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Silver-Russel Syndrome (Srs) : A Review Of Current Concepts

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ABSTRACT: *Russell-Silver syndrome is a growth disorder characterized by slow growth before and after birth. Many children with Russell-Silver syndrome have a small, triangular face with distinctive facial features including a prominent forehead, a narrow chin, a small jaw, and down-turned corners of the mouth*

KEYWORDS: *Silver-Russel syndrome,*

I. INTRODUCTION

Russell-Silver syndrome (OMIM number- #180860) is a growth disorder characterized by slow growth before and after birth. Babies with this condition have a low birth weight and often fail to grow and gain weight at the expected rate (failure to thrive). Its Synonyms are RUSSELL-SILVER SYNDROME, SILVER-RUSSELL DWARFISM. Name of the analyzed genes or DNA/chromosome segments is 11p15.5 [1,2]

II. PREVALENCE AND INCIDENCE

Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence) unknown. , Prevalence in the ethnic group of the investigated person is Unknown. Estimated prvelence is 1 in 75,000 to 100,000 people. Prenatal diagnosis is rarely required for SRS but may occasionally be requested in cases of a familial chromosomal rearrangement affecting chromosomes 11p15 and 7, or in cases of trisomy 7 mosaicism in CVS.

Analytical sensitivity
(Proportion of positive tests if the genotype is present)

UPD(7)mat 11p15.5 ICR 1 hypomethylation	Nearly 100%*
Duplication of Maternal chromosome11p15.5	Nearly 100%
UPD(11p15)mat	Nearly 100%
Imbalanced Cryptic chromosomal aberrations	**
Lowgrade mosaics might not be detected	
** Depends on the method used	

Analytical specificity
(Proportion of negative tests if the genotype is not present)

Nearly 100%.

III. REVIEW:

Based on the clinical features, this syndrome was first described by Silver and colleagues in 1953[3] who found certain features of the syndrome in 2 unrelated children and, soon afterwards, by Russell in 1954 [4] in 5 unrelated children.In their reports the affected children had characteristic facies, low birthweight, asymmetry, and growth retardation.

In 1999, Price et al [5], reevaluated 57 patients who were previously diagnosed with definite or likely SRS and also proposed five criteria for diagnosis of SRS. .In their findings 50 patients had clinical features in the broad definition spectrum of the syndrome.Additional findings were generalized camptodactyly in11 patients. 25 patients were males of which 13 had to be treated with genital surgery for hypospadias and inguinal hernia.Uniparental Disomy of chromosome 7 was seen in 4 of 42 subjects who went through molecular analysis.In 1995 Kotzot et al [6] investigated 35 patients with PCR markers for UPD7 and maternal disomy was seen in 4 cases.Cytogenetic and molecular genetic studies have also been done for Chromosome 1 ,X ,11 besides exclusion studies and Genotype/Phenotype correlations by various authors. In 2011 Gronuland et al [7] identified ophthalmologic abnormalities in17 of 18 children with SRS. So far, about 400 patients have been described with mild phenotypes to classic phenotypes.Most commonly seen is hypomethylation in the chromosome 11p15 imprinting center 1 (IC1).In studies on Inheritance pattern,Rimoin(1969)[8], Nyhan and Sakati(1976) [9] and Samn et al(1990)[10] described monozygotic twins with concordant silver dwarfism and discordant for RSS respectively. Some authors reported familial cases(Fuleihan et al 1971)(Bartholdi et al 2009) [11], while still others reported cases in generations of a family.(Duncan et al 1990)[12]

IV. ETIOPATHOGENESIS

A number sign (#) is used with this entry because 20 to 60% of cases of Silver-Russell syndrome (SRS) are caused by the epigenetic changes of DNA -hypomethylation at the telomeric imprinting control region (ICR1) on chromosome 11p15, involving the H19 (103280) and IGF2 (147470) genes. About 10% of cases are due to maternal uniparental disomy of chromosome 7.[12] Opposite epimutations, namely hypermethylation at the same region on 11p15, are observed in about 5 to 10% of patients with Beckwith-Wiedemann syndrome (BWS; 130650), an overgrowth syndrome .[11]

Pathophysiology

Typical features include intrauterine growth retardation, difficulty in feeding,failure to thrive, or postnatal growth retardation. Adequate catch-up growth often does not occur, and final adult height still is less than normal . Clinical features are usually more clearly manifest in infants and young children but, not in older children The male-to-female ratio is equal.. In a significant number of children with the syndrome Growth hormone abnormalities like insufficiency or spontaneous hormone secretion and subnormal responses to provocative growth hormone stimulation testing have been reported. Other features include :

Facial dimorphism with small triangular facies and normal head circumference but less head length making it looks disproportionately larger. Intelligence may be normal or there may be learning disability. Asymmetric Limbs with camptodactyly (ie, fixed flexion of digits) or clinodactyly (ie, incurving) of one or more fingers may be present.

Oral manifestations:

- Children Experience difficulty having milk
- They have exceptional face features including a small triangular in shape face, notable nasal link, and Unusually small, wide mouth; downturned corners of the mouth; and/or an abnormally small jaw .
- Kids with Russell-Silver affliction have a problem **eating enough calories** from fat for development, parents may figure out how to enhance calorie consumption, as well as special high-calorie formulations may be provided.

Physical Features:
Head circumference- normal
Sclera- blue
Facies- small and triangular
Forehead- high
Jaw- small with micrognathia
Nasal bridge- prominent Corners of mouth- down-turning

Therefore,**Signs** include:

- Small, pointed chin
- Thin, wide mouth
- Triangle-shaped face with broad forehead

Growth and skeletal changes:

- Prenatal onset short stature (final height ≤ -3.6 SD)
- Late closure of anterior fontanelle
- Asymmetry, usually of the limbs
- Hemihypertrophy
- Clinodactyly of the fifth finger
- Camptodactyly
- Syndactyly of second and third toes
- Sprengel deformity or other hand anomalies

Genital anomalies:

- Hypospadias
- Posterior urethral valves

Radiographic findings(hand)

Although no single finding is pathognomic, some findings are - Delayed bone age, ivory epiphyses of the distal phalanges, small middle phalanx of the fifth finger (80%), pseudoepiphyses at the base of the second metacarpal. [5]

Occasional findings

- Cardiac defects
- Malignancy (eg, craniopharyngioma, testicular seminoma, hepatocellular carcinoma, Wilms tumor)
  Assisted reproduction technologies (ART) may increase the risk of imprinting disorders such as Silver-Russell syndrome

Diagnostic Clinical criteria:
Although not clearly established some of those recently proposed criteria subsequent to study of a group of homogenous patients are:

- Birthweight less than or equal to -2 standard deviations (SD) from the mean
- Poor postnatal growth, less than or equal to -2 SD from the mean at diagnosis
- Preservation of occipitofrontal circumference
- Classic facial phenotype
- Asymmetry
- Low birthweight (≤ -2 SD)
- Feeding difficulties during infancy
- Tendency for fasting hypoglycemia during infancy and early childhood
- Tendency for increased sweating during infancy, particularly on the head and upper trunk
- Developmental delay
- Poor head control during infancy caused by relatively large size of head compared to a small body
- Motor impairment caused by lack of muscle bulk and strength
- Impairment of cognitive abilities (language, arithmetic) during childhood in about 50% of patien

Differential Diagnoses

- Fanconi Syndrome
- Fetal Alcohol Syndrome

Diagnostic Analytical Methods(Investigations)

Methylation-specific PCR of parental blood to evaluate for uniparental disomy of chromosome 7 and hypomethylation at chromosome 11p15 , microsatellite typing, methylation-specific MLPA, chromosomal microarray or karyotyping

Hand Radiograph findings may be-

- Delayed bone age
- Ivory epiphyses of distal phalanges
- Small middle phalanx of the fifth finger in 80% of patients with Silver-Russell syndrome
- Pseudoepiphyses at base of second metacarpal

Treatment :

Calorie intake monitoring

Recombinant human growth hormone (rhGH) therapy given via daily subcutaneous injections. will help the kid grow much more, but she or he is still smaller than typical size. Recommended dose is 0.48 mg/kg/wk if the growth of the child is not aequate by the age of 2 years.

Sometimes physical therapy maybe beneficial

Early treatment programs with regard to small children are of help, since a few kids with Russell-Silver affliction will have trouble with vocabulary and mathematics skills.

Prognosis : Older children and adults do not show typical features as clearly as infants or younger children. Intelligence may be normal, although the patient may have a learning disability.

Possible Complications

- Self esteem and emotional problems related to appearance
- Chewing or speaking difficulty if jaw is very small
- Learning disabilitie
- Hepatocellular Carcinomas

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