment include improved body composition, motor development and appetite, reduced hypoglycaemia risk and increased height. Clinicians should be aware of possible premature adrenarche, relatively early and rapid central puberty and insulin resistance. Treatment with gonadotropin releasing hormone analogues can delay progression of central puberty and preserve adult height potential. Long-term follow up is essential to determine the natural history and optimal management in adulthood.

**INTRODUCTION**

Silver-Russell syndrome (SRS, OMIM #180860; or Russell-Silver syndrome, RSS) is a rare, though well-recognised, condition associated with pre- and postnatal growth retardation. It was first described by Silver et al. 3 and Russell 4, who independently described a subset of children with low birth weight, postnatal short stature, characteristic facial features and body asymmetry. Almost all patients with SRS are born small for gestational age (SGA) (refer to Box 1 for definitions). The aetiology of intrauterine growth retardation (IUGR) and SGA is extremely heterogeneous. Children with SRS can be distinguished from those with idiopathic IUGR/SGA and postnatal growth failure by the presence of other characteristic features, including relative macrocephaly, prominent forehead, asymmetry and feeding difficulties 5-8.

**Box 1: Definitions**

**Small for gestational age (SGA)**

Weight and/or length less than -2SD for gestational age at birth, based on accurate anthropometry at birth (including weight, length and head circumference) and reference data from a relevant population 1.

**Intrauterine growth retardation (IUGR)**

Also known as intrauterine growth restriction, this diagnosis is based on at least two ultrasound measurements at least two weeks apart, with fetal weight below 10th percentile for gestational age. IUGR may or may not result in a baby born SGA 2.

**Silver-Russell syndrome (SRS)**

A distinct syndromic growth disorder in which pre- and post-natal growth failure are associated with other characteristic features, including relative macrocephaly at birth, protruding forehead in early life, body asymmetry and significant feeding difficulties. Almost all children with SRS are born SGA. Postnatal catch-up growth is not seen in the vast majority of children with SRS.

The published incidence of SRS ranges from 1:30,000 to 1:100,000 9. A recent study in Estonia 10 estimated an incidence of 1/70,000, but included only molecularly confirmed cases, which may have resulted in under-diagnosis. Overall, SRS is probably more common than some previous estimates have suggested, though the exact incidence remains unknown.

An underlying molecular cause can currently be identified in around 60% of patients clinically diagnosed with SRS. The most common underlying mechanisms are loss of methylation on chromosome 11p15 (11p15 LOM) in 30-60% of cases, and maternal uniparental disomy for chromosome 7 (upd(7)mat) in ~5-10% 6, 11, 12. However, in a significant proportion of patients the molecular aetiology remains unknown.

Although there is considerable overlap in the clinical care of individuals born SGA and those with SRS, there are many management issues which are specific to SRS. These include significant feeding difficulties, severe postnatal growth failure with no catch-up, recurrent hypoglycaemia, premature adrenarche, relatively early and rapid puberty, insulin resistance and body asymmetry. Identification of the molecular cause in many cases has also raised questions regarding management in individual molecular subtypes of SRS. Since evidence from controlled trials is limited, a consensus meeting was organised to develop guidelines for diagnosis and management of patients with SRS.

**METHODS**

Forty-one task force members from 16 countries, chosen for their publication record and expertise in SRS, collaborated to develop this consensus statement. Members were chosen for their publication record and expertise in SRS. They included paediatric endocrinologists, clinical geneticists, molecular geneticists, a gastroenterologist and five non-voting, parent support group representatives. Participants included nominated representatives from four international paediatric endocrine societies. All participants signed a conflict of interest declaration, and the consensus was supported by academic funding, without pharmaceutical support. A Delphi-like consensus methodology was adopted 13. A comprehensive literature search was conducted using PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and the search terms “Silver Russell syndrome” and “Russell Silver syndrome". Additional relevant articles on SGA, differential diagnoses and growth hormone (GH) were also identified. A comprehensive review of over 600 articles formed the basis of discussion by three working groups. These groups focused on clinical diagnosis, molecular testing or clinical management, with 11, 10 and 16 members, respectively. (Individual working group membership is provided with the list of authors). Preparations for the consensus took place over 10 months, including two preparatory meetings and regular teleconference discussions between the working group members. At the final consensus meeting, propositions and recommendations were considered by participants and discussed in plenary sessions, allowing reformulation of the recommendations if necessary. Where published data were unavailable or insufficient, experts’ clinical experiences and opinions were considered. Finally, all experts voted on the recommendations of each working group using the following system:

|  |  |
| --- | --- |
| **A** | Evidence or general agreement allow full agreement with the recommendation |
| **B** | Evidence or general agreement are in favour of the recommendation |
| **C** | Evidence or general agreement are weak for the recommendation |
| **D** | There is not enough evidence or general agreement to agree with the recommendation |

Depending on the proportion of votes received, the strength of the recommendation was recorded as follows:

|  |  |
| --- | --- |
| **+** | 26-49% of the votes |
| **++** | 50-69% of the votes |
| **+++** | ≥70% of the votes |

**CLINICAL DIAGNOSIS**

SRS currently remains a clinical diagnosis based on a combination of characteristic features. Molecular testing can confirm the diagnosis in around 60% of cases. This allows stratification of patients with SRS into subgroups, leading to appropriate management. However, there remains a significant proportion of patients with characteristic clinical features in whom molecular investigations are negative. For these patients an established clinical diagnosis allows access to appropriate support groups, treatment including GH, and further research into the underlying incidence, natural history and aetiology of the SRS phenotype.

The diagnosis of SRS can, however, be difficult, as the condition varies widely in severity among affected individuals and many of its features are non-specific. Until now, there has been no consensus on its clinical definition. Historically this has probably led to under and over-diagnosis, particularly by clinicians unfamiliar with SRS.

Several clinical scoring systems for SRS have been proposed, reflecting the challenge in reaching a confident diagnosis 6, 7, 14-17. All use similar criteria, but vary in the number and definition of diagnostic features required for diagnosis. The relative sensitivity and specificity of these scoring systems have been compared in patients with confirmed molecular diagnoses 16, 17.

**Netchine-Harbison clinical scoring system**

The Netchine-Harbison clinical scoring system (NH-CSS) (Table 1) recently proposed by Azzi et al. 17 is the only system developed using prospective data. Four of the six criteria are objective; protruding forehead and feeding difficulties remain subjective, though clear clinical definitions are given. When compared with other systems on the same cohort, the NH-CSS proved more sensitive (98%) than previous systems 6, 16. It also had the highest negative predictive value (89%), providing a high degree of confidence that patients who have less than 4 out of 6 clinical criteria for diagnosis are truly unaffected by SRS. The system is easy to use in a busy clinical setting. It is also flexible enough to use even if data are incomplete, which is important as diagnosis is often made in infancy, before information about postnatal growth and BMI is available.

In common with other clinical scoring systems, the NH-CSS has a low specificity (36%) 17, potentially resulting in false positive results where the diagnosis is based purely on clinical findings. Relative macrocephaly and protruding forehead are the two features in the NH-CSS which distinguish best between SRS and non-SRS SGA (see supplemental table 1) 6, 17-20. To maintain confidence in the clinical diagnosis if all molecular testing is normal, we recommend that only patients scoring at least 4/6, including both prominent forehead *and* relative macrocephaly, should be diagnosed as ‘clinical SRS’ (previously known as ‘idiopathic SRS’)- see the decision tree for investigation and diagnosis of SRS, figure 1.

**Diagnosis in late childhood/ adulthood**

All scoring systems for SRS have been developed and validated in paediatric cohorts. However, an increasing number of adults with a historical diagnosis of SRS are being seen, particularly concerning offspring risk. In these patients, clinical diagnosis is frequently challenged by lack of early growth data. An attempt should be made to obtain photographs of the individual aged 1-3 years, especially the face in profile, as well as measurements at birth and in the first two years. No current evidence exists to support an alternative approach to diagnosis in older individuals.

**Additional clinical features**

Besides the clinical features in the NH-CSS, several others are recognised in association with SRS, as shown in Table 2 and Supplementary Table 1 online. These characteristics are not specific to SRS, and may be present in non-SRS children born SGA, though at a lower frequency. However, a few occur at a much higher rate in children with SRS 6, 17, 18. These include low muscle mass, crowded/irregular teeth, micrognathia, down-turned mouth, clinodactyly and excessive sweating.

***Recommendations***

* 1. *SRS should remain primarily a clinical diagnosis. Molecular testing is useful for the confirmation and stratification of diagnosis in SRS. Lack of a positive molecular result does not exclude the diagnosis of SRS. (A+++)*
  2. *The decision tree (Figure 1) based on the Netchine-Harbison clinical scoring system (NH-CSS), should be adopted for the investigation and diagnosis of SRS. (A++)*
  3. *In children under two years, adolescents and adults, a reduced threshold for molecular testing may be required due to missing data. (A++)*

**MOLECULAR DIAGNOSIS**

**Decision tree for investigation and diagnosis of SRS (Figure 1)**

A positive molecular test result provides useful confirmation of the clinical diagnosis. It also allows stratification into a specific molecular sub-group which, in turn, can help guide appropriate management. However, many patients are referred for molecular testing with few, or atypical, features of SRS, leading to low diagnostic yields and incurring unnecessary expense 21. We therefore recommend the use of the decision tree in Figure 1 to aid in the investigation and diagnosis of SRS.

Some patients, particularly those with upd(7)mat, have fewer typical clinical features of SRS 6, 7, 15, 18, 22, 23. In the cohort reported by Azzi et al. 17, one of the nine patients scoring 3/6 (and therefore predicted ‘unlikely to have SRS’) had upd(7)mat. The threshold recommended in the decision tree for molecular testing (≥3/6) is therefore lower than that needed for clinical diagnosis of SRS (≥ 4/6).

Conversely, in the same cohort, no positive molecular diagnoses were made in patients scoring less than 3/6 17. Other studies have also excluded 11p15 LOM and upd(7)mat in patients born SGA with postnatal growth retardation (PNGR) but without additional features of SRS 6, 12, 24. We therefore do not recommend testing for SRS in patients scoring less than 3/6. It is worth noting that a small number of asymmetric patients have been reported with 11p15 LOM without associated growth retardation, likely due to tissue mosaicism 22, 23, 25. Although these patients would score less than 3/6, it is difficult to justify a clinical diagnosis of SRS in these patients.

**Chromosome 11p15**

Both SRS and the overgrowth condition Beckwith-Wiedemann syndrome (BWS) are associated with molecular abnormalities of chromosome 11p15.5, which contains two imprinted domains (Figure 2). Imprinting of the telomeric domain, which is strongly implicated in SRS 26, 27, is controlled by the paternally-methylated imprinting control region H19/IGF2 IG-DMR (previously known as IC1, ICR1 and H19 DMR). The centromeric domain contains the maternally-expressed growth repressor *CDKN1C,* whose imprinting is controlled by the maternally-methylated imprinting control region KCNQ1OT1 TSS-DMR (previously known as IC2, ICR2, LIT1, KvDMR1). Figure 3 summarises the more common molecular changes of chromosome 11p15 associated with SRS. Hypomethylation of the H19/IGF2 IG-DMR results in reduced paternal *IGF2* and increased maternal *H19* expression, leading to growth restriction 11. Numerous copy number variants (CNVs) involving the 11p15.5 region have been reported, with phenotype dependent on size, location and parental origin 26, 28 (supplementary table 2 online).

Molecular testing must robustly and accurately measure DNA methylation of CpG dinucleotides at H19/IGF2 IG-DMR 29. Assays involve either bisulphite analysis 30-32, or enzymatic methods, such as methylation-specific multiplex ligation-mediated PCR amplification (MS-MLPA) or Southern blotting 11, 33. The most common test in diagnostic use is MS-MLPA, which is economical on DNA, cost-effective and allows parallel analysis of copy number and DNA methylation 33, 34. Hypomethylation of H19/IGF2 IG-DMR is frequently incomplete and low levels of hypomethylation may elude detection. Methylation patterns may vary between different tissues (leucocytes, buccal swab and skin fibroblasts) 23, 35, 36 and may explain cases where molecular diagnosis is negative in blood.

Although copy number change can be detected by MS-MLPA, additional array analysis may be effective in characterising the size and gene content of any CNV identified.

**Chromosome 7**

Maternal uniparental disomy for chromosome 7 (upd(7)mat) occurs in ≤10% of individuals with SRS 37, 38. The SRS phenotype of upd(7)mat is thought to result from altered expression of imprinted growth-regulatory gene(s) 39. upd(7)mat may also unmask recessive disorders (such as cystic fibrosis) due to pathogenic mutations in regions of isodisomy 40-42.

Candidate SRS regions have been suggested through identification of patients with segmental upd(7)mat or CNVs (including 43-50; supplementary table 3). Currently, the primary candidate SRS genes on chromosome 7 (chr7) are *GRB10* (7p12.1) and *MEST* (7q32).

Microsatellite analysis was the first diagnostic test for upd(7)mat 37, 38; however, it cannot detect imprinting defects (epimutations), and requires DNA from at least one parent. DNA methylation analysis, including *at least* the imprinted GRB10 alt-TSS DMR and MEST alt-TSS DMR, can identify upd(7)mat, epimutations, CNVs, and segmental or whole-chromosome variations. DNA methylation analysis, for example by MS-MLPA, is economical on DNA, cost-effective and compatible with parallel analysis of 11p15 32, 51, 52.

### Additional testing

If testing for both 11p15 and chr7 are negative, additional molecular testing may be considered:

*Copy number variants*

Over 30 different pathogenic CNVs have been described in patients with suspected SRS (17, 53, 54, reviewed in Fokstuen and Kotzot 55; a LOVD entry for structural variations is currently in submission). These patients commonly have more severe developmental delay and/or intellectual disability than is typically seen in SRS. Some fulfil the NH-CSS for diagnosis; others either do not meet NH-CSS criteria, or insufficient data are given to assess this. Although features of SRS can be present in individuals with a pathogenic CNV, clinical diagnosis of SRS is not helpful in these cases and management needs to be tailored specifically to the phenotypic consequences of the individual CNV.

While either array-CGH or SNP array can be used to detect CNVs, SNP array can also detect regions of segmental isodisomy 56.

*Chromosome 14q32 abnormalities*

Molecular abnormalities at the paternally-methylated imprinted locus on chromosome 14q32 include upd(14)mat, paternal microdeletions and hypomethylation of the DLK1/GTL2 IG-DMR (also referred to by terms including MEG3-DMR, 14q32 DMR, IG-DMR). These result in Temple syndrome (TS14), which has clinical overlap with SRS 57, 58, including being born SGA, PNGR, hypotonia, motor delay, and early puberty 57.

In cohorts of SRS patients tested, a small number of patients have been found to have TS14: 1/127 by Poole et al. 59, 2/85 by Kagami et al. 58 and 1/26 by Azzi et al. 17. However, the true incidence of 14q32 abnormalities in patients meeting the NH-CSS criteria for diagnosis remains unknown.

upd*(20)mat and* upd*(16)mat*

Patients with both upd(20)mat and upd(16)mat have occasionally been detected among cohorts of patients investigated for pre- and postnatal growth failure or SRS 17, 59, 60. However, none of eight patients recently described with upd(20)mat had relative macrocephaly or asymmetry 61.

*CDKN1C and IGF2 mutation*

*CDKN1C* and *IGF2* are the coding genes on chromosome 11p15 responsible for the growth anomalies in SRS and BWS, but coding variants in these genes are rare. Maternally-transmitted SRS was described in a four-generation family with *CDKN1C* gain of function mutation 62, and paternally-transmitted SRS in a family with *IGF2* loss of function mutation 63. However, no additional mutations have been reported to date in sporadic or familial SRS cases 62, 64, 65. Sequence analysis of either gene could be considered, particularly in familial cases of SRS where the inheritance pattern is consistent.

*Multi-locus imprinting disturbance (MLID)*

Multi-locus imprinting disturbance (MLID) has been demonstrated in a significant proportion (15-38%) of individuals with 11p15 LOM 35, 59, 66-68. High-density methylation arrays have revealed methylation changes involving both (maternally- and paternally) imprinted and non-imprinted loci 69, 70; but, despite welcome advances in genome-wide methylation screening 69, 71, 72, standardisation is required to ensure accurate description of MLID and comparison between cohorts.

The effect of MLID on clinical phenotype remains unclear. No difference in growth parameters was found at birth or at two years between 11p15 LOM patients with and without MLID 66. Although developmental delay and congenital anomalies were reported in patients with MLID, this may have been affected by ascertainment bias 59.

In principle MLID may be caused by *trans*-acting genetic mutations affecting the acquisition or maintenance of imprints, but in practice, very few have been identified 73, 74. Though yet to be identified, such mutations may also be present in siblings with SRS with MLID.

Overall, the effect of MLID on clinical phenotype and its relevance for genetic counselling remain uncertain. Further information is needed before recommending testing for MLID outside the research setting.

***Recommendations***

*2.1 Molecular genetic testing should be performed by a health professional experienced in the field of imprinting disorders. Consistent and logical nomenclature should be adopted in publications and in test reporting. (A+++)*

*2.2 First-line molecular testing should include DNA methylation analysis of the H19/IGF2 IG-DMR and KCNQ1OT1 TSS DMR. (A+++)*

*2.3 First-line molecular testing should include analysis of DNA methylation at the GRB10 alt-TSS DMR and the MEST alt-TSS DMR. (A+++)*

*2.4 In case of a positive test result at either 11p15 or chr7, then a discrimination between epimutation, CNV and* upd *should be considered in order to estimate recurrence risk. (A+++)*

*2.5 After exclusion of changes in 11p15 and chr7, a clinical decision should be sought about the direction of further testing. Depending upon the clinical features and family history of the patient, further testing may include CNV analysis and DNA methylation analysis at chromosome 14q32. Testing may also be considered for very rare molecular anomalies, including upd(20)mat, upd(16)mat, CDKN1C and IGF2 mutation and analysis of further tissues to detect somatic mosaicism. (A++)*

*2.6 When an underlying pathogenic CNV is identified, the diagnosis should focus on this, even if features of SRS are present. (A+)*

**(EPI)GENOTYPE-PHENOTYPE CORRELATION**

The frequency of individual features in specific SRS subgroups (11p15 LOM, upd(7)mat and clinical SRS) and non-SRS SGA patients, where data are available, are shown in Supplementary Table 1 online. Genotype/phenotype studies of SRS indicate considerable overlap in clinical phenotype between (epi)genotypes and these are generally clinically indistinguishable. However, some features are more common in particular molecular subgroups 6, 15, 17-19, 22, 75.

Patients with 11p15 LOM tend to have lower birth length and weight, more frequent body asymmetry, and more frequent congenital anomalies. Neurocognitive problems are more frequent in patients with upd(7)mat than those with 11p15 LOM or clinical SRS 17, 18, 22 (see “Neurocognitive problems” below).

Patients with 11p15 duplication encompassing H19/IGF2 IG-DMR and KCNQ1OT1 TSS-DMR have a SRS phenotype, though usually without asymmetry and with an increased likelihood of developmental delay. Of 15 patients reported, four were noted to have hearing loss 76.

**Differential diagnosis**

The differential diagnosis of children with short stature of prenatal onset includes many syndromic diagnoses and chromosomal rearrangements. Particular features should prompt consideration of diagnoses other than SRS. These include relative microcephaly (head circumference SDS below height and weight SDS), significant global developmental delay or intellectual disability (without a related explanation such as documented hypoglycaemia), absence of severe feeding difficulties, and/or the presence of additional congenital anomalies, facial dysmorphism or other features atypical for SRS. Disproportionate short stature is suggestive of skeletal dysplasia. Photosensitive skin rash or recurrent bronchopulmonary infections should prompt investigation for chromosome breakage disorders. Since SRS is generally sporadic, a family history of growth failure and/or consanguinity may suggest an alternative underlying diagnosis.

The clinical features of the most important/likely differential diagnoses are summarised in Tables 3 and 4.

A correct diagnosis can have extremely important implications for management. Response to GH treatment, if given, varies depending on the underlying syndromic diagnosis. GH treatment is contraindicated in patients with chromosome breakage disorders, such as Bloom syndrome, due to the associated risk of malignancy. GH treatment in SHORT syndrome has been reported to precipitate insulin resistance and subsequent type 2 diabetes mellitus 77.

Three patients have been reported with clinical features of SRS but a molecular diagnosis of osteogenesis imperfecta (OI), with *COL1A1* mutation 78, 79.

***Recommendations***

*3.1 An alternative syndromic diagnosis, and specific investigation for this, should be particularly considered in patients with any of the following: additional features atypical for SRS, family history of growth failure and/or consanguinity. (A+++)*

*3.2 Patients with features of SRS overlapping with OI should have a skeletal survey to look for additional evidence for OI, with consideration of COL1A1/2 gene testing. (A++)*

**MANAGEMENT**

SRS leads to a wide spectrum of abnormal physical characteristics and functional abnormalities. Multi-disciplinary follow-up and early, specific intervention are necessary for optimum management of this group of patients.

***Recommendation***

*4.1 Patients with SRS should receive multi-disciplinary care in a centre of expertise in SRS in co-ordination with their local centre. The multi-disciplinary team should be composed of paediatric sub-specialists such as an endocrinologist (co-ordinator), gastroenterologist, dietician, clinical geneticist, craniofacial team, orthopaedic surgeon, neurologist, speech and language therapist and psychologist. (A+++)*

**Early feeding and nutritional support**

The typical newborn with SRS has length SDS below weight SDS; but after birth, due to poor appetite, feeding difficulties and gastrointestinal problems, weight SDS drops below the length SDS 6, 19, 75, 80. Over time, progressive failure to thrive (FTT) can result in a calorie-related length deficit.

Feeding difficulties and FTT are significantly more frequent in SRS than in SGA children without SRS 6, 19. FTT in SRS is likely due to a combination of factors, including feeding difficulties (poor appetite, oromotor issues and the resulting low caloric intake) as well as functional and structural gastrointestinal problems. Digestive problems or malnutrition occur in over 70% of patients with SRS 81, including severe gastroesophageal reflux (GER) in 55%, often resulting in persistent vomiting after the age of one year. Constipation is also common, particularly in later childhood.

Cyproheptadine used as an appetite stimulant improves weight gain in other paediatric conditions 82, 83 however specific studies of its use in SRS are needed.

The main therapeutic goals for the first two years of life are nutritional support, prevention of hypoglycaemia, and recovery of any calorie-related length/height deficit, which should be addressed before initiation of GH therapy (see ‘Prevention of hypoglycaemia’ and ‘GH therapy’ below). However, careful monitoring is needed, especially during non-volitional feeding, because rapid catch-up weight gain in children born SGA has been related to increased risk of metabolic and cardiovascular disease in later life 84

Children with SRS have an abnormal body composition with low muscle mass, and are typically light for their length/height 5, 17, 85, 86. From our experience, there is a narrow target for healthy nutritional status, which is dependent upon individual innate muscle mass and even slight over-nourishment (e.g weight > 90% of ideal weight for length/height) can rapidly increase relative fat mass. Suggested targets for children aged 2-4 years preparing for GH therapy are: (1) weight 75-85% of the 50th centile weight for length/height and/or (2) BMI 12-14 kg/m2, using height measurements on the longer side if there is significant leg length discrepancy (see ‘GH therapy section, below). A weight below 70% of the ideal weight for length/height compromises growth velocity, despite GH treatment. For older children, the optimal target BMI will depend on their muscle mass. Exceptions are:

1. 11p15 LOM patients with a very low muscle mass and significant asymmetry who are typically replete at a lower BMI (11-12 kg/m2).
2. upd(7)mat patients with near normal muscle mass who are usually replete at a higher BMI (14-15 kg/m2).

***Recommendations***

*5.1 Nutritional goals in the first years of life: We recommend nutritional repletion\* with awareness of possible hazards of rapid postnatal catch-up leading to later metabolic risk. (A +++)*

*5.2 Ask for and/or screen early for gut dysmotility (GER, delayed gastric emptying and constipation) in all children. (A+++)*

*5.3 Diagnose and treat any oromotor and/or sensory issues impacting oral intake. (A+++)*

*5.4 In cases of severe feeding failure unresponsive to standard care, anatomical or functional disorders of the GI tract, such as malrotation, should be excluded. (A+++)*

*5.5 Avoid enteral feeding by nasogastric or gastrostomy tube (GT) in a child capable of eating where there is adequate nutritional repletion. (A+++)*

*5.6 In cases of extreme feeding difficulties/GER, consider enteral feeding by GT (with/without fundoplication) or low profile transgastric jejunostomy as a last resort to protect against hypoglycaemia and/or malnutrition. (A+++)*

*5.7 In the case of enteral feeding, prevent excessive weight gain in both volitionally and non-volitionally fed children. (A++)*

*\*Note: Low muscle mass makes typical BMI targets excessive in this population.*

*Targets currently used in some centres include:*

* + - * *Waterlow score 75-85% 87*
      * *Weight-for-length SDS -2 to -1 in first year of life*
      * *BMI target SDS between -2 to -1 after first year of life*

**Prevention of hypoglycaemia**

Young children with SRS 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. The incidence of hypoglycaemia is approximately 27% 22, with a high frequency of spontaneous, asymptomatic nocturnal hypoglycaemia 88.

Monitoring of urinary ketones is usually effective in pre-empting fasting and activity/illness related hypoglycaemia. This can be used to determine the “safe fasting time” for a child, which will change with age. Night time hypoglycaemia can be prevented by adding to the last evening feed either high molecular weight glucose polymer (for infants under 10 months) or uncooked corn starch (for older infants and children particularly at risk). Dental hygiene is important as complex carbohydrates can promote caries 89. Severe, non-fasting and non-ketotic hypoglycaemia should always be identified and investigated further.

For episodes of pre-operative fasting or febrile illness, intravenous (IV) glucose (10% dextrose) may be required. Children with SRS may need longer periods of gut rest before oral or enteral feeding because of their gut dysmotility and intrinsic feeding defect. It is advisable to have an absence of ketonuria following at least 12 hours of feeding, without IV support, before discharge.

When hypoglycaemia remains a problem, early GH therapy should be considered 90, 91 (see ‘GH therapy’ section, below).

***Recommendations***

*6.1 Monitoring for ketonuria at home is useful to determine which children need intervention for impending hypoglycaemia. (A++)\**

*6.2 Develop a plan with the child’s local paediatrician and emergency room for rapid admission and IV dextrose treatment when the child is ill. (A++)*

*6.3 Admit children with SRS to hospital early in the course of an illness associated with ketonuria/hypoglycaemia and do not discharge them until they are metabolically stable and can be adequately fed. (A++)*

*6.4 Glucagon is not recommended to correct hypoglycaemia, because of poor glycogen stores and limited ability for gluconeogenesis. (A+++)*

*6.5 Provide parents with an emergency guidance plan for illnesses. (A+++)*

*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. (A+++)*

*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) (A++)*
* *Placement of a gastrostomy/jejunjunostomy tube. (A++)*

*\*Note: Children with a history of hypoglycaemia who do not have appropriate ketone response will require formal fasting studies.*

**Surgery and anaesthesia**

Surgery should be carefully planned due to the increased risk of fasting hypoglycaemia 92. Due to their diminished weight-for-height ratio, low BMI and large head, young patients with SRS are at risk of hypothermia in a cool operating room 93. Many children with SRS also have abnormal tooth distribution and a small mandible, affecting airway visualization and intubation 94. Finally, young children with SRS who are malnourished may not heal well following surgery.

***Recommendations***

*7.1 Review SRS-related issues with the anaesthetist and surgeon in advance. (A+++)*

*7.2 Consider admission the night before surgery for early administration of IV dextrose prior to surgery to avoid ketonuria and hypoglycaemia. (A++)*

*7.3 Schedule first on the surgical list where possible. (A++)*

*7.4 Monitor blood glucose and administer IV dextrose during and after surgery. Do not discharge until ketonuria is absent and the child can sustain themselves on oral/enteral feeding. (A++)*

*7.5 Follow the intra-operative temperature maintenance protocol appropriate for the patient’s size, not age. (A+++)*

*7.6 Delay elective surgery until the child is adequately nourished. (B+)*

*7.7 Be aware of the high risk of post-surgical malnutrition and follow appropriate guidelines. (A+)*

**Growth hormone treatment**

Though data on adult height (AH) in untreated patients with SRS are limited, SRS is associated with significant reduction in AH (around -3 SDS) (supplementary table 4 online). SRS is an indication for growth-promoting GH treatment under the SGA registered licence. It is worth noting, however, that SRS was the only syndrome to be included in theclinical trials of GH in short children born SGA that led to the U.S. Food and Drug Administration (FDA) and European Agency for the Evaluation of Medicinal Products (EMEA) SGA indications for GH therapy in 2001 and 2003, respectively95-99.

Overall, clinical trials for SGA (in which SRS patients were included) demonstrated a satisfactory growth responseandincrease in predicted AH of 7-11 cm at pharmacological doses of GH. Until recently however, the response in subjects with SRS was not investigated separately. A recent Dutch longitudinal study analysed response to GH among 62 children diagnosed clinically with SRS using the NHSS compared to 227 short, non-syndromic children born SGA. Overall the study showed similar response to GH in patients with SRS compared to non-SRS children born SGA (mean total height gains of 1.30 [1.0] SDS and 1.26 [0.8] SDS, respectively), although the final AH attained in subjects with SRS was lower (mean AH -2.17 [0.8] SDS versus -1.65 [0.8] SDS for non-SRS children born SGA) 86. Although the mean height at start of GH treatment in patients with SRS was significantly lower than in those without SRS, it was shown that all SRS subtypes benefited from GH treatment, with a trend towards increased height gain in subjects with upd(7)mat or clinical SRS. In addition, some interim 100 and long-term 101, 102 studies have focused on response to GH specifically in SRS, albeit without a control group of non-SRS short children born SGA. Strong predictors of the short- and long-term responses to GH were age and height SDS at start of GH treatment (both inversely related) 101-103. However the Rakover study of 33 SRS patients lacked data on AH. Mean total height gain ranged from +1.2 to +1.4 SDS for GH doses of 35–70 µg/kg/d, comparable with non-syndromic SGA 95, 101, 102. In 2007, an SGA consensus statement advocated early treatment with GH for children born SGA, including SRS, with severe growth retardation (height SDS ≤2.5; age 2–4 years; dose 35–70 µg/kg/d) 1.

Additional potential benefits of GH treatment are increases in appetite, lean body mass and muscle power, resulting in improved mobility 85, 104. In patients with Prader-Willi syndrome (PWS), another imprinting disorder, use of GH from infancy results in increased lean body mass and motor development, and decreased fat mass 105, 106; consequently GH is now recommended from early childhood in this condition.

Classical GH deficiency is neither a common nor a relevant cause of short stature in SRS, nor predictive of the response to GH treatment in children born SGA 101, 103, 107. Furthermore, given the risk of hypoglycaemia associated with fasting required for GH testing, there may be added risks to testing children with SRS.

For most children with SRS, an increase in height velocity of ≥3 cm/year is the lower limit of an effective response range 1. The growth response depends on the patient's age, GH dose, height deficit, rate of weight gain and confounding problems such as intercurrent illness and scoliosis.

IGF-I levels in response to GH treatment in patients with SRS are difficult to interpret. Children with 11p15 LOM have significantly higher IGF-I levels than upd(7)mat and other children born SGA, suggesting an element of IGF-I resistance 75, 108. Basal serum levels of IGF-I in the upper quartile of the normal age-related range or higher can be expected in children with SRS, especially those with 11p15 LOM 75. Serum levels of IGFBP-3 in children with 11p15 LOM are also elevated 108. IGF-I levels may rise significantly above the reference range in children with SRS on standard doses of GH 86, 108. Further studies are needed to understand how best to use IGF-I and IGFBP-3 serum levels to monitor GH dose in children with SRS and IGF-I resistance.

Comprehensive reviews on the use of GH in children born SGA have concluded that GH treatment appears to be safe and effective 109. Adverse events due to GH treatment are no more frequent in children with SRS than non-syndromic SGA 86, 110 and no specific precautions are advised.

### *Recommendations*

*8.1 Defer GH treatment until caloric deficits are addressed. (A++)*

*8.2 Avoid GH stimulation testing. (A++)*

*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. (A++)*

*8.4 Treat with GH as soon as possible; starting at age 2-4 years is adequate for the majority of patients, though with due consideration of the exceptions listed below\*. (A++)*

*8.5 Start GH at a dose of approximately 35 μg/kg/day. Use the lowest dose that results in catch-up growth. (A+++)*

*8.6 Terminate GH when height velocity is < 2 cm/year over a 6-month period and bone age > 14 years (females) or > 17 years (males). (A++)*

*8.7 If response to GH is poor, re-evaluate the underlying diagnosis, GH dose, IGF-I response, adherence to therapy and other confounding systemic problems. (A+++)*

*8.8 Monitor circulating IGF-I and IGFBP-3 levels at least yearly during GH treatment. (A++)*

*\*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/d) 1.*

*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 shortly lead to gastrostomy if there is no improvement*
* *Severe muscular hypotonia*

Bone age advancement and puberty

Published literature on the natural history of bone age (BA) progression in patients with SRS is limited. Early BA delay is followed by rapid advancement 5, 80, 110. Pubertal onset is usually within the normal range but at the younger end of the spectrum 5, 75, 86, 111. Almost all patients with SRS begin puberty with a delayed BA. Most then experience rapid BA advancement, typically around eight to nine years but sometimes much younger, especially in non-volitionally fed children. Adrenarche can be early and aggressive in comparison to children born with non-SRS SGA, particularly in those with 11p15 LOM 112.

Our experience is that in patients with SRS and early adrenarche, the onset of central puberty may be earlier and the tempo faster than expected. This further accelerates BA maturation, leading to an attenuated pubertal growth spurt and compromised AH. Children with upd(7)mat are more likely to progress to central puberty first, at the younger end of the normal range (mean starting age 9.5 years) 112 (I. Netchine, unpublished data). Rapid increase in BMI may also exacerbate the tendency to early adrenarche and central puberty 113-115.

The window for effective GH treatment appears to be shorter in SRS unless early sex hormone exposure is suppressed. Puberty has been shown to start significantly earlier in patients with SRS (at 10.2 years versus 11.2 years in girls with SRS and non-SRS SGA respectively, and at 11.4 years versus 12.0 years in boys with SRS and non-SRS SGA respectively) 86. Furthermore a steeper decline in height SDS from the onset of puberty until AH was seen, contributing to lower AH at a younger age. Of note, however, is that in 17 patients with SRS in this study, puberty was postponed for two years with gonadotrophin releasing hormone analogue (GnRHa) due to a low predicted AH. Although the use of GnRHa was not an outcome measure in this particular study, its effect on final AH has been analysed by the same investigators in a separate study of patients with SGA, which included children with SRS 116, 117, suggesting that the combination of GnRHa, started at the initiation of puberty and continued for at least two years, along with GH treatment, improves AH in patients born SGA with a poor AH prognosis. A retrospective study of GnRHa treatment specifically in patients with SRS did not detect an effect of GnRHa on AH, but this therapy was used in only 16 patients out of 37 and was not standardised 102. Further studies are required to specifically look at its effects in patients with SRS.

Aromatase catalyses the rate-limiting step in the conversion of androstenedione to oestrone and testosterone to oestradiol. In cases of adrenarche with advancing BA, but without central puberty, third-generation aromatase inhibitors (such as anastrazole) could potentially be helpful to prevent rapid bone maturation but are currently not indicated for growth disorders 118. An 18 month double-blind clinical trial is currently underway to study the efficacy and tolerance of treatment with anastrazole to slow bone maturation related to pathological adrenarche in patients with SRS and Prader-Willi Syndrome (<https://clinicaltrials.gov/ct2/show/NCT01520467>).

***Recommendations***

*9.1 Monitor for signs of premature adrenarche, relatively early and accelerated central puberty, and insulin resistance. (A+++)*

*9.2 Monitor and anticipate acceleration of bone age especially from mid childhood. (A++)*

*9.3 Consider personalised treatment with GnRHa for at least 2 years in children with evidence of central puberty (starting no later than 12 years in girls and 13 years in boys) to preserve adult height potential. (A++)*

**Prevention of long-term metabolic complications**

Individuals born with a low birth weight are at increased risk of adult health problems including coronary heart disease 119-121, hypertension, dyslipidaemia, insulin resistance and obesity (metabolic syndrome) 122-125. Studies of children born SGA indicate that those who have rapid or disproportionate catch-up in weight are at particularly high risk 115, 126, 127.

Insulin resistance in younger, pre-pubertal children with SRS can be atypical and difficult to detect in the fasting state, though impaired glucose tolerance may be confirmed on formal oral glucose tolerance testing. Insulin resistance becomes more classical in the pubertal or post-pubertal age groups with elevation in fasting glucose and insulin levels and potential evolution to type 2 diabetes 128, 129.

Overall, GH appears to have positive metabolic effects in children born SGA, although specific data on such effects in SRS are lacking. Many studies of long-term GH treatment in children born SGA have shown positive outcomes, including increased lean body mass, reduced fat mass, decreased blood pressure and improvement in lipid profile 104, 116, 130, 131, which may last after discontinuation of therapy 131, 132.

In a recent study of 110 children born SGA treated with GH, those with the highest baseline IGF-I levels were the least insulin sensitive. Gains in height and IGF-I response were positively associated with insulin secretion 133. In SRS, children with 11p15 LOM appear to be at a higher metabolic risk due to poor muscle mass and elevated IGF-I levels compared to upd(7)mat and other children born SGA 17, 18, 75, 86. Further research is therefore required on the long-term effects of GH on body composition and metabolic parameters in SRS and its various genotypes.

***Recommendations***

*10.1 Avoid excessive or rapid weight gain to prevent increase in insulin resistance, which is associated with early and rapidly advancing adrenarche, early central puberty, and, in girls, later risk of PCOS phenotype. (A++)*

*10.2 Raise awareness among gastroenterologists, dieticians, neonatologists, paediatricians and primary health care providers of the importance of not overfeeding this group of children. (A+++)*

*10.3 Advise parents, grandparents and care-givers about the risk of insulin resistance associated with intrauterine growth retardation and overfeeding. (A+++)*

*10.4 Screen for physical and biochemical indicators of insulin resistance during GH treatment, especially in the child with low muscle mass and high baseline IGF-I. (A+)*

*10.5 In those with clinical signs of insulin resistance, consider formal assessment of insulin sensitivity with a 2-hour oral glucose tolerance test including insulin and C-peptide levels (A++)*

*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. (A+++)*

**Neurocognitive problems**

Motor and speech delay are common in children with SRS in general (Table 2). Motor delay may be related to reduced muscle bulk and relatively large head size. Verbal dyspraxia and more global developmental delay or learning difficulty, usually mild, have been described in some children, particularly those with upd(7)mat 14, 17, 18, 22, 134. Autistic spectrum disorder has also been reported more frequently in this sub-group 17. Myoclonus-dystonia in patients with upd(7)mat is probably associated with altered expression of the paternally-expressed *SGCE* gene on chromosome 7q21 22, 42, 135, 136.

***Recommendations***

*11.1 Refer infants and children with SRS for a developmental assessment when necessary to ensure appropriate intervention as early as possible. (A+++)*

*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. (A+++)*

*11.3 Monitor children with upd(7)mat for signs of verbal/oromotor dyspraxia and/or signs of autistic spectrum disorders. (A+++)*

*11.4 Inform parents about increased risk of speech, oromotor and learning disabilities (especially in those with upd(7)mat). (A+++)*

*11.5 Follow school-age children for any learning difficulties, psychosocial challenges and/or cognitive delay, to allow appropriate intervention. (A+++)*

**Orthopaedic problems**

Orthopaedic problems seen in association with SRS include limb/body asymmetry, scoliosis, hip dysplasia and hand/foot anomalies (table 2).

**Limb asymmetry** can affect arms, legs or both. In seven patients with clinically-diagnosed SRS, limb length discrepancy was not significantly affected by GH treatment 137. Limb lengthening surgery performed to equalize limb lengths in patients with SRS showed positive results 138.

**Scoliosis** has been reported in 9-36% of individuals with SRS 22, 139, 140. The causal relationship to leg length asymmetry is not clear 139, 140. Associated back pain has been reported inconsistently 7, 139. GH therapy may be associated with worsening of existing scoliosis; however there is no established causality 141. Of interest, a study in a large group of children with PWS has clearly shown that GH therapy does not influence onset and progression of scoliosis 142.

**Hip dysplasia** has been reported in 3-12% of patients with SRS 22, 139.

***Recommendations***

*12.1 Where necessary, refer to a paediatric orthopaedic surgeon for collaborative management of body asymmetry, limb length discrepancy and scoliosis. (A+++)*

*12.2 Routinely examine all patients with SRS for scoliosis. (A+++)*

*12.3 Prior to initiation of GH, refer patients with scoliosis to the orthopaedic team and monitor while on GH. (A+++)*

*12.4 Evaluate leg length asymmetry regularly and consider orthopaedic management if necessary. (A++)*

**Maxillofacial abnormalities and sleep disordered breathing**

SRS is characterized by craniofacial disproportion, resulting in a triangular-shaped face. 94 Delayed dental eruption, microdontia, absence of secondary teeth and blunted condyles have all been reported in patients with SRS 143, 144.

In our experience, the upper jaw arch is frequently narrow and crowded, but in the lower arch crowding may be severe, with displacement of lower incisors into a lingual position. Micrognathia is frequent, with lack of mandibular growth, resulting in a small, pointed chin and an overbite. Children with significant facial asymmetry may have a crossbite that impairs normal chewing. Velopharyngeal insufficiency with/without a submucous cleft is quite common in 11p15 LOM SRS 22. Otitis media is frequent in young children with SRS 7 and appears to be improved by orthodontic treatment 145.

Orthodontic intervention in children with SRS can help normalize oropharangeal function and facial appearance. An experienced craniofacial team, including orthodontists, plastic surgeons and ENT surgeons is ideal. Multiple orthodontic techniques have been successfully employed 146. Currently, rapid palatal expansion is the most effective technique to change the shape of the face and decrease otitis media.

Many patients with SRS report excessive daytimefatigue, snoring and/or disrupted sleep. However, there are very limited data regarding sleep problems, including sleep disordered breathing (SDB), in association with SRS. A retrospective study identified mild SDB in 74% of patients with SRS, (not exacerbated with GH therapy) 147 and manuscript in preparation. Further studies are necessary.

***Recommendations***

*13.1 Develop a referral relationship with a maxillofacial team or orthodontist who has experience caring for patients with SRS. (A++)*

*13.2 Refer patients to the maxillofacial team for assessment after eruption of primary dentition when necessary. (A++)*

*13.3 Encourage early orthodontic intervention and compliance with follow-up. (A+)*

*13.4 Screen for symptoms of sleep disordered breathing (SDB) (such as snoring, apnoeas, excessive daytime fatigue, disrupted sleep, agitation). (A++)*

*13.5 Refer patients with suspected SDB to the appropriate specialist for evaluation of obstructive sleep apnoea. (A++)*

**Other congenital anomalies**

Congenital anomalies are described in a significant minority of patients with SRS, particularly those with 11p15 LOM (supplementary table 1 online). Genital abnormalities, including cryptorchidism and hypospadias, occur frequently in boys 18, 22. Mayer-Rokitansky-Kuster-Hauser syndrome in females is characterised by congenital hypoplasia or aplasia of the uterus and upper part of the vagina 18, 20, 148, 149. Structural renal anomalies 20, 22 and congenital heart defects 6, 20, 22, 150 have also been reported.

***Recommendations***

*14.1 Investigate genital abnormalities in boys. (A+++)*

*14.2 Investigate girls with primary amenorrhoea for Mayer-Rokitansky-Kuster-Hauser* *syndrome. (A+++)*

**Adulthood**

Very little information exists in the literature regarding the long-term natural history of SRS. The majority of individuals with SRS are not routinely followed up, and the small number of adults reported have 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 115, 127, 151 (see above). Medical problems reported in patients with 11p15 LOM include hypertension, dilated cardiomyopathy, type 2 diabetes, hypercholesterolaemia, fatty liver infiltration, elevated glucose levels and raised HbA1c 128, 129, 152 but these reports may not be representative.

***Recommendations***

*15.1 Consider medical follow-up of adolescents and young adult patients with SRS or develop collaboration with a general/internal medicine team for follow-up. (A+++)*

*15.2 Avoid losing contact with adult SRS patients, to facilitate their participation in and potential benefit from future clinical research. (A+++)*

**GENETIC COUNSELLING**

Accurate genetic counselling depends on the underlying molecular cause. 11p15 LOM is associated with a low recurrence and offspring risk, though empirical figures are not available. Three sibships with 11p15 LOM are reported in the literature 15, 22, but the underlying mechanism is unknown in all three. The potential for a familial *trans*-acting gene mutation suggests a possibly elevated recurrence risk in SRS patients with MLID; however, evidence to support this does not yet exist.

Rare familial cases of SRS have been reported with underlying mechanisms including:

* maternally inherited 11p15 duplication (26, 28 and supplementary table 2 online),
* maternally inherited *CDKN1C* gain of function mutations 62,
* paternally inherited *IGF2* loss of function mutations 63.

In these families, recurrence risk may be up to 50%. Investigation for underlying CNVs in patients with 11p15 LOM is therefore important.

upd(7)mat is associated with a low recurrence and offspring risk (if the karyotype of the patient is normal).

Data are limited regarding recurrence risk for parents of children with clinically diagnosed SRS, though the overall risk seems likely to be low. Similarly, the offspring risk for individuals with clinically diagnosed SRS is likely to be low.

***Recommendation***

*16.1 Genetic counselling should be performed by a health professional experienced in the field of imprinting disorders. Since 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. (A+++)*

**CONCLUSIONS**

Children with SRS and their families face challenges from birth to adulthood. In addition to the problems associated with being born SGA, clinicians treating patients with SRS need to be aware of syndrome-specific management issues. These include significant feeding difficulties, severe postnatal growth failure with no catch-up, recurrent hypoglycaemia, premature adrenarche, relatively early and rapid puberty, insulin resistance, body asymmetry, orthodontic issues, sleep disordered breathing and the potential for other congenital anomalies.

Presented here are the first international consensus guidelines for the diagnosis and management of SRS, based on published evidence and expert opinion. A summary of all 72 recommendations, including the decision tree for the investigation and diagnosis of SRS, is available as supplementary information online.

These management recommendations apply to all patients clinically diagnosed with SRS, both with and without a molecularly confirmed diagnosis. Identification of the underlying molecular subtype can, however, guide treatment with regard to specific risk factors. Management should involve a multi-disciplinary approach and close parental guidance. A practical checklist for use in routine clinical follow up of these patients is proposed in Table 5.

As there are limited published data specific to SRS, many questions remain (Box 2). International collaboration and further research is urgently needed to better inform the investigation and management of patients with SRS in the future.

**Declaration of interest**

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**Table 1: Netchine-Harbison clinical scoring system**

Clinical diagnosis is considered if patient scores at least 4 out of 6 from the following criteria:

|  |  |
| --- | --- |
| **Clinical criteria** | **Definition** |
| SGA (birth weight and/or birth length) | ≤ -2SDS for gestational age |
| Postnatal growth failure | Height at 24±1 months ≤ -2SDS  *or*  Height ≤ -2SDS 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 < 0.5cm with at least two other asymmetrical body parts (one non-face) |
| Feeding difficulties and/or low BMI | BMI ≤ -2SDS at 24 months OR current use of a feeding tube OR cyproheptadine for appetite stimulation |

*\*Protruding forehead is equivalent to ‘prominent forehead’ 153.*

Abbreviations: BMI, body mass index; LLD, leg length discrepancy; SGA, small for gestational age.

**Table 2: Additional clinical features of SRS**

|  |  |  |
| --- | --- | --- |
| **Clinical feature** | **Frequency**  **% (total no. patients)** | **Reference** |
| Triangular face | 94 (164) | 18-20 |
| 5th finger clinodactyly | 75 (319) | 6, 17-20, 22 |
| Shoulder dimples | 66 (61) | 17 |
| Micrognathia | 62 (115) | 18, 20, 22 |
| Low muscle mass | 56 (103) | 17, 18 |
| Excessive sweating | 54 (106) | 18, 22 |
| Low-set &/ or posteriorly rotated ears | 49 (266) | 17-19, 22 |
| Down-turned mouth | 48 (176) | 17, 18, 20, 22 |
| High pitched/ squeaky voice | 45 (26) | 18 |
| Prominent heels | 44 (61) | 17 |
| Delayed closure of fontanelle | 43 (47) | 20, 22 |
| Male genital abnormalities | 40 (85) | 17, 18, 20, 22 |
| Speech delay | 40 (189) | 18, 19, 22 |
| Irregular/ crowded teeth | 37 (195) | 18-20, 22 |
| Motor delay | 37 (254) | 6, 18-20, 22 |
| Syndactyly of toes | 30 (264) | 17-19, 22 |
| Hypoglycaemia | 22 (103) | 6, 22 |
| Scoliosis &/or kyphosis | 18 (227) | 18, 22, 140 |

**Table 3- Differential diagnosis of SRS in patients with relative microcephaly**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| *Syndrome*  *#OMIM no.* | **Bloom Syndrome**  **#210900** | **Nijmegen breakage syndrome**  **#251260** | **MOPD II**  **#210720** | **Meier-Gorlin syndrome**  **#224690,61380, 613803, 613804, 613805** | ***IGF1R* mutation/ deletion**  **#147370**  **#612626** | ***IGF1* mutation**  **#147440** |
| *Birth weight SDS* | Mean -4.6 | Mean -1.6 | Mean -3.9 | Mean -3.8 | -1.5 to -4.9 | -2.5 to -4.5 |
| *Adult height range (cm)* | Males:  128-164  Females:  115-160 | Males:  161-172  Females:  150-165 | Mean 96 | Males:  136-157  Females:  127-150 | *IGF1R* mutation:  1 female - 140  2 males - 133 and 170 | 1 male: 117 |
| *Cognitive function* | Usually normal | At pre-school age IQ normal/ borderline;  progressive deterioration to moderate MR | Variable:  none / mild ID (majority), occasionally severe ID | 90% normal IQ, occasionally mild/ moderate ID | Variable: normal (~50%), mild ID (25%), moderate/ severe ID (25%) | Severe ID |
| *Facial features* | Narrow face with underdeveloped malar area and mandible, relatively prominent nose,  sun sensitive telangiectasia in malar distribution | Receding forehead, prominent mid-face, small mandible, up-slanting palpebral fissures, long nose and philtrum, large ears | Prominent, long, broad nose with hypoplastic tip, low insertion of columella, prominent eyes in infancy, micrognathia | Microtia, narrow, beaked nose with low insertion of columella, small mouth, retrognathia | *IGF1R* mutation: often normal; triangular face, micrognathia  15q26-qter deletion: micrognathia | No consistent features reported |
| *Other features* | Patchy areas of hypo- and hyper-pigmented skin, feeding difficulties, high tumour risk (44% develop cancer by age 25), hypogonadism, type 2 diabetes mellitus, immunodeficiency, chromosomal instability with increased frequency of sister chromatid exchange | Severe, progressive microcephaly,  immunodeficiency, cancer predisposition, chromosomal instability and rearrangements, café au lait spots, premature ovarian failure | Mean OFC at birth -4.6 SDS, progressive microcephaly, mesomelic limb shortening, progressive metaphyseal bone dysplasia, hip dysplasia, acanthosis nigricans, insulin resistance, cryptorchidism, intracranial aneurysm, dental anomalies, squeaky voice | Patellar hypoplasia, pulmonary emphysema, cryptorchidism, mammary hypoplasia (post-pubertal 100%), hypoplastic labiae | *IGF1R* mutation:pectus excavatum, 5th finger clinodactyly, short fingers  15q26-qter deletion:  5th finger clinodactyly, short fingers, talipes, congenital heart disease, renal anomalies | Sensorineural deafness |
| *Inheritance/ molecular abnormality* | Autosomal recessive  Mutations in *RECQL3*  High prevalence in Ashkenazi Jewish population | Autosomal recessive  Mutations in *NBN*  High prevalence in Slavic population | Autosomal recessive  Mutations in *PCNT* | Autosomal recessive  Mutations in *ORC1, ORC4, ORC6, CDT1, CDC6* | *IGF1R* mutation: majority autosomal dominant; compound heterozygosity reported in 2 cases | Autosomal recessive  Mutations in *IGF1* |

Abbreviations: ID, intellectual disability; MOPD II, microcephalic osteodysplastic primordial dwarfism type II; OFC, occipito-frontal circumference

**Table 4: Differential diagnosis of SRS in patients with relative normocephaly/ macrocephaly**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| *Syndrome*  *#OMIM no.* | **3-M Syndrome**  **#273750** | **Mulibrey Nanism**  **#253250** | **SHORT syndrome**  **#269880** | **Floating Harbour syndrome**  **#136140** | **IMAGe**  **Syndrome**  **#614732** |
| *Birth weight SDS* | Mean: -3.1 | Mean: -2·8  (range -4.0 to 0.5) | Mean: -3.3 | Mean: -2.5 | -2.0 to -4.0 |
| *Adult height range (cm)* | 115-150 | 136-150 | Mean 154 | Female:  98-156  Male:  106-164 | 1 male: 160  1 female: 143 |
| *Cognitive function* | Normal | Mild motor and speech delay only | Normal | Delayed speech. Intellect variable: normal to significant ID | Normal/ mild ID |
| *Facial features* | Anteverted nares, full lips, mid-face hypoplasia, long philtrum | Triangular face, frontal bossing | Micrognathia, high broad forehead, triangular-shaped face, deep-set eyes, prominent nose, low-set posteriorly rotated ears, hypoplastic nasal alae, facial lipodystrophy, thin hair | Triangular face, deep-set eyes, long eyelashes, bulbous nose, wide columella, short philtrum, thin lips | Frontal bossing, low-set ears, flat nasal bridge, short nose |
| *Other features* | Prominent heels (also in upd(7)mat), short broad neck, pectus deformity, short thorax, winged scapulae, hyperlordosis, hip dysplasia, subtle radiographic changes (slender long bones, tall vertebral bodies) | Hepatomegaly, yellow spots on retina, progressive restrictive perimyocarditis, insulin resistance, high pitched voice, slender long bones with thick cortex and narrow medullar channels, shallow sella turcica, increased tumour risk (particularly Wilms and ovarian stromal tumours) | Rieger anomaly, dental delay, partial lipodystrophy, transparent skin, dimples on elbows and buttocks, herniae, 5th finger clinodactyly, hyperextensible joints, hypogonadism, high pitched voice, type 2 diabetes, nephrocalcinosis, thin gracile bones, | Delayed speech development with expressive language delay, significantly delayed bone age, broad fingertips | Congenital adrenal hypoplasia, metaphyseal and/or epiphyseal dysplasia, male genital anomalies |
| *Inheritance/ molecular abnormality* | Autosomal recessive  Mutations in *CUL7*, *OBSL1, CCDC8* | Autosomal recessive  Mutations in *TRIM37*  High prevalence in Finnish population | Autosomal dominant  Mutations in *PIK3R1* | Autosomal dominant  Mutations in *SRCAP* | Imprinted –  Maternally inherited mutations in *CDKN1C* |

Abbreviation: ID, intellectual disability

**Table 5: Clinical checklist for management of patients with SRS**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | At diagnosis | 0-2  years | 2-10 years | 10-18 years |
| Document molecular subtype |  |  |  |  |
| Provide support group information |  |  |  |  |
| Genetic counselling for parents |  |  |  |  |
| **Feeding and growth** |  |  |  |  |
| Exclude feeding difficulties |  |  | □ | □ |
| Ensure nutritional repletion |  |  |  |  |
| Screen for gut dysmotility |  |  | □ | □ |
| Screen for oromotor/sensory issues |  | □ | □ | □ |
| Avoid rapid postnatal/childhood weight gain |  |  |  |  |
| Measure head circumference |  |  |  |  |
| Measure and monitor linear growth |  |  |  |  |
| Calculate and monitor BMI |  |  |  |  |
| Screen for symptoms/signs of hypoglycaemia |  |  | □ | □ |
| Consider growth hormone treatment |  | □ |  |  |
| Monitor IGF-I/IGFBP3 levels (≥ yearly) |  | □ |  |  |
| Monitor clinically (± biochemically) for insulin resistance |  | N/A |  |  |
| **Adrenarche and Puberty** |  |  |  |  |
| Monitor clinically for early adrenarche |  |  |  | N/A |
| Anticipate early bone age advancement |  | N/A |  |  |
| Consider treatment of early/rapid central puberty |  | N/A |  | □ |
| **Other medical** |  |  |  |  |
| Monitor for symptoms of sleep disordered breathing |  |  |  |  |
| Orthodontic/dental |  | □ |  |  |
| ENT |  | □ | □ | □ |
| **Neurodevelopment** |  |  |  |  |
| Developmental assessment |  |  | □ | □ |
| Screen for myoclonus-dystonia\* |  |  |  |  |
| Speech & language evaluation |  |  |  | □ |
| School progress |  | N/A | □ | □ |
| Monitor for speech, motor and cognitive difficulties |  | □ |  | □ |
| Psychosocial evaluation |  | N/A | □ | □ |
| **Musculoskeletal** |  |  |  |  |
| Limb length discrepancy/ asymmetry |  | □ | □ | □ |
| Scoliosis |  | □ | □ | □ |
| Screen for hip dysplasia |  |  | □ | □ |

N/A not applicable;

Assessment recommended (unless N/A to age group)

□ Assessment may be considered, depending on the clinical features of the patient

\*upd(7)mat only

**Box 2: Future research directions for SRS**

**Clinical**

* Incidence/ prevalence
* Frequency of associated features (eg: scoliosis, sleep disordered breathing, developmental delay, behavioural issues)
* Frequency and associated phenotype of molecular subtypes
  + 11p15, UPD(7)mat
  + MLID
  + 14q32 abnormalities, UPD(20)mat, UPD(16)mat
* Clinical overlap with other imprinting disorders

**Molecular**

* Development of testing methodology
* Identification of additional molecular causes in clinically diagnosed SRS patients
* Prenatal testing: methodology, ethical implications

**Management**

* Use of cyproheptadine as appetite stimulant
* Optimal timing of GH use
* Interpretation of IGF-I levels
* Role of aromatase inhibitors to control bone age advancement
* GnRH analogue inhibition of central puberty
* Control of postnatal weight gain
* Limb lengthening

**SRS in adulthood**

* Natural history, including risk of metabolic syndrome
* Quality of life indicators
* Reproductive issues (ART, recurrence risk associated with MLID)

Abbreviations: ART, assisted reproductive technology; GH, growth hormone; GnRH, gonadotrophin-releasing hormone; IGF1, insulin-like growth factor 1; MLID, multi-locus imprinting disturbance

**Figure legends:**

Figure1: decision tree for investigation and diagnosis of SRS. Diagnostic questions in blue boxes; recommended molecular testing in yellow boxes. Green boxes: diagnosis of SRS confirmed; pink boxes: diagnosis not confirmed. Abbreviations: CNV, copy number variant. NH‑CSS, Netchine-Harbison clinical scoring system; SRS, Silver-Russell syndrome.

Figure 2A: representation of the 11p15 region, showing both centromeric and telomeric domains. Only the imprinted genes that are implicated in the pathophysiology of SRS are represented. Blue boxes: paternally expressed genes (the growth promoter *IGF2* and the long non coding RNA (lncRNA) *KCNQ1OT1*). Pink boxes: maternally expressed genes (the growth inhibitor *CDKN1C*, the ion channel *KCNQ1* and the non-coding RNA *H19*). Circles: Differentially methylated regions (DMRs). Black circles: methylated DMRs. White circles: unmethylated ICRs.

Figure 2B: structure of the *IGF2*/*H19* DMR: this DMR contains short repetitive blocks of sequence and harbours seven binding sites for the zinc finger protein CTCF (green). Multiple enhancer elements (grey ovals) distal to *H19* are shared between *H19* and *IGF2*, able to increase expression of either. Binding of CTCF to the unmethylated maternal DMR blocks interactions between the *IGF2* promoter and enhancers downstream of *H19*, resulting in maternal *H19* expression. Conversely, methylation of ICR1 on the paternal allele prevents CTCF binding, allowing interaction between the *IGF2* promoter and distal enhancers, and thus paternal *IGF2* expression 154, 155.

Figure 3: mutations and epimutations of the imprinted region at chromosome 11p15 associated with SRS. The structure of the 11p15 region is represented as in figure 2. Paternal hypomethylation of *H19*/IGF2 IG-DMR results in loss of paternal *IGF2* and gain of maternal *H19* expression, leading to a growth restriction phenotype 11. Less commonly, maternal duplication of the centromeric or both domains results in growth retardation due to increased dosage of *CDKN1C*; however, smaller CNVs should be classified with caution due to the complex regulation of the region 29.Rare familial cases have been associated with maternal *CDKN1C* gain of function mutation (green cross) 62 or paternal *IGF2* loss of function mutation (red cross)63.

**Summary of Boxes & Tables:**

Box 1: Definitions

Box 2: Questions for future research

Table 1: Netchine-Harbison clinical scoring system (NH CSS)

Table 2: Frequency of features in SRS

Table 3: Differential diagnosis – relative microcephaly

Table 4: Differential diagnosis – normo-/relative macrocephaly

Table 5: Clinical checklist for management of patients with SRS

**Supplementary Information:**

Summary of recommendations

Table 1: Frequency of features in different subtypes of SRS and non-SRS SGA

Table 2: Genetic variants on chromosome 11p15

Table 3: Genetic variants on chromosome 7

Table 4: Adult height data in untreated patients with SRS

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