NEUROFIBROMATOSIS
(VON RECKLINGHAUSEN DISEASE)

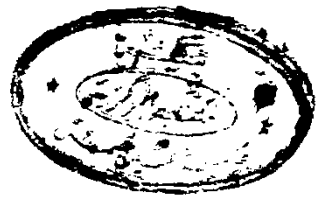
Submitted in Partial Fulfillment
for Master Degree in Ophthalmology

By

Hussein Salah El Din El Nahass

M. B.; B. ch

Supervised by



Professor Dr. Anwar El Masry
Professor of Ophthalmology
Faculty of Medicine
Ain Shams University

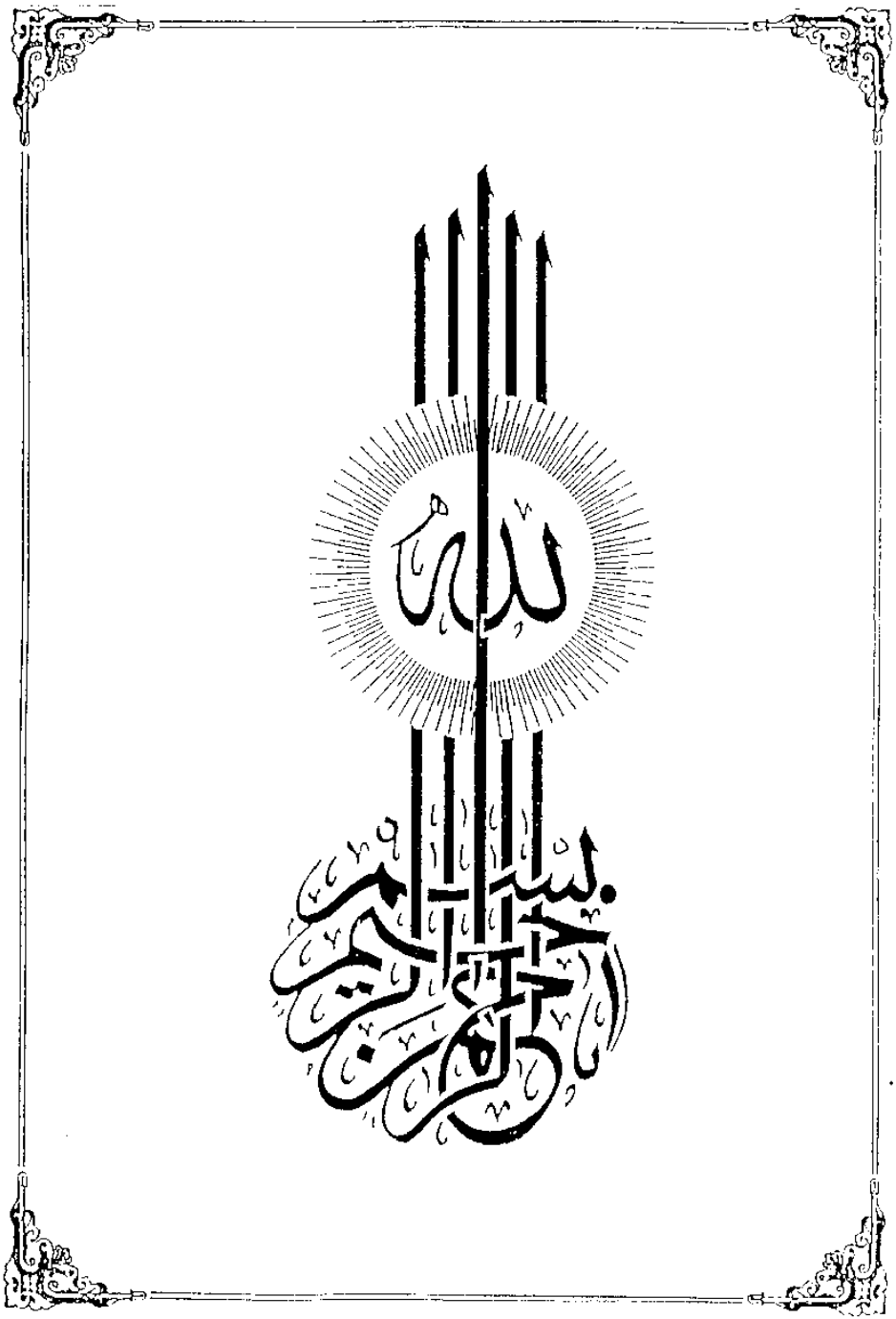
Cairo - Egypt

1988

ACKNOWLEDGEMENT

I wish to express my deepest gratitude and appreciation to Prof. Dr. **Anwar El Masry**, Professor of Ophthalmology, Ain Shams University, for supervising the details of this work, for his encouragement, unlimited support and helpful criticism.

I would like to take this opportunity to extend my thanks and appreciation to all the Professors and staff members of the Ophthalmic Department, Ain Shams University, who contributed in deepening my knowledge in ophthalmology.



CONTENTS

INTRODUCTION TO PHAKOMATOSIS

Introduction to phakomatosis:-

During embryogenesis, the neural crest contributes to both the nervous system and skin, the skin receiving melanocytes, Schwann cell and neuro-axons of dorsal root and autonomic ganglia. Consequently developmental abnormalities involving the neural crest, whether inherited or induced by other factors, often lead to coexistent neurological and cutaneous anomalies. These anomalies may arise at several stages of embryologic development and involve cytogenesis, organogenesis and histogenesis (Shelley et al, 1981).

Abnormal tissue organization (dysplasia) of the neural crest leads to a large group of neuro-cutaneous disorders called phakomatosis. The term phakomatosis was originally given to the retinal lesions by van Der Hoeve 1881. It is derived from the Greek word (phakos) meaning mother cyst, mole, or freckle. The phakomatosis have ectodermal and mesodermal abnormalities and differ mainly in the period of embryogenesis affected by mal-development (Adams, 1979).

van Der Hoeve, in 1923, used the term phakomatosis to comprise the two neuro-ectodermal phakomatosis:

- von Recklinghausen disease,
- Tuberous sclerosis.

In 1932, he added the two mesodermal (vascular) phakomatosis which are:

- Sturge - Weber syndrome.
- von Hippel-Lindau syndrome.

The term phakomatosis is purely morphological and descriptive without pathogenetical or histopathological basis.

He stated that the phakomatosis have four cardinal features:

1) Small spots (phakos) on the skin and mucous membranes in any part of the body.

2) Localized tumor-like hyperplastic formations of different types (phakomata)

3) True tumor arising from undifferentiated embryonic cells, which subsequently become active and form blastomata (phako- blastomata) such as neuro-blastomata and even malignant tumors.

4) Other congenital malformations

In 1963, Francois added other syndromes to the four classical phakomatosis. Consequently he classified phakomatosis as follows:-

I- Neuro-ectodermal phakomatosis which includes:-

1) von Recklinghausen disease.

2) Tuberous sclerosis (Bourneville's disease).

3) Neuro-cutaneous melanosis.

4) Bloch-Sulzeberger syndrome (incontinentia pigmenti).

5) Gorlin-Goltz syndrome (naevoid basal cell epithelioma)

II- Mesodermal (vascular) phakomatosis which includes:-

1) Crianofacial or trigeminal angiomatosis with cerebral calcification (Sturge-Weker-Dimitri-Kalischer syndrome).

2) von Hippel Lindau syndrome

3) Klippel-Trenaunay-Weber syndrome

4) Familial telangiectasia (Osler-Rendu-Weber disease).

5) Ataxia-telangiectasia (Louis-Bar disease).

NEUROFIBROMATOSIS
OF
VON RECKLINGHAUSEN

CHAPTER II

Neurofibromatosis of von Recklinghausen

- Definition
- Historical background

Neurofibromatosis of von Recklinghausen

* Definition (Adams 1979):-

Neurofibromatosis is one of a neuro-ectodermal phakomatosis, which are a result of developmental disturbances of the primordial neuro-epithelium or of cells migrating from neural crest to various parts of the body.

It is a comparatively uncommon hereditary disease in which skin, nervous system, bones, endocrine glands, and sometimes other organs are the site of a variety of congenital abnormalities, often taking the form of benign tumor growth.

The typical clinical picture consists of multiple circumscribed areas of increased skin pigmentation accompanied by dermal and neural tumors of various sizes and shapes (Adams, 1979).

Historical background:-

The condition known as multiple idiopathic neuromas was the object of a monograph by smith (1849).

But it was von Recklinghausen who, in 1882, gave a definitive account of its clinical and pathological features who deserves the credit for its complete identification as a

nosologic entity.

The report of Crowe et al, in 1956, provides the most complete analysis of genetic data, they investigated 107 families from whom 223 cases had neurofibromatosis, and reported that in eleven families, the disease was transmitted in three generations, 50% of these patients had affected relatives, thus dominant transmission was assumed, In 137 cases, the diagnosis was made for the first time and must have been due to a new mutation.

The name of von Recklinghausen disease is after Friedrich Daniel von Recklinghausen (1833 - 1910), the famous pathologist who studied medicine in Berlin, graduated in 1855 and there for six years he was an assistant to the greatest of all pathologists, Rudolf Virchow: there after he occupied chairs of pathology successively at Koigsburg (1865), Wuzburg (1866 - 1872) and Strasburg (1872 - 1906).

His greatest work was on the pathology of bone, but left his mark on almost every branch of pathology. He was the first to describe hyaline and fatty degeneration of muscle, his work on infarction and embolism was revolutionary, he named the condition of heamochromatosis, all in addition to his detailed researches on adenomyomata of the uterus and neurofibromatosis (Duke-Elder and Dobree 1967).

CHAPTER III

PATHOGENESIS OF NEUROFIBROMATOSIS AND CLINICAL CLASSIFICATION

Pathogenesis of neurofibromatosis and clinical classification

Incidence and epidemiology:-

* Neel (1954), in the institute of Human biology at the university of Michigan calculated the frequency of the disease to be 30 to 40 per 100.000 and expected one case in every 2.500 to 3.300 birth. It is an inherited neuro-ectodermal abnormality determined by a dominant gene which arises frequently by mutation (Canale and Bebin, 1972).

The disease has been observed in all races in different parts of the world. Males and females are about equally affected (Adams, 1979).

* Study of distribution of paternal and maternal ages for 187 patients with neurofibromatosis showed that the mean paternal age was 32.8 years, and the mean maternal age was 27.4 years; both being significantly greater than for central population. It also showed that the paternal age is a factor in origin of new mutation (Riccardi et al, 1984).

Aetiology:-

* Neurofibromatosis is the result of the action of an abnormal gene. Its location in the human karyotype of chromosomes remains unknown. Chromosomal count and morphological features do not deviate from normal (Schimke, 1977).

* There are hyperplastic foci involving the sheath elements (Schwann cells and perineural fibroblasts) around the cranial, spinal, and peripheral nerves, the galia and meninges around the brain and spinal cord (Mobley et al, 1977).

* In areas of tumorous dysplasia, the stimulus for cell growth is abnormally strong, leading to proliferation of cells with faulty disorganization and mutation (Reed, 1977).

* Tumors could reflect a localized over-production of nerve growth factor (N.G.F), which is a protein that experimentally provokes exuberant hyperplastic and hypertrophic outgrowth of nerve fibres in chick embryo ganglia. Elevated N.G.F has been suspected in patients with neurofibromatosis, but not confirmed (Mobley et al, 1977).

* A recent study done by Riopelle et al (1984) suggests that human serum does contain non - nerve - growth factor and neuronal growth factors, but the levels of those factors do