Clinical spectrum of Silver - Russell syndrome

Sapna N. K. Varma, Balagopal R. Varma[1]

Abstract

Silver - Russell syndrome is a clinically and genetically heterogenous condition characterized by severe intrauterine and postnatal growth retardation, craniofacial disproportion and normal intelligence downward curvature of the corner of the mouth, syndactyly and webbed fingers. Diagnosis of Silver - Russell syndrome remains clinical; no definite etiology or specific tests have been established. In the recent years, it has been shown that more than 38% of patients have hypomethylation in the imprinting control region 1 of 11p15 and one-tenth of patients carry a maternal uniparental disomy of chromosome seven. The pathophysiological mechanisms resulting in the Silver - Russell phenotype remain unknown despite the recent progress in deciphering the molecular defects associated with this condition. This case report describes the clinical features of Silver - Russell syndrome in a father and daughter.

Keywords: Postnatal growth retardation, Silver - Russell syndrome, short stature

Introduction

Russell - Silver syndrome is a pattern of malformation first described by Silver *et al*.,[1] in 1953 and then by Russell[2] in 1954. Silver *et al*.,[1] reported two unrelated children with congenital hemihypertrophy, low birth weight, short stature and raised gonadotrophins. Russell described five unrelated children with extreme intrauterine growth retardation and characteristic facial features. These children were short for age and two cases had body asymmetry. The characteristic features described by him were triangular shaped face with a broad forehead, pointed and small chin together with wide, thin shark – like mouth. Although each author emphasized rather different features, the composite features have been identified as Silver - Russell syndrome.[3] Attempts to separate Silver syndrome from Russell syndrome, depending on whether asymmetry is present or absent have not generally been accepted.

Departments of Orthodontics and Dentofacial Orthopaedics and [1]Pediatric Dentistry, Amrita School of Dentistry, Kochi, Kerala, India

Correspondence: Prof. Sapna Varma N. K, Department of Orthodontics and Dentofacial Orthopaedics, Amrita School of Dentistry, AIMS Campus, Ponekkara, Kochi - 682 041, Kerala, India.
E-mail: sapnavarma@aims.amrita.edu

Access this article online	
Quick Response Code:	Website: www.contempclindent.org
	DOI: 10.4103/0976-237X.118346

This syndrome remains a clinical diagnosis as no etiology or specific tests have been established.[4] This clinically heterogenous syndrome is characterized by short stature without catch - up growth, normal head size for age, a distinctive triangular face with prominent forehead, low set ears and clinodactyly of fifth fingers.[5] Over the years, many clinical signs have been added. However, no consensus definition has yet been established making a clinical diagnosis difficult. Rare cytogenetic abnormalities were found in patients with this syndrome. Maternal uniparetal disomy for chromosome 7 was found in 5-10% of patients. Loss of methylation of 11p15 imprinting center region 1 telomeric domains have been identified in more than 35% of patients with Silver - Russell syndrome.[6]

Case Report

A 12-year-old female patient presented with global developmental delay and facial dysmorphism. Her chief complaint was irregularly arranged teeth. On examination, her height was 125 cm (<3rd %) and having the following features: Hypertelorism, triangular face, low set ears, scanty eyebrows, depressed nasal bridge, frontal bossing, poor vision of the right eye, crowding of upper and lower dental arches [Figures 1 and 2]. She was found to have an ear tag on the right ear and a pit on the left ear [Figure 3]. However, she did not have any hearing difficulties. She reported intolerance to heat and poor sweating ability. She had clinodactyly of the fingers and disproportionate toes [Figure 3]. She had trouble in running at school.

Her facial features were leptoprosopic facial form having a facial index of 173.4 with the increase in lower facial third, convex profile, posterior divergence, hyperactive mentalis and shallow mentolabial sulcus. She had incompetent lips with interlabial gap of 10 mm. On intra oral examination, she had high arch palate and lower midline shifted to the left by 3 mm. The maxillary and mantibular dentition crowding was 8 mm and 4 mm respectively. She had Class I molar

relationship on the right side and end - on the relationship on the left side. Canine relationship was Class II on both sides. She had an overjet of 3 mm and openbite of 6 mm. She was found to have crossbite in relation to the left posterior region. Cephalometric analysis indicated increased cranial base angle, decreased anterior and posterior cranial base length. Maxilla was retropositioned relative to cranium. Mandibular skeletal base was retrognathic to cranium. In short, she had Class II skeletal base, vertical growth pattern and deficient chin.

The father of this patient also had similar features [Figure 1]. The father was short. His ears were low set and had pits in both right and left ears. He also had hypertelorism, scanty eyebrows and hair on head absent, slanting eyes and poor sweating and heat intolerance. Mother and sibling of the patient were normal. Routine chromosome analysis of daughter and father indicated normal karyotypes.

Hematological investigations of the 12-year-old patient where carried out. Hematological values were within normal limits. Based on the history, clinical examination and investigation findings, a diagnosis of Silver - Russell syndrome was made. Differential diagnoses considered were Fetal Alcohol syndrome, Bloom syndrome and Robinow syndrome.

Patient was advised regarding growth hormone therapy and orthodontic correction of malocclusion. The orthodontic treatment plan was to have a period of rapid maxillary expansion followed by fixed orthodontic therapy. The phase of rapid maxillary expansion is completed [Figure 4].

Discussion

The incidence of Silver - Russell syndrome range from 1 in 3,000 to 100,000 live births and it occurs in all racial groups. More than 500 cases have been reported with equal predilection to male and female.[7] Russell hypothesized an intrauterine challenge or stress at 6 and 7 weeks of gestation although Gorlin *et al*., suggested either an end-organ unresponsiveness to growth hormone or a biostructural abnormality in growth hormone molecule. Marks *et al*.,[8] in 1977 has quoted studies which suggested that there is a spontaneous single gene and autosomal dominant mutation. None of these hypotheses has been confirmed.[8] The etiology is yet to be fully understood.

Individuals with Silver - Russell syndrome are short in stature. Intrauterine growth retardation 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.[9] Children with this syndrome have also been reported to have craniofacial disproportion, low birth weight, asymmetry, clinodactyly of the fifth finger, webbed fingers, normal intelligence, low set ears, term gestation and downward curvature of the corners of the mouth. Patient who reported to our department also had normal intelligence, short stature, craniofacial disproportion, webbed fingers and low set ears. The other features often reported in the literature are frontal bossing, syndactyly of feet and disproportionately short arms. The above-mentioned features were also present in our patient. Visual disturbance was reported as a rare finding by Perkins and Hoang-Xuan[4] and Sreedevi *et al*.[10] Poor vision of the right eye was reported in our patient.

Bartholdi *et al*.,[11] studied the methylation pattern at the H 19 – insulin-like growth factor 2 locus in 201 patients with suspected Russell - Silver syndrome. Methylation defects were found to be restricted to patients who fulfilled the diagnostic criteria for Russell - Silver syndrome. They detected epimutations in an affected father and his likewise affected daughter. The father of our patient also had very similar features. The father was short in stature and having normal intelligence. He had low set ears with ear pits. He had scanty hair on head, scanty eyebrow, hypertelorism, slanting eyes, poor sweating and heat intolerance.

The five core clinical diagnostic criteria of Silver - Russell syndrome are:

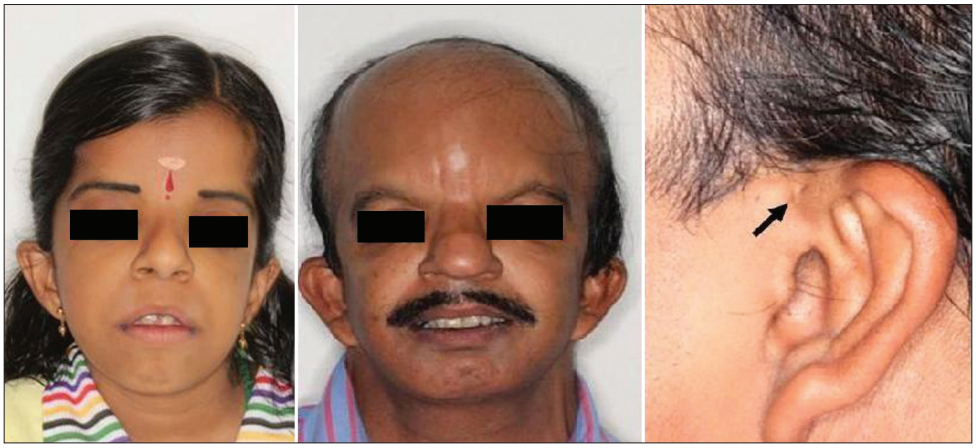

Figure 1: Triangular face with low set ears and hypertelorism of the 12-year-old girl and her father

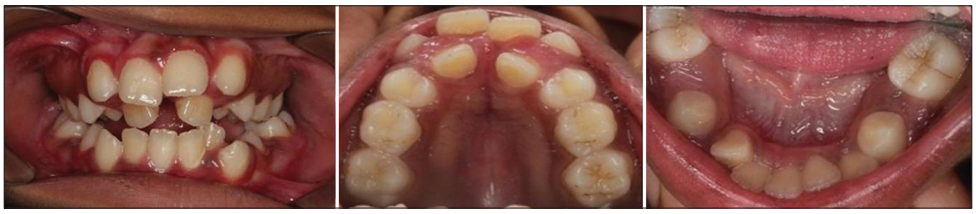

Figure 2: Crowded dentition with open bite

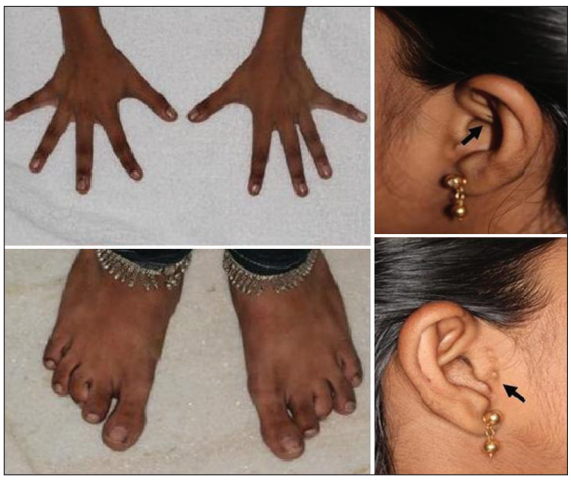

Figure 3: Ear tag on the right ear and pit on the left ear and webbed fingers and disproportionate toes

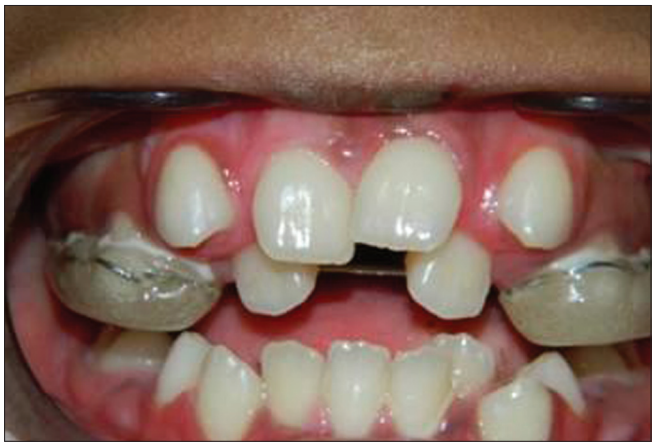

Figure 4: Rapid maxillary expansion

- Intra uterine retardation
- Poor post natal growth
- Preservation of occipitofrontal circumference
- Classic facial phenotype
- Asymmetry.

Due to clinical and genetic heterogeneities of this syndrome, patients who have four out of the above mentioned five features, could be diagnosed with Silver - Russell syndrome.[12]

Conclusion

Silver - Russell syndrome is said to be probably under diagnosed due to the broad range of features. The main features are severe intrauterine and postnatal growth retardation, relative macrocephaly and a characteristic small triangular face. The disease is associated with additional dysmorphic features such as fifth finger clinodactyly and webbed fingers. The accuracy of clinical diagnosis is influenced by the clinicain's skill in recognizing and noting the clinical features of a patient. Early diagnosis facilitates timely administration of general and orthodontic treatment options. This will facilitate healthy and good psychological development in a child with this condition.

References

1. Silver HK, Kiyasu W, George J, Deamer WC. Syndrome of congenital hemihypertrophy, shortness of stature, and elevated urinary gonadotropins. Pediatrics 1953;12:368-76.
2. Russell A. A syndrome of intra-uterine dwarfism recognizable at birth with cranio-facial dysostosis, disproportionately short arms, and other anomalies (5 examples). Proc R Soc Med 1954;47:1040-4.
3. Black J. Low birth weight dwarfism. Arch Dis Child 1961;36:633-44.
4. Perkins RM, Hoang-Xuan MT. The Russell-Silver syndrome: A case report and brief review of the literature. Pediatr Dermatol 2002;19:546-9.
5. Gucev ZS, Tasic V, Jancevska A, Kirovski I. A case of Silver-Russell syndrome (SRS): Multiple pituitary hormone deficiency, lack of H19 hypomethylation and favourable growth hormone (GH) treatment response. J Genet 2009;88:239-43.
6. Eggermann T, Eggermann K, Schönherr N. Growth retardation versus overgrowth: Silver-Russell syndrome is genetically opposite to Beckwith-Wiedemann syndrome. Trends Genet 2008;24:195-204.
7. Kumar S, Jain A, Agrawal S, Chandran S. Silver-russell syndrome: A case report. Cases J 2008;1:304.
8. Marks LJ, Bergeson PS. The Silver-Russel syndrome: A case with sexual ambiguity, and a review of literature. Am J Dis Child 1977;131:447-51.
9. Eggermann T, Gonzalez D, Spengler S, Arslan-Kirchner M, Binder G, Schönherr N. Broad clinical spectrum in Silver-Russell syndrome and consequences for genetic testing in growth retardation. Pediatrics 2009;123:e929-31.
10. Sreedevi P, Chaudhary S, Agnihotri PG, Reddy PB, Nagaveni NB. Russell-Silver syndrome: A case report with review of literature. J Ind Acad Oral Med Radiol 2011;23:73-5.
11. Bartholdi D, Krajewska-Walasek M, Ounap K, Gaspar H, Chrzanowska KH, Ilyana H, *et al*. Epigenetic mutations of the imprinted IGF2-H19 domain in Silver-Russell syndrome (SRS): Results from a large cohort of patients with SRS and SRS-like phenotypes. J Med Genet 2009;46:192-7.
12. Price SM, Stanhope R, Garrett C, Preece MA, Trembath RC. The spectrum of Silver-Russell syndrome: A clinical and molecular genetic study and new diagnostic criteria. J Med Genet 1999;36:837-42.

How to cite this article: Varma SN, Varma BR. Clinical spectrum of silver - Russell syndrome. Contemp Clin Dent 2013;4:363-5.

Source of Support: Nil. **Conflict of Interest:** None declared.