Case Report

Russell–Silver Syndrome – A Case Report from Iraq

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Abstract

Russell–Silver syndrome (RSS) is an uncommon but clinically important genetic disorder defined by specific dysmorphic features such as relative macrocephaly at birth, body asymmetry, intrauterine growth restriction, and postnatal growth failure. RSS is diagnosed clinically when ≥4/6 Netchine–Harbison Clinical Scoring System criteria are met. Maternal uniparental disomy of chromosome 7 and lack of methylation of chromosome 11p15 are the most common causes of RSS. To maximize growth and developmental results, early detection and diagnosis of RSS are essential for starting appropriate therapies, such as growth hormone therapy. In this case report, we describe a 4 years and 3 months old girl from Iraq who presented with growth failure and distinct dysmorphic characteristics suggestive of RSS. We want to focus the light on the importance of clinical diagnosis for RSS (by history and physical examination) rather than depending solely on genetic testing, especially in countries where genetic diagnosis is restricted and of considerable cost.

Keywords: Clinical diagnosis, clinodactyly, growth, growth hormone, Russell–Silver syndrome

Introduction

Russell–Silver syndrome (RSS) is an uncommon but clinically important genetic disorder defined by specific dysmorphic features such as relative macrocephaly at birth, body asymmetry, intrauterine growth restriction, and postnatal growth failure. Since Russell and Silver's first 1953 description, the syndrome has come to be understood as a complicated disorder with a range of clinical presentations.[1,2] The incidence of RSS ranges from 1 in 3000 to 1 in 100,000 live births and both sexes and all races are equally affected.[2] RSS is diagnosed clinically when ≥ 4/6 Netchine–Harbison Clinical Scoring System (NH-CSS) criteria are met [Table 1]. Maternal uniparental disomy of chromosome 7 and lack of methylation of chromosome 11p15 are the most common causes of RSS.[3]

In this case report, we describe a 4 years and 3 months old girl from Iraq who presented with growth failure and distinct dysmorphic characteristics suggestive of RSS.

Case Report

A 4 years and 3 months old female child presented to the Endocrinology Department at National Diabetes Center/ Mustansiriyah University, with a history of poor height and weight gain.

Access this article online

Quick Response Code:

Website: http://www.mmjonweb.org

DOI: 10.4103/mj.mj_51_24

Other than having an extremely low appetite, she has no history of chronic medical conditions. With no maternal history of chronic illnesses, she was delivered by cesarean section at 37 weeks of gestation, weighing 1700 g at birth which is far below the fifth centile for her gestational age. The patient had mild neonatal jaundice that did not require any kind of intervention, neither a history of hypoglycemia, convulsions, or admission to the neonatal intensive care unit. However, her parents reported that she had experienced feeding difficulties in her 1st year of life, which gradually resolved as she grew older. Although her gross and fine motor skills were developing normally, they felt that she lacked intelligence and she had poor attention. The patient was the sole child of her parents who were positively consanguineous; neither the paternal nor maternal side of the family had any relatives with a similar history.

On physical examination, the girl was alert and cooperative. Her weight was 10.5 kg (−4.4 standard deviation [SD]), her

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Submitted: 20-Sep-2024 **Revised:** 02-Dec-2024 **Accepted:** 03-Dec-2024 **Published:** 19-Jun-2026

How to cite this article: Abdullah WH, Alabedi RF, Hussein MA. Russell–Silver syndrome – A case report from Iraq. Mustansiriya Med J 2026;24:75-8.

head circumference was 51 cm (+1.0 SD), her height was 88.5 cm (−3.4 SD), and her body mass index of 13.4 kg/m² (−2.0 SD), all growth measurements were plotted on CDC growth charts. Her features include a triangular face, low-set prominent ears, a large forehead with relative macrocephaly, mandibular hypoplasia, micrognathia, crowded teeth with a high arched palate, and bilateral clinodactyly in the fifth finger [Figure 1a and b]. There was no obvious asymmetry in the proportions of the body, and the toes were normal. Genitalia appeared normal. Neurological examination was uneventful.

Among differential diagnoses are chronic illnesses causing failure to thrive such as hypothyroidism and celiac disease, in addition to growth hormone deficiency (GHD). Investigations revealed normal results including complete blood picture, renal function test, general urine examination, thyroid function test, celiac screen serology, growth hormone assay, and echo study.

Table 1: Netchine–Harbison Clinical Scoring System for clinical diagnosis of Russell–Silver syndrome[3]

Clinical criteria	Definition
SGA	Birth weight and/or length ≤−2 SD for gestational age
Postnatal growth failure	At 24±1 month, height ≤−2 SD score
Relative macrocephaly at birth	At birth, head circumference was ≥1.5 SD
Prominent forehead	From a side viewpoint, the forehead protrudes beyond the facial plane
Body asymmetry	≥0.5 cm difference in leg length, arm asymmetry, or <0.5 cm difference in leg length with a minimum of two more asymmetrical body parts (one nonface)
Low BMI and/or feeding difficulties	When using a feeding tube or cyproheptadine for appetite stimulation, or when the BMI was ≤−2 SD score at 24 months

Those who fit ≥4/6 clinical criteria should be suspected of having RSS. Molecule testing is required to confirm the diagnosis in patients who exhibit a high degree of suspicion and meet at least three clinical criteria

BMI: Body mass index, SD: Standard deviation, RSS: Russell–Silver syndrome, SGA: Small for gestational age

Figure 1: (a) Clinical image of the patient with triangular facies, prominent forehead. (b) Bilateral fifth fingers clinodactyly

Bone age was 3.5 years; it is assessed by Greulich and Pyle method [Figure 2].

The following are the five main clinical diagnostic criteria for RSS: (1) intrauterine retardation; (2) poor postnatal growth; (3) preservation of occipitofrontal circumference; (4) typical facial phenotype, and (5) body asymmetry particularly in the extremities. Patients can be diagnosed with RSS if their characteristics match four of these five criteria.[2] Our patient presented in this case fulfilled four of five of the abovementioned criteria. Regarding the NH-CSS,[3] she scored 4/6 suggesting a clinical diagnosis of RSS. Still, molecular testing is the gold slander for diagnosis, unfortunately, it was expensive for the family and they cannot afford it, so we depend on the clinical diagnosis.

Recombinant GH was commenced for the indexed case under the small for gestational age license.

Discussion

RSS is a distinctive illness both genetically and clinically. Its physical characteristics are peculiar. Growth failure is the most common sign. From birth, children with RSS exhibit varying signs and symptoms, and their phenotypic characteristics range from mild to typical.[4] Molecular testing allows for the confirmation of the diagnosis in about 60% of cases; in the remaining 40%, the diagnosis remains unclear. It is possible that there are yet unidentified epigenetic reasons.[3,5]

The NH-CSS can be used to produce a "clinical RSS" diagnosis based on clinical criteria; as it is not necessary to find a molecular defect to diagnose RSS.[3] Our patient had low birth weight, poor postnatal growth, macrocephaly, prominent forehead, feeding difficulties, and clinodactyly of bilateral fifth finger. The diagnosis was made on the basis of clinical evidence.

There was no hemihypertrophy in our indexed case. About 60% of documented RSS patients have visible limb asymmetry.[2] Mahindrakar *et al*. described a 13-year-old boy who has had

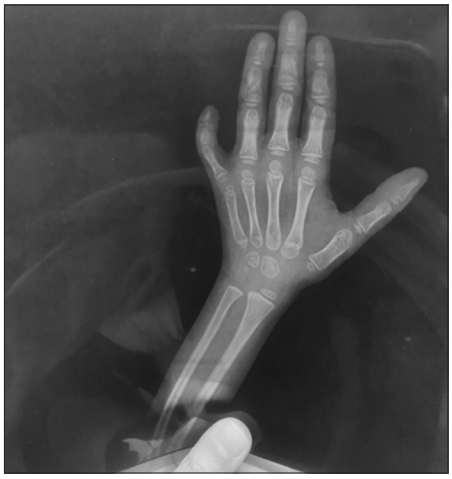

Figure 2: Left wrist and hand X-ray for bone age

hemihypertrophy of the left side of his body since birth, among other RSS characteristics.[6] The asymmetry in the length of the upper extremities was also present in another RSS patient, who was a 9-year-old kid from Iran, as described by Mahdian *et al*.[2]

A major characteristic of RSS is its short stature. Childhood growth failure is ongoing. In the absence of GH therapy, the mean final height is − 3.6 SDs below the mean for normal growing kids of the same age and gender. GHD is frequent in RSS, as are aberrations in nocturnal GH pulses.[1] The US Food and Drug Administration has approved the use of somatropin therapy for children with RSS,[7] thus even though the GH essay in our patient was normal, she is receiving GH as primary treatment. Studies have compared the effects of GHs in SGA and RSS. For example, a study by Smeets *et al*.[8] discovered that SGA and RSS children responded to GHs equally well regarding height gain.

An interesting association with RSS is hypoglycemia, which is one of the distinctive features that have not been adequately clarified.[9] Reduced body mass, which is frequently caused by low appetite and feeding issues, decreased calorie intake, and, in some children, GH insufficiency were all contributing causes to hypoglycemia in children with RSS.[10] Of the 53 children with RSS, 32% exhibited clinical symptoms suggestive of hypoglycemia, and 13% had hypoglycemia that was biochemically confirmed. Sixty-seven percent of the moms reported discomfort over their children's excessive perspiration, particularly at night.[11] In our case, the family denied any suggestive symptoms of hypoglycemia.

In patients with RSS, gastrointestinal problems such as esophagitis, reflux disease, vomiting, constipation, and failure to thrive are frequently experienced. One large study identified gastrointestinal insults including feeding disorders and/or malnutrition in 77% of infants with RSS, and 55% of children had severe gastroesophageal reflux.[12]

Oral and dental anomalies are frequent. Dental crowding, microdontia, and high-arched palate as a result of tiny mouth and relative micrognathia, all are features observed in RSS patients.[13,14] It seems that dental crowding and overbite are the most prevalent orofacial symptoms.[15]

Our patient had experienced a lack of intelligence and poor attention. Learning difficulties as well as developmental delays, such as those involving the motor, cognitive, and speech domains, are more common in children diagnosed with RSS.[16]

Furthermore, reports of males with micropenis and girls with internal genitourinary anomalies (such as Mayer–Rokitansky–Kuster–Hauser syndrome) had been made in RSS.[17] Abdominal and pelvic ultrasound in our patient was normal.

The management of RSS involves not only GH medication but also a high-calorie diet, nutritional support, and limb lengthening/shoe lifts in more severe cases. Orthodontic procedures can help children with RSS to improve their oropharyngeal function and facial appearance.[2] It is nice to encourage patients with RSS to participate in adaptive sports or special Olympics to ensure appropriate social involvement and connect families with local resources.[18]

We want by explanation of this case report to focus light on the importance of clinical diagnosis for RSS (by history and physical examination) rather than depending solely on genetic testing, especially in countries where genetic diagnosis is restricted and of considerable cost.

Conclusions

RSS is an uncommon genetic disorder characterized by intrauterine growth retardation, postnatal growth failure, and specific dysmorphic features. To maximize growth and developmental results, early detection and diagnosis of RSS are essential for starting appropriate therapies, such as GH therapy. Even in countries where genetic diagnosis is restricted, clinical diagnosis and treatment of RSS are still feasible.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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