NEUROFIBROMATOSIS

ESSAY

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Master Degree in

ORTHOPAEDIC SURGERY

BY

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UNDER SUPERVISION OF

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بسم الله الرحمن الرحيم

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صدق الله العظيم
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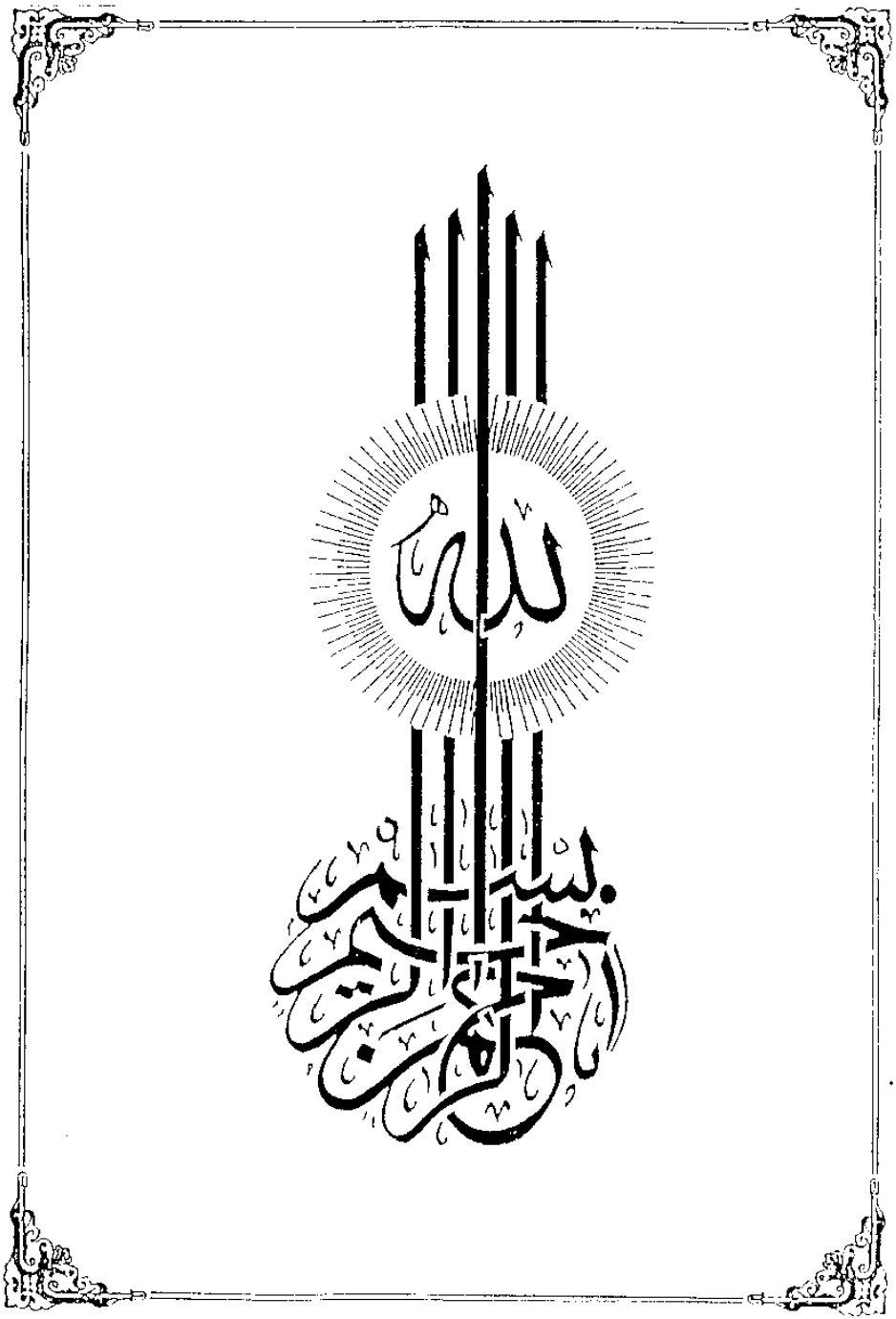

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Neurofibromatosis(NF) is the most common neurocutaneous syndrome, affecting approximately 1 in 3000 individuals. It is a hamartomatous disorder involving neural crest derived cells and is characterized by multiple areas of skin pigmentation in association with overgrowth of nerve sheaths and fibrous tissue elements (neurofibromata). This disease is inherited in an autosomal dominant manner; however, new mutations account for at least 50 percent of cases of the syndrome. Severity and rate of progression vary markedly from one individual to the next, and the protean manifestations of NF make it quite difficult to describe a "typical" clinical picture or natural history of the disease. The expression of any one feature does not correlate with the severity or presence of any other feature. There are several forms of NF. Classically NF consists of a clinical triad that includes cutaneous lesions, mental deficiency and skeletal deformities.

Recent years have witnessed the recognition that there are at least two distinct forms of NF:

NF1 or Von Recklinghausen's NF (previously called peripheral NF) and NF2 or bilateral acoustic NF

(previously called central NF). Accounts of NF prior to 1988 may have been confused by the inclusion of cases of both types.

In this essay, orthopaedic manifestations of NF will be discussed in details. These manifestations include scoliosis which develops in 30 percent of patients and occasionally hypertrophy of one limb. The Nerve Tumors themselves may be palpable or may cause symptoms when situated in a confined space such as the spinal canal. Occasionally, X-ray reveals pressure erosion of bone; rarely, one of the tumours undergoes malignant change. Neurofibromatosis has other curious skeletal associations including disturbance of bone growth, anomalies of bone architecture and pseudoarthrosis of the tibia.

Surgically, NF represents a challenging problem to all orthopaedic surgeons, the procedures themselves are difficult and the prognosis is guarded.

AETIOLOGY & GENETIC FACTORS IN NEUROFIBROMATOSIS

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Neurofibromatosis (NF) is the most common single-gene disorder of the nervous system **(Ionasescu and Zellweger, 1983).** NF is a disease of protean manifestations and involves tissues of ectodermal and mesodermal origin. The condition particularly affects the skin, subcutis, peripheral nerves, and the skeleton. Von Recklinghausen in 1882 was the first to describe the neural involvement within affected tissues, and this early description led to the association of his name with the classic form of NF. Modern terminology has divided NF into two types: NF-1 and NF-2 **(DiSimone and Berman, 1989).**

NF-1, classically Von Recklinghausen's disease or peripheral NF, is inherited as an autosomal-dominant trait affecting one in 3000 individuals **(Holt, 1978).**

It has variable penetrance and a 50% mutation rate. Manifestations vary, resulting in minor or major cosmetic disfigurement and likewise varying levels of physical disability. **Crowe et al. (1956)** have established diagnostic criteria for classic NF (or NF-1); these include manifestations of two or more of the following;(1)a positive

family history; (2) a positive tissue biopsy; (3) a minimum of six cafe-au-lait spots, each at least 1.5 cm in diameters (4) multiple subcutaneous neurofibromas; and (5) characteristic bone lesions, such as pseudoarthrosis of the tibia, hemihypertrophy, or a short segment sharp scoliotic curvature.

NF-1 patients occasionally require treatment by orthopedic surgeons for skeletal pathology **(Laws and Pallis, 1963).** Less known by orthopedists is NF-2 (classically central NF). These are patients with schwann cell tumours arising from the inferior vestibular nerve.

NF-2 is a rare autosomal-dominant disease with an incidence of one in 50,000 individuals. The most recent diagnostic criteria proposed for NF-2 are (1) bilateral acoustic neuromas on a first-degree relative with NF-2 and (2) either a unilateral eighth-nerve mass or two of the following: meningioma, glioma, schwannoma, neurofibroma, and juvenile posterior subcapsular lenticular opacity.

Large gene size is known to be associated with high mutation rate as in Duchenne muscular dystrophy, to date, there is no enough evidence to support a similar theory in

NF, which is also known for high mutation rate **(Barker et al., 1987)**. In one half of NF-1 cases, there is no family history of NF and examination of first-degree relatives (parent, sibling, offspring) is negative. These cases probably represent new mutations. The high mutation rate suggests that NF-1 is a heterogenous entity caused by several mutations and may be a large gene. Other subtypes remain to be described. Nerve growth factor and glial growth factor may play a role in the pathogenesis of the disorders **(Schenkein et al., 1974)**.

Another question concerns the malignant transformation potential of some neurofibromas. Are there separate structural genes (oncogenes) coding for these tumours, or is there a loss of the normal regulatory function in schwann cell growth with reactivation of nerve growth factors? It has been shown that schwann cells in neurofibromas unlike normal schwann cells, have cell surface receptors for nerve growth factor (NGF) **(Davis, 1988)**. This does not reflect an intrinsic abnormality. Rather,schwann cells in neurofibromas probably have lost contact with nearby cells (axons) and become activated. Such a process is likely to be gene encoded and may be involved in formation of neurofibromas, schwannoma, or dedifferentiation into neurofibrosarcomas **(Woods et al., 1986)**.

Gene linkage research may give better understanding of the increased incidence of leukemia, rhabdomyosarcoma, and Wilms' tumour in NF patients. Also, NF patients have an increased incidence of radiation-induced neoplasia, especially neurofibrosarcoma **(Huson et al., 1986).**

Even though all cells in an NF patient have the same gene code, why do only certain cells form cafe-au-lait spots or neurofibromas? A gene pool with two events, possibly separate alleles, has been proposed for phenotypic expression in NF patients (i.e some cells express cafe-au-lait spots or neurofibromas, but other cells do not).

Those who have studied neurofibromas closely fail to find DNA lesions to support this two-event gene hypothesis. It has been proposed that non genetic factors may be responsible for triggering neurofibroma formation. During puberty and pregnancy, preexisting tumours have been observed to enlarge. Studies have shown that tumours in NF patients develop more often in nerves that have a greater number of estrogen receptors **(Ratner, 1988).**

Current estimates of mental retardation in NF range up to 8%, versus 3% for the general population. Non verbal forms of learning disability appear much more common in NF

versus the general population **(Davis, 1988)**. It is presently unknown whether genetics play a clear role in learning disability and NF.

Chromosome Location

NF-1

Linkage analysis of 15 utah kindred has revealed a gene locus for NF-1 in the pericentric region of chromosome 17 **(DiSimone and Berman, 1989)**. Additional independent work has shown independent segregation a long chromosome 17 of ß-NGF, with its possible role in disinhibition of schwann cell (NF) proliferation and the gene locus for NF-1. Earlier evidence of a possible linkage of NF-1 genes to the myotonic dystrophy locus on chromosome 19 is now believed to be exclusionary **(Huson et al., 1986)**.

NF-2

Much of the information about the frequency of occurrence and the natural history of NF-2 has been derived from studies of one large Pennsylvania family begun by Gardner and his colleagues more than 50 years ago **(Young et al., 1970)**. More recent studies of another large kindred allowed gene linkage DNA markers to localize the NF-2 gene to somewhere near the center of the long arm of chromosome 22.