Russell-Silver Syndrome: A Case Report with Review of Literature

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ABSTRACT
Russell-Silver syndrome is a disorder present at birth characterized by low birth weight, poor postnatal growth, craniofacial disproportion, clinodactyly, normal intelligence, downward curvature of the corner of the mouth, syndactyly, cafe-au-lait spots, cryptorchidism, etc. Episodes of hypoglycemia is an important feature in the diagnosis of RSS. Diagnosis of RSS remains clinical as no definite etiology or specific test has been established. It appears to be sporadic in most instances and has been noted to occur in all racial groups. We report to you one such case of an 11-year-old boy who presented with most of the features mentioned above. Early diagnosis of such cases is essential to overcome the psychological trauma to the patient.

Keywords: Intrauterine growth retardation, Short stature, Cryptorchidism, Russell-Silver syndrome.

INTRODUCTION
Russell-Silver syndrome is a pattern of malformation first described by Silver et al in 1953 based on two cases and then by Russell in 1954 based on seven cases.1,2 It remains a clinical diagnosis, as no etiology or specific test has been established.1,3 It is a congenital disorder of short stature having features of triangular-shaped face, broad forehead, pointed, small chin, wide-thin mouth, clinodactyly and hypoglycemia.4 We report to you one such case of postnatal growth retardation.

CASE REPORT
A 12-year-old male patient reported with a chief complaint of crowding of upper and lower anterior teeth. History of present illness revealed that the deciduous anterior teeth erupted in cross-bite relationship. As the permanent teeth erupted, some of them erupted properly but few were still in cross-bite relation. Past medical history revealed that he was born with low birth weight (1.7 kg), hypoglycemia, small genitalia and growth hormone deficiency (6.23 ng/dl). He was operated for cryptorchidism. His family history revealed that his maternal uncle and his cousin were having similar features. He has an younger brother who was born normally. General physical examination revealed short stature, triangular facies with frontal bossing, hypertelorism, downslanting eyes, low set ears, light brown stains on the face (Figs 1 and 2). Examination of hands revealed webbed fingers with clinodactyly of fifth finger (Fig. 3). Intraoral examination revealed micrognathia with crowding of upper and lower anterior teeth, palatally erupted 12 and 22, cross-bite in relation to both the lateral incisors, erupting 13 and 23 (Fig. 4). There was deep palatal vault (Fig. 5). There was Angle’s class I malocclusion with crowding of upper and lower anterior teeth.

Hematological and radiological investigations were carried out. Serum alkaline phosphatase was 245 IU/L. Other values were within normal limits. Based on history, clinical examination and investigative findings, a diagnosis of Russell-Silver syndrome was given. Robinow syndrome, Bloom syndrome and Fetal alcohol syndrome were considered in differential diagnosis. Patient was advised to go for growth hormone therapy and orthodontic correction of the malaligned teeth.

DISCUSSION
The occurrence of Russell-Silver syndrome appears to be sporadic in most instances has been noted to occur in all racial groups. Maternal uniparental disomy of chromosome 7, in which a child...
has inherited both copies of a region of the chromosome from the mother, has been shown to play a role. It is important to note that no single explanation to date can account for the heterogeneity of the phenotypic findings.\textsuperscript{1,5} Russell hypothesized an intrauterine challenge or stress at 6 to 7 weeks of gestation, while Gotlin et al suggested either an end-organ unresponsiveness to growth hormone or a biostructural abnormality in growth hormone molecule. Fuleihan et al and Garies et al have suggested that there is a spontaneous single-gene and autosomal dominant mutation. None of these theories have been confirmed.\textsuperscript{6} The etiology has yet to be fully elucidated.

The incidence ranges from one in 3,000 to one in 100,000 live births. Worldwide more than 500 cases have been reported with equal male and female ratio.\textsuperscript{7} Russell-Silver syndrome has been noted to occur in all racial groups.\textsuperscript{1} Intrauterine growth retardation (IUGR) results in reduction in total body cell mass and after birth growth proceeds normally with the child always remaining small in comparison with their peers. Insufficient growth hormone secretion has been suggested as a contributory factor in some studies.\textsuperscript{2}

Findings that have been described in over 50% of all patients with Russell-Silver syndrome are short stature, craniofacial disproportion, low birth weight, asymmetry, clinodactyly of (incurved) fifth finger, normal intelligence, term gestation and downward curvature of the corners of the mouth (shark mouth).\textsuperscript{6-9} Our patient was also having normal intelligence with short stature, low birth weight, clinodactyly of fifth finger, etc. In 10 to 50% of the cases have shortened fifth digit, pseudohydrocephalus, frontal bossing, delayed early motor development, delayed skeletal maturation, cryptorchidism, elevated urinary gonadotropin levels, syndactyly of feet, disproportionately short arms, cafe-au-lait spots, maternal difficulties during pregnancy.\textsuperscript{6} Our patient had most of the above-mentioned features like frontal bossing, slightly delayed skeletal maturation, cryptorchidism, cafe-au-lait spots. The finding of disproportionately short arms has been inadequately pursued in the literature. In large series of Tanna et al, there was no disturbance of upper-lower limb length relationship.\textsuperscript{6}

Major intraoral features of this syndrome that have been reported are a high arched palate, delayed tooth eruption, microdontia, hypodontia and crowding.\textsuperscript{10} Episodes of hypoglycemia is also an important feature in the diagnosis of RSS.\textsuperscript{11} In our patient, the episodes of hypoglycemia occurred twice. First time it was when patient was not even one day old and the second time when he was 9-year-old for which he was admitted to hospital and got treatment for hypoglycemia. One theory for hypoglycemia is that it is due to the rapid depletion of limited hepatic glycogen stores, especially in small for gestational-age neonates.\textsuperscript{8} One rare finding found in our case was visual disturbance which was also mentioned by Robert et al.\textsuperscript{1}
Diagnosis of RSS remains clinical as no definite etiology or specific tests has been established.\textsuperscript{1,3} The five core clinical diagnostic criteria are:

1. Intrauterine retardation
2. Poor postnatal growth
3. Preservation of occipitofrontal circumference
4. Classic facial phenotype
5. Asymmetry (especially of the extremities).

Due to the clinical and genetic heterogeneities of this syndrome, patients whose features fulfill four of these five criteria could be diagnosed with Russell-Silver syndrome.\textsuperscript{12,13}

Little has been published on therapeutic options for patients with RSS. General treatment includes growth hormone therapy, high calorie diet, limb lengthening/shoe lift.\textsuperscript{5} One study targeting small-for-gestational-age children treated RSS patients as a subset with growth hormone and demonstrated favorable responses. Research performed by Azcona et al has shown that growth hormone therapy improves short-term growth acceleration in patients with RSS despite adequate endogenous levels of the hormone.\textsuperscript{1}

Rokover and others found that younger, shorter individuals had the greatest increase in height; standard deviation scores over 3 years. The finding of a better response in younger children suggests that early commencement of growth hormone may be indicated in RSS.\textsuperscript{5} Growth hormone has been used in the treatment of children with growth hormone deficiency for more than 20 years. Such physiological replacement treatment increases growth velocity and allows the restoration of growth prognosis from the onset of treatment, but in standard dose regimens of between 12 and 15 IU/m\textsuperscript{2}/week does not improve final height prognosis beyond the potential at the start of treatment, growth hormone treatment allows that potential to be attained. The pharmacological use of growth hormone in children with short stature has been in the dose range of 15 to 30 IU/m\textsuperscript{2}/week, although 40 IU/m\textsuperscript{2}/week has been used in children without changes in glucose tolerance.

IUGR may be associated with postnatal growth failure and result in a final height in the region of – 3.6 SD score. The pattern of growth in such children continues to be abnormal from intrauterine life through to full maturity. Growth in the first two years of life, which is predominantly dependent on nutrition and growth factors rather than growth hormone, is subnormal. Growth in the middle childhood years, which is predominantly growth hormone dependent, may be due to abnormalities in quality and quantity of endogenous growth hormone secretion. The adolescent growth spurt usually occurs early and is reduced in magnitude.

Previous authors have reported an increase in growth velocity in some children with short stature secondary to IUGR but have used growth hormone doses between 30 and 65 IU/m\textsuperscript{2}/week. The relatively poor response may have been due to the frequency of administration being only two or three times per week. Using a more optimal frequency of daily administration, a satisfactory growth response has been reported using a lower dose regimen. The children who were treated with higher dose regimen grew much faster.

The growth spurt of puberty is abnormal in children with IUGR, the onset of puberty occurs earlier and there is a lower peak height velocity than in normal children. It may be advantageous to delay the onset and duration of puberty using a gonadotropin releasing hormone analogue to permit a longer period for growth in prepuberty and puberty.\textsuperscript{14}

**REFERENCES**