Case report:

Achondroplasia: “a common cause of dwarfism”

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Abstract

Achondroplasia is a common cause of dwarfism. A couple (having a height 2-2.5 feet) was complaining repeatedly for otitis. Both of them were investigated. Radiological report showed many bony deformities. Extremely deformed bony structure produces many problems in carrying out daily activities. Both of them were having Achondroplasia. Still early treatment for bony abnormalities and proper education will help these patients. With proper mental preparation and will power patient can enjoy a happy life. This couple was happy with their marital life. They have 2 sons with normal bony structure. Early detection of Achondroplasia helps the patient as well as parents to make the patient’s life less miserable. Proper treatment for the mental trauma is also an important part of the treatment.

Key words: Achondroplasia, dwarfism, otitis.

Background:

Achondroplasia is one of a group of disorders called chondrodystrophies (cartilage maldevelopment) or osteochondrodysplasias (any disorder of cartilage and bone growth).

Cause: Achondroplasia may be inherited as an autosomal dominant trait, which means that if a child gets the defective gene from one parent, the child will have the disorder. If one parent has Achondroplasia, the infant has a 50% chance of inheriting the disorder. If both parents have the condition, the infant’s chances of being affected increase to 75%.

Sporadic mutation is seen in approximately 80% of cases. The disorder itself is caused by a change in the gene for fibroblast growth factor receptor 3 (FGFR3), which causes an abnormality of cartilage formation and this leads to severely shortened bones. The prevalence is approximately 1 in 25,000. The effect is genetically dominant, with one mutant copy of the FGFR3 gene being sufficient to cause Achondroplasia, while two copies of the mutant gene are invariably fatal (recessive lethal) before or shortly after birth (known as a lethal allele). A person with Achondroplasia thus has a 50% chance of passing dwarfism to each of their offspring. People with Achondroplasia can be born to parents that do not have the condition due to spontaneous mutation. New gene mutations leading to Achondroplasia are associated with increasing paternal age (over 35 years old). Studies have demonstrated that new gene mutations for Achondroplasia are exclusively inherited from the father and occur during spermatogenesis; it is theorized that oogenesis has some regulatory mechanism that prevents the mutation occurring in females.

Males affected more frequently than females. Patients are of normal intelligence with normal motor
function. However, they may have specific neurologic deficits.

**Pathology**

The disease results from a mutation in the fibroblast growth factor gene 3 (FGFR3) located on chromosome 4p16.3 which causes abnormal cartilage formation. All bones that form by enchondral ossification are affected. Bones that form by membranous ossification are not affected, thus allowing the skull vault to develop normally.

**Presentation**

**Improporionate dwarfism**

- Shortening of the proximal(upper) limbs (called rhizomelic shortening)
- Short fingers and toes
- Large head with prominent forehead
- Small midface with a flattened nasal bridge
- Spinal kyphosis (convex curvature) or lordosis (concave curvature)
- Varus (bowleg) or valgus (knock knee) deformities
- Frequently have ear infections (due to Eustachian tube blockages), sleep apnea (which can be central or obstructive), and hydrocephalus

**Diagnosis**

Antenatally it is difficult to diagnose Achondroplasia until the 3rd trimester.

Achondroplasia can be detected before birth by the use of prenatal ultrasound. A DNA test can be performed before birth to detect homozygosity, wherein two copies of the mutant gene are inherited, a lethal condition leading to stillbirths. Clinical features include megaloecephaly, short limbs, prominent forehead, thoracolumbar kyphosis and mid-facial hypoplasia. Complications like dental malocclusion, hydrocephalus and repeated otitis media can be observed. The risk of death in infancy is increased due to the likelihood of compression of the spinal cord with or without upper airway obstruction.

**Radiographic features**

Almost all the bones of the skeleton are affected, and hence all parts of the body have bony changes with secondary soft tissue changes. Antenatally it is difficult to diagnose achondroplastic features until the 3rd trimester.

A skeletal survey is useful to confirm the diagnosis of Achondroplasia. The skull is large, with a narrow foramen magnum, and relatively small skull base. The vertebral bodies are short and flattened with relatively large intervertebral disk height, and there is congenitally narrowed spinal canal. The iliac wings are small and squared, with a narrow sciatic notch and horizontal acetabular roof. The tubular bones are short and thick with metaphyseal cupping and flaring and irregular growth plates. Fibular overgrowth is present. The hand is broad with short metacarpals and phalanges, and a trident configuration. The ribs are short with cupped anterior ends. If the radiographic features are not classic, a search for a different diagnosis should be entertained. Because of the extremely deformed bone structure, people with Achondroplasia are often "double jointed".

The diagnosis can be made by fetal ultrasound by progressive discordance between the femur length and biparietal diameter by age. The trident hand (A trident hand is a description where the hands are short with stubby fingers, with a separation between the middle and ring fingers) configuration can be seen if the fingers are fully extended.
Treatment

At present, there is no known treatment for Achondroplasia, even though the cause of the mutation in the growth factor receptor has been found. Although used by those without Achondroplasia to aid in growth, human growth hormone does not help people with Achondroplasia. However, if desired, the controversial surgery of limb-lengthening will lengthen the legs and arms of someone with Achondroplasia. But according to some, the best results appear within the first and second year of GH therapy. After the second year of GH therapy, beneficial bone growth decreases. Therefore, GH therapy is not a satisfactory long term treatment.

Gene based therapy may possibly serve as a future treatment option. BioMarin Pharmaceutical Inc. recently announced the initiation of a Phase 1 study in healthy volunteers for BMN-111, an analog of C-type Natriuretic Peptide (CNP), for the treatment of Achondroplasia. To counteract the effects caused by the activating FGFR3 mutation, BioMarin has developed a stabilized version of C-type natriuretic peptide (BMN-111), a natural human peptide that is a positive regulator of bone growth. BMN-111 binds to its own receptor which initiates intracellular signals that ultimately inhibit the overactive FGFR3 pathway. Daily subcutaneous injections of BMN-111 in mouse models of the disease have demonstrated the ability of this drug to correct the dwarf phenotype.

Fig 1. Mutations in the FGFR3 gene located on chromosome 4p16.

Fig 2. Lordosis-Lordosis is excessive curvature in the lumbar portion of the spine.

Fig 3. Scoliosis and Kyphosis.
Exams and Tests
During pregnancy, a prenatal ultrasound may show excessive amniotic fluid surrounding the unborn infant. Examination of the infant after birth shows increased front-to-back head size. There may be signs of hydrocephalus ("water on the brain").

Treatment
There is no specific treatment for Achondroplasia. Related abnormalities, including spinal stenosis and spinal cord compression, should be treated when they cause problems.

Outlook (Prognosis)
People with Achondroplasia seldom reach 5 feet in height. Intelligence is in the normal range. Infants who receive the abnormal gene from both parents do not often live beyond a few months.

When to Contact a Medical Professional
If there is a family history of Achondroplasia and you plan to have children, you may find it helpful to speak to your health care provider.

Prevention
Genetic counseling may be helpful for prospective parents when one or both have Achondroplasia. However, because Achondroplasia most often develops spontaneously, prevention is not always possible.

References


