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 [1].

It was first described by Silver and co-workers in 1953, then independently by Russell in 1954 [2, 3].

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 [4]

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 [1]. In addition, there is a further class of mutations which are copy number variations affecting different chromosomes, mainly 11p15 and 7 [5].

Presenting features [6]

SRS is primarily a clinical diagnosis but molecular testing enables confirmation of the clinical diagnosis and defines the subtype [7]. As many of the features of this condition are nonspecific, clinical diagnosis of SRS remains difficult [8].

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.
- 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

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