Silver-Russell Syndrome

Synonyms: Russell-Silver syndrome, Russell-Silver dwarfism, Silver's syndrome

Definition

Silver-Russell syndrome (SRS) is a clinically and genetically heterogeneous condition characterised by severe intrauterine and postnatal growth restriction, craniofacial disproportion and normal intelligence, downward curvature of the corner of the mouth, syndactyly and webbed fingers. It was first described by Silver and co-workers in 1953, then independently by Russell in 1954.

Epidemiology

Incidence

This is very rare. Reported cases since the discovery of the syndrome number in the hundreds but it is likely to be underdiagnosed. Estimates of incidence vary from 1 in 75,000 births to 1 in 100,000.

Genetics

The condition occurs sporadically and, in many cases, no genetic cause can be clearly identified. SRS is genetically heterogeneous. In recent years, it has been shown that more than 38% of patients have hypomethylation in the imprinting control region 1 of 11p15 and around 10% of patients carry a maternal uniparental disomy of chromosome 7. In addition, there is a further class of mutations which are copy number variations affecting different chromosomes, mainly 11p15 and 7.

Presenting features

SRS is primarily a clinical diagnosis but molecular testing enables confirmation of the clinical diagnosis and defines the subtype. As many of the features of this condition are nonspecific, clinical diagnosis of SRS remains difficult.

In general the features of the syndrome are most pronounced in young children and become less obvious as the patient becomes older.

The face is characteristically small and triangular; however, the head circumference is usually normal for age. This, combined with short stature, gives the appearance of having a large head.

Growth

- Birth weight less than 2 standard deviation (SD) from mean.
- Poor postnatal growth - less than 2 SD from mean at diagnosis.
- Normal occipitofrontal circumference despite growth restriction.
- Asymmetrical patterns of growth.
- The average height for affected males is about 151 cm and about 140 cm for affected females.

Facies

- Normal head circumference but characteristic small, triangular face.
- Blue sclerae.
- High forehead tapering to micrognathic jaw.
- Prominent nasal bridge and down-turned corners of mouth.

Gastrointestinal/metabolic difficulties

- Feeding difficulties during infancy, including gastro-oesophageal reflux, oesophagitis, food aversion, poor appetite and faltering growth.
- Tendency to fasting hypoglycaemia during infancy, as a result of feeding difficulties.

Developmental abnormalities
- Poor head control in infancy, due to a relatively large head compared with the neck/trunk. Motor impairment due to poor muscle mass/function.
- About half have learning difficulties, particularly problems with arithmetic and language.

**Skeletal abnormalities**
- Late closure of the anterior fontanelle.
- Limb asymmetry and hemihypertrophy.
- Clinodactyly (incurving) of the little finger.
- Camptodactyly (fixed flexion) of fingers.
- Syndactyly (fusion) of toes.
- Sprengel's neck deformity - unilateral shortening and webbing to trunk.
  X-ray abnormalities include:
  - Delayed bone age.
  - 'Ivory' epiphyses of distal phalanges.
  - Small middle phalanx of the little finger - present in 4 out of 5 cases.
  - Pseudo-epiphyses at the base of second metacarpal.

**Miscellaneous features**
- Increased sweating affecting the head and upper trunk.
- Urogenital anomalies - hypospadias, posterior urethral valves.
- Cardiac abnormalities.
- Tendency to tumours such as Wilms' tumour, hepatocellular carcinoma, testicular seminoma and craniopharyngioma.

**Differential diagnosis**
- Causes of intrauterine growth restriction and faltering growth.
- Fetal alcohol syndrome and Fanconi's syndrome also present similarly.

**Investigations**
- Karyotyping of a child and both parents to look for known underlying genetic abnormalities.
- Radiographs of the hand may detect typical skeletal abnormalities.

**Management**
- Growth can be improved by optimising nutrition:
  - Enteral feeding may be needed.
  - Short stature in SRS can be treated by use of pharmacological doses of recombinant growth hormone, resulting in good short-term catch-up\(^8\).
- Early use of physiotherapy.
- Educational support.

**Prognosis**
The prognosis is generally good but morbidity is very variable and will depend on the severity of associated features.

There have been no long-term follow-up studies of sufficient numbers of those with the condition to define life expectancy, morbidity and mortality definitively.

**Further reading & references**
- Russell Silver Syndrome (RSS), Intrauterine Growth Retardation (IUGR), Small for Gestational Age (SGA); Child Growth Foundation
