O MUNDO DA SAÚDE

14q24.1 DELETION: phenotypic characteristics and response to the use of recombinant human growth hormone

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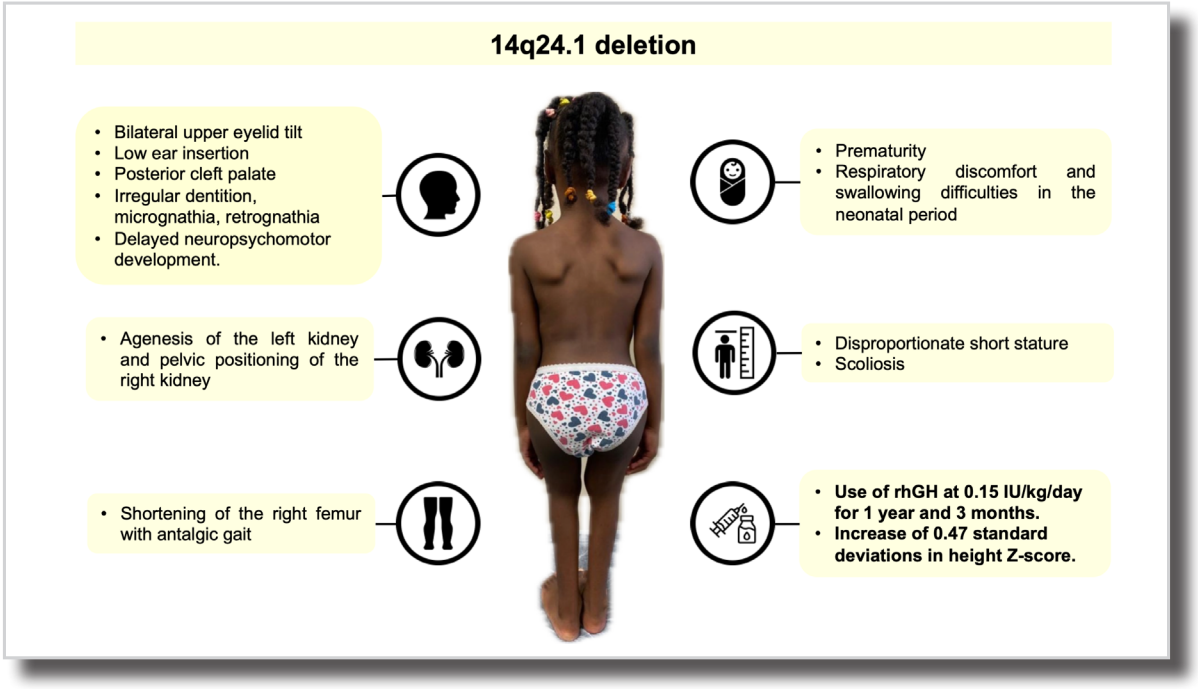
DOI: 10.15343/0104-7809.202448e15712023I

Graphic Abstract



Abstract

Structural chromosomal changes on chromosome 14 are uncommon and can lead to a diverse spectrum of clinical manifestations, including hypotonia, delayed psychomotor development, cognitive deficits, and facial dysmorphisms. The specific phenotype is influenced by the location, extent, and breakpoints of the deletion. This case report aims to detail the phenotype and genotype of a preschooler with 14q24.1 deletion, in addition to documenting the response to treatment with recombinant human growth hormone (rhGH). The patient, a premature female, born with appropriate measurements for gestational age and daughter of non-consanguineous parents, presented respiratory discomfort and swallowing difficulties in the neonatal period, requiring gastrostomy until the first year of life. Between birth and two years and six months, she presented a reduction in growth speed and disproportionate short stature. Bilateral upper eyelid tilt, low ear insertion, posterior cleft palate, irregular dentition, micrognathia, retrognathia, scoliosis, shortening of the right femur with antalgic gait, agenesis of the left kidney and pelvic positioning of the right kidney were also observed. Furthermore, the patient exhibited delayed neuropsychomotor development. Genetic analysis revealed a deletion on the long arm of chromosome 14 of approximately 231 Kb. With rhGH treatment, an improvement in growth rate and final height was observed. The clinical evolution of the case indicates that the administration of rhGH, associated with strict clinical monitoring and treatment of comorbidities, can contribute to the improvement of anthropometric parameters.

Keywords: Genetics. Chromosome 14. Growth Hormone.

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INTRODUCTION

Chromosomal deletion represents a structural change that results in the loss of genetic material, occurring due to a break in a specific region of the chromosome. This leads to the loss of genes and the consequent manifestation of a series of distinct phenotypic characteristics[1].

Deletions on chromosome 14 are rare, and the phenotype that is presented is determined by the location, size and specific point of the deletion. These characteristics often include hypotonia, delayed neuropsychomotor development, failure to thrive and facial dysmorphisms, which can significantly affect patients' quality of life[2].

Diagnostic confirmation of a deletion of chromosome 14 is achieved through advanced molecular studies, such as the SNP-array (Single Nucleotide Polymorphism array), which allows the detection of gains and losses of genetic material with a much higher resolution than that offered by conventional analysis of chromosomal karyotypes[3].

The prognosis of individuals with chromosome 14 deletion is shaped by age at diagnosis and the severity of the clinical condition, and is also influenced by the early initiation of interventions for associated comorbidities, which requires a multidisciplinary treatment strategy[4].

In cases where there is a growth deficit, therapy with somatropin, or recombinant human growth hormone (rhGH), aims to normalize the growth rate, allowing a height proportional to the patient's age and sex to be achieved, respecting their genetic potential. rhGH stimulates the synthesis of IGF-1 (insulin-like growth factor 1), promoting the proliferation of prechondrocytes, osteoblast hypertrophy and bone remodeling. Additionally, this treatment has beneficial metabolic effects, such as reducing body fat and increasing lean mass[5].

Therefore, this case report aims to describe the phenotype and genotype of a preschool-aged child with 14q24.1 deletion, as well as record his response to treatment with rhGH.

CASE REPORT

According to the clinical history, a female preschooler, from the city of São Paulo – Brazil, was born prematurely at 32 weeks of gestation and had adequate measurements for her gestational age: weight of 1.560g, length of 41cm and head circumference of 33cm. In the neonatal period, she faced respiratory distress, which resulted in a prolonged stay in the intensive care unit for 57 days. Due to generalized hypotonia and changes in swallowing, there was a need to perform a gastrostomy. This intervention was maintained until the age of one year, when it was possible to transition to full oral feeding.

Regarding family history, the parents are not consanguineous and both are under 40 years old; the patient is an only child. No cases of congenital malformations, genetic syndromes or cancer were reported in the family.

From birth to two years and six months, she developed reduced growth speed, disproportionate short stature (height Z-score -4.28 standard deviations) and body mass index within the normal range (Z-score 0.85 standard deviations). At two years and six months, on physical examination, bilateral upper eyelid tilt, low ear implantation, posterior cleft palate, irregular teeth, micrognathia and retrognathia, scoliosis and shortening of the right femur were observed - Figure 1. Despite the dysmorphisms, the patient did not present microcephaly. She had no changes in the cardiorespiratory examination or abdominal examination, and had no palpable masses or visceromegaly. Due to the shorte-

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ning of her lower limbs, she had an antalgic gait without other joint changes. Furthermore, the patient had isolated premature thelarche at 6 months (Tanner staging M3P1) with progressive regression of breast size and had typical female genitalia.

Regarding neuropsychomotor development, the patient exhibits a change in gait; however, there are no language changes. Moreover, a learning deficit was observed in the school environment.

Although basal levels of IGF1 (Insulin-like growth factor 1) and IGFBP3 (Insulin-like growth factor binding protein 3) were adequate for age and sex, the growth hormone stimulation test with clonidine was responsive, while the with glucagon it was not. Additionally, there was a vitamin D deficiency, which was later corrected with cholecalciferol supplementation.

On simple radiographs, the presence of coxa vara and slightly shallow acetabulum was observed, as well as accentuation of physiological lordosis, lumbar scoliosis and a medial curvature of the femur - Figure 2. Furthermore, the patient's bone age radiograph was compatible with their chronological age. Ultrasonography of the abdomen and pelvis identified the presence of a right kidney in a pelvic position and agenesis of the left kidney.

In the SNP-Array examination, through a peripheral blood sample, a pathogenic deletion of approximately 231 Kb on chromosome 14 was identified (arr[hg19] 14q24.1(68,264,139-68,495,136)x1), confirming the patient's diagnosis. It should be noted that the parents' karyotype was normal.

Considering the patient's low growth rate and significantly reduced height, as well as her non-responsiveness to the GH stimulation test with glucagon, treatment with rhGH was initiated to enhance growth and optimize final height. Treatment began at six years and eight months, with the maximum recommended daily dose of 0.15 IU/kg/day. During follow-up, no side effects or clinical complications related to therapy were observed. After one year and three months of continuous treatment, there was a satisfactory height response, with an increase of 0.47 standard deviations. During this period, no signs of pubertal advancement were detected. To date, the patient has received care from the specialties of pediatric endocrinology, medical genetics, pediatric nephrology and pediatric urology.

Figure 1 - A: shortening of the right femur, B: mild scoliosis and winged scapulae; C: arched eyebrows, bulbous nose, micrognathia and retrognathia, and irregular teeth.

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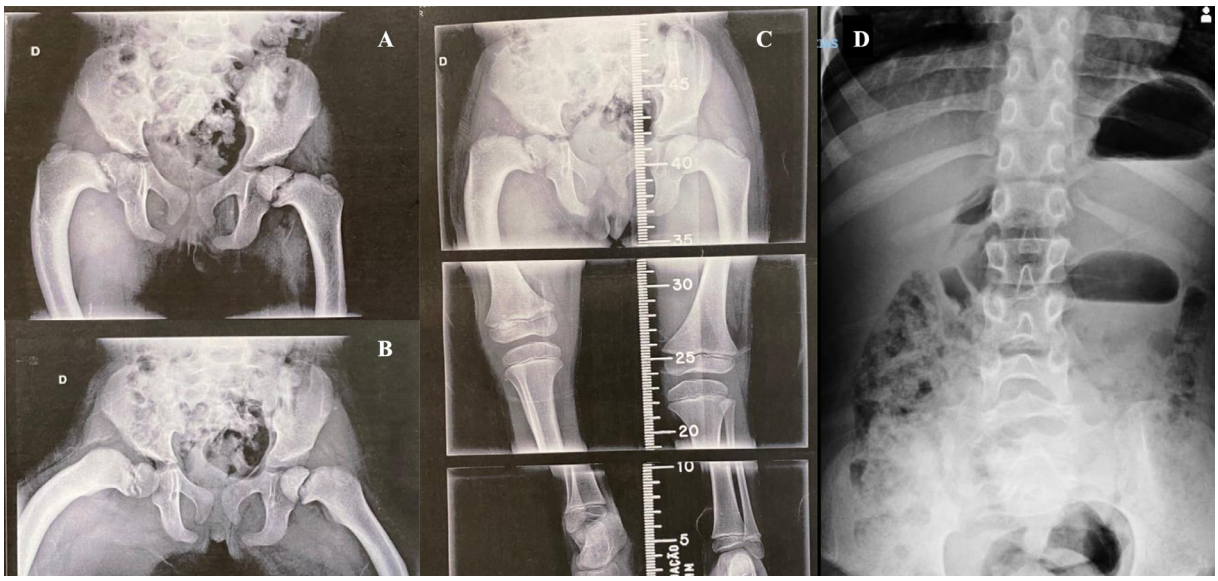

Figure 2 - A and B: Coxa varas, acetabulum discreetly shallow; C: asymmetry of the lower limbs with shortening and medial curvature of the right femur. D: mild scoliosis in the lumbar spine.

DISCUSSION

Deletion of chromosome 14 is an extremely heterogeneous condition, and this case report illustrates the phenotype associated with the location, size and point where the deletion occurs. These deletions on chromosome 14 are rare and are often associated with characteristics such as microcephaly, elongated face, muscular hypotonia, and postnatal growth retardation. Most previous case reports are associated with terminal regions of chromosome 14[6-8].

Therefore, the combination of dysmorphic facial features, disproportionate short stature with limb asymmetry and scoliosis, in addition to left renal agenesis, may be associated with the location of the deletion in the 14q24.1 region found in the patient described[2,9].

Among the various clinical manifestations, the patient had severe short stature (height Z-score -4.28). Due to significant growth deficit and low growth speed, treatment with rhGH was started at a dose of 0.15 IU/kg/day, with regular use and good patient compliance. After 15 months of treatment, the patient had a height score equivalent to -3.81, showing a gain of 0.47 standard deviations in height, without associated pubertal progression. Despite the satisfactory response to the use of the medication in the patient affected by chromosome 14 deletion, its mechanism of action still needs to be elucidated. rhGH binds to the growth hormone receptor after subcutaneous administration, activating the JAK-STAT (Janus kinase/signal transducers and activators of transcription) signaling pathway, and promoting the synthesis and release of IGF-1 in the liver and other tissues. IGF-1 stimulates cartilage cells in growth plates, increasing cell proliferation and maturation, which results in linear growth of long bones and increased height. Therefore, the height gain observed in the patient may indicate a partial deficiency or resistance to growth hormone, which was possibly overcome with treatment, given that she had baseline levels of IGF1 and IGFBP3 appropriate for her age and sex and a clonidine responsive growth hormone stimulation test[10,11].

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Furthermore, it is crucial to carefully monitor rhGH treatment to assess long-term effects and possible adverse reactions. Associations have been reported between polymorphisms at the 14q24.1 locus and an increased risk of breast cancer, as well as a case of chromosomal deletion at 14q related to acute lymphoblastic leukemia. However, the use of rhGH has not shown a significant increase in the risk of developing new neoplasms or recurrence of pre-existing oncological conditions, especially in patients with isolated GH deficiency and idiopathic short stature. Morbidity and mortality appear to be more related to the underlying pathology of treated patients than to the use of rhGH. However, additional studies are needed to reinforce the evidence on the benefits and safety of prolonged use of rhGH in individuals with chromosome 14 deletion[5,12-15].

Therefore, the interdisciplinary approach, involving specialists in pediatric endocrinology, medical genetics, pediatric nephrology and pediatric urology, is essential to ensure effective clinical management of patients with chromosome 14 deletion. This care strategy allows for early identification of complications and adjustment treatment as needed, contributing to improving patients' quality of life.

CONCLUSION

Deletion on chromosome 14 can result in a heterogeneous phenotype, including skeletal alterations that impact the height gain of patients. Regular and multidisciplinary follow-up, combined with the use of rhGH, has proven beneficial for growth velocity, thus contributing to the improvement of the quality of life of these individuals.

CRediT author statement

Conceptualization: Canedo, JVR; Colares Neto, GP. Methodology: Canedo, JVR; Colares Neto, GP. Validation: Canedo, JVR; Colares Neto, GP. Investigation: Canedo, JVR; Miguel, LP; Toda, ACS; Pontes, MF; Diniz, MJCS; Zambardino, FBG. Resources: Canedo, JVR; Miguel, LP; Toda, ACS; Pontes, MF; Diniz, MJCS; Zambardino, FBG. Writing-original draft preparation: Canedo, JVR; Miguel, LP; Toda, ACS; Pontes, MF; Diniz, MJCS; Zambardino, FBG. Writing-review and editing: Colares Neto, GP. Visualization: Canedo, JVR; Colares Neto, GP. Supervision: Colares Neto, GP. Project Administration: Colares Neto, GP.

All authors have read and agreed with the published version of the manuscript.

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Received: 08 november 2023.
Accepted: 22 april 2024.
Published: 27 june 2024.