CASE OF SILVER- RUSSEL SYNDROME PRESENTING WITH SHORT STATURE AND THE INFLUENCE OF GROWTH HORMONE ON GROWTH

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ABSTRACT

The Silver-Russell syndrome (SRS) is a rare inherited disorder whose pathogenesis remains controversial. The diagnosis mainly depends upon the characteristic signs, including in-utero growth retardation, postnatal short stature, relative macrocephaly, triangular facies, clinodactyly of the fifth finger and asymmetry of the body. In this case report, we focused on a patient with SRS, who came to OPD clinic with failure to thrive and delayed speech. The child presented with evident poor height and weight gain, relative macrocephaly. The specific SRS features in this patient included flat feet and clinodactyly. In the subsequent follow-up, the patient revealed a few alterations in the craniofacial anomalies, but with heightened intellectual, psychological issues and failure to gain weight/height. The treatment with growth hormone resulted into considerable increase in height and weight emphasizing that growth hormone has some beneficial effect on the growth velocity. The pediatricians in the developing countries should know the clinical diagnostic score for SRS and other congenital malformations to diagnose SRS as they are deprived of access to molecular or genetic diagnostics.

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INTRODUCTION

SRS is defined as a rare syndrome of growth disorder in which growth failure before and after birth are associated with other distinct features, including relative macrocrania at birth, frontal bossing in the early infancy, body asymmetry and significant feeding difficulties. SRS children are small for gestational age (SGA). Postnatal catch-up growth rarely occurs children with SRS[1]. Cases of "sudden" infant deaths have been reported[5]. These deaths, often carry the suspicion of infanticide, which is a common occurrence with infants having congenital malformations. This rare genetic disease ranks are estimated to affect 1–30/100,000 individuals, with a prevalence of 1–9/1,000,000 live births. Globally, only around 400 cases have been reported until date[3]. The disease equally affects all races and both the sexes[4,6]. Although adolescents and adults with Silver-Russel syndrome will be shorter than average, the syndrome does not have significant impact on life expectancy. Historically, in 1953, Silver et al first described this disease, followed by Russell in 1954[6].

Silver et al. described two children with congenital hemi-hypertrophy, low birth weight, short height and increased urinary gonadotropins. Russell [7], however, reported five children with intrauterine growth failure and anomalies of the skull and face. The two phenotypes were later identified as a single entity and the disease was thus classified as SRS, using both their names. From the perspective of heredity, transmission

is observed to be sporadic or autosomal dominant, Advances in Pediatric Research 1 Nagalo et al. 2018 [4]

At present, the two genotypic anomalies clearly recognizable in the initial stage of the disease include loss of methylation (LOM) on chromosome 11p15, imprinting the centre region 1 (ICR 1) and the maternal uniparental chromosome 7 disomy (upd(7) mat) . The 11p15 ICR1 bears the genes responsible for the growth-regulating proteins, and the LOM in this region induces characteristic growth retardation in SRS. 50% of the SRS cases have unknown etiology. The clinical diagnosis of SRS is quite difficult, as several other syndromes show similar phenotypical characteristics[8]. Finally, although as a congenital affliction, there is no cure for SRS, prevention through genetic counselling is useful in familial cases of SRS. Treatment with human growth hormone (hGH), significantly improves growth and ultimate height in IUGR cases regardless of the cause of IUGR. Growth hormone treatment is often considered for a child with SRS who has not achieved adequate catch-up growth by the age of 2 years.

CASE REPORT

The child named Mustafa born on 24. 4.13 visited the OPD for consultation at the age of 04 years with failure to gain weight and height, on 29 November, 20017. According to his medical history, he is the outcome of a normal mono-fetal pregnancy without any complications that culminated in normal delivery at term. At birth, his weight was 2k g and body length 43 cm, with the head circumference (HC) of 32 cm. Mother gave history of feeding difficulties as inadequate, slow feeding and frequent regurgitation. During the course of interrogation, it was revealed that the patient suffered from language and cognition development delay. He had delayed closure of anterior fontanel. He is a product of consanguineous marriage. His father aged 25 years, is a sales man in a grocery store and the mother is a housewife of age 22 years, G2 P1. He has one elder sister in apparently good health.

The weight and height were 9kg and 75cm well below the 3rd percentile, the mid-parental height was 164 cm or 64% height percentile. He had triangular face, frontal bossing, hypertelorism, kypho-lordosis, bilateral clinodactyly of the fifth finger and camptodactyly of the fourth right finger (Figure 3).

Both his feet were flat. No cytogenetic or molecular investigations were performed. The signs are summarized in the table. No growth hormone treatment was given initially and he was closely followed for growth velocity for 1 year. When the second examination was performed on 27 April, 2018, Mustafa was of age 5 years. The mother complained of short stature and poor weight gain despite having a good appetite. On examination, the patient weight was 9.8 kg, height 78cm and HC 50cm, indicating no significant change in the growth parameters in the last one year. The patient had strong muscles, the anterior fontanel was closed, but the craniofacial and extremities anomalies remain unchanged. There was no difference in the length of limbs. The palate was high arched and the teeth showed decay and overcrowding. The bonage was 3.5 years. At this stage we decided Growth hormone therapy subcutaneously on daily basis in a dose of 0.3mg/kg/week in divided doses on daily basis, which is still continuing and has shown desirable results in the form of gain in weight and height particularly. Now he is 7 years old grade 01 student with a height and weight of 95cm and 13.5 kg respectively (a gain of 7-8cm/year in height and 2kg/kg in weight) . The dose of growth hormone was progressively increased from 1.2units/day to 1.7 units/day because of unsatisfactory increment in height initially. Psychologically, he feels ostracized by his classmates, which has given him a complex. The changes in the height and weight before and after the growth hormone therapy are shown in the growth chart.

Summary of the phenotype of the Silver–Russell syndrome in the patient

Table 1 Summary of clinical signs of patient (case)

S. No	Clinical signs	+/-
1	Small for gestational age	+
2	Post-natal growth failure	+
3	Relative macrocephaly, frontal bossing	+
4	Body asymmetry	-
5	Feeding difficulties	+
6	Triangular face	+
7	Fifth finger clinodactyly	+
8	Microgonathia	+
9	Low muscle mass	+
10	Low set ears	+
11	Speech delay	+
12	Motor delay	+
13	Delayed closure of anterior fontanel	+
14	Irregular / crowded teeth	+
15	Syndactly of toes	-
16	Hypoglycemia	-
17	Flat foot	+
18	Kyphosis/lordosis/scoliosis	+
19	Clubbing of digits	-

Figure 1. The Silver–Russell syndrome in the patient showing the triangular face characteristic with relative macrocephaly, frontal bossing, mandibular hypoplasia and small chin.

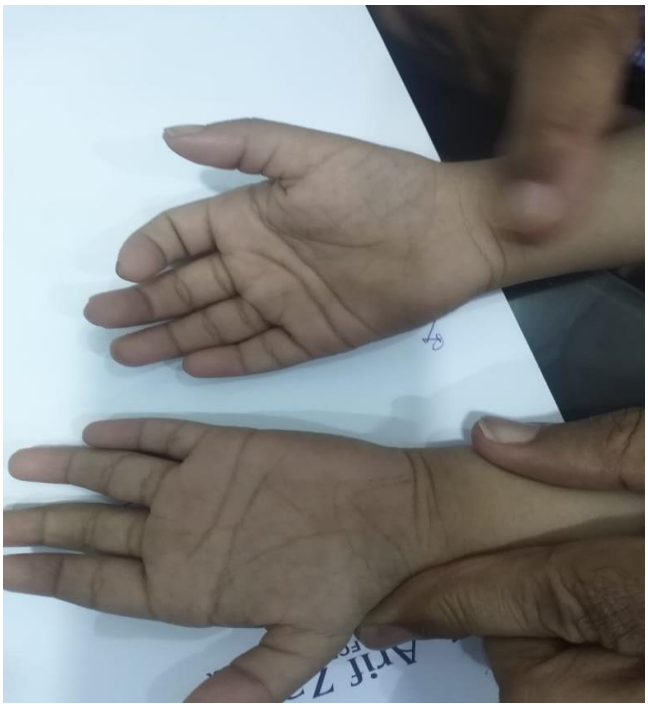

Figure 3. showing clinodactyly of fifth finger and camptodactyly fourth right finger

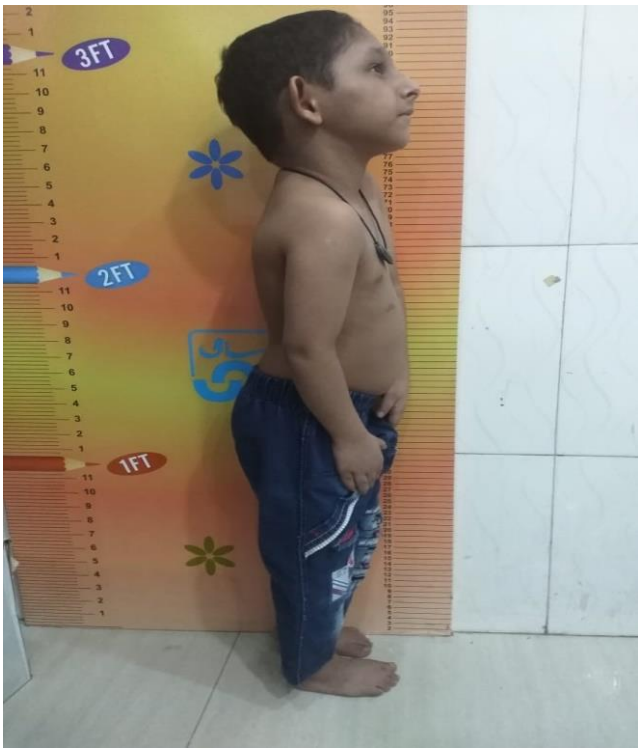

Figure 2. Mustafa at the age of 7 years showing lumbar lordosis and a height of 95cm

Figure 4. triangular face, relative macrocephaly and small face, microgonathia in SRS.

DISCUSSION

The short stature is a common complaint with which the children visit a pediatrician. Most of the children have genetic or constitutional short stature while the others have causes like hypothyroidism, hypopituitarism, IUGR, Prematurity, and syndromic causes e.g: turner syndrome, Noonan syndrome, Silver Russel syndrome, Prader willi syndrome, achondroplasia etc. Our patient had typical features of Silver Russel syndrome as summarized in table 1.

In studies carried out by Netchine, 2007[10] clinical sign frequency was: Growth birth weight ≤ -2 SD 94%, height at examination ≤ -2 SD 85%, relative macrocephaly 84.6%, body asymmetry 64%. development global retardation 23.4%, triangular facies 76%, bulging forehead 92%, micro/retrognathia 67%, dental anomalies 28-64%, down-turned corners of the mouth 50-57%, Low-set ears 40%. Other clinical sign clinodactyly 5th finger 64%, syndactyly 2/3 toes 20-23%, camptodactyly 16-25% arthrogryposis 0-1%1 café-au-lait spots 17.9%, feeding difficulties 82%, hypoglycaemia 15.4%, gastro-oesophageal reflux 12.5%, delayed closure of fontanel 36-43%, associated congenital malformations 10-36%.

To minimize the risk of over/underestimation of SRS cases and enable easier diagnosis, several clinical scores have been proposed [5, 22.] The diagnosis of the Silver-Russell syndrome was established according to the"Netchine–Harbinson clinical scoring system" (NH-CSS) NH-CSS). . The NH-CSS was proposed by Azzi et al.[19] and includes six criteria: (1) prenatal growth retardation; (2) postnatal growth retardation; (3) relative macrocephaly at birth; (4) protruding forehead; (5) body asymmetry; and (6) feeding difficulties and/or low BMI. Infrequent, uncommon, or rare anomalies may be associated with SRS, such as endocrine [23], urogenital, skin [6], heart[24], neurological[23,28,] and psychiatric [30] anomalies, besides the appearance of tumors [1,4]. When compared to other scores, NHCSS offers the advantage of high sensitivity (97.9%), low specificity (36.4%) and high negative (88.9%) and positive (76.7%) predictive values in addition to being easy to use. Molecular tests can confirm the diagnosis of SRS in around 60% of patients [20]. This means that a negative result does not exclude the diagnosis of SRS. Hence, the experts recommend that the diagnosis of SRS remains essentially clinical. We unfortunately could not collect molecular test evidence to confirm the genotype of the SRS in this patient.

SRS patients do not show the post-natal catch-up growth that occurs normally in SGA infants. They have slow growth in the initial three years of life and then it remains parallel to the groth curve but below the third percentile[3]. Abnormalities of spontaneous growth hormone secretion and inadequate responses to provocative growth hormone stimulation have been described in a considerable number of children with SRS.

Treatment with human GH has been known to significantly increase growth and final height in IUGR cases irrespective of the underlying cause. Growth hormone therapy is often recommended for a child with SRS who has failed to show adequate catch-up growth by the age of 2 years Treatment with growth hormone has benefited children with SRS, even in the absence of growth hormone deficiency including cosiderable growth acceleration and better final height and persistent normal growth rate after the cessation of growth hormone therapy[33]. A recent study of final height in 26 children with SRS treated with long term growth hormone (median 9.8 years) showed a substantial improvement in growth with a ultimate height of -1.3 SDS. A greater increase in final height was observed in children with lower heights at begining of treatment [18]. We started treating our patient with growth hormone at the age of about 4 years and increased the dose of growth hormone after noticing poor response to initial doses. The height increased by about 17cm in 03 years.

If treatment with growth hormones is not administered, the final adult height gets reduced to 142.5–145 cm in males and 146.5 cm in females [20]

CONCLUSION

As established in the above case presentation, GH treatment has a considerable impact on improving the ultimate growth outcome. There was a significant improvement noted in height which clearly endorses the use of rhGH therapy in children with SRS and other disorders of short stature even in the absence of GHD. Assessment of RSS children for GHD must be done since it frequently accompanies SRS and based on adequate evidence, it can be treated with rHGH.

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