Clinical, Radiological and Molecular Studies of Egyptian children with Achondroplasia

Thesis submitted for the partial fulfillment of M.Sc. Degree in Pediatrics

Presented by

Ghada Ahmed Otaify
M.B.B.Ch

Supervised by

Professor Dr. Mona Hassan Hafez
Professor of Pediatrics
Cairo University

Assistant Professor Dr. Sahar Nasr Saleem
Associate Professor of Radiology
Cairo University

Assistant Professor Dr. Mona Sabry Aglan
Assistant Research Professor of Clinical Genetics
Clinical Genetics Department
Human Genetics and Genome Research Division
National Research Centre

Faculty of Medicine
Cairo University
2008

﴿سَنريهم آيَاتنَا فى الآفَاق وفى أنفسهم حَتى يتَبَينَ لَهم أنه الحَق﴾

«أية ٥٣ من سورة فصلت»

Acknowledgment

This thesis would not have been possible if it were not for the aid and assistance of many people to whom I am grateful.

I have been very fortunate with my supervisors, who complemented each other wonderfully well.

First I would like to thank **Dr. Mona Hassan Hafez** Professor of Pediatrics, Faculty of Medicine, Cairo University. It was a great honor for me to be supervised by her. Her assistance and advice, extraordinary kindness and smooth and simple way in supervising the data throughout this work are very much appreciated.

Also I would like to express my thanks and gratitude to **Dr. Sahar Nasr Selim** Associate Professor of Radiology, Cairo University for her helpful advice and accurate supervision throughout this work.

My deep appreciation and grateful thanks is expressed to **Dr. Mona Sabry Aglan** Assistant Research Professor of Clinical Genetics, National Research Centre, for highly meticulous supervision, great effort, hard work, great patience, continuous encouragement and sincere concern. Nevertheless, she cannot be credited for all what she did for me.

My study could not have been completed without the active participation, continuous advice and meticulous supervision of **Dr. Alice Kamal Abdel-Aleem** Professor of Molecular Human Genetics, National Research Centre to whom I am greatly indebted.

Thanks to **Dr. Laila Hosny,** Professor of Clinical Genetics, National Research Centre, for the generosity with which she helped me in the anthropometric measurements.

I would like to express my everlasting gratitude to **Dr. Samia El Temtamy**, Professor of Human Genetics, and the head of Limb and Skeletal anomaly Clinic, National Research Centre, for her generous support and scientific advice.

I can't forget in this occasion to thank all the staff members of Human Genetic Department, National Research centre, Cairo for their help and cooperation.

I am forever grateful to my parents and my brother who always sincerely offer advice, continuous support and encouragement through the whole of my life.

I would like also to express my thanks to my friends who have been very supportive all the time.

Last but not least, this work wouldn’t have been done without the patients who were involved in this study, to whom I am very thankful and grateful.

Abstract

Achondroplasia **(**OMIM #100800**)** is the most common form of non lethal skeletal dysplasia

The condition has been recognised for centuries, with examples seen in art from ancient Egypt

It is a fully penetrant autosomal dominant disorder and the majority of cases appear sporadically resulting from de novo mutation associated with advanced paternal age

The phenotype of achondroplasia is related to a disturbance in endochondral bone formation, due to a mutation in the fibroblast growth factor receptor-3 (FGFR3)

KEY WORDS:

Achondro plasia – dysplesia – dominant - fibroblast

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ABBREVIATION

3D : three dimensional
3D HCT : 3D helical computer tomography
A : adenine
AAPCG : American Academy of Pediatrics Committee on Genetics
ACH : achondroplasia
AD : autosomal dominant
AP : Anteroposterior
BMI : body mass index
C : cytosine
CCJ : craniocervical junction
cf-DNA : cell free DNA
CNP : C-type natriuretic peptide
COMP gene : cartilage oligomeric matrix protein gene
CPAP : continuous positive airway pressure
CSF : cerebrospinal fluid
CT : Computed Tomography
CVS : chorionic villus sampling
DNA : Deoxyribonucleic acid
F : female
FGFR3 : fibroblast growth factor receptor3
Fig. : figure
G : guanine
GH : Growth hormone
HC : head circumference
Ht : height
HYP : hypochondroplasia
IQ : intelligence quotient
Kg : kilogram cm: centimeter
L : laminas
LBW : low birth weight
LPA : Little People of America
LS : lower segment
M : male
m : month
m^2 : square meter

MALDI-TOF MS : Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry
MAPK : microtubule associated protein kinases
MRA : magnetic resonance angiography
MRI : Magnetic Resonance Imaging
MRV : Magnetic resonance venography
NRC : National Research Centre
OM : otitis media
OMIM : On Line Mendelian Inheritance In Man
P : pedicles
PCR : Polymerase Chain Reaction
PSACH : Pseudoachondroplasia
SADDAN : severe achondroplasia with developmental delay and acanthosis nigricans
SDS : standard deviation score
SP : spinous process
TD : Thanatophoric dysplasia
TM : transmembrane
TP : transverse processes
URTI : upper respiratory tract infection
US/LS : upper segment/lower segment
US : upper segment
UV : ultra violet
-ve : negative
VB : vertebral body
Wt : weight
y : year

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INTRODUCTION

The skeletal dysplasias form a large group of hereditary disorders characterized by abnormal growth and malformations of bone and cartilage.

Achondroplasia **(OMIM #100800)** is the most common form of non lethal skeletal dysplasia and the mutation causing it might be the most common disease-causing mutation to arise de novo in human beings. **(Shiang et al, 1994)**

The condition has been recognised for centuries, with examples seen in art from ancient Egypt, Greece, and Rome. (**Kozma, 2006)**

The incidence rate ranges between 1/15,000 and 1/ 40,000 live births. **Achondroplasia is overdiagnosed in many newborn infants with a skeletal dysplasia.**

It is a fully penetrant autosomal dominant disorder and the majority of cases **appear sporadically resulting from de novo mutation associated with advanced paternal age (Shotelersuk et al., 2001, Vajo et al., 2000)**.

The phenotype of achondroplasia is related to a disturbance in endochondral bone formation, due to a mutation in the fibroblast growth factor receptor-3 (FGFR3). **(Bagci et al., 2006).** Consequently, affected individuals exhibit Characteristic clinical and radiological features. **(Trotter and Hall, 2005)**

AIM OF THE WORK

1. Proper diagnosis of cases with achondroplasia and its differentiation from other skeletal dysplasias with disproportionate short stature and Study of social and family factors that may predispose to de novo cases.

2. Evaluation of body physique in correlation with the severity and age of the studied cases.

3. Evaluation of the characteristic radiological signs in achondroplastic patients as a main tool for diagnosis.

4. Molecular analysis of FGF3 in the studied sample to esnsure and differentiate clinically diagnosed achondroplasia from other related skeletal dysplasias.

5. Provide proper genetic counseling concerning nature, inheritance, recurrence risk and implications of the disease to help the affected families make informed medical and personal decisions.

BACKGROUND AND REVIEW OF LITERATURES

1- The Skeletal System:

A skeleton is an inner framework made of bone and cartilage. Bones are the hard material of the skeleton. At birth the human skeleton is made up of 275 different bones. With body maturation some of these bones, such as wrist and ankle bones, fuse together leaving only 206 bones in the adult body.

The Skeletal System serves many important functions; it provides the shape and form for our bodies in addition to supporting and protecting vital organs, providing a system of muscle levers that allow body movement and producing blood for the body and storing minerals.

The human skeleton is divided into two distinct parts; the axial skeleton that consists of the skull, sternum, ribs and vertebral column and the appendicular skeleton that is composed of bones that anchor the appendages to the axial skeleton including the upper extremities, the lower extremities, the shoulder girdle and the pelvic girdle. The sacrum and coccyx are considered part of the vertebral column.

The bones of the human body fall into four general categories: long bones, short bones, flat bones, and irregular bones. Long bones are longer than they are wide and work as levers. The bones of the upper and lower extremities (e.g. humerus, tibia, femur, ulna, metacarpals, etc.) are of this type. Short bones are short, cube-shaped, and found in the wrists and ankles. Flat bones have broad surfaces for protection of organs and attachment of

muscles (e.g. ribs, cranial bones, bones of shoulder girdle). Irregular bones are all others that do not fall into the previous categories. They have varied shapes, sizes, and surface features and include the bones of the vertebrae and a few in the skull. **(http://emuseum.mnsu.edu/biology/humananatomy/skeletal/skeletalsystem.html)**.

2- Skeletal Dysplasias:

Skeletal dysplasias form a large group of hereditary disorders characterized by abnormal growth and malformations of bone and cartilage. The clinical severity ranges from mildly affected short stature to lethal forms. In **1992, Spranger** classified approximately 200 different skeletal dysplasias based on the clinical and radiographic features in addition to the mode of genetic transmission. With the rapid accumulation of knowledge concerning defective genes and proteins causing this group of disorders, new classifications emerged; including the Classification by the International Working Group on Constitutional Diseases of Bone based on the mutations in the same group gene taking into consideration the clinical and radiological findings **(Hall, 2002)**. This classification was revised and updated by the group of the International Skeletal Dysplasia Society providing an overview of recognized entities with skeletal involvement and of the underlying gene defects. Three hundred seventy-two different conditions were included and placed in 37 groups defined by molecular, biochemical and/or radiographic criteria **(Superti-Furga et al, 2007)**. It is important to notice that the clinical manifestations and radiological investigations are crucial for the differential diagnosis in skeletal dysplasias. However, prenatal diagnosis and postnatal