CHAPTER I
INTRODUCTION AND OBJECTIVES
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During the past few years there has been great interest in the study of diseases of muscle as well as the fundamental aspects of muscle structure and function. Muscle biopsy has become increasingly a popular diagnostic technique and the modern myology revolves around the techniques related to histochemistry, electron microscopy and immunopathology, to understand the structure and functional correlation.

Neuromuscular disorders are those conditions in which the patients symptoms result from abnormalities in the lower motor neuron, the neuromuscular junction and the voluntary muscles themselves. Amongst the various neuromuscular disorders, the infantile neuromuscular disorders constitute a high proportion. Many of these infantile disorders are rare and unknown in the adult population.

Normal muscle activity in young infants is evident mainly in their tone and posture. Hence in muscle disease, hypotonia is the dominant clinical feature presenting in the first year of life. However, hypotonia is also the earliest sign of many systemic illness and disorders of central nervous system as well. Some of the neuromuscular disorders producing infantile hypotonia and motor weakness include:

(a) spinal muscular atrophy type - 1 (Werdnig - Hoffmann
disease) and the relatively benign form - Spinal muscular atrophy type - 2; (b) congenital muscular dystrophy; (c) different forms of congenital myopathies and (d) metabolic myopathies presenting in early infancy and childhood. Amongst these infantile neuromuscular disorders, the congenital myopathies tend to be rather benign when compared to other conditions causing weakness at birth, by their relatively slow progression or static nature of the neuromuscular disability. However, patients with congenital myopathies present at birth with marked weakness and hypotonia. During the initial stages, they may be indistinguishable from conditions such as infantile Spinal muscular atrophy - 1 (Werding - Hoffmann disease) which carries a grave prognosis. An accurate diagnosis and classification is therefore essential for prognostication. All neuromuscular disorders have a genetic component to their etiology. The recognition of the genetic heterogeneity within a clinically homogeneous group is important for a number of reasons. Neuromuscular disorders are invariably disabling, rarely treatable and never curable. The only approach is therefore genetic counseling.

Since these infantile neuromuscular disorders share many clinical features in common, they pose problem to the neurologists in arriving at a definitive diagnosis. Histochemical and electron microscopic findings in muscle
biopsy serves as the most discriminative diagnostic tool as these disorders show definite morphological characteristics.

Many authors consider abnormalities of embryonic development as possible cause for the infantile neuromuscular diseases. Infantile spinal muscular atrophies are considered to be denervation atrophies, due to the loss of anterior horn cells. However, persistence of foetal myofibres until infancy has also been reported as a pathogenetic mechanism (Hausmanowa-Petrusewicz and Fidzianska, 1974; Fidzianska, 1976, Saito, 1985). Some of the congenital myopathies are also considered to be due to abnormalities in the embryonic development of muscle and hence, such conditions are designated as 'dysmaturation myopathies'. Fibres with central nuclei in centronuclear myopathy (one of the congenital myopathies) and the small fibres of infantile spinal muscular atrophies and congenital muscular dystrophy are often considered as foetal myotubes resulting from arrest in maturation. Whether these small fibres are morphologically altered due to the disease process thus resembling the foetal myotubes or they represent arrested foetal myotubes, is an unresolved issue.

Even though various reports suggest persistence of foetal muscle in infantile neuromuscular disorders, studies on comparative evaluation with normal human foetal muscles during development are limited (Spiro et al., 1966,
Hausmanowa-Petrusewicz and Fidzianska, 1974, Fidzinanska, 1976, Korenyi-Both and Marosan, 1979, Saito 1985). A comprehensive study of various parameters is therefore needed for better understanding of the pathogenesis of these infantile neuromuscular disorders.

There are very few studies on infantile neuromuscular disorders available in Indian literature. Barucha et al., (1966) discussed the clinical and histological features of fifty eight infants in their study. However, Electrophysiological, histochemical and electron microscopic studies were not included. Anisya (DM thesis, 1988), conducted clinical electrophysiological, histochemical and electron microscopic study of floppy infant syndrome at our centre. In the recent years work on neuromuscular disorders utilizing histochemical and electron microscopic techniques are being undertaken at a few centres in India. However, information on comparative study of infantile neuromuscular disorders and foetal skeletal muscle during development is not available in Indian literature.

The present work utilizing histological, enzymehistochemical and electron microscopic techniques was therefore carried out with the following objectives:

1) To study the sequence of morphological changes in development of human skeletal muscle at different gestational ages.
2) To delineate the various infantile neuromuscular disorders.

3) To compare the morphological features of skeletal muscle in infantile neuromuscular disorders with those of normal muscle obtained from human foetuses at different gestational ages.

4) To determine whether the morphological characteristics of muscle in infantile spinal muscular atrophies, congenital muscular dystrophy and congenital myopathies are similar to those of foetal muscle at any developmental stage.

5) To ascertain the role of primary myopathic change and effect of denervation in the evolution of each of the above mentioned conditions.

The classification proposed by Dudley (1989) adopted in our study is enclosed in appendix. Infantile spinal muscular atrophy (ISMA) is not included under congenital diseases of muscle as it is grouped under spinal muscular atrophy.

The work done is presented in different chapters as indicated below:

The material and methods employed are given in Chapter 2. The morphological structure of normal skeletal muscle is provided in Chapter 3. Development of human skeletal muscle with review of literature, observations and discussions is provided in Chapter 4. The study on different
infantile neuromuscular disorders is presented with relevant review of literature, observation and discussions in Chapters 5, 6, 7 and 8. This is followed by a general discussion on the observations made in different infantile neuromuscular disorders with a comparison with human foetuses and Summary and Conclusions.