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A rare cause of short stature - A case report

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Abstract

Silver-Russell Syndrome is a rare and clinically diverse condition characterized by growth restriction and various dysmorphias. Genetic testing confirms the diagnosis in up to 60% of cases, commonly revealing hypomethylation of the imprinted control region 1 (ICR1) on chromosome 11p15. This case report presents a five-year-old girl with SRS due to a *de novo* pathogenic variant (c.100G>A p.(Gly34Ser)) in the Insulin Growth Factor-2 (IGF2) gene. Despite normal thyroid function under levothyroxine, her height consistently fell below the third percentile. Clinical exome sequencing identified the IGF2 variant on the paternal chromosome, establishing the Silver-Russell Syndrome diagnosis. The child is undergoing follow-up with levothyroxine and growth hormone treatment. This case underscores the importance of genetic testing in diagnosing and managing short stature conditions, particularly in revealing rare etiologies like IGF2 variants. The Netchine-Harison Clinical Scoring System aids in clinical diagnosis, while an interdisciplinary approach tailored to comorbidities is crucial for effective management. The prognosis for SRS is generally favorable, emphasizing the significance of genetic alterations in short stature for clinical follow-up and family genetic counseling.

Keywords: Growth hormone, IGF2, insulin growth factor-2, silver-russell syndrome, short stature

Introduction

The Silver-Russell Syndrome (SRS) is a clinically diverse condition characterized by severe intrauterine growth restriction, inadequate postnatal growth, craniofacial dysmorphias such as a triangular face with micrognathia and narrow chin and prominent forehead, body asymmetry, and numerous other minor malformations: fifth-finger clinodactyly and/or brachydactyly, delayed closure of anterior fontanelle, dental crowding, down-turned corners of the mouth, shoulder dimples, scoliosis and genitourinary anomalies. Other associated characteristics include excessive sweating, fasting hypoglycemia and speech and motor delay [1-11]. Some phenotypic features become less pronounced with growth, becoming more subtle in adolescence and adulthood [1]. It is a rare condition with an estimated incidence ranging from 1:30,000 to 1:100,000 individuals [1-3, 5-6, 9, 11].

Genetic tests enable confirmation of the clinical diagnosis in up to 60% of the patients, with hypomethylation of the imprinted control region 1 (ICR1) on chromosome 11p15 being the most observed pathogenic mechanism (35-50%). In approximately 7-10% of patients, the identified alteration is maternal uniparental disomy of chromosome 7 (mUPD7) [1-11]. In other cases, duplications, deletions, or translocations involving the imprinting centers region on chromosome 11p15.5 or chromosome 7 may be identified. More infrequently, individuals with pathogenic variants in *CDKN1C*, Insulin Growth Factor-2 (*IGF2*), among other genes, have been documented [1, 3, 6, 8-11]. The authors present a case of a child with SRS due to a *de novo* pathogenic variant in *IGF2*.

Case Description

A five-year-old girl is the first and only daughter of non-consanguineous parents. The father is in good health, while the mother has Hashimoto thyroiditis; both parents have heights within the standard range. Family members on both maternal and paternal sides exhibit short stature of unknown etiology.

The child was born at term, weighing 2890 grams (Percentile 15-50; -2 < standard deviation (SD) < 0), measuring 45.5 cm (Percentile 3, SD < -2), with a head circumference of 35 cm (Percentile 85; SD=+1)

In the neonatal screening, she was diagnosed with congenital hypothyroidism (TSH 67 mIU/L). She underwent a neck ultrasound that revealed a normal-volume thyroid and she was started on levothyroxine.

During subsequent follow-up consultations, it was noticed that the child's height was not increasing as expected. Since birth, her height has consistently fallen below the third percentile, as depicted in the growth charts (Figure 1).

On physical examination, in addition to her short stature, she presented with minor dysmorphism such as a prominent forehead, large eyes, and anteverted nostrils. Analytically, she exhibited normal thyroid function (under levothyroxine 25 mcg/day), IGF-1 at 50 ng/mL (normal range: 55-248 ng/mL), IGFBP-3 at 3.7 ug/mL (normal range: 1.1-6.5 ug/mL), negative celiac disease screening, and a clonidine stimulation test with a peak of 8.17 ng/mL (normal >7 ug/mL). Karyotype, NGS multigene panel for congenital hypothyroidism, and molecular study for hypochondroplasia were all negative.

Following a multidisciplinary discussion, it was decided to carry out a clinical exome sequencing, which identified the variant c.100G >A P. (Gly34Ser) in heterozygosity in the *IGF2* gene (NM_000612.6), classified as likely pathogenic. Genetic testing of the parents revealed that the variant occurred de novo on the paternal chromosome, establishing the diagnosis of SRS. The child continues to receive follow-up consultations with no new occurrences and is currently being treated with levothyroxine and growth hormone. Cardiac ultrasound was normal.

Discussion

Our case delineates a rare etiology of SRS, specifically an *IGF2* pathogenic variant. Current knowledge about *IGF2* is limited, making it among the least understood growth factors. Primarily expressed during the embryonic period, *IGF2* levels markedly decrease after birth. The *IGF2* gene undergoes imprinting, with expression occurring solely from the paternal allele [7-8, 10].

In the presented case, the child exhibited short stature and minor dimorphic characteristics, such as a prominent forehead. She lacked some other SRS characteristics, such as hemihypertrophy, feeding difficulties, and demonstrated positive neurodevelopmental progress.

Diagnosis relies on clinical suspicion, adherence to diagnostic criteria, and genetic testing. The Netchine-Harbison Clinical Scoring System (NH-CSS) serves as a sensitive diagnostic tool (table 1). Clinical diagnosis is established in an individual meeting at least four NH-CSS clinical criteria, with other disorders ruled out [1-6]. Approximately 40% of individuals undergoing molecular testing after scoring four of six on NH-CSS will have non diagnostic laboratory studies [1]. In our case, the child met four criteria, making SRS highly probable.

Genetic testing for SRS encompasses various available tests due to its genetic heterogeneity. Common molecular mechanisms include hypo methylation of imprinting control region 1 on chromosome 11p15 and maternal uniparental disomy of chromosome 7 [1-6, 11]. Less commonly, pathogenic variants in *IGF2* may cause SRS when present on the paternal allele [1, 7-8, 11]. In our case, a de novo pathogenic variant in the paternal allele of *IGF2* was identified as the cause of SRS.

Concerning treatment, an interdisciplinary approach is crucial, tailored to the patient's comorbidities. Notably,

lower-limb length discrepancies exceeding 2 cm require intervention, and psychological counseling may be employed as needed to address psychosocial and body image concerns [1-2, 5-6].

The use of growth hormone (GH) treatment in SRS remains a subject of discussion, as it is indicated under the "small for gestational age (SGA)" license. Some authors advocate for its use in SRS, independent of SGA status, citing benefits such as significant growth acceleration, improved final height, and sustained normal growth rate post-GH therapy discontinuation [1-3, 8-11]. In our case, considering the child's growth falling below the third percentile, GH treatment was presented to the GH committee and approved; consequently, she is currently undergoing GH treatment.

SRS prognosis is generally favorable, with a life expectancy comparable to individuals without SRS. It is a lifelong condition with manageable comorbidities [2-3]. This clinical case underscores the significance of genetic alterations in short stature, emphasizing the importance of their diagnosis for clinical follow-up, prognosis, and family genetic counseling.

Conclusion

In conclusion, this manuscript sheds light on a rare etiology of SRS by presenting a case involving a de novo pathogenic variant in the *IGF2* gene. When approaching a child with short stature, it is of primordial importance to find its etiology because depending on it, the child might be eligible for growth hormone treatment.

Declaration of Interests

The authors have no conflicts of interest to declare.

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