Original Research Paper

Volume - 10 | Issue - 12 | December - 2020 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Nursing

ACHONDROPLASIA- CASE REPORT

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ABSTRACT Achondroplasia is a disorder of bone growth that prevents the changing of cartilage (particularly in the long bones of the arms and legs) to bone. It is characterized by dwarfism, limited range of motion at the elbows, macrocephaly, small fingers, and normal intelligence. Achondroplasia can cause health complications such as interruption of breathing , obesity, recurrent ear infections, lordosis. More serious problems include a narrowing of the spinal canal that can compress the upper part of the spinal cord and a buildup of fluid in the brain . Some people with achondroplasia may have delayed motor development , but cognition is normal. Achondroplasia is caused by mutations in the FGFR3 gene. Inheritance is autosomal dominant. Treatment may include medication with growth hormone, and surgery aimed to correct the spine, or bone problems, as well, as to reduce the pressure inside the brain in cases of hydrocephaly. Prognosis with achondroplasia is good except in cases of spinal compression at the neck.

KEYWORDS : Achondroplasia, Dwarfism, Macrocephaly

INTRODUCTION

Achondroplasia is a genetic disorder affecting bone development that results in short-limb dwarfism. It is the most common form of short-limb dwarfism, in which bone tissue does not develop properly, especially the long bones of the arms and legs. Affects about 1 in 25,000 individuals of all ethnic groups. The word achondroplasia literally means "without cartilage formation."

CAUSE

Achondroplasia is a single gene disorder caused by mutations in the FGFR3 gene on chromosome4. Inheritance is autosomal dominant

INHERITANCE

Most cases of achondroplasia are not inherited. When it is inherited, it follows an autosomal dominant pattern of inheritance. About 80% of individuals who have achondroplasia have parents with average stature and are born with the condition as a result of a new gene alteration. Each individual with achondroplasia has a 50% chance, with each pregnancy, to pass on the mutated gene.

PATHOLOGY

FGFR3 gene encodes the instructions for making a protein called fibroblast growth factor receptor 3 (FGFR3). FGFR3 protein in bone cells helps control bone growth by limiting a process called ossification, which controls the formation of bone from cartilage. The bones of embryos are made largely of cartilage, so they are soft. Ossification uses calcium to create hard, strong bone, as the child grow. When growth factors bind to the FGFR3 protein it is activated (switched on) and FGFR3 is able to regulate the process of ossification. Mutations in the FGFR3 gene lead to a change in the FGFR3 protein, specifically, the amino acid glycine is replaced with the amino acid arginine. This results in the FGFR3 protein being absent or damaged so that it cannot interact with external growth factors and therefore cannot control ossification. This results in problems during bone development where cartilage fails to turn into bone.

SYMPTOMS

Achondroplasia is characterized by short stature, short limbs, and rhizomelic disproportion, macrocephaly, and midfacial retrusion. Affected children have delayed development and often take longer to learn to sit, crawl and walk than their unaffected peers. They may also develop a curved spine and bowed legs. Those individuals reach a maximum height of 120 cm (four feet). Other characteristics are a small chest, thoracolumbar kyphosis, lumbar hyperlordosis, limited elbow extension, short fingers, and trident configuration of the hands. Patients may also show hypermobile hips and knees, bowing of the mesial segment of the legs as well as hypotonia. Adults can suffer from back and leg pain. Abnormal development of the head may result in hearing loss and infections. Affected patients experience various orthopedic and neurological complications and might face multiple medical and non-medical challenges in their daily life

DIAGNOSIS

Achondroplasia is generally diagnosed by X-ray, bone measurement during physical examination. The molecular techniques are the only available methods to confirm the diagnosis of achondroplasia. Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) technique to detect the gene mutations. Clinical and radiological features are only suggestive and not confirmatory. Prenatal diagnosis is recommended if one or both of the parents are already affected.

Prenatal Testing and Preimplantation Genetic Testing

High-risk pregnancy. A high-risk pregnancy is one in which one or both parents have achondroplasia. Once the FGFR3 pathogenic variant has been identified in the affected parent or parents, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. Noninvasive prenatal diagnosis using cell-free fetal DNA in maternal serum with high sensitivity and specificity has been reported.

Low-risk pregnancy. Routine prenatal ultrasound examination may identify short fetal limbs and raise the possibility of achondroplasia in a fetus not known to be at increased risk. Ultrasound findings of achondroplasia generally are not apparent until 24 weeks' gestation, although widening of the femoral diaphysis-metaphysis angle may allow earlier detection.

In recent years, advanced methods of diagnosing achondroplasia have also been explored. One is the use of high resolution melting (HRM), a new, rapid, and inexpensive method of molecular detection to screen for genetic mutations. HRM analysis can provide an improved approach over RFLP-PCR in terms of detecting FGFR3 mutations in patients with achondroplasia. Denaturing high performance liquid chromatography (DHPLC) is another common method to diagnose achondroplasia.

SURVIVAL

Most of those with achondroplasia will have a normal or near normal life expectancy. However, there is an increased risk for premature death related not only to sudden unexpected deaths in infancy but also, it appears, to cardiovascular complications in mid-adult life. Overall, average life span is about 10 years less than that of the general population. A recently completed study confirms that the highest standard mortality rates are in those less than 4 years of age. However, in addition, that multicenter mortality study shows that there has been a dramatic decrease in deaths, including sudden unexpected deaths, in young children with achondroplasia, most likely secondary to recognition of their special risks and aggressive evaluation and intervention related to the cranio cervical junction.

TREATMENT

There is no cure for achondroplasia. Growth hormones can help people with achondroplasia to achieve moderate growth in some children. Surgery is a treatment option in some cases to increase leg length by up to 30 cm, prevent spinal compression, or correct bowed legs. In some people with achondroplasia it may be necessary to drain fluid from the head to relieve pressure on the brain.

In the last decade, a number of new approaches have emerged, due to

the advance in the knowledge of the pathogenesis of achondroplasia and related disorders. The research is concentrated in suppressing FGFR3 signals. Among the possible treatments are included the chemical inhibition of receptor signaling, the antibody blockade of receptor activation, and the alteration of pathways that modulate the downstream propagation of FGFR3 signal.

Recent adavancements in the management of achondroplasia

An Experimental drug can encourage bone growth in children with dwarfism. Researchers report that an experimental drug called vosoritide, which interferes with certain proteins that block bone growth, allowed the average annual growth rate to increase in a study of 35 children and teenagers with achondroplasia. The patients' average boost in height to about 6 centimeters (2.4 inches) per year is close to growth rates among children of average stature, and the side effects of the drug were mostly mild, according to the researchers. Results of the four-year study are summarized online June 18 in the "New England Journal of Medicine." An increase in the annual growth rate alone may have a positive effect on some patients' quality of life. For other patients, now and in the future, the hope is that the altered bone growth throughout the body could ease the problems, such as sleep apnea, neurological and leg and back problems, and improve their quality of life. The results of the study show an impact on growth, and this effect is sustained, at least over nearly four years in this trial. The potential long-term benefit will take more time to observe.

TransCon CNP (C-type natriuretic peptide (CNP-38)) is in clinical development for the treatment of comorbidities associated with achondroplasia, single subcutaneous injections of the unconjugated CNP-38 molecule or a daily CNP-39 molecule (same amino acid sequence as Vosoritide). Genetic overexpression of C-type natriuretic peptide (CNP), a positive regulator of endochondral bone growth, prevents dwarfism in mouse models of ACH.

SURVEILLANCE

Monitor height, weight, and head circumference in childhood using growth curves standardized for achondroplasia; evaluation of developmental milestones throughout infancy and childhood using achondroplasia-specific standards; baseline neuroimaging of craniocervical junction and brain in infancy; neurologic examinations monitoring for signs of cervical myelopathy; monitor for signs and symptoms of sleep apnea; hearing evaluation as a newborn and tympanometric and behavioral audiometric evaluation by age approximately one year; monitor for middle ear problems or evidence of hearing loss in childhood; clinical assessment for kyphosis and bowed legs, with radiographic evaluation and referral to an orthopedist if necessary; in adults, clinical history and neurologic examination to screen for spinal stenosis with development of any new signs or symptoms or at least every three to five years; discuss social adjustment at each visit with primary care provider. Modification in the school and work setting to optimize function; educational support in socialization and school adjustment.

CONCLUSION

Achondroplasia is chronically debilitating. As molecular genetic techniques develop, the pathogenesis of this condition will be studied , and more effective treatments are anticipated for patients with achondroplasia . The diagnosis of achondroplasia and its consequences may influence the daily life of the entire family because they have to adapt to the child's special needs. Hence special efforts are needed to address patients' and parent's quality of life needs..

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