



e-ISSN: 2319-8753 | p-ISSN: 2320-6710

IJRSET

International Journal of Innovative Research in
SCIENCE | ENGINEERING | TECHNOLOGY

INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH

IN SCIENCE | ENGINEERING | TECHNOLOGY

Volume 10, Issue 1, January 2021

ISSN INTERNATIONAL
STANDARD
SERIAL
NUMBER
INDIA

Impact Factor: 7.512

9940 572 462

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A Systematic Review on Rare Syndrome Achondroplasia

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ABSTRACT : Achondroplasia is a Greek word which means “Without cartilage formation”. Achondroplasia is the most common form of short limb dwarfism in human beings. It is the most common non-lethal skeletal dysplasia and it is a disorder of bone growth. Achondroplasia occurs in approximately one in every 15,000 to one in 40,000 live births. It occurs as a result of spontaneous genetic mutation in 80% of patients; In the remaining 20% it is inherited from a parent. Most cases of dwarfism are caused by a genetic mutation which follows an autosomal dominant inheritance pattern. Achondroplasia is caused by mutations in FGFR3 gene which is responsible for making a protein (fibroblast growth factor receptor -3). This protein is useful in the production of collagen and other structural components in tissues and bones. People with achondroplasia have short arms and legs, an enlarged head and an average sized torso. It can be diagnosed before birth by prenatal ultrasound and a DNA testing. After birth it can be diagnosed with a physical examination. There is no known cure for achondroplasia but treatment can help. Achondroplasia patients may be treated with growth hormones and in some cases surgeries and other potential therapies are used to lengthen legs. This review provides the detailed study of achondroplasia.

KEYWORDS : Dwarfism, skeletal dysplasia, FGFR-3 gene, prenatal ultrasound, DNA testing, Achondroplasia.

I. INTRODUCTION

Achondroplasia is a disorder of bone formation primarily affecting the long bones of the extremities and the base of skull resulting in characteristic features of short extremities, a large head and trident shaped hands.

- The term Achondroplasia was proposed by Jules Porrott in the year 1878 to describe a condition of children and adults with disproportionate short stature.
- It is the most common form of dwarfism in humans.
- It occurs with a frequency of one in 15-25000, of them 80% of cases are sporadic.
- The average adult height for patients with achondroplasia is 131cm for men and 124cm for women.

II. CAUSES

a. Genetic basis

1. A single gene mapped to short arm of chromosome 4 is responsible for achondroplasia and is transmitted as an autosomal dominant trait.
2. When any of the parent has achondroplasia the chance of transmitting to each child is 20%.
3. If both the parents have achondroplasia 50% chance of having child with achondroplasia.
4. 25% chance of having a child who inherits altered FGFR3 has severe form and often still born or die shortly after death.

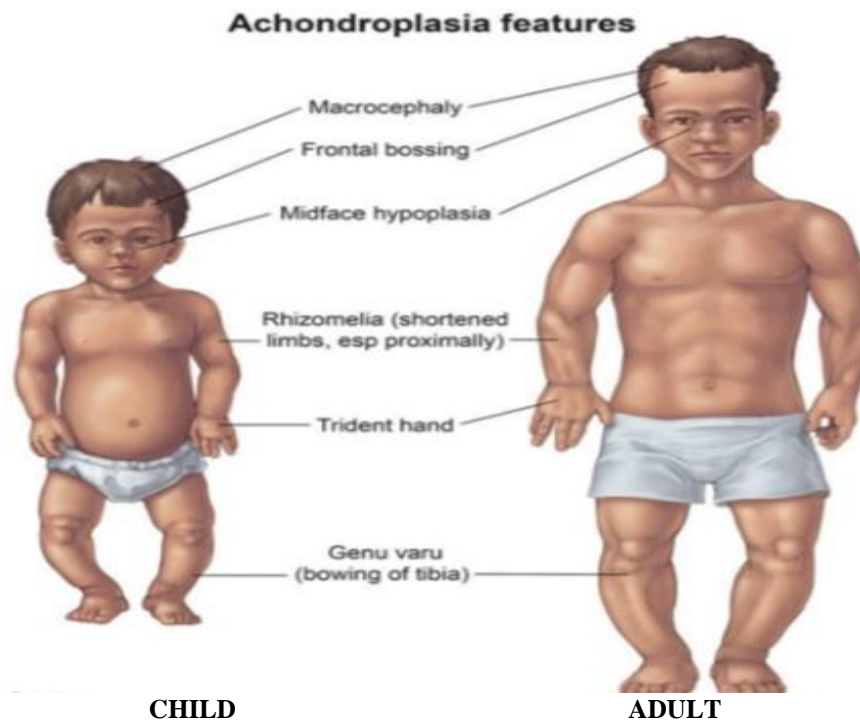
b. Molecular basis

1. Fibroblast growth factors (FGFs) are structurally related proteins associated with cell growth, migration, wound healing and angiogenesis, their function is mediated by FGF receptors.

2. Mutation in FGFR3 on chromosome 4 is responsible for achondroplasia.
3. The primary function of FGFR3 is to limit osteogenesis.
4. Mutations in this gene causes decrease in thickness of hypertrophic cell achondroplasia one resulting in diminution in endochondral bone growth.

III. SIGNS AND SYMPTOMS

- ✓ Small stature
- ✓ Short limbs and rhizomatic disproportion(arms and thighs)
- ✓ Macrocephaly (prominent fore head)
- ✓ Mid facial retrusion – under development of cartilaginous bones of face resulting in flattening of mid face and a flat nasal bridge.
- ✓ Thoracolumbar kyphosis (abnormal rounding of spine)
- ✓ Short fingers and trident configuration of hands
- ✓ Misshaped spine
- ✓ Bowed legs (Genu varum)
- ✓ Hydrocephalus
- ✓ Recurrent otitis media
- ✓ Sleep apnea



IV. DIAGNOSIS

- **Diagnosis during pregnancy**
 - Hydrocephalus or an abnormally large head.
 - Genetic tests to look for the defective FGFR3 gene in a sample of amniotic fluid.
- **Diagnosis after child birth**
 - By physical observation
 - X-rays that measure length of infants bones
 - Blood tests to look for defective FGFR3 gene
- **Other diagnostic tests**
 - Hearing exam
 - Sleep study for sleep apnea

V. TREATMENT

- ✓ There is no known cure or specific treatment for achondroplasia. But treatment can be done to relieve problems caused by achondroplasia.
- ✓ Growth hormone has been widely used in children with achondroplasia. Children receive treatment with injections of a synthetic version of hormone until they reach a maximum adult height.
- ✓ Vosoritide is an experimental drug. It is a synthetic version of C-type natriuretic peptide present in humans, which binds to a specific receptor on the surface of chondrocytes, a type of cartilage found in the growth plates of bones. The vosoritide receptor sends a signal to the fibroblast to deny the flow of negative growth factors that were triggered by the mutations in the FGFR3 gene.
- ✓ The advanced surgical limb lengthening procedures resulted in a significant increase in patient height over a 24 months period.
- ✓ Spinal canal decompression is the most common surgical strategy to treat spinal stenosis in patients with achondroplasia and it can also reduce lumbar stenosis.
- ✓ Antibiotics are given for ear infections.
- ✓ By maintaining a healthy weight, airways are clear and reduce sleep apnea symptoms.
- ✓ In case of hydrocephalus, the pediatric neurosurgeon will perform a ventriculo-peritoneal shunt to relieve the accumulation of CSF in the child's ventricles.

VI. COMPLICATIONS

- ✓ Cervicomedullary compression – Marked thickening and abnormal anterior extension of the posterior rim of the foramen magnum
- ✓ Spinal Stenosis – It is a narrowing of the space within spine, which puts pressure on the nerves that travel through spine
- ✓ Hyperlordosis – A curving inward of the lower back
- ✓ Ear infections such as Otitis media
- ✓ Bowed legs
- ✓ Restrictive and obstructive lung disease
- ✓ Crowded teeth

VII. CONCLUSION

Achondroplasia is the most common form of dwarfism which occurs in both sexes and all races, although there are over 200 types of dwarfism 2/3rd have achondroplasia which is caused by a mutation of FGFR3 gene on the chromosome 4 resulting in the appearance of disproportionate features, midface deficiency, bowed legs, short height, where there is no specific or permanent treatment available and symptomatic treatment is given. Growth hormones and surgery may be able to lengthen limbs to reach maximum adult height.

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