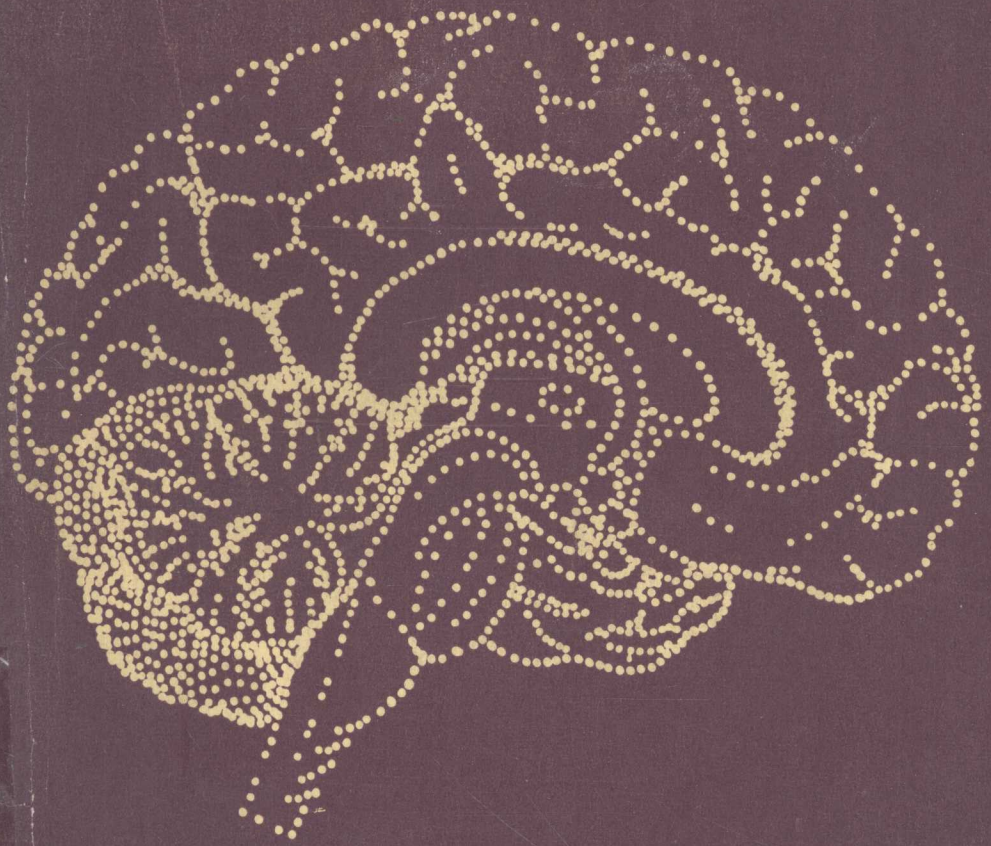
Advances in Neurology

Volume 17:

Treatment of Neuromuscular Diseases

Edited by
R. C. Griggs and R. T. Moxley



Advances in Neurology
Volume 17

Treatment of Neuromuscular Diseases

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Raven Press ▪ New York

Raven Press, 1140 Avenue of the Americas, New York, New York 10036

Made in the United States of America

International Standard Book Number 0-89004-113-x
Library of Congress Catalog Card Number 75-43197

Library of Congress Cataloging in Publication Data
Main entry under title:

Treatment of neuromuscular diseases.

(Advances in neurology; v. 17)
Bibliography
Includes index.
1. Neuromuscular diseases—Congresses. I. Griggs, Robert C. II. Moxley, Richard T. III. Series.
[DNLM: 1. Neuromuscular diseases—Therapy—Congresses. 2. Neuromuscular diseases—Diagnosis—Congresses. W1 AD684H v. 17 / WE550 T784 1976]
RC321.A276 vol. 17 [RC925] 616.8'08s [616.7'4] 75-43197
ISBN 0-89004-113-X

Foreword

This volume on the Treatment of Neuromuscular Diseases coincides with the fiftieth anniversary of the University of Rochester School of Medicine, the twenty-fifth anniversary of the founding of the Muscular Dystrophy Association Clinic at Rochester, and the tenth anniversary of the establishment of the Department of Neurology at the medical school.

Fifty years ago, there was almost nothing known about muscle disease except for the clinical descriptions and some broad classifications of the muscle dystrophies. Twenty-five years ago, steroid therapy was becoming popular, and it was found effective in the then-named menopausal muscular dystrophy which proved to be inflammatory. Ten years ago, more specific mechanisms for the muscle disorders were being found with the fructifying union of biochemistry, physiology, immunology, and neurology.

A few years ago, it would have been an impertinence to discuss treatment of these disorders. It will become obvious that great strides have taken place, but it will be equally obvious that we have a way to go. New treatments will come only as we come to understand the basic mechanisms of normal and abnormal neuromuscular function. The arrangement of this symposium emphasizes the logical move from disordered structure and function to efforts to correct these abnormalities.

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Preface

This volume commemorates the 50th anniversary of the University of Rochester School of Medicine and Dentistry.

It presents information on the evaluation and management of patients with neuromuscular diseases, as well as a review of areas of research likely to lead to advances in the treatment and understanding of these conditions. Introductory chapters focus on the approach to the neuromuscular diseases and the evaluation of the weak patient. Subsequent chapters review the management of those neuromuscular diseases for which treatment is available including myasthenia gravis, polymyositis, dermatomyositis, periodic paralysis, myotonia, and neuropathies. Genetic counseling is discussed and the management of pulmonary, cardiac, and orthopedic complications of the progressive neuromuscular diseases is reviewed. Additional sections present an overview of areas of investigation likely to lead to new therapy for neuromuscular diseases including discussions of immunologic, histologic, electrophysiologic, biochemical, and metabolic studies.

The volume is not intended to be a comprehensive text on either clinical or investigative aspects of neuromuscular disease but to serve as a "state of the art" discussion of current and future therapy. The volume is written by clinicians and investigators experienced in all aspects of the treatment of neuromuscular disease and is aimed at the physician who sees patients with neuromuscular disease as either a major or occasional portion of his practice. It is also pertinent for those with a special investigative interest in neuromuscular disease since much of the work is either previously unpublished or unavailable in a single source.

The Editors

Advances in Neurology Series

Vol. 17: Treatment of Neuromuscular Diseases
R. C. Griggs and R. T. Moxley, III, editors. 392 pp., 1977.

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Contents

Advances in Neurology, Vol. 17, edited by
R. C. Griggs and R. T. Moxley, III. Raven Press,
New York © 1977.

Perspectives on the Treatment of Neuromuscular Disease

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INTRODUCTION

The contributors to this volume consider recent major advances in the treatment of the neuromuscular diseases. This chapter presents a brief overview of the classification of neuromuscular disease and summarizes the approach to the patient suspected of having neuromuscular disease in the light of current therapy. A number of considerations in the management of neuromuscular disease not discussed elsewhere in the volume are reviewed briefly. The following chapter by Moxley highlights those research areas in which significant therapeutic advances may be looked for in the near future.

CLASSIFICATION OF THE NEUROMUSCULAR DISEASES

The traditional subdivision of the motor unit into four parts, although oversimplified and perhaps naive in the light of current speculation as to etiology of a number of so-called myopathies, has merit in providing an approach to the diagnosis and evaluation of patients with neuromuscular disease. Table 1 summarizes the clinical features of characteristic examples of (a) anterior horn cell disease, (b) peripheral neuropathy, (c) neuromuscular junction disease, and (d) myopathy. It should be noted that the anterior horn cell, the peripheral nerve, and the proximal portion of the neuromuscular junction are, in fact, all part of one cell—the anterior horn cell and its peripheral extension. The subdivision into the four traditional categories of neuromuscular disease is, therefore, somewhat arbitrary, and it has been increasingly recognized that a defect apparently limited to the distal portion of the anterior horn cell may, in fact, reflect more proximal pathology in the neuron.

The classification of neuromuscular diseases into these categories has been based on specific electromyographic and muscle biopsy patterns. This has in large part been due to a meager basic understanding of the etiology of these conditions. Nonetheless, because disease nosology has been drawn

TABLE 1. *Classification of the neuromuscular diseases*

Site of involvement	Anterior horn cell	Peripheral nerve	Neuromuscular junction	Muscle
Example	Amyotrophic lateral sclerosis	Nutritional neuropathy	Myasthenia gravis	Polymyositis
Distribution of weakness	Asymmetric limb or bulbar	Symmetrical distal	Extraocular, bulbar, proximal limb	Symmetrical proximal limb, bulbar
Atrophy	Marked early	Moderate	Usually slight	Slight early, severe late
Sensory symptoms	Cramps	Paresthesias, hypoesthesia	None	Aching
Characteristic features	Fasciculations	Tremor	Diurnal fluctuation	
Reflexes	Variable (depends on degree of upper motor neuron involvement)	Decreased out of proportion to strength	Normal	Parallel strength

along these lines, it is reasonable to maintain this subdivision if only as a framework for discussion of evaluation and management.

RECOGNITION OF NEUROMUSCULAR DISEASE

Physicians experienced in the diagnosis of neuromuscular diseases have come to realize that the most difficult part of the management of neuromuscular disease is recognizing the appropriate diagnostic category for a given patient. Thus, a large number of patients are seen with complaints of "weakness," "cramps," or "stiffness," which defy specific diagnosis. On the other hand, a smaller but impressive number of patients endure true cramps, myoglobinuria, fatigue, myotonia, or other symptoms and are subjected to the hazards of general anesthesia, contraindicated medications, or severe exercise during athletic or military training without diagnosis being established.

Symptoms Suggesting Neuromuscular Disease

"Weakness," the finding common to the majority of neuromuscular diseases, is surprisingly uncommon as a chief complaint. Patients more characteristically complain of an inability to perform a specific activity at home or work, such as lifting an object of specific weight that previously was easily managed, rising from a chair, or climbing a flight of stairs. In children, parents may note that a child does not achieve specific motor skills at an age comparable to his peers or older siblings. Although a complaint of "weakness" or "fatigue" can occur in myasthenia gravis and occasionally in other neuromuscular diseases, such complaints more commonly reflect a cause outside the motor unit such as anemia, congestive heart failure, or depression. Limb weakness is often of insidious onset whereas ocular and bulbar weakness is more often abrupt in presentation since a deficit such as diplopia, dysphonia, dysphagia, or ptosis is difficult to ignore for more than a brief time.

If the history supports a loss of muscle function, a number of complaints are important including (a) diurnal fluctuation in strength, (b) pain, (c) cramps, (d) stiffness, (e) fasciculations, and (f) paresthesias. Fluctuation in strength is characteristic of disorders of neuromuscular transmission in which strength is usually worse later in the day. Muscle pain, cramps, or stiffness are surprisingly uncommon in diseases of muscle, although they may occur in a minority of patients with dermatomyositis or polymyositis and characteristically in disorders of glycogen and lipid metabolism. Pain and cramps are more often seen in patients with anterior horn cell or peripheral nerve disease. Fasciculations in a weak patient are usually indicative of anterior horn cell or less commonly peripheral neuropathic disease. Paresthesias point to peripheral neuropathy but may also occur

in the Eaton-Lambert syndrome. As isolated presenting complaints, however, symptoms such as fatigue, pain, cramps, and fasciculations do not usually indicate neuromuscular disease. Thus, although patients with diseases of the neuromuscular junction such as myasthenia gravis or the Eaton-Lambert syndrome characteristically have fatigue, this complaint in isolation also indicates disease remote from the neuromuscular system. Muscle pain, cramps, or stiffness are often without clear diagnostic significance, and fasciculations are often benign in the patient without weakness.

Inability to establish diagnosis in patients with these complaints may not necessarily indicate that no disease is present. In fact, patients with the recently characterized disorders such as the glycogen and lipid storage disease discussed by DiMauro and Eastwood (*this volume*) defied diagnosis until quite recently and were often felt to have complaints on a psychogenic basis. The existence of forme frustes of a number of neuromuscular diseases such as myotonic dystrophy, facioscapulohumeral dystrophy, and Fabry's disease should also raise concern that patients with undiagnosed complaints could represent such a situation. Similarly, the recent recognition that occasional carriers of neuromuscular disease such as Duchenne and Becker dystrophy may manifest moderately severe features of the illness (22,24) raises the possibility that heterozygotes of other recessive conditions could have moderate and undiagnosable symptoms.

In addition to those complaints clearly referable to the neuromuscular system, a number of other clinical findings should raise the possibility of neuromuscular disease, including (a) skeletal deformity, such as scoliosis, club foot, or pes cavus; (b) unexplained dyspnea owing to respiratory insufficiency; and (c) cardiac disease suspected to be related to myopathy. Neuromuscular diseases with multisystem involvement, such as myotonic dystrophy or the collagen diseases, may also present with complaints outside the peripheral neuromuscular system. Often the symptoms point to pathology in the central nervous system, joints, eyes, or elsewhere.

Examination of the Patient with Neuromuscular Disease

Patient examination is considered in detail by Brooke (*this volume*). He emphasizes the activities that normal individuals can perform and stresses functional testing of patients in these activities. "Formal testing" using the Medical Research Council 0 to 5 scale is often difficult to interpret in terms of the question, "Is weakness present?" Formal testing is notoriously unreliable in sequential follow-up of a patient, and although sometimes helpful, it should never substitute for functional testing. Functional testing permits (a) reproducible evaluation by more than one examiner; (b) assessment of strength by history (for example, by telephone); (c) allowance for differences because of age, size, gender, and to some extent, physical conditioning; and (d) sequential follow-up during therapeutic trial. A sys-

tem of sequential functional testing such as that described by Brooke is essential for the evaluation of any patient with neuromuscular disease undergoing treatment.

Laboratory Evaluation

As summarized in Table 2, evaluation of patients with neuromuscular disease is directed toward determining: (a) which of the four categories of neuromuscular diseases best describes the patient; and (b) what specific condition in this category he resembles. To answer these questions, one must perform certain laboratory evaluations. All patients should have serum "muscle enzyme" determinations (serum glutamic oxaloacetic transaminase, lactate dehydrogenase, and creatine phosphokinase), electrocardiogram, and a screening pulmonary function test. Most should have electrophysiological studies as discussed by McQuillen (*this volume*). Muscle biopsy (see Chapter 10) and nerve biopsy (see Chapter 14) are indicated in selected patients. Taken together, these tests usually permit determination of whether an illness is due to muscle or nerve disease. A number of other specific tests may be indicated in selected cases such as immunologic studies, endocrine evaluation, or metabolic studies.

In the patient with a potentially treatable neuromuscular disease, laboratory criteria to permit sequential follow-up are of obvious importance. Although most of the diagnostic techniques summarized in Table 2 permit some degree of reliability for sequential follow-up during the treatment, several have marked limitations. Muscle biopsy, for example, represents only a relatively small number of fibers, and marked variation can occur because of sampling error (1). Even within muscles sampled from the same patient at the same time, muscle pathology can vary from normal to severely abnormal in adjacent sites or in identical muscles from different limbs. Nerve conductions (10) and creatine phosphokinase (16) similarly have a considerable degree of spontaneous variation that has not been well characterized for many conditions. Thus, there remains a need for additional criteria for the sequential follow-up of the course of neuromuscular disease in terms of both following therapy and documenting the natural history of illness.

SUMMARY OF THE MANAGEMENT OF THE NEUROMUSCULAR DISEASES

Anterior Horn Cell

Although none of the anterior horn cell diseases is amenable to specific therapy, much can be done to help patients with these diseases.

TABLE 2. *Laboratory evaluation of patients with neuromuscular disease—characteristic findings*

Site of involvement	Anterior horn cell	Peripheral neuropathy	Neuromuscular junction	Myopathies
Example	Amyotrophic lateral sclerosis	Nutritional neuropathy	Myasthenia gravis	Polymyositis
Creatine phosphokinase	Normal or slightly elevated	Normal	Normal	Elevated
Electromyography	Recruited motor units, number decreased; size and duration increased; spontaneous activity marked	Recruited motor units, number normal or decreased; size and duration often increased; spontaneous activity usually abnormal	Recruited motor units, normal number initially; size and duration normal; spontaneous activity normal	Motor units recruited more rapidly than normal, size of potential decreased; spontaneous activity occasionally abnormal
Motor nerve conduction velocity	Early—normal	Usually normal or slightly slowed in axonal neuropathy—usually slowed in demyelinating neuropathy	Normal	Normal
Repetitive nerve stimulation	Usually normal	Usually normal	Decremental response	Normal
Muscle biopsy	Early—single-fiber atrophy; late—grouped atrophy, fiber type grouping	Same as anterior horn cell although grouped atrophy less striking	Variable—slight or moderate atrophy frequent	Muscle necrosis, phagocytosis; inflammatory reaction