Summary of recommendations

Clinical diagnosis of SRS

1.1 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+++)

1.2 The flow chart (Figure 1), based on the NH-CSS, should be adopted for the investigation and diagnosis of SRS. (A++)

1.3 In children aged <2 years, adolescents and adults, a reduced threshold for molecular testing might be required due to missing data. (A++)

Molecular testing

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 chromosome 7, discrimination between epimutation, CNV and upd should be considered to estimate recurrence risk. (A+++)

2.5 After exclusion of changes in 11p15 and chromosome 7, a clinical decision should be sought about the direction of further testing. Depending on the clinical features and family history of the patient, further testing might include CNV analysis and DNA methylation analysis at chromosome 14q32. Testing might also be considered for very rare molecular anomalies, including upd(20)mat, upd(16)mat and mutations in CDKN1C and IGF2, as well as analysis of further tissues to detect somatic mosaicism. (A++)

2.6 When an underlying pathogenic CNV is identified, the diagnosis should focus on this finding, even if features of SRS are present. (A+)
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-Harbison clinical scoring system; SRS, Silver–Russell syndrome.
**Differential diagnosis**

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

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

**Multidisciplinary care**

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. (A+++)

**Early feeding and 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. (A+++)

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

5.3 Diagnose and treat any oromotor and/or sensory issues that affect oral intake of food. (A+++)

5.4 In patients with severe feeding failure who are unresponsive to standard care, anatomical or functional disorders of the gastrointestinal tract, such as malrotation, should be excluded. (A+++)

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

5.6 In cases of extreme feeding difficulties or gastrooesophageal reflux, consider enteral feeding by gastrostomy tube (with or 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 nonvolitionally fed children. (A++)
Low muscle mass makes typical BMI targets excessive in this population. Targets currently used in some centres include: Waterlow score 75–85%; 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

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 intravenous 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 or 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 tube or jejunostomy tube. (A++)

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

Surgery and anaesthesia

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

7.2 Consider admission the night before surgery for early administration of intravenous dextrose before 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 intravenous dextrose during and after surgery. Do not discharge until ketonuria is absent and the child can sustain themselves on oral or enteral feeding. (A++)

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

* Netchine et al. (doi:10.1038/nrendo.2016.138)
7.6 Delay elective surgery until the child is adequately nourished. (B+)

7.7 Be aware of the high risk of malnutrition after surgery and follow appropriate guidelines. (A+)

**Growth hormone treatment**

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; however, due consideration should be given to the exceptions listed below*. (A++)

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

8.6 Terminate GH therapy when height velocity is <2 cm per year over a 6-month period and bone age is >14 years (female patients) or >17 years (male patients). (A++)

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. (A+++)

8.8 Monitor circulating levels of IGF1 and IGFBP3 at least yearly during GH treatment. (A++)

*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)^2. 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**

9.1 Monitor for signs of premature adrenarche, fairly 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 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. (A++)
Prevention of 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. (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 children with low muscle mass and high baseline levels of IGF1. (A+)

10.5 In patients with clinical signs of insulin resistance, consider formal assessment of insulin sensitivity with a 2-h oral glucose tolerance test including measurement of 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

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

Orthopaedic problems

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 Before initiation of GH therapy, refer patients with scoliosis to the orthopaedic team and monitor while receiving GH. (A+++)
12.4 Evaluate leg length asymmetry regularly and consider orthopaedic management if necessary. (A++)

**Maxillofacial anomalies and sleep disordered breathing**

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 (such as snoring, apnoeas, excessive daytime fatigue, disrupted sleep and agitation). (A++)

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

**Other congenital anomalies**

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

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

**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. (A+++)

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

**Genetic counselling**

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. (A+++)

**References**
