Case Report with Review of Literature

Russell Silver syndrome: A perspective on growth and the influence of growth hormone therapy

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ABSTRACT

A 6 years male child was referred to our Endocrinology clinic with complaints of failure to thrive and he displayed the characteristic features of Russell Silver Syndrome which included short stature, relative macrocephaly, triangular facies and bilateral clinodactyly. He had a birth weight of 2.14 kg and an expected target height of 170 cm. He was subjected to a hormonal analysis which revealed a normal thyroid profile, but low serum markers of growth namely IGF-1=68 ng/ml (52-297 ng/ml) and basal growth hormone (GH) (1.5 µg/l). No defects were detected on MRI of the sella. Therefore a growth hormone stimulation test with Clonidine was performed which confirmed complete GH deficiency (at 0 min=0.16 µg/l, 60 min=0.27 µg/l, 120 min=4.73 µg/l). He was commenced on rhGH therapy at 8 years of age (height=102 cm, SDS=-4.53), due to financial restraints. Following initiation of GH therapy (1.5 IU/day) for 19 months, a height gain of 15 cm was obtained (Height=117 cm, SDS=-3.05). Bone age at 9 yr. was between 7-8 years.

Key words: Growth hormone therapy, Russell Silver syndrome, short stature

Introduction

Russell Silver Syndrome (RSS) is a heterogenous syndrome, characterized by intrauterine and postnatal growth retardation with relative macrocephaly (sparing of cranial growth), triangular face, bilateral clinodactyly, congenital body asymmetry and feeding difficulties [Figures 1 and 2]. It is a rare genetic cause of syndromic short stature which is occasionally associated with growth hormone deficiency [Figures 3 and 4].

Genetic pathogenesis

The clinical manifestations of RSS are accounted for by abnormalities in genomic imprinting. Epigenetics refers to chromatin modifications, which do not affect the DNA sequence itself, resulting in the regulation of gene expression. Epigenetic changes are crucial for development (allowing the differentiation of different cell types), as well as for X-chromosome inactivation and genomic imprinting. These epigenetic alterations contribute to the phenomenon of genomic imprinting wherein a certain cluster of genes undergo methylation resulting in differentially methylated regions (DMR's) also referred to as Imprinting control regions (ICR's). These imprinted genes are responsible for the synchronized regulation of gene expression and hence play pivotal roles in fetal and placental growth. Paternally expressed genes enhance growth whereas maternally expressed genes restrain growth. Imprinting errors in RSS involve mainly imprinting centers situated on chromosomes 7 and 11p15. Maternal Uniparental Disomy of chromosome 7 (mUPD7) accounts for 7-10% of these cases. Human chromosome 11p15 contains a cluster of imprinted genes that includes paternally expressed genes (IGF2 and KCNQ1OT1) and maternally expressed genes (such as CDKN1C and H19). Hypomethylation of IGF2/H19 which constitute IC1 (Imprinting Center 1), is responsible for 60% of RSS cases.[1]

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How Does Genomic Imprinting Contribute to Growth Retardation In RSS?

IGF-II has a fundamental role in fetal growth, being

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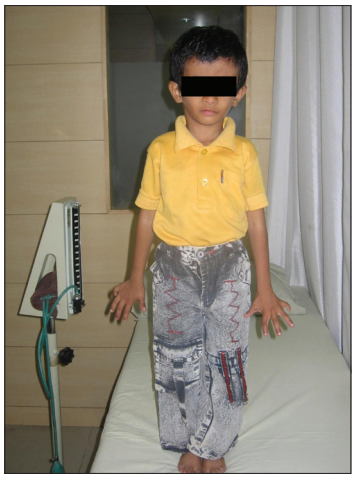

Figure 1: Phenotypic appearance portraying short stature with pseudomacrocephaly, triangular facies and body asymmetry

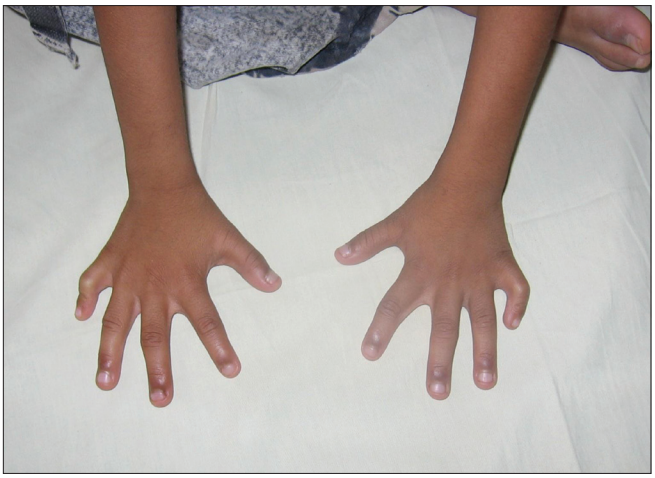

Figure 2: Bilateral fifth-finger clinodactyly

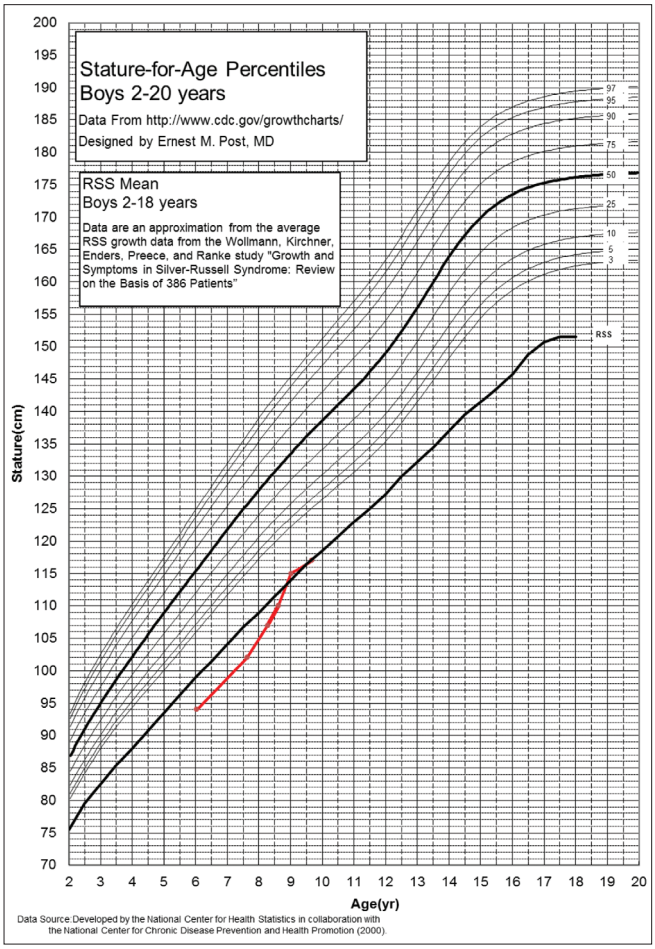

Figure 3: RSS Growth Chart of the case in review (Courtesy of The Magic Foundation) http://www.magicfoundation.org/www/docs/7.799

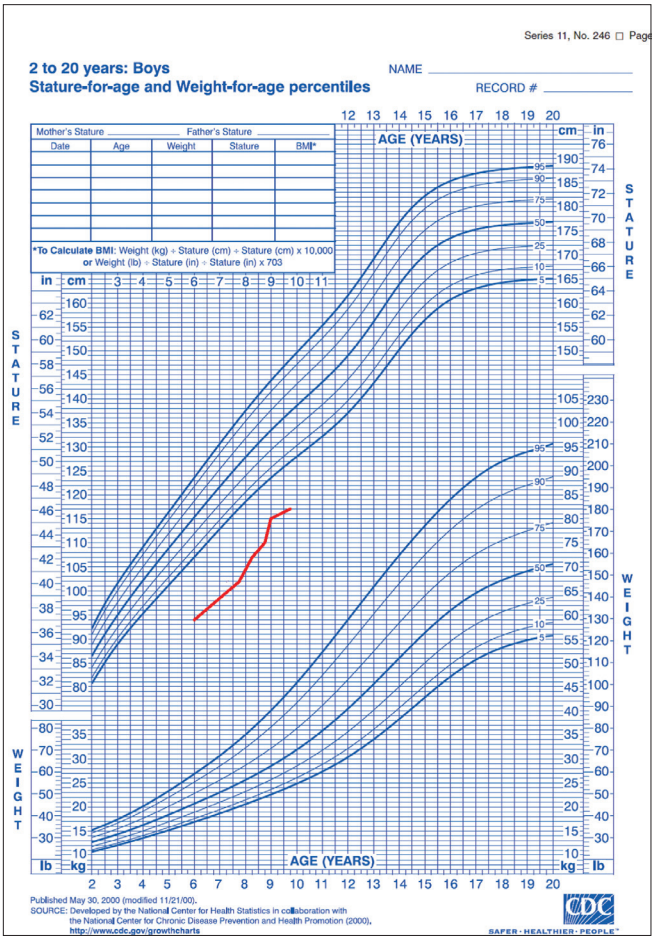

Figure 4: Growth Chart depicting the growth curve before and after rhGH replacement therapy (For the case in review)

predominantly paternally expressed in the placenta during the antenatal period. After birth, serum IGF-II is mainly produced in the liver where IGF2 imprinting is relaxed. Reduced IGF2 expression with ICR1 hypomethylation may therefore have its main effect on prenatal growth. IGF-II may also remain low in the tissues postnatally despite normal serum IGF-II levels.[2]

The growth failure associated with mUPD7 arises from altered expression of an imprinted gene (s) on chromosome 7. This could be either over-expression of a maternally expressed growth suppressor or under expression of a paternally expressed growth promoter.[2] The specific genes responsible for mUPD7 have not yet been identified.

Nature of growth in Russell Silver Syndrome

The hallmark of RSS is short stature. The birth weight of affected infants is typically two or more SD below the mean, and postnatal growth two or more SD below the mean for length or height. Growth velocity is normal in children with RSS. However, RSS patients do not experience the catch up growth that is normally seen in SGA infants. The growth in the first three years of life is slow, and from this point on it remains parallel to the curve but below the third percentile.[3] The average adult height attained, without GH therapy, is 151.2 cm (-7.8 SD) in males and 139.9 cm (-9 SD) in females.[4] They also have characteristics of abnormal growth hormone pulsatility, absence of catch-down growth after growth hormone therapy and inappropriate advancement of bone age during the middle childhood years.

Abnormalities of spontaneous growth hormone secretion and subnormal responses to provocative growth hormone stimulation have been reported in a significant number of children with RSS. One possible mechanism evident from a previous study is that the IGFBP-3 increase in children with 11p15-RSS, in response to GH therapy, was more pronounced than the increase of IGF-I, indicating a disordered Co-regulation of the growth factor and its major binding protein.[5]

Impact of rhGH therapy in Russell Silver Syndrome

Human GH therapy has been known to significantly improve growth and final height in IUGR cases regardless of the underlying etiology. Growth hormone therapy is often considered for a child with RSS who has not acquired adequate catch-up growth at the age of 2 years.

In particular, children with RSS have benefited from growth hormone supplementation even in the absence of growth hormone deficiency,[6] including significant growth acceleration and improved final height[7] and continued normal growth rate after the discontinuation of growth hormone therapy.[8] A recent study of final height in 26 children with SRS treated with long term growth hormone (median 9.8 years) showed a significant improvement in growth with a final height of -1.3 SDS. A greater increment in final height was observed in those patients with lower heights at start of treatment.[9]

Interestingly, catch-up growth could also be enhanced by incrementing the dose of GH therapy.

Even when GH therapy was initiated in GH deficient children diagnosed later in life, the outcome was found to be satisfactory.[10]

Conclusion

As demonstrated in the above case presentation, GH therapy has a tremendous impact on improving the final growth outcome. There was a significant improvement noted in the SDS score for height which clearly validates the use of rhGH therapy in children with RSS and other causes of short stature even in the absence of GHD. Assessment of RSS children for GHD should thus be advocated since it is a frequent accompaniment of RSS and based on potential evidence, it can be rectified with rHGH treatment.

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