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Silver Russell Syndrome: A case report and review

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Summary

Silver–Russell syndrome (SRS) is a rare congenital genomic imprinting disorder characterized by prenatal and postnatal growth retardation, craniofacial dysmorphism, body asymmetry, and multisystem involvement. Due to marked phenotypic variability and nonspecific clinical findings, diagnosis is often challenging, particularly in the absence of molecular confirmation. Reports focusing on dental and orofacial manifestations of SRS are limited. A 6-year-old boy presented with multiple carious teeth and malocclusion. General examination revealed short stature, slender build, triangular facial appearance with frontal bossing, downturned corners of the mouth, low-set auricles, and clinodactyly of the fifth finger. Intraoral examination showed early mixed dentition, hypodontia, mandibular crowding, and deep palatal vault. Radiographic evaluation demonstrated missing permanent tooth buds, delayed skeletal maturation, clinodactyly, and characteristic craniofacial disproportion. Based on clinical and radiographic findings, a diagnosis of Silver–Russell syndrome was established. Dental management and parent counselling were done. Early recognition of the craniofacial and dental features of SRS by pediatric dentists is crucial for timely diagnosis and multidisciplinary management, which can significantly improve functional outcomes and quality of life.

Keywords: *Genomic Imprinting, Genotype-Phenotype Correlation, Silver-Russell Syndrome (SRS)c*

Introduction

Silver-Russell syndrome (SRS) is a well-described congenital genomic imprinting disorder, which is clinically represented by severe prenatal and postnatal growth alterations, craniofacial dysmorphia, notable asymmetry seen in face, body, and limbs, metabolic, endocrinological, and neurological issues. It is a rarely seen genetic condition with an estimated prevalence of 1/100,000[1,2]. Most cases are sporadic without any familial background[3]. Nonetheless, there have been documented occurrences of X-linked, autosomal recessive, or autosomal dominant inheritance patterns connected to assisted reproductive technologies. Molecular etiology can be found in over 60% of instances with SRS[3]. The etiopathogenesis primarily responsible included hypomethylation of the paternal allele at the ICR 1 in 50 % of

cases[4]. The oral manifestations include microdontia, congenitally missing lateral incisors and second premolars, occurrence of deciduous double molars, and more frequently seen is crowding of teeth in the mandibular arch[5]. As most of these symptoms are nonspecific, diagnosing SRS can be challenging as each patient's level of illness differs greatly[2]. The clinical spectrum varies tremendously for very severe SRS phenotype to individuals with very mild features presenting only asymmetry or hemihypoplasia. As a result, the clinical diagnosis of SRS is not always easy and depends on the experience of the clinician. As the patient ages, the appearances of the patient tend to diminish, making it challenging to identify in older children and adults. To correctly diagnose the case of SRS, numerous scoring systems had been used[6]. Many research groups have proposed clinical characteristic score methods for SRS clinical diagnosis and/or identification of prospective patients for genetic testing. Unfortunately, no widely accepted clinical scoring system has been established[7].

We have limited information in dental literature regarding the management of orofacial deformities of patients with SRS. Its management is based on symptomatic treatment, growth hormone use, and/or bone lengthening surgery in the hope of relieving the psychological suffering of patients[8]. Therefore this case is reported wherein the diagnosis of SRS was made based on clinical signs. In this article we also discuss various clinical features and etiopathogenetic etiology of this rare syndrome.

Case presentation

A 6-year-old child presented to the department of Pediatric and Preventive Dentistry with the major concern of several carious teeth and malocclusion. On physical examination, the boy was alert and cooperative and demonstrated low stature and slender build. The child also had a small triangular shaped face, with broad frontal part of cranium and downturned corners of the lips. The child had also presented with auricle that are positioned slightly lower than the normal position (Figure 1a) No abnormalities in feet and limbs were reported (Figure 1b). The examination of the hands showed the presence of clinodactyly and finger webbing. The fifth finger had an inward curvature (Figure 1c).

Figure 1a: Frontal view; 1b: Extraoral view; 1c: Hands showing inward curvature of fifth finger

The parent also reported that the child had slower developmental milestones. No abnormalities were reported regarding the hearing ability of the child and in the tone of the voice. From the birth history, it was reported that the patient had a low birth weight measuring 1.5 kg. According to the child's mother, as no other abnormalities were detected other than the low birth weight, there was no history of hospitalization. No familial history of Silver Russell Syndrome was reported.

The child displayed normal level of intelligence and psychomotor development according to his age.

Oral examination

An intraoral evaluation revealed an early mixed dentition with multiple carious and some restored primary teeth. Left maxillary first permanent molars had erupted. We also noted discrepancy between the arch length and tooth size in mandibular arch along with deep vault palatal arch. It was also noted that 74 and 84 were missing due to exfoliation/extraction. Due to high caries index of the patient, there was root stump of 54. The patient's oral hygiene was poor. Along with all these dental findings, a grade II mobile 82 and displaced 83 was observed. All the mandibular primary anterior teeth were also found to be worn out (Figure 2).

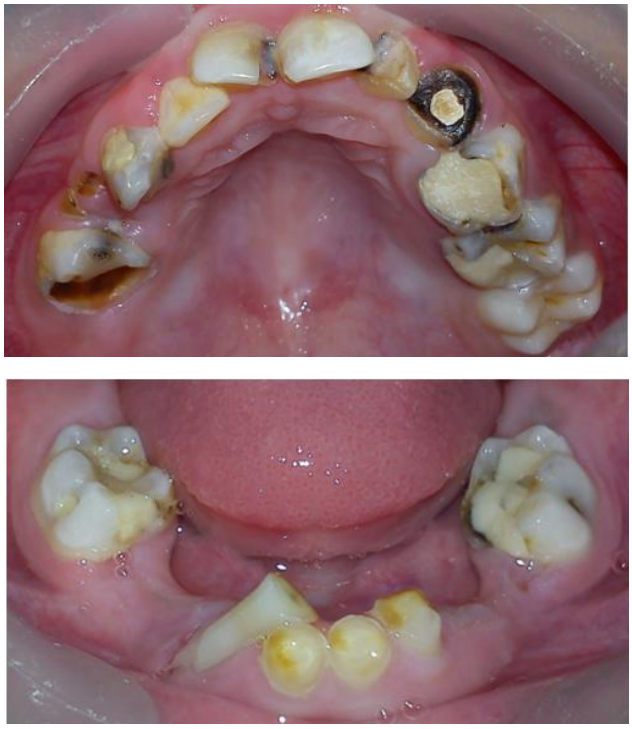
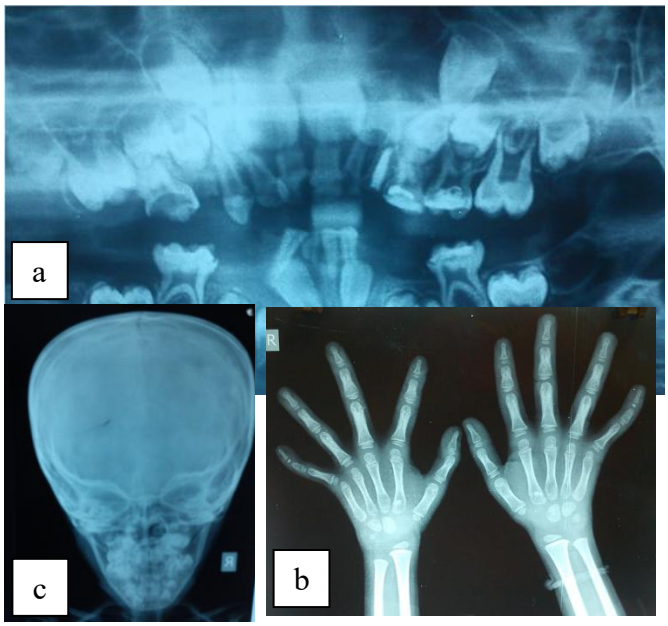


Figure 2: Intra oral view of maxillary and mandibular arche

Radiological evaluation

Radiographic evaluation involved an OPG, Hand-wrist and PA skull radiograph. From the OPG taken, we can notice that tooth germ of 42 and 32 are missing along with multiple missing primary teeth such as 84,85,72,73,75 (Figure 3a).

Figure 1a: OPG; 1b: PA Skull View demonstrating triangular shaped face; 1c: Hand



radiograph showing clinodactyly and finger webbing

The Hand wrist radiograph confirmed the presence of clinodactyly (Figure 3b). The craniofacial disproportion, and a triangle shaped face anatomy were well portrayed in the PA skull (Figure 3c).

Diagnosis and treatment planning

From clinical and radiographic findings, it was concluded that the patient has Silver Russell Syndrome (SRS). Genetic investigations were not performed as the parents were reluctant to give consent for further investigation. Glass Ionomer Cement Restoration was planned for multiple carious teeth. Topical applications of Sodium fluoride varnish were suggested every 3 months to increase the remineralizing efficiency and decrease the decalcification of teeth. The patient was suggested to have a good nutritious diet, and proper oral hygiene instructions were given to maintain good dental health. The parents were guided about the genetic condition of the patient, and they were referred for Growth Hormone (GH) Therapy.

Table1: Parameters considered in Diagnostic Criteria of SRS based on different scoring systems.

Parameters considered in various scoring systems	Scoring systems
Birth weight and/or length ≤–2 SD[a]	1-6
Height ≤–2 SD at or after 2 years of age[a]	1-6
Relative macrocephaly at birth[a]	2-6
Body, face, and/or limb asymmetry[a]	1-6
Classic facial phenotype: prominent forehead, triangular face, downturned corners of the mouth and micrognathia, or protruding forehead only[a]	1-4,6
Feeding difficulties[a]	4,6
Normal cognitive development	3
Clinodactyly	1,3
Genital anomalies (e.g., cryptorchidism, hypospadias)	3
Others (e.g., brachymesophalangy, syndactylous toes, inguinal hernia, pigmentary changes)	1

Note: *There are 6 scoring systems for SRS: 1 = Lai et al., 1994; 2 = Price et al., 1999; 3 = Bartholdi et al., 2009; 4 = Netchine et al., 2007; 5 = Dias et al., 2013, and 6 = Azzi et al., 2015, [a] Most sensitive scoring system for SRS – the so-called Netchine-Harbinson clinical scoring system.*[22]

Discussion

Clinical manifestations of Russell Silver Syndrome

Growth: The average birth weight of an infant suffering from Russell Silver Syndrome weighs below the 3rd percentile (<-2SD) even full term. Weight frequently continues to drop after delivery, straying further from the usual range. During childhood and adolescents, growth velocity for length/height remains slower than usual and there is no "catch-up" growth. At an early age, the bone ages of most RSS kids are reduced[6]. Still, it should be considered that not all patients have intrauterine growth restriction (IUGR), as it has been shown that overall, 78% of patients had a birth weight ≤-2 SD with a wide range[9].

Asymmetry: Asymmetry can affect the trunk, face, and/or limbs. Many children with RSS have asymmetrical body, which indicates that one side of their body is smaller than the other. This is caused by hemi hypotrophy (underdevelopment of one side of the body). The degree and severity of asymmetry vary greatly. Asymmetry is often evident in only one leg or arm length, however in certain instances, one full side of the body is afflicted. As a result, individuals can develop issues with balance and walking[10].

Craniofacial features: Children with the condition frequently have distinctive craniofacial characteristics, especially during infancy and early childhood. A "large-head-for-body" is an extremely prevalent observation. The term "head sparing" or "relative macrocephaly" refers to the fact that the head circumference is always much larger on the growth curve than either weight or length. This contributes to the classic triangle face shape found in children with RSS, combined with the tendency for the jaw to be tiny (micrognathia). A forehead that protrudes out when the face is viewed from the side is another typical facial feature. An unusually large forehead, which protrudes out when the face is viewed from the side, is another typical facial characteristic. Additional craniofacial characteristics linked with RSS include bluish staining of the whites of the eyes (blue sclera) during infancy, a tiny mouth, downturned angles of the mouth, and a high, narrow palatal arch. A variety of dental abnormalities have been reported including absence of teeth, abnormally small teeth (microdontia), and crowding of the

teeth[11]. Small and undeveloped jaws, a narrow chin, and a high arched mouth are further characteristics[12]. A "set back" lower jaw overbite are most frequently found. The high-arched palate and undeveloped jaws cause crowding and malocclusion[13]. Due to muscle weakness and the unique shape of the palate, these children may experience sucking and feeding difficulties. Speech and language development might also be delayed

Neurodevelopment: A lack of muscle tone (hypotonia) and unusually big heads, particularly during infancy and toddlerhood, can cause disruptions in motor development abilities. It is also typical for infants with maternal uniparental disomy of chromosome to experience difficulties in developing their speech. The overwhelming majority of infants with RSS are averagely intelligent. However, there is evidence that the various genetic subtypes of RSS differ in the incidence of learning and/or behavioral issues, including autism spectrum disorder, with a higher risk for children with mother uniparental disomy of chromosome[14].

Growth failure constitutes a significant defect from a pathophysiological standpoint. Intrauterine growth retardation, feeding difficulties, malnutrition, and postnatal stunting are typical symptoms that are present. Patients who are affected do not put on weight or grow in a manner that is appropriate and their growth is unbalanced[15]. Little hands as well as feet are typical, and the fifth finger clinodactyly. Low strength muscles and retarded motor coordination are both very frequent. Cognitive impairment may be present in some circumstances[15,16].

As the facial length is often shorter than normal and the head seems to be excessively huge, children with little triangular faces and normal head circumference tend to look dysmorphic[17,18]. Premature birth, a late skeletal age, and limb lengths that are shorter than body height are further characteristics. Camptodactyly (fixed flexion of the digits) or clinodactyly (incurving) of one or more fingers may be present in asymmetrical limbs. Another defining trait of the syndrome is the sporadic occurrence of hypoglycemia[18].

Diagnosis of Russell Silver Syndrome

For clinical diagnosis, different diagnostic scoring systems have been developed. The first diagnostic scoring system was reported by Lai et al. (1994)[14] followed by Price et al. (1999)[15]; Netchine et al. (2007)[19]; Bartholdi et al. (2009)[20]; Dias et al. (2013)[21]; Azzi et al. (2015)[22] (Table 1). The most emphasized clinical manifestations described by all of them are growth related: birth weight and/or length ≤-2 SD, height ≤-2 SD at 2 years of age or later, relative macrocephaly at least at birth except Lai et al., 1994[14], and body and/or limb asymmetry. Price et al[15] stated that to establish the presence of SRS, the individual must demonstrate the five critical criteria listed below:

1. Birth weight is less than or equal to -2 standard deviations from the population mean
2. Postnatal growth is less than or equal to SD from the mean value at diagnosis[22]
3. Maintenance of occipitofrontal head size
4. Distinctive facial characteristics
5. Asymmetry of the skeleton.

Common Radiographic Findings

Different radiographic methods such as hand wrist radiograph and cervical radiograph are being used to access the growth of a patient. In hand wrist radiography it revealed retarded skeletal maturity, normally shaped epiphyses showing uniform increase in density, with no radiologic evidence of medullary structure of the distal phalanges, short middle phalanx of the fifth finger (80%) along with clinodactyly, secondary ossification at the base of the second metacarpal[23,24].

Common Line of Treatment Protocol

Management of SRS requires a multidisciplinary approach with paediatric dentists, orthodontists, endocrinologists, gastroenterologists, dieticians, clinical geneticist, craniofacial team, orthopedic surgeon, neurologist, speech therapist, and psychologist [3]. As long as severe face deformity is not clinically evident, it is wise to maintain the patient's appearance. Moreover, in such patients there is a delay in dentofacial development, hence creating extra space in mandibular anterior regions with orthopedic therapy during the restricted normal growth period, could benefit the patient, thus avoiding any subsequent surgical intervention[25]. Prosthetic rehabilitation with removable partial dentures or dental implants is primary option of therapy in patients with hypodontia. Since these procedures require impression making, which could be troublesome in young patients. The impression trays can be customized, and proper behavior management techniques should be applied as the patient may refuse the treatment.

Growth hormone treatment serves as the initial form of therapy for a person with SRS who has not demonstrated appropriate development at the age of 2 years. The US Food and Drug Administration in 2001 approved the use of growth hormones for such patients. Recombinant human growth hormone (rhGH) is administered daily through subcutaneous injection at a dosage of 0.48 mg/kg every week. Early intervention, such as physical therapy, is advantageous, and as the child becomes older, special education classes are required [3].

Children frequently need additional dental treatment, such as fluoride therapy and assistance with oral cleanliness to achieve quality of life. Between the ages of 7 and 9, a child should see an orthodontist diagnose any dental irregularities or malocclusions and schedule any required orthodontic treatment. They may also consult with a speech therapist. Early feeding and nutritional support are especially important to address low birth weight, low muscle mass, and poor appetite. Monitoring levels of urinary ketones is usually effective in pre-empting hypoglycemia related to fasting, activity or illness [3]. The patient requires regular follow ups and early, specific, intervention for an efficient management of multiple physical and functional abnormalities.

Conclusion

Silver Russell Syndrome management requires multidisciplinary approach. There is a lack of knowledge amongst dental professionals concerning this syndrome. More awareness programs are needed to facilitate successful diagnosis and treatment.

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