Neuromuscular Disorders

Treatment and Management

TULIO E. BERTORINI

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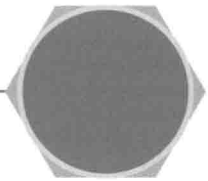
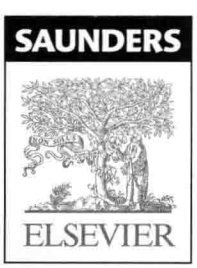


Neuromuscular Disorders: Treatment and Management

Tulio E. Bertorini, MD

Professor of Neurology and Pathology
University of Tennessee, Center for the Health Sciences, Memphis
Chief of Neurology, Methodist University Hospital
Director, Wesley Neurology Clinic and Muscular Dystrophy and ALS Clinic
Memphis, Tennessee



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1600 John F. Kennedy Boulevard
Suite 1800
Philadelphia, PA 19103-2899

NEUROMUSCULAR DISORDERS: TREATMENT AND MANAGEMENT ISBN: 978-1-4377-0372-6

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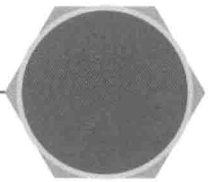
Library of Congress Cataloging-in-Publication Data
Neuromuscular disorders: treatment and management / [edited by] Tulio E. Bertorini. —1st ed.
p. ; cm.
Includes bibliographical references.
ISBN 978-1-4377-0372-6
1. Neuromuscular diseases. I. Bertorini, Tulio E.
[DNLM: 1. Neuromuscular Diseases—therapy. WE 550 N49443 2010]
RC925.5.N474 2011
616.7′44—dc22

2010010083

Acquisitions Editor: Adrianne Brigido
Developmental Editor: Taylor Ball
Design Direction: Lou Forgione

Printed in China

Last digit is the print number: 9 8 7 6 5 4 3 2 1



Neuromuscular Disorders: Treatment and Management

This work is dedicated to the members of my loving family: to my father, Nicolas; the memory of my mother, Enriqueta; my wife, Emma; my daughter, Paola and her husband Jason; my sons, Tulio and Francisco, and their girlfriends, Stacy and Paulinha; as well as my grandson, Nicolas.

Also, I want to dedicate this book to the families of my collaborators and particularly to the memory of my friend, excellent clinician and researcher, Lisa Krivickas, MD, who collaborated in this book and who recently passed away.

Preface

Recent advances in the understanding of the genetics and basic mechanisms of neuromuscular diseases have been both rapid and spectacular. Furthermore, these advances have resulted in an expansion of the methods used for diagnosis—from routine clinical histologic and electrophysiologic tests to more specific techniques, such as biochemical and Western Blot analysis, and, most important, molecular genetic testing. These modern techniques have begun to replace more costly and painful procedures for some patients.

Innovations in the field of molecular genetics have led to the identification of certain protein deficiencies and thus to the design of replacement therapy for some conditions. Examples include enzyme replacement with recombinant alpha-glucosidase for Pompe disease and agalsidase for Fabry disease. Another important advance in the understanding of neuromuscular disorders has been the recognition of the pathways of the cascade of immune mechanisms of autoimmune diseases. This understanding allows us to treat these disorders with newer immunosuppressants and selective monoclonal antibodies that target specific molecules of this cascade. These treatments hold promise for better patient care, but more knowledge of possible adverse effects is needed. At times monoclonal antibodies have been found to cause autoimmune disorders, further complicating therapy.

Although the goal of our specialty is to find cures or effective treatments for neuromuscular disorders, the management of symptoms to improve quality of life is still paramount. The control of pain in the treatment of dysautonomic symptoms and the management of muscle hyperactivity in the myotonias are examples.

Ambulation and survival can be prolonged with well-planned rehabilitation programs, orthopaedic surgery, and proper early management of cardiac, respiratory, and gastrointestinal complications, particularly in patients with motor neuron diseases and muscular dystrophy. Prolonged survival has changed the care of these patients. For example, in the past patients with Duchenne muscular dystrophy generally died of respiratory failure before they developed symptomatic cardiac disease; now they are living longer and require aggressive treatment of their cardiac complications to further prolong their lives.

Many excellent textbooks and treatises dedicated to the understanding of the basic mechanisms of clinical and laboratory diagnoses of neuromuscular diseases also include discussions of treatment but this information is not comprehensive. In this text we aim to cover the current treatment and management of these subjects and to discuss promising experimental therapies. Also included are discussions of the prevention and treatment of neuromuscular complications of medical conditions and surgery.

The introductory chapter is a brief overview of the approach to diagnosis and treatment in patients with neuromuscular disease—information that we hope will be helpful to young clinicians. The next several chapters discuss complications of neuromuscular disorders and their general management, such as rehabilitation, orthopaedic surgery, and cardiac, gastrointestinal, and respiratory care, as well as the treatment of painful neuropathy and dysautonomia. The balance of the chapters cover specific diseases as well as the basic mechanisms of these disorders.

The information in each chapter is intended to complement that in others, although occasionally there are minor repetitions. When possible, evidence-based treatment recommendations are given, particularly for the more common conditions, though we emphasize that the treatment of all patients should be individualized. For less common disorders, for which controlled trials have not yet been published, recommendations are based on published information and the authors' experience.

I am honored and grateful for the collaboration of an excellent group of renowned specialists. They have generously contributed their time and expertise to make what we hope is a textbook that is useful for all physicians who care for patients with neuromuscular disorders.

Tulio E. Bertorini, MD

Acknowledgments

For their untiring editorial assistance, I want to express my sincere appreciation to Rachel Young, RN, BS, BSN, my research coordinator, and to Kay Daugherty, medical editor of the Campbell Foundation.

I thank Mariallen Shadle for her work on the excellent histologic slides and Cindy Culver for transcription of the manuscripts.

The compilation of my Introduction was completed with the help of Rachel Young, Mariallen Shadle, and Kay Daugherty.

Recognition is extended to Taylor Ball and Adrianne Brigido of Elsevier and to Peggy Gordon of P. M. Gordon Associates.

My appreciation is also extended to Wesley Neurology Clinic, Methodist Hospitals of Memphis, and The University of Tennessee Health Science Center for continuous support.

I wish in particular to express my gratitude to the authors and collaborators of the various chapters of this work, with a special thanks to their families, as they have sacrificed their time together to participate in the preparation of this book. I also wish to thank Drs. Genaro Palmieri, Abbas Kitabchi, and Cesar Magsino for their insightful comments regarding Chapter 20, on endocrine disorders.

Finally, to all of our patients, whom we hope will benefit from the knowledge we continue to gain.

Tulio E. Bertorini, MD

Contributors

Bassam A. Bassam, MD
Professor of Neurology
Director of Neuromuscular and EMG Laboratory
University of South Alabama
College of Medicine
Attending and Professor of Neurology
University of South Alabama Medical Center
Mobile, Alabama
Chapters 10 and 20

Tulio E. Bertorini, MD
Professor of Neurology and Pathology
University of Tennessee, Center for the Health Sciences, Memphis
Chief of Neurology, Methodist University Hospital
Director, Wesley Neurology Clinic and Muscular Dystrophy and ALS Clinic
Memphis, Tennessee
Chapters 1, 7, 10, and 20

William W. Campbell, Jr., MD
Professor and Chairman
Uniformed Services University of Health Sciences
Chief, Clinical Neurophysiology
Walter Reed Army Medical Center
Bethesda, Maryland
Chapter 16

Vinay Chaudhry, MD
Professor of Neurology
Vice Chair, Clinical Affairs
Johns Hopkins University School of Medicine
Baltimore, Maryland
Chapter 13

Marinos C. Dalakas, MD
Professor, Clinical Neurosciences
Chief, Neuromuscular Diseases Service
Imperial College, London
Hammersmith Hospital Campus
London, England
Chief, Neuroimmunology Unit
Department of Pathophysiology
University of Athens Medical School
Athens, Greece
Chapter 21

Marcus Deschauer, MD
Neurologische Klinik
Universitat Halle-Wittenberg
Halle, Germany
Chapter 22

Diana M. Escolar, MD
Associate Professor of Neurology
John Hopkins School of Medicine
Center for Genetic Muscle Disorders
Kennedy Krieger Institute
Baltimore, Maryland
Chapter 19

Christopher H. Gibbons, MD, MMSc
Assistant Professor of Neurology
Harvard Medical School
Staff Neurologist
Beth Israel Deaconess Medical Center
Director, Diabetic Neuropathy Clinic
Joslin Diabetes Center
Boston, Massachusetts
Chapter 5

Daniel M. Goodenberger, MD
Professor and Chairman
Department of Medicine
University of Nevada School of Medicine
Las Vegas, Nevada
Chapter 2

Nivia Hernandez-Ramos, MD
Neuromuscular Medicine Program
Division of Neurology
University of Puerto Rico School of Medicine
San Juan, Puerto Rico
Chapter 15

Susan T. Iannaccone, MD
Jimmy Elizabeth Westcott Distinguished Chair in Pediatric Neurology
Professor of Neurology and Pediatrics
University of Texas Southwestern Medical Center
Director of Pediatric Neurology
Children's Medical Center
Chair, Section on Child Neurology
American Academy of Neurology
Dallas, Texas
Chapter 12

Cristian Ionita, MD
Assistant Professor of Pediatrics
University of Arkansas for Medical Sciences
Director of Neuromuscular Diagnostic Clinic
Arkansas Children's Hospital
Little Rock, Arkansas
Chapter 12

Mohammad K. Ismail, MD
Program Director
Gastroenterology Fellowship and Training
University of Tennessee, Memphis
Chief of Gastroenterology
Methodist University Hospital
Memphis, Tennessee
Chapter 4

Lisa S. Krivickas, MD†
Associate Professor of Physical Medicine and Rehabilitation
Harvard Medical School
Associate Chair of Academic Affairs
Associate Chief of Physical Medicine and Rehabilitation
Massachusetts General Hospital
Boston, Massachusetts
Chapter 8

Robert T. Leshner, MD
Professor of Neurology and Pediatrics
Children's National Medical Center
George Washington University
Washington, DC
Chapter 19

Yingjun David Li, MD
Consulting Neurologist
Methodist Le Bonheur Healthcare
Memphis, Tennessee
Chapter 10

Thomas E. Lloyd, MD, PhD
Assistant Professor
Department of Neurology
The Johns Hopkins School of Medicine
Baltimore, Maryland
Chapter 13

†Deceased

Catherine Lomen-Hoerth, MD, PhD
Associate Professor of Neurology
University of California, San Francisco
San Francisco, California
Chapter 11

Carlos A. Luciano, MD
Professor of Neurology
Director, Neuromuscular Medicine Program
Division of Neurology
University of Puerto Rico School of Medicine
San Juan, Puerto Rico
Chapter 15

Daniel L. Menkes, MD
Director of Clinical Neurophysiology
University of Connecticut Health Center
Farmington, Connecticut
Chapter 6

Christopher W. Mitchell, MD
Neurologist
West Tennessee Neurosciences
Jackson, Tennessee
Chapters 7 and 10

Pushpa Narayanaswami, MD
Instructor of Neurology
Division of Neuromuscular Diseases
Department of Neurology
Harvard Medical School
Beth Israel Deaconess Medical Center
Boston, Massachusetts
Chapter 17

Peter O'Carroll, MD
Fellow, Clinical Neurophysiology
The University of Tennessee Health Science Center
Memphis, Tennessee
Chapter 19

Shin J. Oh, MD
Distinguished Professor of Neurology
Department of Neurology and Pathology
University of Alabama at Birmingham
Birmingham, Alabama
Chapter 18

Nicholas J. Silvestri, MD
Assistant Professor of Neurology
State University of New York at Buffalo School of Medicine
Staff Neurologist
Erie County Medical Center
Buffalo, New York
Chapter 5

Zachary Simmons, MD
Professor of Neurology
The Pennsylvania State University School of Medicine
Director, Neuromuscular Program and ALS Center
Penn State Hershey Medical Center
Hershey, Pennsylvania
Chapter 14

Christopher F. Spurney, MD
Assistant Professor of Pediatrics
Division of Cardiology
Children's National Heart Institute
Children's National Medical Center
Washington, DC
Chapter 3

Matthias Vorgerd, MD
Associate Professor of Neurology
Bergmannsheil GmbH
Department of Neurology, Ruhr-University Bochum
Neuromuscular Center
Bochum, Germany
Chapter 22

William C. Warner, Jr., MD
Professor, Department of Orthopaedic Surgery
University of Tennessee Center for the Health Sciences
LeBonheur Children's Medical Center
Campbell Clinic, Inc.
Memphis, Tennessee
Chapter 9

Dorothy Weiss, MD, EdM
Clinical Fellow, Physical Medicine and Rehabilitation
Chief Resident, Spaulding Rehabilitation Hospital
Harvard Medical School
Boston, Massachusetts
Chapter 8

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PART

General Principles in the Treatment and Management of Neuromuscular Disorders

Tulio E. Bertorini, MD

1

Introduction: Evaluation of Patients with Neuromuscular Disorders

This book is dedicated to the treatment of neuromuscular disorders (NMDs), which include those that affect the anterior horn cells, nerve roots, plexi, peripheral nerves, neuromuscular junction, and muscles (Fig. 1-1).[1] These disorders may be caused by genetic defects or may be acquired, as in autoimmune diseases; they also may be secondary to general medical conditions or may arise as complications of surgery. To make therapeutic decisions about these disorders, clinicians should be able to recognize their clinical presentation and characteristics. This chapter provides a brief introduction to the evaluation of patients with NMDs.

Medical History and Symptoms

The evaluation should include obtaining detailed medical and family histories as well as identifying possible complicating factors. In children, information should be obtained on the prenatal period and delivery, especially if the patient was a "floppy baby," and details of the patient's developmental milestones should be recorded.[1,2]

Identifying general medical problems is important because some NMDs are associated with other conditions, such as, for example, endocrine and connective tissue diseases. Medications also should be considered, because many are known to produce neurologic complications.

Muscle weakness is a common symptom, except in patients with sensory or autonomic neuropathy or in some radiculopathies and entrapment syndromes. The rate of progression varies, and in some conditions, such as Guillain-Barré syndrome (GBS), electrolyte imbalance, toxic neuropathy, and myopathy associated with rhabdomyolysis, it is rapid (Box 1-1). In disorders of neuromuscular transmission, such as myasthenia gravis (MG), weakness fluctuates during the day. In periodic paralysis, weakness is recurrent,[3] whereas in other disorders, such as muscular dystrophies, or in hereditary and some autoimmune neuropathies, it is subacute or chronic (Box 1-2).[3,4]

The distribution of weakness also is important in diagnosis; for example, it is proximal in spinal muscular atrophies and most myopathies, except for some rare disorders in which it is more distal. In myopathies, weakness usually is symmetric, although asymmetry can be seen in some cases, as in fascioscapulohumeral dystrophy. In polyneuropathies, this characteristically begins in the legs, but may initially manifest more prominently in the upper extremities, as in multifocal neuropathy, brachial plexopathies, and cervical spinal canal disorders as well as in amyotrophic lateral sclerosis (ALS). This follows the territory of roots or nerves in radiculopathies and focal neuropathies.[4]

Dysphagia, diplopia, and droopy eyelids also help to identify NMDs because they occur in some myopathies and also in disorders of neuromuscular transmission, such as MG. Symptoms of respiratory difficulty should be recognized and treated promptly because this can be the first manifestation of a disorder such as MG, GBS, ALS, and myopathies, such as acid maltase deficiency, whereas in other disorders, it appears at later stages.[4,5]

Difficulty combing the hair and placing objects in high cabinets commonly occurs in patients with shoulder-girdle weakness, whereas difficulty writing and grasping objects indicates involvement of the forearm and hand muscles, as in ALS and inclusion body myositis. Weakness of the hip extensors usually causes inability to rise from a low chair or a toilet seat, whereas difficulty ascending stairs indicates dysfunction of the hip flexors and quadriceps muscles. More severe weakness of the quadriceps muscles occurs in inclusion body myositis, causing difficulty descending stairs.[3,6] When the distal muscles are affected, foot drop may cause a steppage gait and difficulty negotiating curves or changing courses, as seen in polyneuropathies, distal dystrophies, and ALS.

Muscle stiffness, tightness, and spasms occur as a result of spasticity in disorders affecting the upper motor neuron, but these also occur in patients with motor unit hyperactivity, such as "stiff-person" and Isaac syndromes or the myotonias. Those with inflammatory myopathies, polymyalgia rheumatica, fasciitis, and hypothyroidism also complain of stiff limbs. Cramping at rest or during exercise is a prominent symptom of cramp-fasciculation syndrome[7] and also some neuropathies. In metabolic myopathies, this usually occurs during or after exercise, or after fasting in some cases. Fatigue is common in disorders of neuromuscular transmission, such as Eaton-Lambert syndrome (ELS) and MG, but also in myopathies, even though weakness is the major symptom. In ELS, there may be temporary improvement after brief exercise.

Numbness and decreased sensation as well as paresthesias and neuropathic pain are symptoms of peripheral neuropathies.[8] These symptoms are localized in the affected areas in those with radiculopathies, plexopathies, and entrapment neuropathies. Autonomic dysfunction can occur in some neuropathies and also in ELS.

Physical Examination

A careful general physical examination is essential to arrive at a diagnosis, and the clinician should assess cardiac and lung function, examine the eyes for cataracts and retinal disease, and check for hearing loss,

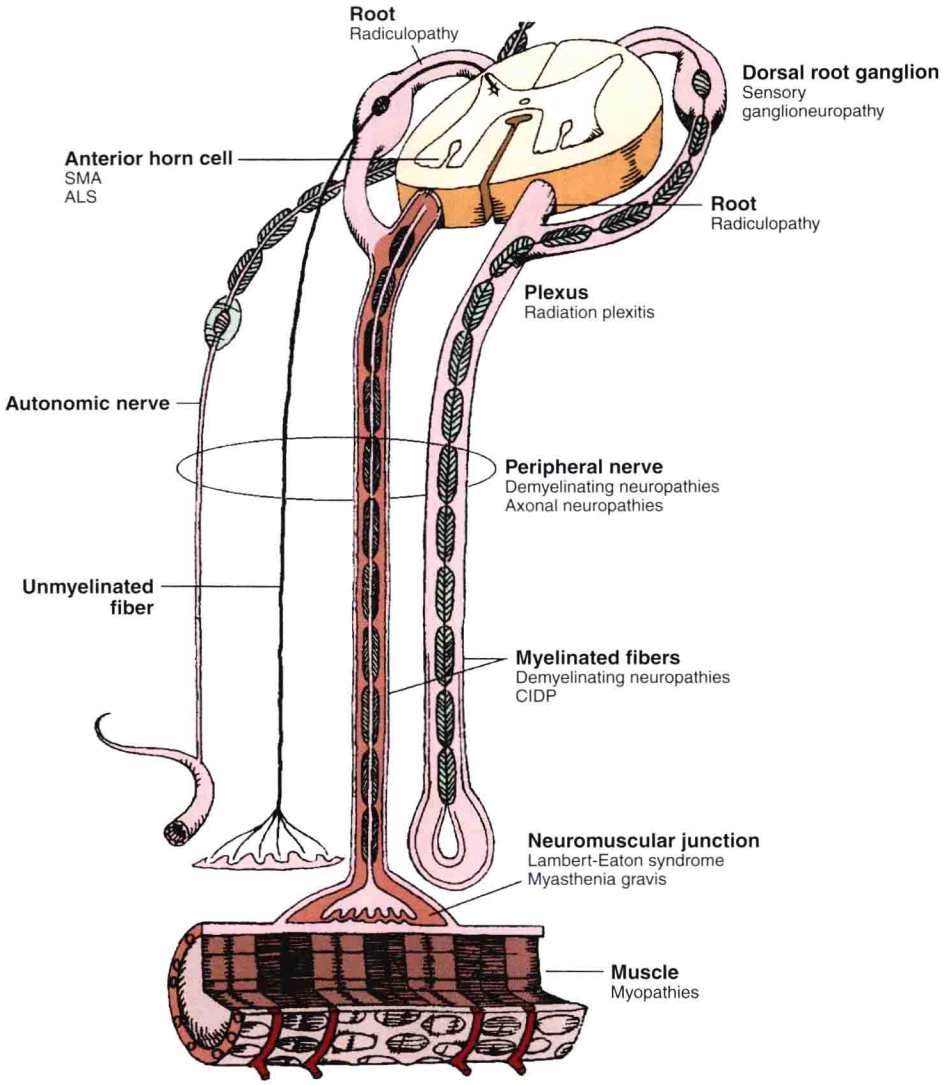

Figure 1-1 Anatomic elements of the peripheral nervous system and related neurologic disorders. ALS, amyotrophic lateral sclerosis; CIDP, chronic inflammatory demyelinating polyneuropathy; SMA, spinal muscular atrophy. (Adapted from Bertorini TE: Overview and classification of neuromuscular disorders. In Bertorini TE, ed: *Clinical Evaluation and Diagnostic Tests for Neuromuscular Disorders*, Woburn, MA, 2002, Butterworth-Heinemann, pp 1–13.)

Box 1-1 Neuromuscular Disorders That May Present with Acute Generalized Weakness

Motor Neuron Diseases

Poliomyelitis
Amyotrophic lateral sclerosis (rarely)

Neuropathies

Guillain-Barré syndrome and variants
Porphyria, particularly acute intermittent
Dinoflagellate toxins
Diphtheria
Arsenic poisoning and other acute toxic neuropathies

Disorders of Neuromuscular Transmission

Botulism and other biologic toxins (black widow spider bites, snake bites)
Organophosphate poisoning
Eaton-Lambert myasthenic syndrome
Hypermagnesemia
Myasthenia gravis

Myopathies

Rhabdomyolysis (from various causes, including metabolic, toxic, and infectious)
Polymyositis/dermatomyositis
Infectious myositis (e.g., trichinosis, toxoplasmosis)
Electrolyte imbalance (e.g., hypohyperkalemia, hypermagnesemia, hypocalcemia, hypercalcemia, hypophosphatemia)
Hyperthyroidism
Toxins
Intensive care myopathy (after immobilization with paralyzing agents and steroids in the intensive care unit)

Box 1-2 Examples of Conditions That Present with Progressive Subacute or Chronic Proximal Muscle Weakness

- Progressive spinal muscular atrophy
- Bulbospinal muscular atrophy (Kennedy disease)
- Amyotrophic lateral sclerosis (sometimes)
- Chronic inflammatory demyelinating neuropathy
- Eaton-Lambert myasthenic syndrome
- Myasthenia gravis
- Endocrine diseases (e.g., hypothyroidism, Cushing disease, hyperparathyroidism)
- Drugs (e.g., steroids, cholesterol-lowering agents, zidovudine, colchicine, chloroquine)
- Toxins (e.g., alcoholic myopathy)
- Electrolyte imbalance
- Congenital myopathies (usually of earlier onset)
- Muscular dystrophies
- Polymyositis and dermatomyositis
- Inclusion body myositis
- Adult "nemaline" or "rod" myopathy
- Mitochondrial myopathy
- Juvenile and adult forms of acid maltase deficiency
- Carnitine deficiency

which is often seen in mitochondrial disorders. Visceromegaly and skin changes are present in some patients with neuropathies, for example, those with POEMS (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*onoclonal gammopathy, *s*kin changes) syndrome. Skin abnormalities can also be seen in connective tissue disorders, whereas patients with dermatomyositis have a characteristic rash.[4]

Intellectual function should be assessed because it could be impaired in some diseases, such as in some cases of ALS and in myotonic dystrophy. During the neurologic examination, posture and muscle strength should be evaluated to determine, for example, whether there is hyperlordosis with proximal atrophy in myopathies or distal atrophy in neuropathies, whether it is symmetric (Fig. 1-2) or focal (Fig. 1-3), or whether it affects the upper or lower extremities more prominently (see Fig. 1-2). The clinician should examine the patient for muscle hypertrophy, which is seen in some dystrophies and disorders of neuromuscular hyperactivity. Examination of muscle tone also is important to determine whether there is focal or generalized hypotonia, particularly in infants (Fig. 1-4 and Box 1-3). Gait analysis includes observation for the characteristic waddling of myopathies, the circumduction of spasticity, the steppage gait of peripheral neuropathy and distal dystrophies, and the ataxic gait in

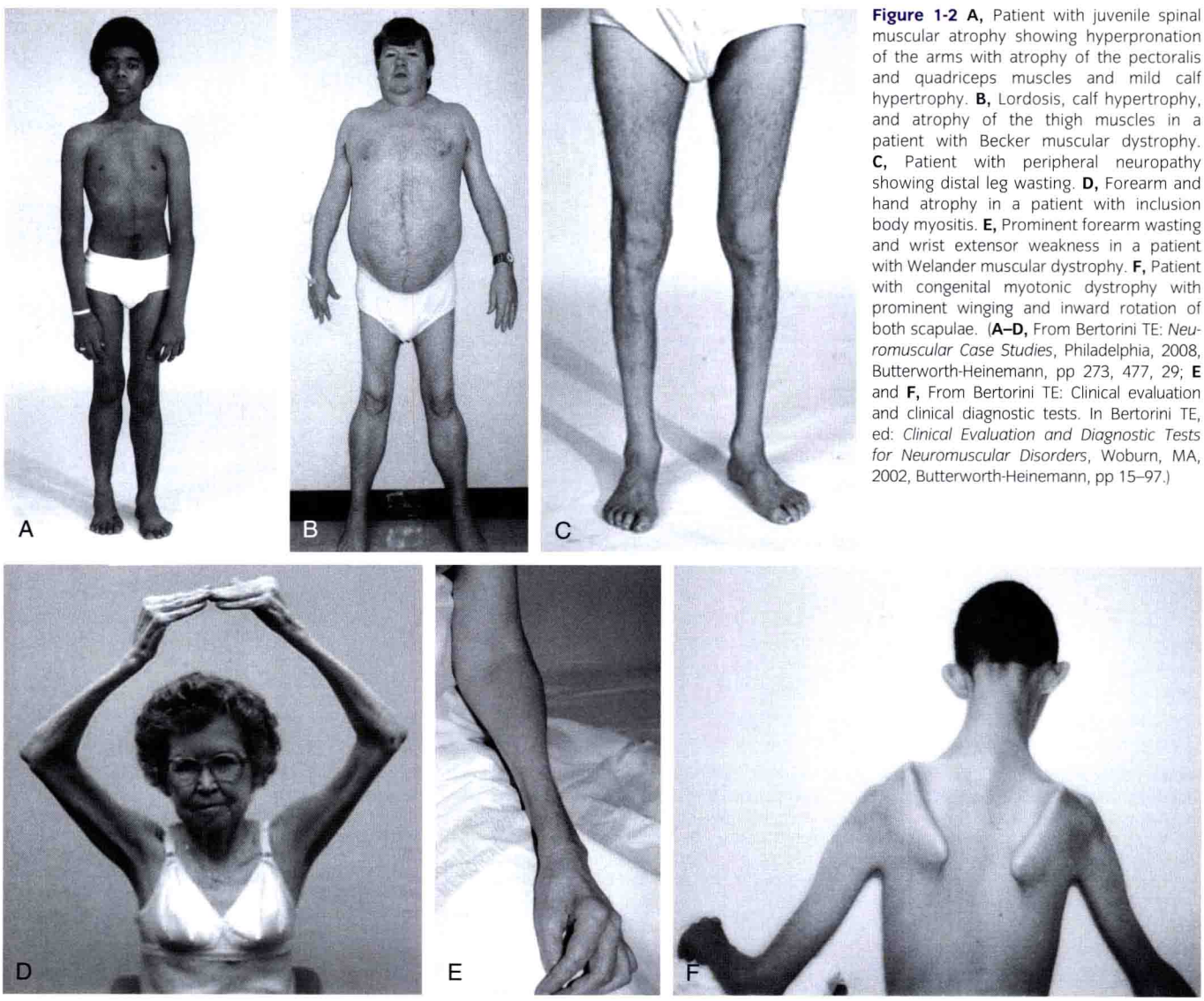

Figure 1-2 **A,** Patient with juvenile spinal muscular atrophy showing hyperpronation of the arms with atrophy of the pectoralis and quadriceps muscles and mild calf hypertrophy. **B,** Lordosis, calf hypertrophy, and atrophy of the thigh muscles in a patient with Becker muscular dystrophy. **C,** Patient with peripheral neuropathy showing distal leg wasting. **D,** Forearm and hand atrophy in a patient with inclusion body myositis. **E,** Prominent forearm wasting and wrist extensor weakness in a patient with Welander muscular dystrophy. **F,** Patient with congenital myotonic dystrophy with prominent winging and inward rotation of both scapulae. (**A–D,** From Bertorini TE: *Neuromuscular Case Studies*, Philadelphia, 2008, Butterworth-Heinemann, pp 273, 477, 29; **E** and **F,** From Bertorini TE: Clinical evaluation and clinical diagnostic tests. In Bertorini TE, ed: *Clinical Evaluation and Diagnostic Tests for Neuromuscular Disorders*, Woburn, MA, 2002, Butterworth-Heinemann, pp 15–97.)