

# A Case Report of Silver-Russell Syndrome in Iran

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**Objectives** Silver-Russell syndrome (SRS) is a rare genetic disorder which is typically characterized by prenatal and postnatal growth failure and asymmetry in the size of the two halves or other parts of the body. Herein, we report accurate diagnosis and management of a patient with SRS.

**Case** Our patient was a 9-year-old boy with short stature and dysmorphic facial profile. The patient was diagnosed with SRS based on clinical and radiographic features such as short stature, triangular face, mandibular hypoplasia and clinodactyly. He was under growth hormone therapy since birth. The orthodontic treatment plan was space management for permanent teeth and growth modification to accelerate mandibular growth potential.

**Conclusion** Early diagnosis and treatment are very important for SRS patients. Growth hormone therapy is often prescribed. It is necessary to persuade these patients to undergo early orthodontic intervention and comply with the follow-up protocol.

**Keywords** Silver-Russell Syndrome; Dwarfism; Fetal Growth Retardation

## Introduction

Silver-Russell syndrome (SRS) which is also named as asymmetry dwarf-dysgenesis syndrome<sup>1</sup>, is defined as “a distinct syndromic growth disorder in which prenatal and postnatal growth failure are concomitant with other characteristic features, including relative macrocephaly at birth, protruding forehead in the early life, body asymmetry and considerable feeding difficulties”<sup>2</sup>.

Silver and Russell were the first to describe a syndrome of intrauterine dwarfism distinguishable at birth. Silver et al. (1953)<sup>3</sup> described two children with congenital hemi-hypertrophy, low birth weight, short stature and increased urinary gonadotropins. Russell (1954)<sup>4</sup>, however, reported five children with intrauterine growth retardation and anomalies of the skull and face. Even as both the authors thought they were describing two different conditions, the two phenotypes were later recognized as a single entity and the disease was thus categorized as SRS, using both their names. The occurrence of SRS ranges from 1 in 3000 to 1 in 100,000 live births.<sup>5</sup> The disease equally affects all races<sup>6-8</sup> and both sexes.<sup>9</sup> This syndrome is almost rare and a few cases have been reported in the recent years (Table 1).

**Table 1- Recent case reports of Silver-Russell syndrome**

Author	Title	Year	County
Cecen, et al <sup>10</sup>	Silver-Russell syndrome and middle cerebral artery infarct: A case report	2014	Turkey
Nagalo, et al <sup>11</sup>	Silver-Russell syndrome with unusual clinical features: A case report	2018	Burkina Faso (West Africa)
Leszinski, et al <sup>12</sup>	A case report and review of the literature indicate that HMGA2 should be added as a disease gene for Silver-Russell syndrome	2018	Germany
Karher and Banda <sup>13</sup>	Behavioral problems in Silver-Russell syndrome – Case report	2017	Serbia
Shiraishi, et al <sup>14</sup>	Russell-Silver syndrome with cleft palate: a case report	2018	Japan

At present, the two genotypic anomalies clearly recognizable in the initial stage of the disease include loss of methylation on chromosome 11p15, imprinting the center region 1<sup>15</sup> and the maternal uni-parental chromosome 7 disomy (upd (7) mat)<sup>16</sup>.

An intrauterine challenge or stress at six or seven weeks of gestation is the Russell's hypothesis; whereas, another hypothesis reported either an end-organ unresponsiveness to growth hormone or biostructural abnormality in growth hormone molecule to be responsible. However, none of these theories have been confirmed. The etiology has yet to be entirely elucidated<sup>17</sup>. Almost all children with SRS are born small for gestational age and postnatal catch up growth is rare in most of them<sup>2</sup>.

The characteristic features described were triangular shaped face with a broad forehead, pointed small chin and a wide thin 'shark-like' mouth. Although each author emphasized rather different features, the composite features have been identified as the Russell-Silver syndrome, and efforts to separate the Silver syndrome from the Russell syndrome, depending on whether asymmetry is existing or not, have not been generally accepted<sup>18</sup>.

Clinically obvious limb asymmetry occurs in about 60% of reported patients. The musculoskeletal manifestations of SRS were studied in 25 cases. The most common manifestations were short stature (25 cases), limb-length discrepancy (23 cases), clinodactyly (19 cases), metacarpal bone and phalangeal abnormalities (13 cases), scoliosis (9 cases), foot syndactyly (5 cases), and developmental dysplasia of the hips (3 cases)<sup>19</sup>.

Because the symptoms of SRS are primarily due to the lack of growth hormone, early diagnosis and treatment of this syndrome is very important to prevent joint deformities and other growth problems. A case of SRS is reported for better understanding of the problem and to evade wrong diagnosis and management.

## Case

A 9-year-old boy with a chief complaint of crowding in his upper and lower dental arch presented to the Orthodontics Department, Shahid Beheshti University of Medical Sciences. He had non-consanguineous parents and his mother reported no complication during pregnancy. He had a younger sister who was born normally. His mother had a history of gestational diabetes, but no medication was prescribed. He was delivered via a Caesarean section at 36 weeks of gestation. At birth, he weighed 1800 g and was 40 cm tall, with the head circumference of 34 cm. His developmental milestones were somewhat delayed (sitting at 1 year and walking at 2 years). Other family members had no history of such type of illness. On physical examination, the boy was alert and cooperative. His weight was 11 kg, his head circumference was 51 cm and his height was 105 cm which was short for his age. His BMI of 9.07 kg/m<sup>2</sup> indicated that he was under weight. He had a poor appetite since childhood. Intelligence and psychomotor development were normal. He had normal speech. He was under speech therapy and physiotherapy from the age of 2.

His skull and face examination revealed triangular face with relative macrocephaly, low-set prominent ears (Figure 1) and mandibular hypoplasia and micrognathia in the profile view (Figure 2).



Figure 1-Triangular face



Figure 2- Mandibular hypoplasia

Posterior-anterior cephalometry revealed asymmetric inferior border of the mandible and mild chin deviation to the right side. Mandibular hypoplasia and high mandibular plane angle were obvious on the lateral cephalogram (Figure 3).

The hands showed bilateral clinodactyly of the fifth finger.

The toes were normal (Figure 4). His right hand was slightly taller than the left one but the length of his legs was equal (Figure 5). Both his feet were flat.



Figure 3- Lateral cephalogram



Figure 4- Clinodactyly of the fifth finger



Figure 5- Short stature and asymmetry in length of upper extremities

He had hypospadias, which is a common congenital disease of the penis with an abnormal ventral opening of the meatus of the urethra. Six operations had been performed to treat this condition.

Head magnetic resonance imaging and electroencephalography disclosed normal results. Routine investigations including blood count and urine were normal. No cytogenetic or molecular investigations were performed.

He had a history of 26 hospitalizations for a variety of reasons such as pancreatitis, pneumonia, malnutrition, asthma, hypospadias, tooth restoration, etc.

Intraoral examination revealed a highly arched palate, restored teeth, micrognathia with severe space deficiency for eruption of permanent teeth, and posterior cross bite (Figure 6). There was no hypodontia or microdontia.



**Figure 6- Severe space deficiency for eruption of permanent teeth**

He was under growth hormone therapy since birth. At the time of visit, the medications had been discontinued. The Netchine-Harison clinical scoring system (NH-CSS) is the only diagnostic scoring system for SRS which is shown in Table 2.

Table 2- Netchine-Harison clinical scoring system	
Clinical criteria	Definition
SGA (birth weight and/or birth length)	$\leq -2$ SDS* for gestational age
Postnatal growth failure	Height at $24 \pm 1$ months $\leq -2$ SDS or height $\leq -2$ SD below mid-parental target height
Relative macrocephaly at birth	Head circumference at birth $\geq 1.5$ SDS above birth weight and/or length SDS
Protruding forehead	Forehead projecting beyond the facial plane on a side view as a toddler (1–3 years)
Body asymmetry	LLD** of $\geq 0.5$ cm or arm asymmetry or LLD $< 0.5$ cm with at least two other asymmetrical body parts (one non-face)
Feeding difficulties and/or low BMI	BMI $\leq -2$ SDS at 24 months or current use of a feeding tube or cyproheptadine for appetite stimulation

\* Schedule for Deficit Syndrome

\*\* Leg length discrepancy

To ensure clinical diagnosis when all molecular testing are normal, it has been recommended that only patients that score at least four of the six criteria, including both prominent forehead and relative macrocephaly, should be diagnosed with “clinical SRS”.

Diagnosis of SRS in our patient was made based on the clinical and radiographic features by the attending pediatrician at birth. No genetic testing was performed for the patient due to the lack of ethical and rational justification.

## Discussion

### Definition and etiology

SRS is a clinically and genetically heterogeneous disorder of growth with a spectrum of further dysmorphic features. It has been reported that 7% to 10% of patients with this

syndrome have a defect in a gene called the maternal uniparental disomy on chromosome 7. Most cases occur in children whose parents have no history of the disease.<sup>5</sup> It is essential to note that no single description to date can account for the heterogeneity of the phenotypic findings.

### Features, diagnosis, and differential diagnosis

Outcomes that have been reported in over 50% of all patients with SRS are short stature, craniofacial disproportion, low birth weight, asymmetry, normal intelligence, downward curvature of the mouth (shark mouth) and clinodactyly of the fifth finger. The described patient in this report also had a short stature, clinodactyly, triangular face, and normal intelligence.

Normal intelligence is the rule in this syndrome. However, there may be some delay in the early motor milestones due to decreased muscle bulk and relatively large head.<sup>5</sup>

Major maxillofacial features that have been described are a highly arched palate, delayed tooth eruption, microdontia, hypodontia, absence of secondary teeth, blunted condyles, and crowding.<sup>20</sup> Crowding might be severe in the lower arch, with displacement of lower incisors into a lingual position. Micrognathia is common, with lack of mandibular growth, which results in a small, pointed chin and an overbite. Velopharyngeal insufficiency with or without a submucosal cleft is common in patients with 11p15 LOM SRS. Otitis media is common in young children with SRS<sup>7</sup> and seems to be improved by orthodontic treatment.<sup>21</sup>

Diagnosis of SRS remains clinical as no certain etiology or specific tests have been established. The five core clinical diagnostic criteria include:

1. Intrauterine retardation
2. Poor postnatal growth
3. Preservation of occipitofrontal circumference
4. Typical facial phenotype
5. Asymmetry specially in the extremities

Patients whose features fulfill the four of these five criteria could be diagnosed with SRS.<sup>6, 22</sup> The patient presented in this paper fulfilled all of the above-mentioned criteria.

The differential diagnosis of SRS includes other syndromes of primordial dwarfism with characteristic facial features such as Bloom syndrome, 3M with intrauterine growth retardation, Nijmegen breakage syndrome, Meier-Gorlin syndrome, Mulibreyanism, SHORT syndrome, fetal alcohol syndrome, floating harbour syndrome, IMAGe syndrome and other chromosomal, endocrine, and metabolic disturbances that would account for the short stature.<sup>23, 24</sup> To differentiate SRS from the other syndromes and conditions, the specific features of SRS should be considered. These include relative microcephaly (Table 1), prominent developmental delay or intellectual disability, absence of severe feeding difficulties and/or the presence of additional congenital anomalies, facial dysmorphism or other atypical features of SRS. The head circumference of our patient was 51 cm which is considered as macrocephaly in comparison with

its normal size. This property rules out syndromes described in Table 3. The lack of intense mental disability makes this syndrome different from many other conditions such as fetal alcohol syndrome.

**Table 3-** Diseases differentiated from SRS by microcephaly

<b>Microcephaly</b>	Bloom syndrome
	MOPD *II
	Fetal alcohol syndrome
	Nijmegen breakage syndrome
	IGF1 mutation
	IGF1R mutation or deletion
	Meier-Gorlin syndrome

\*Microcephalicosteodysplastic primordial dwarfism type II

A precise diagnosis is extremely important for management. Response to growth hormone treatment, if given, differs depending on the underlying syndromic diagnosis.<sup>2</sup> Growth hormone treatment is contraindicated in patients with chromosome breakage disorders, such as Bloom syndrome, due to the associated risk of malignancy.<sup>25</sup>

#### Management and prognosis

The management of SRS is conservative, comprising of growth hormone therapy, high calorie diet, limb lengthening/shoe lift in more severe cases,<sup>26</sup> nutritional support and physical therapy to alleviate the skeletal symptoms. The use of growth hormone was approved by the US Food and Drug Administration in 2001 in children born small for their gestational age who have not yet manifested sufficient catch-up growth at the age of 2 years; however, growth hormone therapy was started in our patient from birth and stopped at the age of five.

Recombinant human growth hormone is given daily via subcutaneous injection at a dose of 0.48 mg/kg per week.<sup>27, 28</sup> Stanhope et al. (1998) showed that growth hormone therapy caused short term growth acceleration in patients with SRS despite adequate endogenous levels of hormone.<sup>27</sup>

After treatment, the body height may increase noticeably in the first year, but decrease progressively over the years. Bone age tends to mature fast, and no finding is available on the effect of recombinant human growth hormone

treatment on the final height of SRS patients.<sup>29</sup> SRS has a comparatively good prognosis. In the absence of growth hormone therapy, the final adult height reaches 142.5 to 145 cm in males and 146.5 cm in females.<sup>21</sup> Johnson and Mokuolu reported cases of “sudden” infant deaths, while fatality is an exception rather than a rule in SRS.<sup>7</sup>

The oropharyngeal function and facial appearance can be improved by orthodontic intervention in children with SRS. Multiple orthodontic techniques such as distraction osteogenesis have been used successfully.<sup>24</sup> Currently, the most effective technique to change the V-shape maxillary arch is rapid palatal expansion.<sup>30</sup> It is recommended to develop a referral relationship with a maxillofacial team or an orthodontist experienced in caring for such patients. Precise history, and clinical and radiographic examination can be sufficient for proper diagnosis.

The orthodontic treatment plan in our patient was space management by extraction of some deciduous teeth, arch expansion and space retaining for eruption of permanent teeth. Growth modification is considered as the next step for the patient.

#### Conclusion

The necessity of early diagnosis and timely treatment is based on the SRS etiology. Since the growth hormone deficiency is the primary reason for joint deformities and other growth problems, it is essential that the syndrome is diagnosed as soon as possible and appropriate treatment is started. It is recommended to develop a referral relationship with a maxillofacial team or an orthodontist experienced in caring for such patients. Precise history, and clinical and radiographic examination can be sufficient for proper diagnosis.

#### Conflict of Interest

Non Declared ■

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