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Growth hormone therapy in child with Russell-Silver: A case report

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Abstract
Russell-Silver syndrome (SRS) is a genetic disorder with unknown etiology; however, some clinical manifestations and diagnostic criteria have been found to diagnose SRS. Here, we report on an 8-year-old girl with short stature and failure to gain weight, who started growth hormone (GH) therapy with good response; she presented with distinctive facial features, bilateral clinodactyly of the fifth finger, and syndactyly of the 2nd and 3rd toes; there are hypo pigmented spots on her back and delay bone age.

Keywords: russell-silver syndrome, short stature, growth hormone, dimorphisms

Introduction
Russell-Silver syndrome (SRS) is a genetic disorder characterized by antenatal and postnatal growth failure [1, 2]. As stated, most cases are of unknown etiology, but about 38% were found to have hypo methylation in chromosome's 11p15's imprinting center 1. Also, 7 to 10% of patients carry a maternal uniparental disomy of chromosome7.Both genders are equally affected, with an estimated occurrence of 1 in 100,000 to 1 in 3000 [3, 4, 5]. Dysmorphic features include a triangular face, relative macrocephaly, clinodactyly of the fifth finger, syndactyly of the second and third toes, and asymmetry between the left and right sides [6, 7].
The US Food and Drug Administration (FDA) approved the use of somatropin therapy for children with SRS [8]. Several studies report that GH treatment is highly effective, along with other modalities, such as "correction of caloric intake" [9]. We present a case of SRS with the beneficial effect of GH therapy in an 8-year-old girl.

Case Report
Our case involves an 8-year-old Saudi girl born at term by first degree cousins, had small birth weight of 1.7kg and a length of 30 cm, both below the third percentile for age and sex. She was presented to the Pediatric Endocrine Clinic one year ago with parental concern about her short stature and poor weight gain, in comparison to her other siblings who were growing normally. She had no past history of chronic disease, infection, trauma, or hemorrhage. The mid-parental height was 164cm above the fifth percentile, with no family history of short stature.
On examination, her height was 108cm, weight 15kg, both below the third percentile. She had dysmorphic features: frontal bossing, a small triangular face, a depressed nasal bridge, an inverted V-shaped mouth, dental problems, bilateral clinodactyly of the fifth finger and syndactyly of the 2nd and 3rd toes. Hypo pigmented spots were also noted on her back.
Her laboratory investigation can be seen in (Table 1). Bone age was corresponded to 6.83-years-old with preserved joint spaces.
Because of GH deficiency and dysmorphic features of SRS, she was started on GH replacement therapy, a daily dose of 30mcg/kg/day with remarkable improvement in height velocity from 1 to 2cm/year to 8cm/year. She was started on a high caloric formula with multivitamins, which showed improvement in weight velocity by 4kg/year.

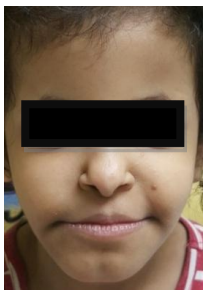
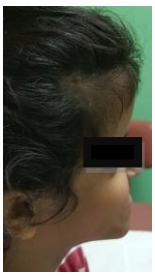


Fig 1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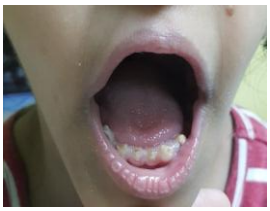
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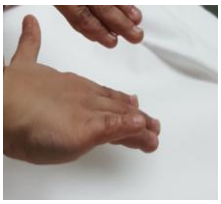
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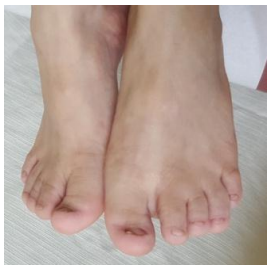
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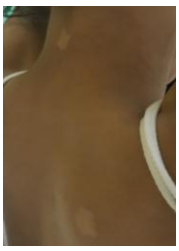
Fig 6

Discussion

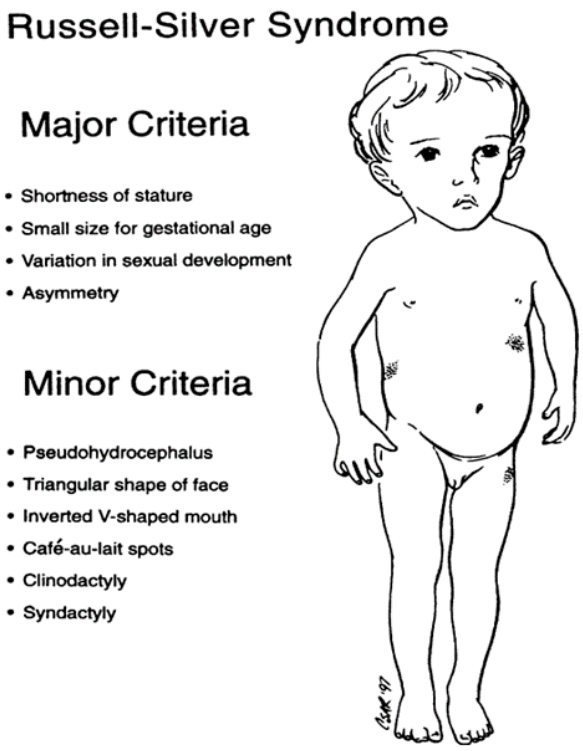

Fig 7: Adopted from Musculoskeletal Manifestations of Russell-Silver Syndrome

The clinical scenario in this case ultimately led to the diagnosis of SRS. As the study noted, SRS or "symmetry-dwarf-dysgenesis syndrome" is a genetic growth disorder with unknown etiology which is present at birth.(1) It was first reported by Silver et al. in 1953, and later by Russellin in 1954.(8) Clinical manifestations are divided into major and minor criteria in order to diagnose the syndrome (Figure 7) [10]. The diagnosis of SRS was addressed in The First International Consensus Statement of 16 members from different countries; this demonstrated that SRS is a clinical diagnosis, and should be based on the Netchine-Harbison clinical scoring system (Table2), in which its diagnosis requires four out of six criteria. Clinical features of SRS can be seen in (Table 3) [11]. Short stature and poor weight gain are apparent in our case, plus characteristic facial features were similar to other cases in the literature [6, 8, 12, 13].

In 2001, the use of GH was approved for children with SRS who were not showing adequate catch-up in growth at 2-years-old [8]. In this index case, she was started on GH therapy, showing remarkable improvement in height and weight. Several studies have found the beneficial effects of GH administration in children with SRS [14, 11, 9, 7]; a study of 26 toddlers, diagnosed with RSS at a median age of 2.9 years, showed significant growth improvement in the final height from –2.7 SDS increasing to –1.3 SDS in SRS children after 10 years of GH treatment. The shorter the patient at the start of treatment, the greater the increment in final height [15]. The first international consensus statement showed several recommendation of using GH in treating SRS such as; delay GH treatment until caloric deficits are addressed and proved that the goals of GH treatment are to improve body composition, motor development and appetite, to reduce the risk of hypoglycemia, and to optimize linear growth [11].

Table 1: Basal hormonal workup

Test	Result	Normal ranger
TSH	1.45 uIU/L	0.27-4.2 uIU/L
FT3	5.3 Pmol/L	2.8-7 Pmol/L
FT4	13.14 Pmol/L	12-22 Pmol/L
FSH	1.91	Less than 2
LH	0.284	Less than 2
Insulin like growth factor1	204	1600-6500 ng/ml
insulin like growth factor binding protein 3	4810 ng/ml	1600-6500 ng/ml

Table 2: Netchine–Harbison clinical scoring system

Clinical criteria	Definition
SGA (birth weight and/or birth length)	≤−2 SDS for gestational age
Postnatal growth failure	Height at24 ± 1 months≤−2 SDS or height≤−2 SDS below mid-parental target height
Relative macrocephaly at birth	Head circumference at birth ≥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 ≥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 ≤−2 SDS at 24 months or current use of a feeding tube or cyproheptadine for appetite stimulation

Table 3: Clinical features of Silver–Russell syndrome

Clinical feature	Frequency %
Triangular face	94%
Fifth finger clinodactyly	75%
Shoulder dimples	66%
Micrognathia	62%
Low muscle mass	56%
Excessive sweating	54%
Low-set and/or posteriorly rotated ears	49%
Down-turned mouth	48%
High pitched or squeaky voice	45%
Prominent heels	44%
Delayed closure of fontanelle	43%
Male genital abnormalities	40%
Speech delay	40%
Irregular or crowded teeth	37%
Motor delay	37%
Syndactyly of toes	30%
Hypoglycaemia	22%
Scoliosis and/or kyphosis	18%

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