

# **STUDY OF THE EYE MANIFESTATIONS WITH GENETIC SKELETAL DISORDERS**

**Thesis Submitted for Partial Fulfillment of  
The Degree of M.D.  
In  
Clinical Genetics**



**By  
Dr. Shahira Riad Nowier**

618.920977  
Sh. R

53270

**Under the Supervision Of  
Prof. Dr. Abdel Khalik Khattab  
Professor of Pediatric & Genetics  
Faculty of Medicine-Ain Shams University**

**Prof. Dr. Mohammed Awad-allah  
Professor of Pediatric & Genetics  
Faculty of Medicine-Ain Shams University**

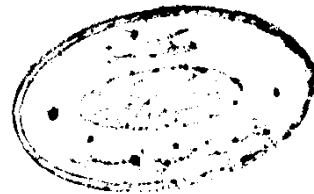
**Prof. Dr. Zeinab M. Osman  
Professor of Ophthalmology  
Institute of Ophthalmic Research**

Handwritten signature and notes in Arabic script.

**Assist. Prof. Dr. Mohammed El Sawy  
Assistant Prof. of Genetics  
Faculty of Medicine-Ain Shams University**

Handwritten signature or initials.

**1994**



## ACKNOWLEDGEMENT

Words fail to express my deepest gratitude and most sincere thanks to Prof. Dr. Abdel khalik khattab. Professor and head of pediatric and genetics department Faculty of Medicine, Ain Shams University for his valuable advice and guidance to accomplish this work.

My special and sincere gratitude to Prof. Dr. Mohammed Awad-Allah Professor of Pediatric and Genetics Faculty of Medicine, Ain Shams University for his continuous guides, greet help and endless encouragement in making this work.

I am greatly thankful to Professor Dr. Zeinab M. Osman Professor and Ophthalmology, Institute of Ophthalmic Research, who was very generous in time and effort during the preparation of this work.

Also, I wish to express my sincere appreciations and deepest gratitude to assistant Professor Dr. Mohammed El-Sawy, assistant Professor of Genetics, for his kind supervision, valuable criticism and generous help and advice.

*Shahira Nowier*



# CONTENTS

	<i>Page</i>
<b>LIST OF TABLES</b>	
<b>LIST OF ABBREVIATIONS</b>	
<b>INTRODUCTION AND AIM OF THE WORK</b>	1
<b>REVIEW OF LITERATURE:</b>	
Embryology, anatomy and physiology of the eye	2
Embryology, anatomy of the skeletal system	10
Eye and skeletal anomalies is chromosomal aberrations	17
Association of eye and bony manifestations in syndromes	34
Eye anomalies with craniofacial malformations	43
Eye and bone disorders in metabolic diseases	51
Eye and skeletal anomalies in heritable connective tissue disorders	58
Eye and skeletal anomalies due to environmental factors	62
<b>SUBJECTS AND METHODS</b>	67
<b>RESULTS</b>	70
<b>DISCUSSION</b>	191
<b>RECOMMENDATIONS</b>	205
<b>ENGLISH SUMMARY</b>	207
<b>REFERENCES</b>	209
<b>ARABIC SUMMARY</b>	

## LIST OF TABLES

No. of Table	Title of Table	Page
1	Distribution of cases with eye and skeletal abnormalities according to the aetiology.	70
2	Frequency of positive phenotypic findings in Down syndrome.	72
3	Showing sex distribution among cases with eye and skeletal abnormalities.	75
4	Showing the parental consanguinity in cases with eye and skeletal abnormalities.	77
5	Showing the degree of consanguinity in positive consanguinous.	79
6	Showing the maternal age distribution at conception in different aetiological groups.	80
7	Showing the comparison between the mean age of our patients at time of presentation to our clinic in the different aetiological groups.	82
8	Showing mental affection in our different groups.	83
9	Cytogenetic findings in chromosomal group.	85
10	Showing eye and bony findings in chromosomal group.	86
11	Percentage of the Genetic syndromes presenting with eye and skeletal manifestations.	106
12	Showing eye and bony findings in examined syndromes.	107
13	Showing the craniofacial disorders presenting with eye and bony abnormalities.	135
14	Distribution frequency of eye and skeletal abnormalities among craniofacial group.	136
15	Showing the metabolic disorders presenting with eye and bony abnormalities.	154

<b>No. of Table</b>	<b>Title of Table</b>	<b>Page</b>
16	Distribution frequency of eye and skeletal abnormalities among the metabolic group.	155
17	Showing teratogenic agents among the teratogenic group with eye and bony abnormalities.	165
18	Showing eye and bony findings due to teratogenic agents.	166
19	Percentage of connective tissue disorders presenting with eye and skeletal abnormalities.	171
20	Frequency of eye and bony abnormalities among connective tissue disorders	172
21	Showing the main eye and bone findings among examined cases.	176
22	Main eye and bony abnormalities in our cases	186
23	Significant association between eye and bony anomalies among our cases	188

## LIST OF ABBREVIATIONS

%	Percent
+/-	Before a chromosome number indicates a gain or loss of whole chromosome, after a chromosome number indicates a gain or loss of that part.
1 <sup>st</sup>	First
2 <sup>nd</sup>	Second
3 <sup>rd</sup>	Third
A.D.	Autosomal dominant
A.R.	Autosomal recessive
X <sup>2</sup>	Chi-square test
CNS	Central nervous system
CT	Computerized tomography
C.T	Connective tissue
C.V.S.	Cardiovascular system
Cm	Centimeter
mm	Millimeter
E.C.G.	Electrocardiogram

E.E.G	Electroencephalogram
gm	Gram
I.Q	Intelligence quotient
M.R.	Mental retardation
S.D.	Standard deviation
STORCH	Syphilis, Toxoplasmosis, rubella, cytomegalovirces and herpes simplex.
Cong.	Congenital
↑	Increase
↓	Decrease
V.S.D	Ventricular septal defect
A.S.D.	Atrial septal defect
Exam.	Examination
&	and
Chr.	Chromosome
No.	Number
D.M.	Diabetes mellitus
Aberr	Aberration

Rt	Right
Lt.	Left
Yr.	Years
gp	group
Synd.	Syndrome
+ve	positive
-ve	negative
Consang	Consanguinity
Post.	Posterior
Ant.	Anterior
Hge	Haemorrhage
G.I.T.	Gastro-intestinal tract
bet.	Between
p	Short arm of chromosome
q	Long arm of chromosome
pt	Patient

# **Introduction and Aim of the Work**

## INTRODUCTION AND AIM OF THE WORK

It has been noticed that many genetically determined disorders as connective tissue disorders, metabolic disorders, genetic syndromes and chromosomal aberrations, show eye manifestations together with skeletal manifestations e.g. Marfan syndrome is a serious connective tissue disorder, it is presented by skeletal manifestations in form of upper segment/ lower segment ratio at 2SD below mean for age, pectus deformity and kyphoscoliosis. The eye anomaly, ectopia lentis may be the key for diagnosis [Tsipauras, 1990].

Also congenital craniofacial abnormalities frequently require ophthalmic evaluation, e.g. in craniosynostosis as in Grouzon syndrome, hypertelorism and exophthalmos are present as eye manifestations which could aid in early diagnosis and early management [Etheridge, 1983].

Our aim in the present work is to study the prevalent forms of congenital eye anomalies associated with skeletal disorders to find out if these abnormalities are related to certain teratogens, metabolic disorders, connective tissue disorders, genetic syndromes or chromosomal aberrations, and to provide data that could be beneficial in early diagnosis and management of cases and in adequate genetic counselling.

# **Review of Literature**

## **EMBRYOLOGY, ANATOMY AND PHYSIOLOGY OF THE EYE**

### **Embryology of the Eye:**

A short general out line of the embryology of the eye is essential to appreciate its anatomy and understand much of its pathology. The central nervous system is developed from the neural groove which invaginates to form the neural tube running longitudinally down the dorsal surface of the embryo.

The eye develops in the 22<sup>nd</sup> day embryo as a diverticulum from the lateral aspect of the fore brain the diverticulum grows out laterally toward the side of the head, and then becomes slightly dilated to form the optic vesicle, while the proximal portion becomes constricted to form the optic stalk. At the same time, a small area of surface ectoderm overlying the optic vesicle thickens to form the lens placode. The lens placode invaginates and sinks below the surface ectoderm to form the lens vesicle. Meanwhile the optic vesicle becomes invaginated to form a double layered optic cup. The inferior edge of optic cup is deficient and this notch is continuous with a groove on the inferior aspect of optic stalk called the optic fissure. Vascular mesenchyme now grows in the optic fissure and takes with it the hyaloid artery. Later the fissure becomes narrowed by growth of its margins around the artery, and by the 7<sup>th</sup> week the fissure closes, forming a narrow tube, the optic canal, inside the optic stalk. By the 5<sup>th</sup> week, the lens vesicle loses contact with the surface ectoderm and lies within the mouth of the optic cup, the edges of which form the future pupil [Sadler, 1985].

### **Retina:**

The retina is divided into two developmental layers.

- 1- The pigmented layer
- 2- The neural layer

#### ***The pigmented Layer:***

This is formed from the outer thinner layer of the optic cup, as a result of the development of pigment granules in the cells in the 5<sup>th</sup> week of development.

#### ***The Neural Layer:***

This is formed from the inner thicker layer of the optic cup.

By the 6<sup>th</sup> month of development, all the layers of the nervous portion of the retina have developed, including the rods and cones. It is thus seen that the inner layer of the optic cup may be divided into small numerous portions near the edge of the cup and a large photosensitive portion, and the two are separated by a wavy line, the ora serrata [Ehler and Brown, 1983].

### **Optic Nerve:**

Walton and Robb, (1970) mentioned that the ganglion cells of the retina develop axons which converge to a point where the optic stalk leaves the posterior surface of the optic cup. Gradually the inner layer encroaches on the cavity of the stalk until the inner and outer layers fuse. The cells of the optic stalk form neuroglial supporting cells to the axons. The cavity of the stalk disappears, the

stalk, together with the optic axons form the optic nerve, the hyaloid artery and vein become the central artery and vein of the retina.

### **Lens:**

As the lens vesicle sinks beneath the level of the surface ectoderm, the cells forming the posterior wall rapidly elongate, lose their nuclei and form a transparent lens fibers. The laminated arrangement of the lens fibers occurs as a result of additional fibers being produced and added to the outer surface of the lens by the division of the cells in the equatorial region of the lens. Meanwhile, vascular mesenchyme is growing into the optic cup and surrounds the developing lens. The mesenchyme immediately adjacent to the lens becomes the lens capsule, which in the earliest stages receives an abundant arterial supply from the hyaloid artery. Later this blood supply regresses and it disappears before birth [Waardenburg, 1961].

### **Ciliary Body and Suspensory Ligaments of the Lens:**

The mesenchyme situated at the edge of the optic cup differentiates to form:

- 1) The connective tissue of the ciliary body.
- 2) The smooth muscle fibers of the ciliary muscles.
- 2) The suspensory ligament of the lens

[Calhoun, 1983].

The two layers of ectoderm forming the edge of the optic cup grow onto the posterior surface of the ciliary muscle and become folded to form the ciliary processes.