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Diagnosis and Management of Achondroplasia in Childhood: Evidence - Based Update and Case Report

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Abstract: ***Achondroplasia is the most common skeletal dysplasia, characterized by disproportionate short stature caused by a mutation in the FGFR3 gene. This alteration leads to abnormal activation of the MAPK signaling pathway, inhibiting chondrocyte proliferation and differentiation in growth plates. Achondroplasia follows an autosomal dominant inheritance pattern with complete penetrance, though most cases result from de novo variants, often linked to advanced paternal age. Globally, its prevalence varies by region, and in Colombia, although recognized as a rare disease, precise epidemiological data are not available. We present the case of a pediatric patient from Colombia diagnosed with achondroplasia through clinical, radiological, and molecular evaluation, confirming the pathogenic heterozygous c.1138G>A (p. Gly380Arg) variant in FGFR3. After identifying open growth plates, eligibility for treatment with vosoritide was established. Vosoritide is the only drug approved by the EMA and FDA to improve growth velocity in these patients. This case highlights the importance of early diagnosis, multidisciplinary management, and access to innovative treatments to enhance the quality of life of individuals with achondroplasia.***

Keywords: short stature, achondroplasia, skeletal dysplasia, FGFR3, case report

1. Introduction

Achondroplasia is the most common skeletal dysplasia and is associated with disproportionate and severe short stature (1) . Achondroplasia is caused by mutations in the Fibroblast Growth Factor Receptor Type 3 (FGFR3) gene, leading to a gain - of - function mutation that activates the MAPK signaling pathway (2) , thus inhibiting the proliferation and differentiation of chondrocytes in the growth plates (3) . The inheritance pattern is autosomal dominant, has a penetrance of 100%, and in up to 80% of cases is caused by a de novo variant which is not inherited from the parents but is highly correlated with advanced paternal age (> 35 years) (4) . If both parents are affected, their children have a 25% chance of normal height, a 50% chance of having achondroplasia (heterozygous), and a 25% chance of having homozygous achondroplasia, which is incompatible with life and causes early neonatal death (5) .

Globally, a meta - analysis estimated a prevalence of 4.6 per 100, 000 births, with significant regional variations (6) , with a prevalence of 1 in 7, 000 and 1 in 30, 000 in South America (7) , 1 in 15, 000 in Europe (8) , and in the United States, between 1 in 10, 000 and 1 in 30, 000. In Colombia, there is no prevalence of achondroplasia other than case series reports, although it is included in the list of orphan diseases (9)

Clinically it is distinguished by characteristic craniofacial features (macrocephaly, frontal prominence, hypoplasia of the central part of the face and depressed nasal bridge), disproportionate short stature with rhizomelic shortening of the arms and legs, brachydactyly, kyphosis and accentuated lumbar lordosis (10) . Clinical, radiographic and molecular findings are combined to establish its diagnosis (analysis for the classic variant 1138 of the FGFR3 gene).

Its treatment should be directed by an experienced multidisciplinary team with experience in the treatment of this type of pathology, and it is essential to carry out strict follow - up during the first two years of life since early guidance can mitigate future complications such as fixed thoracolumbar kyphosis, hearing impairment and language disorders (11) .

2. Case Report

A male patient from Barranquilla, Colombia, was born to a 28 - year - old mother during her second pregnancy. The pregnancy was adequately checked with proper prenatal care, with no maternal infections and no pathological findings on ultrasound evaluations. Delivery was performed via cesarean section at 38 weeks of gestation due to arrested labor. At birth, the patient had a proper Apgar score, weighing 3.5kg, with a length of 48 cm and a head circumference of 32 cm. During the first year of life, he showed proper psychomotor development for his age, achieving cephalic support at 3 months, rolling over at 4 months, sitting at 6 months, crawling at 10 months, and walking at 14 months. There was no significant personal or family history of pathological conditions.

At 15 months of age, he was evaluated for the first time in a pediatric clinic, where findings of short stature with rhizomelic limb shortening, macrocephaly, and frontal bossing were seen. He was referred to a geneticist, who requested a molecular analysis for common variants in the FGFR3 gene. The analysis found the heterozygous pathogenic variant c.1138G>A (p. Gly380Arg) in the FGFR3 gene, confirming the clinical suspicion of autosomal dominant achondroplasia.

A spinal X - ray revealed thoracolumbar kyphosis and vertebral morphological changes, while an X - ray of the

lower limbs showed bilateral genu varum, femorotibial shortening, and metaphyseal widening. At 3 years and 4 months of age, he was evaluated in a pediatric endocrinology clinic after a period of loss to follow - up, weighing 18 kg and measuring 81 cm in length. Given the clinical (see Fig.2), radiological, and genetic findings, a bone age assessment (see Fig.1) was promptly performed, confirming open growth plates. Based on these findings, the patient was considered a suitable candidate for vosoritide therapy, the treatment currently recommended for achondroplasia by the European Medicines Agency (EMA) and the U. S. Food and Drug Administration (FDA).

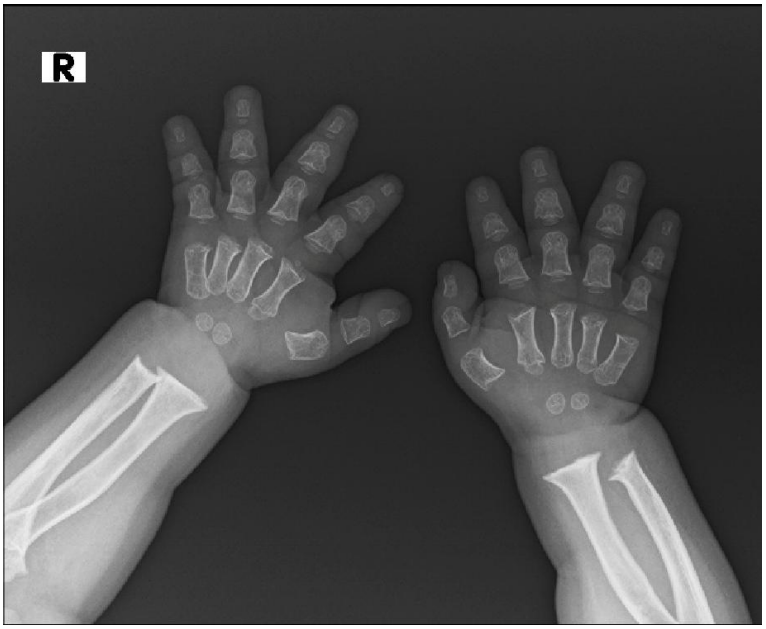

Figure 1: Hand radiographs show shortening of all phalanges and metacarpal bones bilaterally and flattening of the articular surfaces of the radius and ulna. Bilateral negative ulnar variance. Bone age of 1 year and 6 months with a chronological age of 3 years and 4 months.

Figure 2: Broad forehead, midface hypoplasia (small nasal bridge), lumbar hyperlordosis, rhizomelic shortening of limbs with redundant skin folds, genu varum (bowed legs), trident hand.

3. Discussion

Achondroplasia results from point mutation of the gene encoding the transmembrane part of fibroblast growth factor receptor 3 (FGFR3), which is a tyrosine kinase receptor that negatively regulates growth plate activity. In this disorder, the increase in FGFR3 signaling suppresses the maturation and proliferation of chondrocytes in the growth plate resulting in decreased growth plate, reduced trabecular bone volume, and delayed longitudinal bone growth (12)

Two common variants in the FGFR3 gene are responsible for most cases of achondroplasia: 1138G>A (98%) and 1138G>C (15%). Both mutations result in the substitution of glycine with arginine at amino acid 380 (p. Gly380Arg) in the transmembrane domain of FGFR3. (13) . It has an autosomal dominant inheritance pattern, however, 80% of cases are pathogenic de Novo variants, with an important risk factor being advanced paternal age, probably produced during spermatogenesis (14) . When both parents have achondroplasia, 50% of their children are at risk for achondroplasia and 25% for homozygous achondroplasia, which is potentially lethal (5) .

Mutations in the FGFR3 gene can also cause other types of skeletal dysplasia such as hypochondroplasia, thanatophoric dysplasia type I, severe achondroplasia with developmental delay, and acanthosis nigricans and thanatophoric dysplasia type II (15) .

The understanding of the genetic and molecular bases has allowed the development of new therapeutic strategies, such

as the use of C - type natriuretic peptide analogues, which antagonize the mitogen - activated kinase (MAPK) pathway descending FGFR3 and have shown promising results in assorted studies (16) .

4. Diagnosis

Prenatal Stage

Its prenatal diagnosis is complicated, since in the absence of a family history it is generally not suspected until the third trimester of pregnancy where ultrasound shows highly suggestive findings of achondroplasia: Rhizomelic shortening of the limbs, incubation of the femur and slowing of its growth (from week 26), femur length/foot length ratio <1, brachydactyly with trident hand, narrow thorax without pulmonary hypoplasia, prominent forehead, midfacial hypoplasia, flattened nasal bridge, rounded and flat iliac crests and polyhydramnios. However, in cases of high suspicion, genetic study is performed by chorionic villus biopsy from week 12 and amniocentesis from week 15 of gestation (17) . Other non - invasive ways for prenatal detection is the study of the pathogenic variant in FGFR3 in DNA of the fetus extracted from the (healthy) mother which, accompanied by ultrasound, can be a safe and cost - effective form of prenatal diagnosis (18) .

Clinical Manifestations

Patients with achondroplasia have disproportionate short stature with rhizomelic shortening of the limbs, brachydactyly, accentuated lumbar lordosis, and distinctive craniofacial features (macrocephaly, frontal protrusion, saddle nose deformity, and midface retrusion).

Limb Alterations: The limbs have a shortening that is more pronounced in the proximal segments (rhizomelic shortening) so they typically have redundant skin folds that are more noticeable in the upper limbs. The metacarpal bones are short, which makes your hands show a trident - like appearance. Knees often have varus deformities, initially due to joint laxity and later secondary to tibial bowing and peroneal overgrowth (19) .

Thoracolumbar Kifosis: It is seen from the moment of birth, however in most cases it resolves once ambulation begins, only 10 - 15% will have persistent kyphosis that will require a brace or spinal fusion (20) .

Foramen Magnum Stenosis: It is the first spinal manifestation seen in children with achondroplasia and is associated with a high mortality rate, ranging from 2 to 7.5% (21) Among its most frequent clinical manifestations are snoring and periods of sleep apnea. In other cases, dysphagia, lower cranial nerve palsy, hyperreflexia, generalized hypotonia, weakness, and clonus may be seen. On the other hand, cases of hydrocephalus have been reported in less than 5% of patients, attributable to increased venous pressure inside the skull because of stenosis in the jugular foramina (22) .

Hearing Loss: Middle ear dysfunction in patients with achondroplasia has its origin in the anatomical and functional alterations of the Eustachian tubes, which explains why most of these patients experience at least one episode of otitis media during their first year of life, and approximately 90% have it before the age of two. In addition, it is estimated that almost 50% of children with achondroplasia require the placement of ventilation tubes (VTI) in their childhood (23) . If not treated properly, these problems can lead to conductive hearing loss severe enough to interfere with language development. One cohort study reported that 40% of patients with achondroplasia have functionally relevant hearing loss (24) .

Developmental Milestone Delay: Children with achondroplasia have a delay in the appearance of developmental milestones due to their distinctive anatomical features without compromising other areas of development, so there are tools for developmental assessment for these patients validated by Ireland et al. (2012); however, it is expected that Cephalic support is achieved between 4 and 7 months of age, unaided sitting between 9 and 11 months, crawling between 9 and 10 months, and unassisted walking between 16 and 22 months of age (19) . It is recommended to measure the head circumference every 2 - 4 months in the first year of life as any excessive increase associated with neurological signs or symptoms is indicative of craniocervical compression or hydrocephalus (3) .

5. Radiographic Findings

Findings in achondroplasia are easily identifiable by a radiologist and help confirm the clinical diagnosis. Among the most common are (25) :

- Large Calvary and narrowing of the foramen magnum region
- Long, short, robust bones
- Narrow lumbar interpedicular distance
- Hypoplastic iliac wing
- Narrowing of the sacrosciatic notch
- A relatively longer fibula compared to the tibia.
- Short and narrow chest.

Treatment

Until 2021, the only approved treatment for children with achondroplasia was growth hormone, however, this therapy had no impact on final adult height and was found to only increase growth velocity in the first 24 months of treatment (26) . For this reason, various therapies have been developed aimed at the pathophysiology of achondroplasia.

Vosoritide: It is a recombinant C - type natriuretic peptide analogue indicated for patients with achondroplasia from 4 months of age, provided there is genetic confirmation of a mutation in the FGFR3 gene (27) . Its use is authorized by both the EMA and FDA and can be administered until the growth rate falls below 1.5 cm/year or until epiphyseal closure occurs (28) The recommended dose of vosoritide is 15 µg/kg administered subcutaneously once daily. So far, a randomized, placebo - controlled phase 3 clinical trial proved that treatment with Vosoritide resulted in a significant increase in growth velocity compared to placebo, and that its effects are safe and persistent over at least two years of continuous treatment. (29)

Infigratinib: Known as a drug previously used for the management of metastatic intrahepatic cholangiocarcinoma,

it is a selective inhibitor of the FGFR1 - 3 tyrosine kinase available for oral administration. So far, it has been shown to increase growth velocity in phase 3 studies in children with achondroplasia (PROPEL, PROPEL - 2 and PROPEL - 3), it has also been safe, without major safety problems, and has improved the proportion of upper and lower body segments (30) . The recommended dose is 0.25 mg/kg/day, lasting 12 - 18 months.

6. Conclusion

Early diagnosis of achondroplasia is essential for optimizing patient management and improving long - term outcomes. This case emphasizes the importance of a comprehensive, multidisciplinary approach that combines clinical assessment, imaging studies, and genetic testing to ensure diagnostic accuracy. It also highlights the critical role of early and continuous follow - up in finding potential complications and evaluating the suitability of emerging therapies such as Vosoritide, which is a promising advancement in regulating bone growth. This case report provides valuable clinical insights and underscores the importance of continued research into novel therapies that enhance prognosis and quality of life for individuals with achondroplasia.

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