

Recurrence of Achondroplasia

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Abstract:

Achondroplasia, a nonlethal form of chondrodysplasia, is the most common form of short-limb dwarfism. It is inherited as a mendelian autosomal dominant trait with complete penetrance. Approximately 80% of cases are due to new or de novo dominant mutations. An unusual case of recurrent Achondroplasia, in the same couple due to denovo gene mutation, as both parents were healthy and young. Diagnosis was based on prenatal ultrasound and clinical examination of the baby.

Keywords: Achondroplasia, chondrodystrophies, osteochondrodysplasias, kyphosis and lordosis.

Introduction:

Achondroplasia is a disorder of bone growth that causes the most common type of dwarfism. It is one of a group of disorders called chondrodystrophies or osteochondrodysplasias.

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%. However, most cases appear as spontaneous mutations. The prevalence is approximately 1 in 25,000¹. No documented race predilection is noted. Males and females are equally affected.

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.

Case Report:

Mrs. ABC, 24years old lady, married for last 2 years, Para 1+0, Gravida 2, presented in Gynae

OPD, at 27 weeks + 4 days gestational amenorrhea for termination of pregnancy due to Achondroplasia, diagnosed on ultrasound. It was her consanguineous marriage and her previous baby was also Achondroplastic.

In current pregnancy she was booked in a private hospital where she received her antenatal care. Her Pregnancy was confirmed by urine pregnancy test and ultrasound scan. At 25 weeks, ultrasound scan showed intra uterine growth retardation (IUGR) and Achondroplasia. She is Para 1+0 and her previous pregnancy was uneventful and had LSCS at term due to fetal distress, in a private hospital, she delivered a male child, died 5 hrs after birth. On clinical examination baby was diagnosed to have Achondroplasia but no further investigations were performed. Her past medical and surgical history was not significant. There was no history of any genetic disorders or any other congenital anomaly in the family.

As her ultrasound at 25+ weeks revealed single fetus of 25+ weeks with short limbs, short hands and fingers, macrocephaly with frontal bossing and depressed nasal bridge, diagnosed as Achondroplasia. She was advised termination of pregnancy by a private doctor and she was given

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Figure 1:

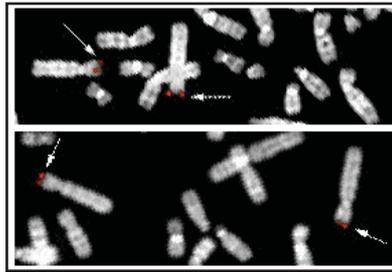


Figure 2:

Tab Misoprostol 200 micrograms orally but termination did not occur in next 3 days so she presented in Gynae OPD for further management.

On examination she was pallor, her vital signs were all normal and abdominal examination revealed height of fundus of 25 cms, fetal parts were palpable and fetal heart sounds were audible. On vaginal examination, cervical os was closed but cervix was soft, short and anteriorly placed most likely due to the effect of Tab Misoprostol cervix was ripening. She was admitted and her routine investigations were performed. Her labor was induced by Intra cervical Foley's catheter and Tab. Misoprostol, 50 micrograms given per vaginally. After eight hours, a female baby of 1 kg, delivered as breech with poor Apgar score. Baby died after 5 mins. On gross examination Achondroplasia confirmed and further radiological investigations were not performed because of family refusal and financial constraints.

Patient remained stable and discharged on second day. Couple was counseled regarding need of proper evaluation in future pregnancy.

Discussion:

Achondroplasia is a disorder of bone growth that causes the most common type of dwarfism. Achondroplasia is one of several congenital conditions with similar presentations, such as osteogenesis imperfecta, multiple epiphyseal dysplasia tarda, achondrogenesis, osteopetrosis, and thanatophoric dysplasia. This makes estimates of prevalence difficult, with changing and subjective diagnostic criteria over time.¹

Achondroplasia occurs as a sporadic mutation in approximately 85% of cases (associated with

advanced paternal age) or may be inherited in an autosomal dominant genetic disorder that is a common cause of dwarfism. However, the mutation can also be completely spontaneous even when neither of the parents of the child are affected with the gene. If both parents of a child have Achondroplasia, and both parents pass on the mutant gene, then it is very unlikely that the homozygous child will live past a few months of its life.²

The disorder itself is caused by a change in the DNA for fibroblast growth factor receptor 3 which causes an abnormality of cartilage formation. Achondroplastic dwarfs have short stature, with an average adult height of 131 cm (4 feet, 3½ inches) for males and 123 cm (4 feet, ½ inch) for females. The prevalence is approximately 1 in 25,000.¹

The disease is related to a mutation in the fibroblast growth factor receptor-3 (FGFR3) gene encoding one member of the FGFR subfamily of tyrosine kinase receptors, which results in constitutive activation of the receptor. FGFR3 is a negative regulator of chondrocytes proliferation and differentiation in growth plate. This mutation induces a disturbance of endochondral bone formation.^{1,2}

People with achondroplasia have one normal copy of the fibroblast growth factor receptor 3 gene and one mutant copy. Two copies of the mutant gene are invariably fatal before or shortly after birth. Only one copy of the gene has to be present for the disorder to occur. Therefore, a person with achondroplasia has a 50% chance of passing on the gene to his or her offspring, meaning that there will be a 50% chance that each child will have achondroplasia. Since it is fatal to have two copies (homozygous), if two people with achondroplasia have a child, there is a 25% chance of the child dying shortly after birth, a 50% chance the child will have achondroplasia, and a 25% chance the child will have an average phenotype. People with achondroplasia can be born to parents that do not have the condition. This is the result of a new mutation.²

New gene mutations leading to achondroplasia are associated with increasing paternal age³ (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 hinders the mutation from originally occurring in females (although females are still readily able to inherit and pass on the mutant allele).

The typical appearance of achondroplastic dwarfism can be seen at birth. Symptoms include; Abnormal hand appearance with persistent space between the long and ring fingers, bowed legs, decreased muscle tone, disproportionately large head-to-body size difference, frontal bossing, shortened arms and legs (especially the upper arm and thigh), short stature (significantly below the average height for a person of the same age and sex), spinal stenosis and spine curvatures called kyphosis and lordosis. The most common rheumatological complications of achondroplasia are medullar and radicular compressions due to spinal stenosis and deformities of the lower limbs.²

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.⁴ In families in which both parents have achondroplasia, prenatal diagnosis may be particularly useful, the aim being to distinguish fatal homozygous achondroplasia from heterozygous achondroplasia (with one copy of the achondroplasia gene) from normal. Diagnosis before birth is accomplished by examining cells obtained by chorionic villus sampling (CVS) or amniocentesis.

Examination of the infant after birth shows increased front-to-back head size and there may be signs of hydrocephalus. X-rays of the long bones can reveal achondroplasia in the newborn.

Achondroplasia is one of several congenital conditions with similar presentations, such as

osteogenesis imperfecta, multiple epiphyseal dysplasia tarda, achondrogenesis, osteopetrosis, and thanatophoric dysplasia. This makes estimates of prevalence difficult, with changing and subjective diagnostic criteria over time. One detailed and long-running study in the Netherlands found that the prevalence determined at birth was only 1.3 per 100,000 live births.⁸ However, another study at the same time found a rate of 1 per 10,000.⁸

At present, there is no known treatment for achondroplasia even though now that the cause of the mutation in the growth factor receptor has been found, therapies and diagnostic methodologies are likely to be looked into and developed.

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.⁵

Usually, the best results appear within the first and second year of therapy.⁶ After the second year of GH therapy, beneficial bone growth decreases.⁷ Therefore, GH therapy is not a satisfactory long term treatment.⁶

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.

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