Indian Journal of Genetics and Molecular Research
Volume 2 Number 2, July - December 2013

Achondroplasia

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Abstract

Achondroplasia is a very rare condition where a child is diagnosed with dwarfism. It is the most common type of dwarfism. It is caused by an autosomal dominant gene. "Little People", as they refer to themselves, are not mentally retarded, nor do they have any other mental disabilities due to the disorder.

Keywords: Achondroplasia; Autosomal dominant gene; Short stature.

Introduction

Achondroplasia is a disease that affects the bone growth in the arms and legs. Achondroplasia, coming from Greek, literally means "without cartilage formation." Sufferers from achondroplasia do possess cartilage. During the development in the womb, cartilage forms into bone. When the development from cartilage to bone is prolonged, the bones take longer to form and this creates a shorter stature. About eighty percent of the suffers from achondroplasia are affected because of the mutation through the process listed above. The other twenty percent are affected through a faulty gene on the number four chromosome. The faulty gene is passed from generation to generation. If only one parent is affected, there is a fifty percent chance a child will be affected. If both parents are affected, then there is a fifty percent chance the child will be affected, a twenty-five percent chance the child will go unaffected, and a twenty-five percent chance that the child will suffer from severe skeletal disfiguration that will be lethal. Typically once a family has produced an affected child, there will be no more affected in the family, although it is not known why this is the case.

Case Summary

10 years girl was admitted in our hospital with complaints of NOT GAINING HEIGHT.

Mother gives history that this boy an uncomplicated spontaneous vaginal delivery, was noticed to have a large head, short arms and feet at birth. Since then he had height less than other children of the same age and hands as well as feet were shorter as compared to children of same age. She also tells that he is the shortest boy in his class.

According to the mother child was not shown to any paediatrician or any other local practitioner. There is no history of any treatment or drugs like androgens, steroids, anti-malignancy drugs taken for the same complaint.

There is no History of:

- Loss of weight, irritability, mental apathy- *Malnutrition*
- Persistent diarrhoea – *Malabsorption*
- Cough, foul smelling sputum- *Suppurative lung disorder*
- Dyspnoea, recurrent respiratory tract

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infections, bluish discoloration of lips and palms or soles-*Cardiovascular disorder*

- Increased thirst, increased or decreased urination-*Renal disorder*
- Intolerance to cold, constipation, hoarseness of voice, decreased activity-*Hypothyroidism*
- Moon face, obesity, headache, vomiting-*Cushing's syndrome*
- Loss of weight and apetite-*Chronic disorder (HIV, TB)*

Our case is first issue of parents, out of their 3 siblings (2 females & a male). History of similar features in a younger sister 7 years age.We admitted the girl to our hospital in paediatric ward for further investigations & management.

On examination,

Anthropometry

Mid Parental Height	: 155+166+13\2= 167 cm
Lower Segment-47 cm	: US\LS=1.2:1 Increased.
Upper Segment-57 cm	
Arm Span–102 cm	
Total Height-104 cm	: Arm Span Less Than Height.
Crown Rump Length	: 56 cm
Total Height\2=52	: Crown Rump Length More Than Sitting Height\2. (Infantile Body Proportions.)
Tip of thumb overshoots tip of shoulder.	: Rizomelia Present.

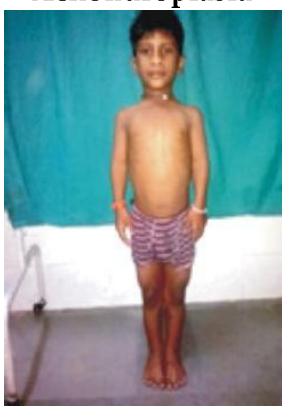
His pulse was 82 beats/minute & blood pressure was 110/66 mmHg. All systemic examinations were within normal limits.

His investigations were as follows:

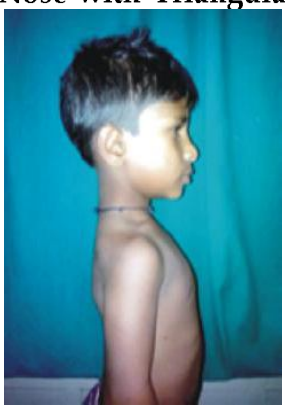
- Hb: 11.1 gm%
- TLC: 8500/cmm
- P – 37, L – 57, E – 05, M – 01, B – 00.
- Platelet count: 2.32 lacs/cmm.
- ESR: 12 mm at end of 1st hr.
- X-ray palm showing Trident Hand Configuration
- X-ray long bones showing metaphyseal cupping and flaring
- X-ray skull showing large skull with small skull base

Discussion

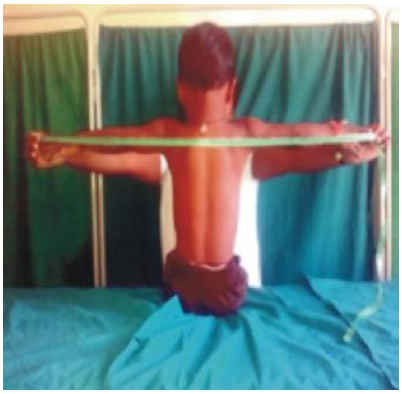
Achondroplasia



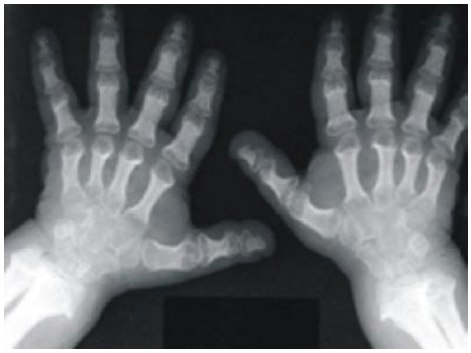
Saddle Nose with Triangular Facies



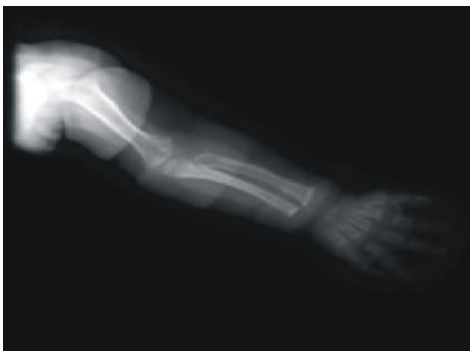
Arm Span



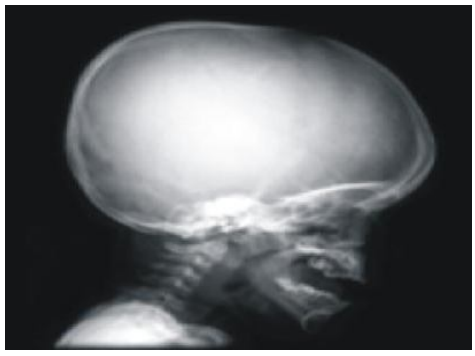
X-ray Palm showing Trident Hand Configuration



X-ray Long Bones showing Metaphyseal Cupping and Flaring



X-ray Skull Large Skull with Small Skull Base



Achondroplasia is a common cause of dwarfism. It occurs as a sporadic mutation in approximately 75% of cases (associated with advanced paternal age) or may be inherited as an autosomal dominant genetic disorder.

People with achondroplasia have short stature, with an average adult height of 131 centimeters (51.5 inches) (4 ft 3.5 in) for males and 123 centimeters (48.4 inches) (4 ft 0.4 in) for females. Achondroplastic adults are known to be as short as 62.8 cm (24.7 inches) [2 ft 0.7 in]. The disorder itself is caused by a change in the DNA for fibroblast growth factor receptor 3 (FGFR3), which causes an abnormality of cartilage formation. 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. The prevalence is approximately 1 in 25,000.[1]

Causes

In normal figures, FGFR3 has a negative regulatory effect on bone growth. In achondroplasia, the mutated form of the receptor is constitutively active and this leads to severely shortened bones.

People with achondroplasia have one normal copy of the FGFR3 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 condition 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 and genotype. 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 age[3] (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). More than 99% of achondroplasia is caused

by two different mutations in the FGFR3. In about 98% of cases, a G to A point mutation at nucleotide 1138 of the FGFR3 gene causes a glycine to arginine substitution (Bellus *et al* 1995, Shiang *et al* 1994, Rousseau *et al* 1996). About 1% of cases are caused by a G to C point mutation at nucleotide 1138. The mutant gene was discovered by John Wasmuth and his colleagues in 1994.

There are two other syndromes with a genetic basis similar to achondroplasia: hypochondroplasia and thanatophoric dysplasia.

Diagnosis

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.

Radiologic Findings

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,[4] 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 configuration can be seen if the fingers are fully extended.

Another distinct characteristic of the syndrome is thoracolumbar gibbus in infancy.

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.[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]

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.

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