CURRENT TRENDS IN MANAGEMENT OF LIMB DEFORMITIES AND SHORTENING IN ACHONDROPLASIA

Essay

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Abstract

Achondroplasia is an inherited disorder of bone growth that cause the Most common type of dwarfism. It is one of the groups of disorders collectively
Called chondrodysplaias.

The Word achondroplasia Was coined by parrot in 1878 to distinguish the disease from rickets With Proportionately Short Ststure . Kaufmann In 1891 , substituted the term Chondrodystrophia Foetalis to imply deficiency of cartilage Proliferation in the growth plate.

Key Words :

Angulation Correction Axis – Achondroplasia .

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Ayman Shaheen

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Contents

List of abbreviations

ACA Angulation Correction Axis
Ach Achondroplasia
BAX Bcl-2 Associated Protein
Bcl-2 Beta Chronic Lymphocytic Leukemia Protein 2
BDD Body Dysmorphic Disorder
CBFA-1 transcription factor Core Binding Factor A-1
cGMP Cyclic Guanosine MonoPhosphate
CNP C-type Natriuretic Peptide
COMP Cartilage Oligomeric Protein
CORA the Center Of Rotation of Angulation
ELL Extensive Limb Lengthening
ERK Extracellular signal-Regulated Kinase
FGFR-3 Fibroblast Growth Factor Receptor-3
FGFs Fibroblast Growth Factors
G380R Glycine to Arginine substitution at 380 codon
GH Growth Hormone
HA pins HydroxyApatite coated pins
ICP IntraCranial Pressure
Ihh Indian Hedgehog
IMNs IntraMedullary Nails
ISKD Intramedullary Skeletal Kinetic Distractor
JLCA Joint Line Convergence Angle
LATN Lengthening And Then Nailing
LDTA Lateral Distal Tibial Angle
LLD Limb-Length Discrepancy
LON Lengthening Over Nail
LPA Little People of America's
LPFA Lateral Proximal Femoral Angel
LRS Limb Reconstruction System device
MAC Multi-Axial Correcting device
MADC Mechanical Axis Deviation Conventional
MADG Mechanical Axis Deviation Ground
MAPK Mitogen Activated Protein Kinase
mLDFA mechanical Lateral Distal Femoral Angle
MMP Matrix MetalloProteinases
MPTA Medial Proximal Tibial Angle
NPR-B Natriuretic Peptide –B receptor
PI3K Phosphatidylinositol phosphate-3-Kinase (serine / threonine kinase; protein kinase B; AKT)
PLCγ PhosphoLipase Cγ
PPTA Posterior Proximal Tibial Angle
PSSD Pressure Specified Sensory Device
PTH Parathyroid hormone
PTHrP Parathyroid hormone related protein
ROM Range Of Motion
SD Standard Deviation
ST Secondary Translation
STAT1 Signal Transducer and Activator of Transcription 1
TCA TibioCalcaneal Angle
TD Thanatophoric Dysplasia
TFL Tensor Fascia Lata
TGF-β Transforming Growth Factor-Beta
TSF Taylor Spatial Frames
VEGF Vascular Endothelial Growth Factor

Introduction

Achondroplasia is an inherited disorder of bone growth that causes the most common type of dwarfism. It is one of the groups of disorders collectively called chondrodysplasias. (**1**)

The word achondroplasia (literally meaning without cartilage formation) was coined by ***Parrot***, in 1878, to distinguish the disease from rickets with proportionately short stature. ***Kaufmann***, in 1891, substituted the term chondrodystrophia foetalis to imply deficiency of cartilage proliferation in the growth plate. (**2**)

Achondroplasia accounts for about 75% of all dwarfism. However, it is a rare condition affecting 1/50,000 of children. Therefore most the achondroplastic children will grow in communities without any peers sharing the same condition. (**3**)

Achondroplasia must be distinguished from other forms of disproportionate short stature, which, until recently, were all called achondroplasia. Indeed, the heterogeneity of disproportionate short stature only began to be appreciated and studied about 40 years ago, leading to the recognition of hundreds of specific clinical entities each with their own clinical and radiographic features, natural history, complications, and genetic basis.(**4**)

The primary manifestations and medical complications of achondroplasia have received much attention over the past four decades and are now well established for childhood and adolescence. By contrast, the natural history is only gradually being delineated for adults, and several new potential complications have been uncovered. (**4**)

Similarly, mutations of the gene for fibroblast growth factor receptor 3 ***(FGFR3),*** were discovered in achondroplasia over a decade ago. The natures of these mutations, as well as the biology of the receptor encoded by ***(FGFR3)***, and the molecular consequences of the mutations on linear bone growth are

becoming better understood. Eventually, this knowledge will probably provide the underpinning for future treatments that will be targeted directly at the molecular disturbances caused by the ***(FGFR3)*** mutations. Even though the most striking feature of achondroplasia involves cartilage growth, the achondroplasia mutation affects many systems. (**4**)

This essay addresses the present state of knowledge about achondroplasia and latest methods of management of lower and upper limb deformities and short stature in patients with achondroplasia. It discusses the following subjects:

1) Etiology and pathogenesis of achondroplasia.
2) Histochemistry and ultrastructure of growth plate of achondroplasia.
3) Clinical picture of achondroplasia.
4) Management of achondroplasia.
5) Correction of deformities and limb-lengthening in achondroplasia (strategies for lengthening - clinical, radiological, and psychological evaluations before lengthening – challenges in anesthesia of achondroplastic patient)
6) Complications of limb-lengthening procedures.

Chapter 1

Etiology and pathogenesis of achondroplasia

The achondroplasia is caused by a point mutation (single base pair substitution) in fibroblast growth factor receptor-3 ***(FGFR-3)*** gene located on short arm of chromosome 4 resulting in single amino acid substitution of arginine for glycine at position 380. Achondroplasia is transmitted as autosomal dominant gene with the double dose being lethal. Still 80% of cases are spontaneous mutation, and these patients are born for normal parents. (5)

The primary defect in achondroplasia is in endochondral ossification with normal periosteal and intramemebranous ossification. The action of the defective receptor appears to control the rate of longitudinal growth, therefore cell columns in growth plate are small and hypertrophic zone is narrow and since the cartilage cell proliferation in growth plate is the engine behind longitudinal growth, there is disproportion between longitudinal and latitudinal growth. (6)

●NORMAL FUNCTION OF *(FGFR-3)* GENE:

The ***(FGFR-3)*** gene provides instructions for making a protein called fibroblast growth factor receptor-3 (**figure 1-1**). This protein (tyrosine kinase in nature) is a part of a family of fibroblast growth factor receptors that share similar structure and functions. These proteins play a role in several important cellular processes, including regulation of cell growth and division, determination of cell type, formation of blood vessels, wound healing, and embryo development. (7)

The ***(FGFR-3)*** protein is a Trans –membrane protein that spans the cell membrane with one end remains inside the cell and the other projects from the outer surface of the cell, this position allow it to interact with specific growth factors outside the cell and to receive signals that control growth and development. When these growth factors attach to ***(FGFR-3)*** protein, this will

triggers a cascade of chemical reactions inside the cell (**figure 1-2**) that instruct the cell to undergo certain changes, such as maturing to take specialized functions. (7)

The ***(FGFR-3)*** protein is involved in development and maintenance of bone and brain tissues. Its function in bones appears to limit endochondral ossification, particularly in long bones by acting negatively on both proliferation and terminal differentiation of growth plate chondrocytes. So the point mutation in achondroplasia is positive mutation causing the protein to be overly active without binding to specific ligand which interferes with skeletal development and leads to the disturbance of growth seen within this disorder. (7)

(FGFR-3) signals affect many cellular events and processes largely through inducing or repressing expression of target genes in a cell-specific context. Four main signaling pathways have been implicated to date: **STAT1** (signal transducer and activator of transcription 1), **MAPK** (mitogen activated protein kinase), **PLCγ** (phospholipase Cγ), **and PI3K** (phosphatidylinositol phosphate-3-kinase; serine/threonine kinase; protein kinase B; AKT) with the first two receiving the most attention. (8)

STAT signals seem to inhibit chondrocyte proliferation, whereas **MAPK** signals negatively affect proliferation, terminal differentiation, and post-mitotic matrix synthesis via both the **p38** and **ERK** (extracellular signal-regulated kinase) pathways. Studies of target gene expression suggest that **FGFs** initiate signals in many pathways that result in the induction of antiproliferative functions and down regulation of growth promoting molecules. (9)

There are also signaling pathways that modulate the strength of ***(FGFR3***) signals. The best defined at present involves C-type natriuretic peptide (**CNP**). Through interaction with its receptor, natriuretic peptide receptor B (**NPR-B**), **CNP** induces accumulation of intracellular cyclic guanosine monophosphate (**cGMP**) antagonizing **MAPK** signaling downstream of **FGFR3** activation. Of note, mutations of **NPR-B** are responsible for acromesomelic dysplasia. Both **CNP** and

NPR-B are expressed in the proliferative and prehypertrophic zones of the growth plate, setting up a potential autocrine or paracrine regulatory circuit. (9)

Furthermore, a **G380R** (glycine to arginine at 380 codon) mutation in ***(FGFR3)***, which results in achondroplasia, induces apoptosis in the chondrogenic cell. This is associated with a decrease in the expression of **PTHrP** (parathyroid hormone related protein), which shares the same receptor with **PTH**, and it is significant that **PTHrP** rescues these cells from apoptosis. Therefore **PTH** is a potential therapeutic agent for achondroplasia. (11)

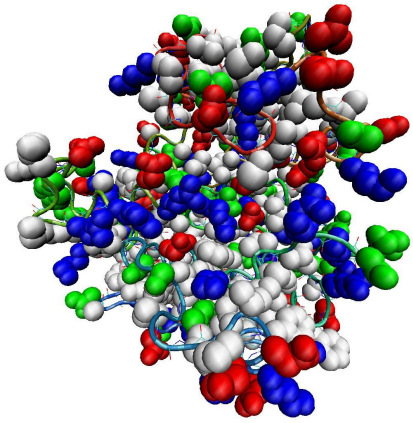

Fig 1-1: model of ***FGFR-3*** (1)

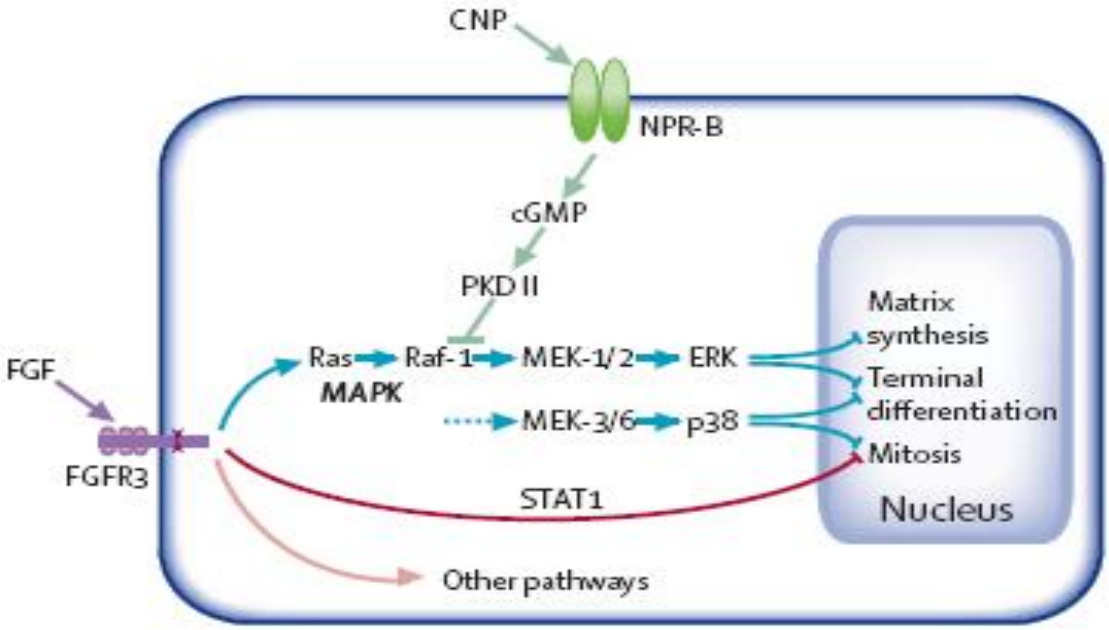

Figure 1-2 : **Signalling pathways of FGFR3 most relevant to growth plate chondrocytes**

FGFR3 signals propagated through STAT1, MAPK-ERK, MAPK-p38, and other pathways inhibit chondrocyte proliferation, post-mitotic matrix synthesis, and terminal (hypertrophic) differentiation. The CNP-NPR-B pathway inhibits the MAPK pathways. (stat1: signal trasducer and activator of transcriptor 1- MAPK mitogen activated protein kinase- CNP C-type natriuretic peptide- NPR-B natriuretic peptide receptor B(1)

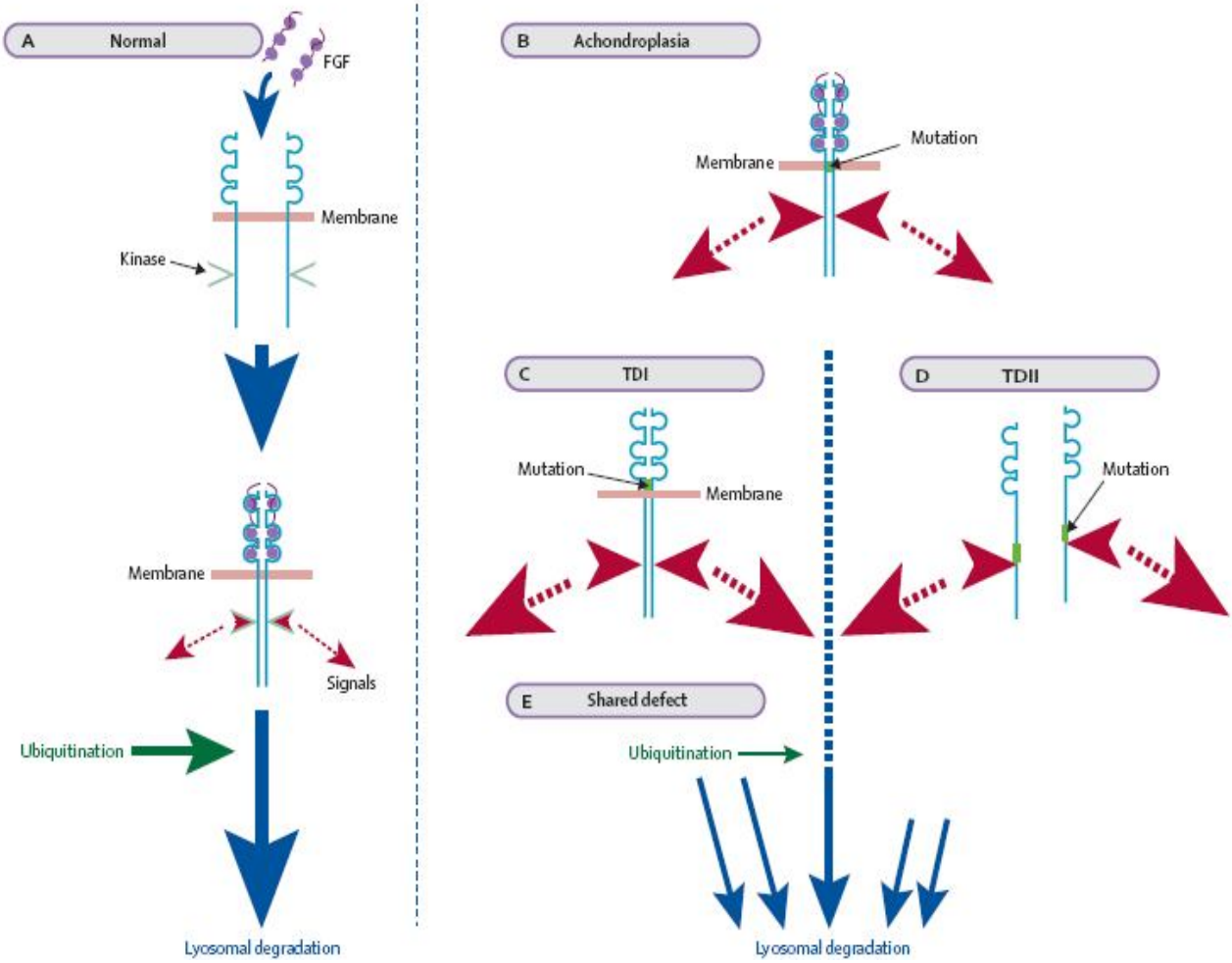

Fig 1- 3: **Proposed mechanisms by which mutations lead to gain of FGFR3 function**

(A) Normally, ligand induces dimerisation of receptor monomers, which activates kinase and initiates propagation of FGFR3 signals. Activated FGFR3 is targeted by ubiquitination to the lysosomes, where they are degraded, and terminating signal propagation soon after activation. (B) FGFR3 dimers are stabilised by mutation (arrow) in transmembrane domain of the receptor in achondroplasia. (C) FGFR3 dimers are induced by formation of disulphide bonds in the proximal extracellular domain (arrow) in thanatophoric dysplasia I. (D) Kinase is constitutively activated by mutation in thanatophoric dysplasia II (and to a lesser extent in severe achondroplasia with developmental delay and acanthosis nigricans and hypochondroplasia). (E) Disturbed ubiquitination, which slows lysosomal targeting and receptor degradation, is shared by mutations that activate FGFR3 kinase activity.(1)

● INCIDENCE AND RISK FACTORS OF ACHONDROPLASIA:

- ***FREQUENCY*:** achondroplasia affects about 1 in every 40,000 children. (This number varies, depending on the source). 80% of all "little people" have achondroplasia. Approximately 150,000 persons have achondroplasia worldwide. The worldwide population of little people is approximately 190,000. (3)
- ***RACE:*** achondroplasia occurs in all the races with equal frequency. (3)
- ***SEX*:** achondroplasia occurs with equal frequency in males and females. (It is inherited in an autosomal dominant manner). (3)
- Penetrance of the altered gene is 100%, meaning that all individuals who have single copy of altered gene have achondroplasia. (6)
- ***PARENTS OF A PROBAND:***
  - More than 80%of individuals with achondroplasia have parents with normal stature as result of *de novo* gene mutation. (6)
  - *De novo* gene mutations are associated with advanced parentral age often defined as over age 35 years. Studies have demonstrated that *de novo* gene mutations causing achondroplasia are exclusively inherited from the father and occurring during spermatogenesis in the unaffected father rather than germline mosaicism.(13)
  - The remaining 20% of individuals with achondroplasia have one or two affected parents. (13)
- ***SIBS OF A PROBAND:***
  - The risk to sibs of a proband depends upon the genetic status of the parents. (6)
  - If the parents have normal stature, the risk to sibs of having achondroplasia is exteremly low. A few instance of parents with normal stature having more than one affected child have being reported supporting the concept of parentral germline mosaicism can occur, albeit

rarely. Germline and somatic mosaicism have been decoumented in a woman of normal stature who has two affected children. (13)

- If one parent has achondroplasia, the risk to sibs is 50% (13)

- ***OFFSPRING OF A PROBAND:***
  - An individual with achondroplasia who has a partner with average stature has a 50% risk of having a child with achondroplasia. (13)
  - When both parents have achondroplasia, the risk to their offspring of having normal stature is 25%, of having achondroplasia is 50%, and having homozygous achondroplasia which is lethal condition is 25%. (13)
  - Homozygous infants usually die a few weeks to just months after birth, while heterozygous newborns are expected to live out normal live spans. (13)

Table 1-1: genetic possibilities of achondroplasia (3)

Affected parent and non affected parent:

	A	**a**
a	**Aa**	**aa**
a	**Aa**	**aa**

-50% chance of having affected child

Both parents are affected:

	A	**a**
A	**AA**	**Aa**
a	**Aa**	**aa**

-50%chance of having affected child

-25% death

●PATHOGENESIS OF ANATOMICAL ABNORMALITIES (*THEORY OF PONSETI):*

After studying iliac crest apophyses and the upper fibular epiphyseal plates of seven achondroplastic children, ***Ponseti*** found that the iliac crest apophysis and its growth plate were nearly histologically normal, on the other hand, the central region of fibular growth plate had cartilage cell clusters separated by wide septa of fibrous matrix which appeared to be very slowly and irregularly resorbed at the vascular front hindering calcification and ossification. Bone formation was normal in the iliac wing and was very stunted in the fibular metaphysis. However, bone formed normally in the fibular head, at the insertions of biceps tendon and collateral knee ligament, and in the periphery under the periosteum where abundant normal periosteal bone spread out in a funnel-shaped fashion underneath the peripheral margins of growth plate and accounted for flaring of the metaphysis. According to these histological observations, ***Ponseti*** saw that the peculiar skeletal development in the child with achondroplasia could be explained. (14)

The defect affects primarily the central region of growth plate while sparing the peripheral ring of the plate. Therefore, the larger the proportion of the central region of growth plates to the peripheral ring, the greater the growth inhibition. The distal femur which has the largest growth plate in lower limb is affected the most and similarly the proximal humerus has the largest growth plate in upper limb so it is affected the most. That is why the proximal parts are affected more than the distal parts of the limbs (rhizomelic disproportionate dwarfism). (14)

The fibula has relatively small growth plate with much higher ratio of peripheral to central growth cartilage compared with adjacent tibia. The growth of the tibia therefore is more affected than that of the fibula resulting in overgrowth of the fibula, and both upper and lower fibular epiphyses are at a higher level than the corresponding tibial epiphyses which causes developmental varus of the proximal and distal joint lines of the tibia, lateral