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CASE REPORT

18q Chromosome Deletion Syndrome associated with Growth Hormone Deficiency

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Chromosome deletion, Human growth hormone, Chromosomes human pair 18.

Abstract

Introduction: The 18q Chromosome Deletion Syndrome is caused by the deletion of the long arm of chromosome 18, and its phenotype is widely variable, with associated short stature. **Case report:** preschooler, female, presented congenital cardiomyopathy, recurrent wheezing, clubfoot, and typical 18q deletion syndrome characteristics, confirmed by chromosomal analysis, depicting chromosomes 18 long arm deletion (46, XX, del (18) (q23)). She manifested severe short stature (initial stature Z score - 4,62) due to growth hormone deficiency, which improved after growth hormone treatment (current stature Z score -2,51). **Discussion:** untreated comorbidities such as congenital cardiomyopathy, orthopedic abnormalities, and steroid usage notably decrease final stature in patients affected by genetic syndromes. However, associated growth hormone deficiency must be investigated and treated to improve stature. **Conclusion:** in 18q23 deletion syndrome, early growth hormone deficiency treatment and comorbidities management increase the patients final height memorably.

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INTRODUCTION

Chromosome 18q deletion syndrome is caused by a deletion in the long arm of chromosome 18. It is a condition with various phenotypic presentations and levels of severity, depending on the location of the deletion and the genes involved. Its prevalence is 1:40,000 live births, and its etiology may be innate with karyotype or hereditary changes. Generally, there are no changes in the parents' karyotype. However, in some cases, a balanced translocation of 18q may occur, without clinical symptoms.[1]

Patients with the syndrome present global developmental delay, behavioral disorders, brain demyelination, hypotonia, hearing loss, short stature, hand and foot malformations, immunoglobulin A deficiency, craniofacial abnormalities, cardiac alterations, and growth hormone deficiency.[1-4]

Regarding growth, most patients have severe short stature with a height Z score below -3 and a low growth rate. Although growth hormone stimulation tests with clonidine or arginine may produce a normal response in some cases, 68% of the patients with the condition are prescribed somatropin, which results in improved final height.[3]

This article presents the case of a patient with 18q deletion syndrome associated with growth hormone deficiency and describes her clinical evolution with the use of somatropin.

CASE DESCRIPTION

A girl born through a cesarean section with a gestational age of 40 weeks, weighing 2,925g, and with a length of 43 cm was categorized as small for gestational age.

Clinical examination revealed she had orbital hypertelorism, low-set ears, global developmental delay, and sensorineural hearing loss. She also had congenital clubfoot, which was orthopedically repaired when the patient was one year old, followed by the use of an orthosis until she was three years old. Right genu valgum was also observed (Figure 1). At three years and four months, the patient was diagnosed with immunoglobulin A deficiency, with episodes of wheezing and atopic dermatitis, and was treated with inhaled and topical corticosteroids. Furthermore, she had symptomatic heart disease, with a 14mm atrial septal defect with hyperflow, which was surgically corrected when she was three years and six months old. The patient also had an umbilical hernia, which was repaired when she was five.

Due to the phenotypic characteristics presented, G-band karyotyping was ordered, which revealed a distal deletion in one of the chromosomes of pair 18 (46, XX, del (18) (q23)) (Figure 1). Karyotyping of the parents did not show chromosomal mutations.

When she was 3 years and 7 months old, the patient was referred to the pediatric endocrinology service for investigation of short stature. She was impubescent and had severe short stature with a Z score for height of -4.62, eutrophic with a Z score for weight of -0.66, and a Z score for body mass index of -0.56. She did not have scoliosis or limb asymmetry.

During the investigation of short stature, computed tomography scans of the head and magnetic resonance imaging of the sella turcica were ordered, which showed no anatomical changes. Her serum IGF-1 levels were within the normal range. However, the growth hormone stimulation test with clonidine showed no response (maximum GH peak of 3.92 ng/mL at 90 minutes; reference value > 5 ng/mL). Her bone age was less than her chronological age (bone age: one year and six months; chronological age: three years and 10 months). She was diagnosed with growth hormone deficiency based on clinical findings, delayed bone age, and lack of response in the growth hormone stimulation test, and was prescribed somatropin.

At the age of six years and two months, she started treatment with somatropin at a dose of 0.12 IU/kg/day or 0.039 mg/kg/day, resulting in an increase in growth rate (from 4.5 cm/year to 9.5 cm/year) and an increase in height Z score after approximately two years of treatment (from -4.35 to -2.51) (Figure 2). When she was nine years old, her bone age was in agreement with her chronological age. When this case report was being finalized, she had not shown signs of pubertal development and was on pubertal staging M1P1. In terms of global development, the patient had adequate motor development and was in the process of becoming literate.

DISCUSSION

Our patient had the typical phenotype of an individual with chromosome 18 deletion syndrome, which includes short stature aggravated by associated comorbidities, such as congenital heart disease, use of inhaled glucocorticoids for wheezing, and orthopedic alterations in the legs. Chronic diseases and environmental factors have a direct impact on growth, affecting both height and growth rate. The presence of uncorrected comorbid conditions in the first years of life contributed significantly to the patient's severe short stature (height Z score -4.62). Therefore, it is important to evaluate both intrinsic and extrinsic factors in cases of 18q23 deletion.[1,5,6]

In the present case, control of chronic diseases and surgery to repair the atrial septal defect and clubfoot were not sufficient for the patient to reach an adequate height for her age and sex. Thus, somatropin was prescribed to improve her Z score for height caused by growth hormone deficiency. After two years and 10 months of treatment with recombinant growth hormone, we saw an increase of +2.11 standard deviations (SD) in the patient's height Z score (initially -4.62 and now -2.51), a result similar to those described by Cody et al. Margaret et al. also reported a good response to somatropin, with an increase in growth rate and normalization of somatomedin C (IGF-1) levels.[3,7,8]

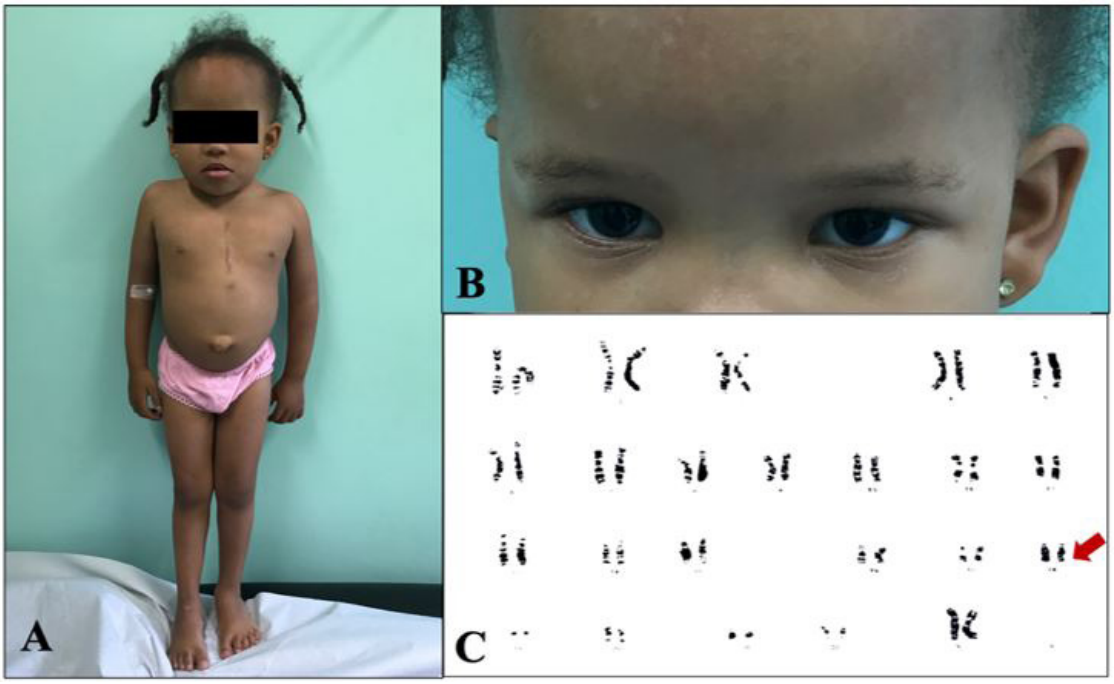

Figure 1. A: Right genu valgum; umbilical protrusion and scar in the sternal region. B) Orbital hypertelorism. C) G-banded karyogram, with the red arrow demonstrating the deletion - 46, XX, del (18) (q23).

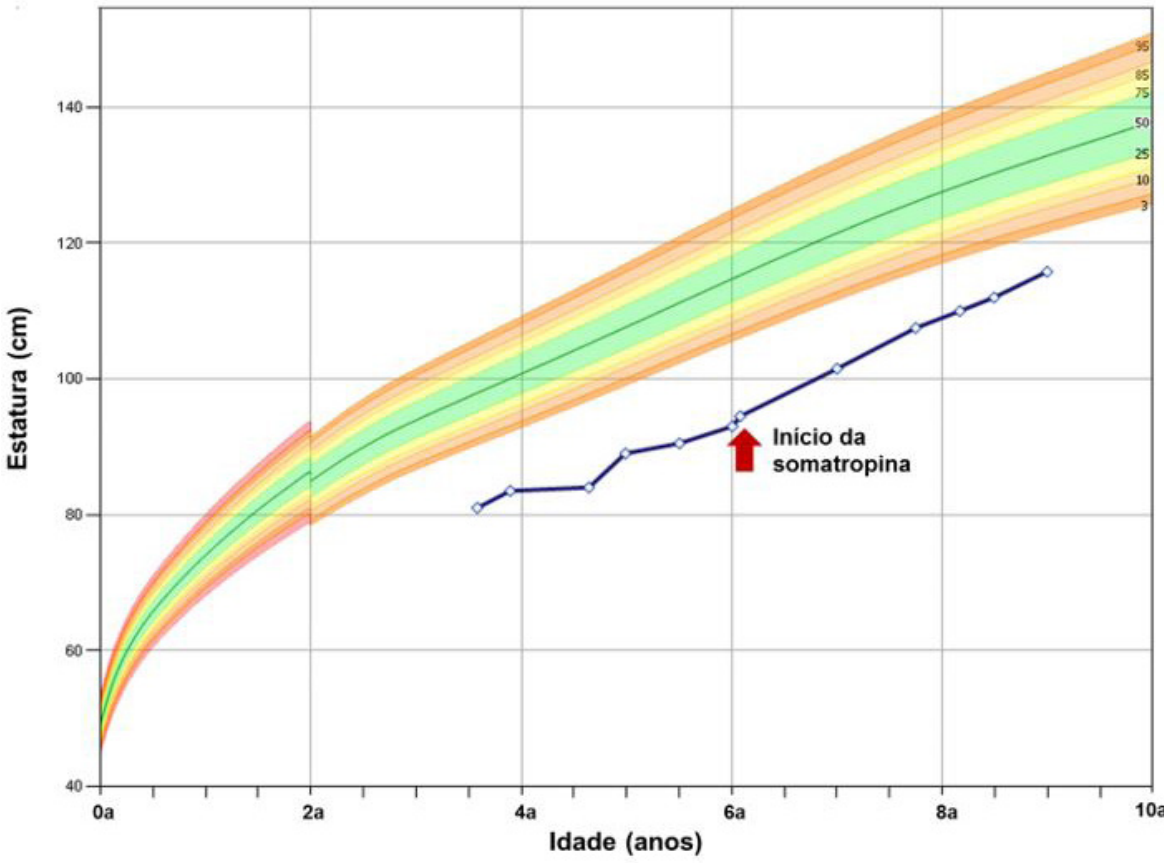

Figure 2. Growth chart from the World Health Organization, demonstrating the gain in height Z score after the start of somatropin.

Furthermore, there is a correlation between genotype and phenotype, in which distal deletions of chromosome 18 may be associated with foot deformities, global developmental delay due to hypomyelination of the central nervous system, and short stature caused by hypothalamic changes and growth hormone deficiency. This association relates to a critical region that covers 2 Mb on chromosome 18q23, between loci 71 and 73 Mb.[6] In this region, galanin receptor type 1 (GALR1) is the candidate gene for the deficiency. Galanin is a neuromodulator that stimulates the secretion of growth hormone, and the reduction in the number of receptors for galanin results in lower production and secretion of growth hormone.[9]

Our patient had global developmental delay, but her performance at school was improving gradually, as was her ability to interact with other children. Although the improvement in the associated comorbidities may have affected the myelination of the central nervous system and her global development, somatropin may also have played a role in her progress. Sartorio et al. and Cody et al. described a significant improvement in the non-verbal Intelligence Quotient of children treated with somatropin compared to untreated controls. The mechanism behind this improvement has not yet been completely understood, but somatropin or one of its mediators appears to play an important role in the development of the central nervous system and cognition.[3,10]

Despite the need for compliance with treatment and the financial burden associated with somatropin, the drug may produce a wide array of systemic improvements, which ultimately improve the patient's quality of life.

CONCLUSION

Our patient with chromosome 18q23 deletion syndrome was provided adequate follow-up, with early identification and treatment of growth hormone deficiency and management of comorbidities associated or not with her condition. These measures resulted in a significant improvement in the patient's height gain.

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