Molecular Basis of Congenital Muscular Diseases

رسالة

Essay

Submitted For Partial Fulfilment of M.S. Degree in Pediatrics

BY

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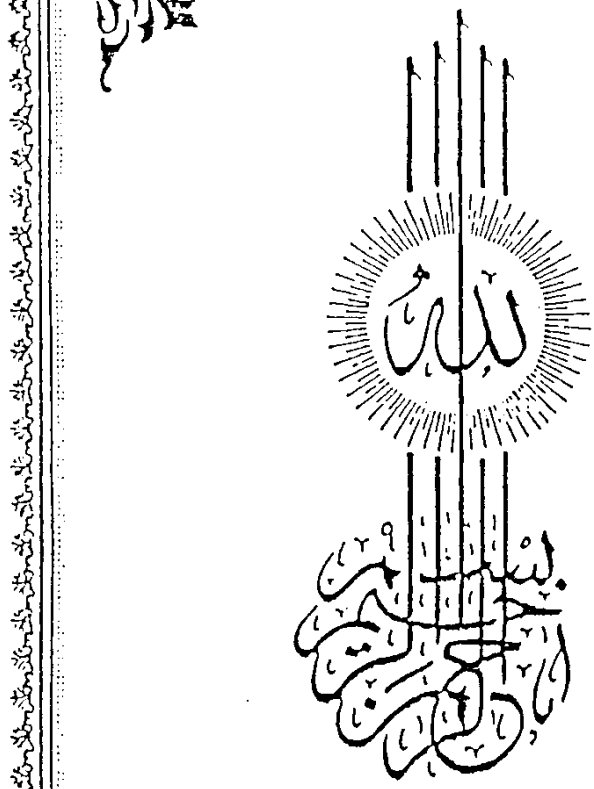

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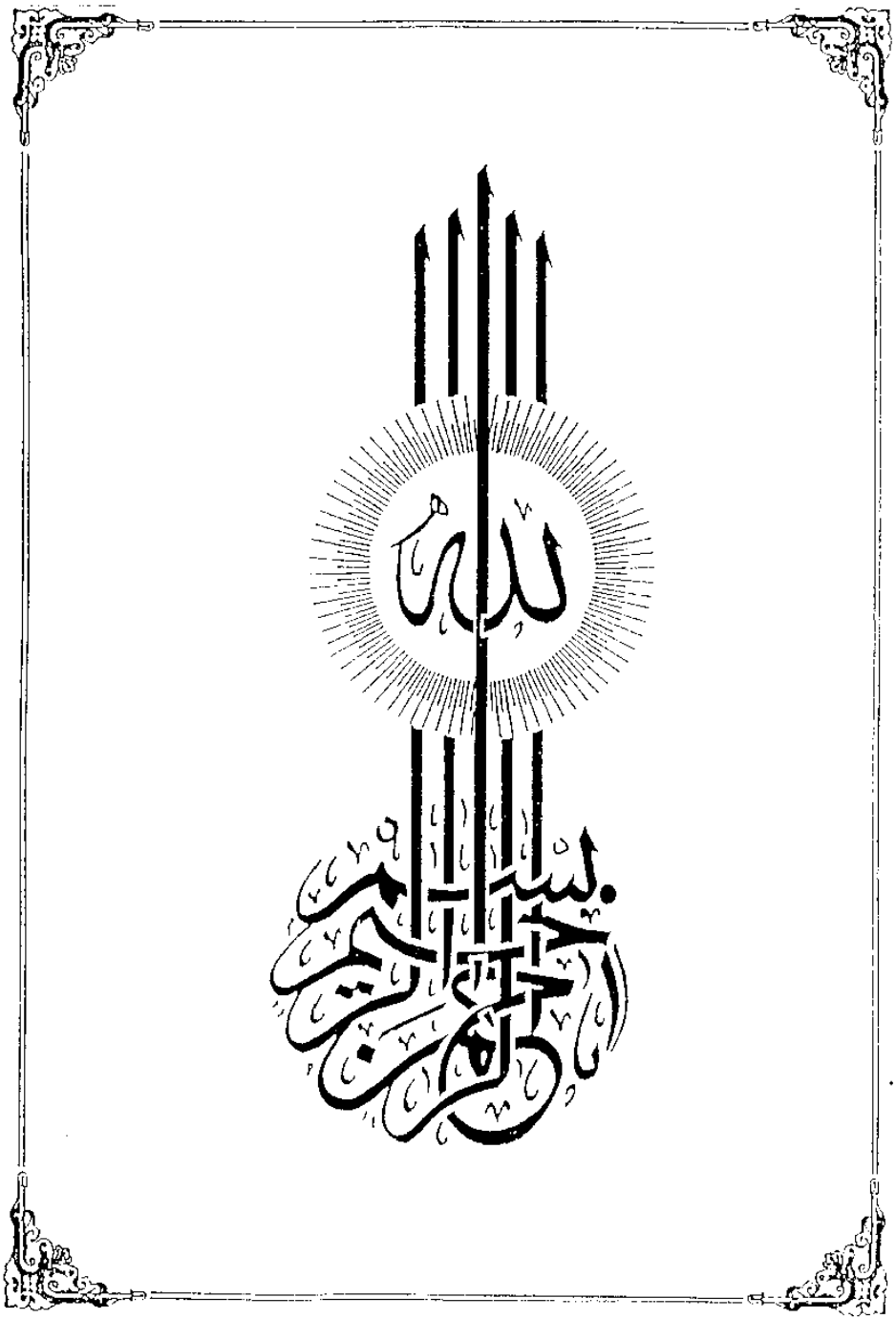

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The Candidate

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LIST OF ABBREVIATIONS

BMD	Becker muscular dystrophy
CPK	Creatine phosphokinase
CTG	Cytosine - thymine - guanine.
DMD	Duchenne muscular dystrophy
DRP	Dystrophin related protein
FSH	Fascioscapulohumeral
LGMD	Limb-girdle muscular dystrophy
DM	Myotonic dystrophy
PCR	Polymerase chain reaction
PFGE	Pulsed-field gel electrophoresis
RFLP	Restriction fragment length polymorphism

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INTRODUCTION

INTRODUCTION

A myopathy is a disorder of skeletal muscle due to disease of the muscle fiber itself (Gillory & Holliday, 1982). The muscle is relatively free from acquired diseases; however, it is a subject to numerous genetic, degenerative, and metabolic disorders (Dubowitz, 1978).

Muscular dystrophies are a group of primary muscle diseases which are genetically determined and usually progressive. Progression of the disease may be relentless and fatal as in the Duchenne form of sex linked recessive muscular dystrophy or with a severe presentation and yet slow or negligible progression as in some cases of congenital muscular dystrophy. Onset may be in utero or at any time up to adult life (Brown, 1992).

Duchenne muscular dystrophy (DMD) is a lethal X-linked recessive disorder affecting approximately 1 in 3500 newborn males (Emery, 1991). In contrast to the mild allelic Becker muscular dystrophy (BMD), DMD is progressive and usually results in death during the second decade of life (Niemann - Seyde, et al., 1992).

A major discovery was achieved when "reverse genetics" technology had revealed the genetic abnormality responsible for DMD. This abnormality was localized to the Xp21 locus in

the human genome (Iannaccone, 1992). The gene disrupted has been cloned and sequenced (Koenig et al., 1988).

The absence of dystrophin in DMD muscles, and its altered size in BMD muscles establishes the disruption of dystrophin as the primary biochemical defect in Duchenne/ Becker muscular dystrophy (Hoffman et al., 1988).

Southern blot analysis of the dystrophin gene using cDNA probes has shown that about 65% of DMD patients have detectable deletions, and another 5% have duplciation (Hu et al., 1988). Large variability in the location and size of deleted segments was observed (Koenig et al., 1989).

The high mutation rate in DMD has long been recognized with approximately one third of cases estimated to result from a new mutation (Bushby, 1992).

Myotonic dystrophy (DM) is a pleiotropic autosomal dominant disease with the highest prevalence among inherited adult neuromuscular diseases (Harper, 1989). The gene for DM has been isolated very recently, and linkage analysis has identified chromosomal localization for FSH dystrophy on 4q, (Aslanidis et al., 1992).

A form of recessive limb-girdle has been localized on 15q, a form of dominant limb girdle on 5q, and Emery-Dreifuss

muscular dystrophy at Xp28 (Bushby, 1992).

Aim of the Essay:

The aim of this essay was to review the literature concerning the recent advances in the molecular basis of congenital muscular diseases. These advances will give us hope in proper dealing with these disorders as regards the diagnosis and therapy.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Differential diagnosis of muscle weakness:

The differential diagnosis of muscle weakness and wasting is a commonly encountered problem in clinical situations. The examiner should consider the distribution of weakness since this is of value in determing etiology. Proximal weakness is usually encountered in myopathies, whereas distal weakness is more likely to have a neurogenic origin (Gillory & Holliday, 1982). The distinguishing characteristics of myopathic and neurogenic disorders are summarized in table (1). The differential diagnosis of weakness is illustrated in Fig. (1).

Clinical disorders of muscles may involve primarily the muscle fiber, or they may be secondary to disease that occurs in other organs (Millichap, 1977).

Table (1): Distinguishing characteristics of myopathic and neurogenic disorders. (Gillory & Holliday, 1982).

	Myopathic	Neurogenic
Signs & Symptoms	Proximal weakness and wasting	Distal weakness and wasting ± Sensory signs & symptoms ± Fasiculations, increased tone, extensor-plantar responses
Serum muscle enzymes	Increased	Normal
Nerve conduction velocities	Normal	Slowed
EMG	Low amplitude polyphasic motor unit	Increased insertion activity, fibrillations and fasiculations
Muscle biopsy	- Variation in fiber diameter - Degeneration of fibers - Increased endomysial connective tissue	- Angular fibers - Pyknotic clumbing - Type I fibers : small - Type II fibers: hypertrophied