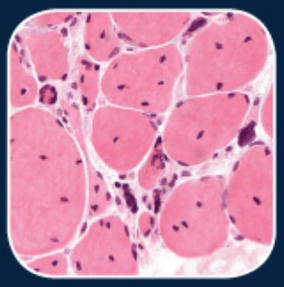

MUSCLE DISEASE

Pathology and Genetics

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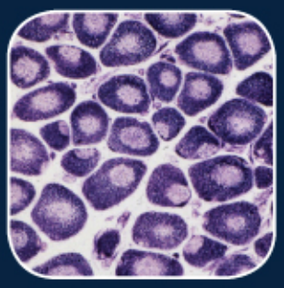

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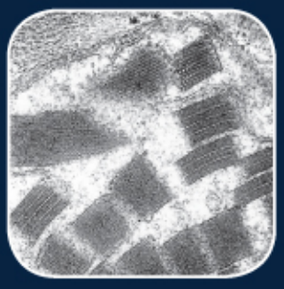
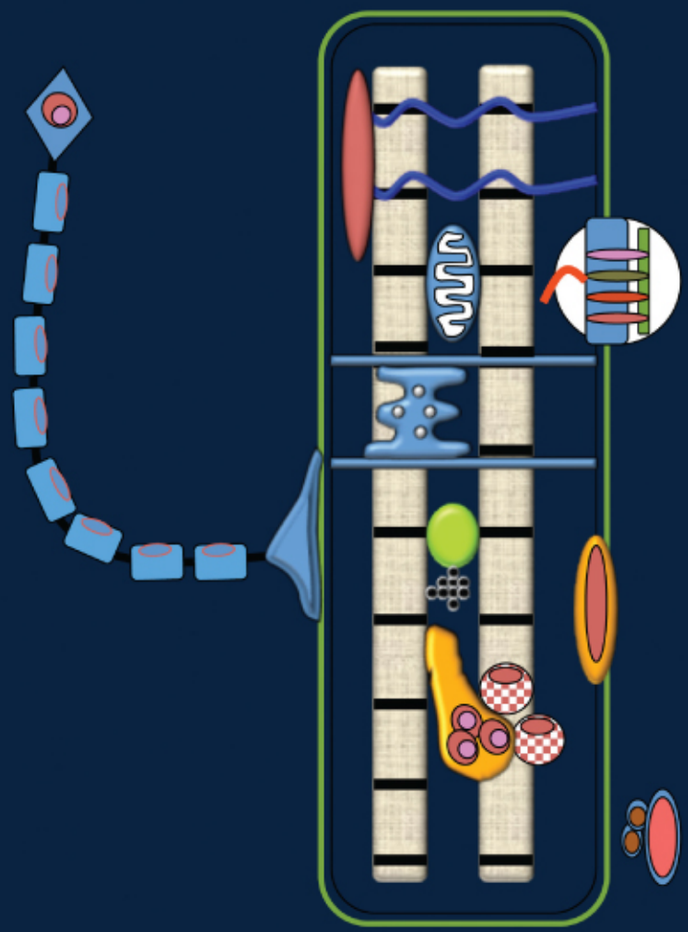
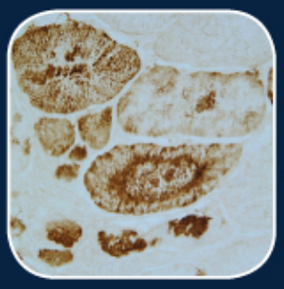
Roy O. Weller







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Muscle Disease

Advisory Editors

Muscle Disease: Pathology and Genetics

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SECOND EDITION

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Wiley-Blackwell is an imprint of John Wiley & Sons, formed by the merger of Wiley's global Scientific, Technical and Medical business with Blackwell Publishing.

Registered office: John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial offices: 9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
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Library of Congress Cataloging-in-Publication Data

Muscle disease : pathology and genetics / edited by Hans H. Goebel, Caroline A. Sewry, Roy O. Weller. – Second edition.
p. ; cm.
Preceded by (work): Structural and molecular basis of skeletal muscle diseases / volume editor, George Karpati. Basel : ISN Neuropath Press, c2002.
Includes bibliographical references and index.
ISBN 978-0-470-67205-1 (hardback : alk. paper) – ISBN 978-1-118-63546-9 – ISBN 978-1-118-63547-6 (Mobi) – ISBN 978-1-118-63548-3 (ePub) – ISBN 978-1-118-63549-0
I. Goebel, H.-H., editor of compilation. II. Sewry, Caroline A., editor of compilation. III. Weller, Roy O., editor of compilation. IV. International Society of Neuropathology, issuing body. V. Structural and molecular basis of skeletal muscle diseases. Preceded by (work):
[DNLM: 1. Muscular Diseases–pathology. 2. Muscular Diseases–genetics. WE 550]
RC927
616.7'4–dc23
2013010900

A catalogue record for this book is available from the British Library.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Cover design by Meaden Creative

Set in 9.25/12pt Minion by Toppan Best-set Premedia Limited, Hong Kong

1 2013

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Preface

The International Society of Neuropathology (ISN) has a major role in promoting education and improving standards of diagnosis and research in diseases of the nervous system. In this activity, the ISN works closely with clinicians, geneticists, basic neuroscientists, biochemists, and immunologists to maintain a broad spectrum of knowledge for the care and treatment of patients with neurological disease. In order to fulfill this objective, the ISN sponsors the research journal *Brain Pathology*, and a series of books devoted to maintaining and improving the standard of neuropathology worldwide.

The initial series of ISN neuropathology books was initiated by Paul Kleihues and published between 2001 and 2005 under the general editorship of Ynvge Olsson. The books comprised *Developmental Neuropathology* edited by Geoffrey A. Golden and Brian Harding (2004), and *Pathology and Genetics of Cerebrovascular Diseases* edited by Hannu Kalimo (2005) and were preceded by the first edition of *Structural and Molecular Basis of Skeletal Muscle Diseases*, edited by George Karpati (2002) and the first edition of *Neurodegeneration: the Molecular Pathology of Dementia and Movement Disorders*, edited by Dennis Dickson (2003). In parallel with the ISN books has been the publication of a series entitled *WHO Classification of Tumours of the Central Nervous System* published by WHO Press. The fourth edition of the brain tumor book, edited by David N. Louis, Hiroko Ohgaki, Otmar D. Wiestler and Webster K. Cavenee, was published in 2007.

With the present series editor, the second edition of *Neurodegeneration: the Molecular Pathology of Dementia and Movement Disorders* was published in 2011 with Dennis W. Dickson and Roy O. Weller as editors; the book was subsequently translated into Spanish as *Neurodegeneración: Patología molecular de la demencia y los trastornos del movimiento* and published by Editorial Médica Panamericana, S.A.

The publication of the second edition of the book on muscle disease, the present volume, entitled *Muscle Disease: Pathology and Genetics*, is in response to the very rapid and significant advances in the field of muscle disease that have occurred over the last decade. For this volume, edited by Hans H. Goebel, Caroline A. Sewry and Roy O. Weller, a team of authors was appointed from an international field of experts after consultation with the Advisory Editors. One of the major challenges has been to assemble a coherent text that reflects the mood of this rapidly changing field of medical science. The main objective of the book is to offer the reader a modern view of the pathology and genetics of muscle disease that will integrate the requirements of clinicians, pathologists, geneticists, and other neuroscientists involved in the investigation, diagnosis, research, management, and treatment of muscle disorders.

Although the clinical classification of muscle disease is extremely valuable in diagnosis and management, such a classification does not allow the adequate expression of modern concepts in the pathology and genetics of muscle disorders. For this reason, the present book has been organized in such a way that the whole spectrum of muscle disease from neurogenic and inflammatory disorders to diseases based upon mutations in a single gene can be covered in a logical sequence. The structure of the present book is based upon the motor unit; the inherited disorders in particular are related to the ultrastructure of the muscle fiber, its organelles, and associated connective tissue elements.

Following an introductory chapter, the first section of the book is devoted to general introductions to the clinical, pathological, and genetic aspects of muscle disease. Subsequent sections detail the pathology and genetics of neurogenic muscle disease and disorders of neuromuscular transmission. Then follows a series of sections based upon the subcellular structures and organelles in the muscle fiber, for example, disorders of the sarcolemma focusing on muscular dystrophies and related diseases; disorders of nuclei, myofibrils, intermediate filaments, and mitochondria. Subsequent sections cover diseases of sarcoplasmic reticulum and T-tubules, cytoplasmic proteins, metabolic and storage disorders and muscle diseases associated with DNA expansions and facioscapulohumeral dystrophy. All-important sections on inflammatory myopathies, toxic myopathies, muscle diseases associated with age, systemic disorders and rare structural abnormalities are grouped together at the end of the book. For ease of navigation through the complex variety of muscle diseases, individual chapters have been organized in a standard format that allows the

reader to easily locate information on individual disease entities in different chapters. Each chapter covers the clinical, pathological, and genetic aspects of each disorder and includes data on experimental muscle disease and, where possible, a vision of future developments and treatment of each disorder.

I would like to thank Professors Hans Goebel and Caroline Sewry for their inspiration in the planning and their efforts in the preparation of the book; their breadth of knowledge and contacts within the field of muscle disease has been outstanding. I would also like to thank the Advisory Editors for their counsel and, wholeheartedly, the authors of individual chapters for the high quality of their contributions. Dr Herbert Budka, as president of ISN, Dr Seth Love as past General Secretary of ISN and Dr David Hilton as the present General Secretary have all been sources of valuable advice and inspiration. The book would not have been possible without the skill and commitment of the staff of the publishers, Wiley-Blackwell, especially Martin Sugden, Jennifer Seward, Rob Blundell and Helen Harvey, whom I sincerely thank.

Finally, who is most likely to benefit from reading and consulting this book? With its integrated approach, the book will be a valuable asset to clinicians, pathologists, geneticists, and neuroscientists involved in the investigation, diagnosis, research, treatment, and management of muscle disease.

Roy O. Weller
Series Editor

List of Abbreviations

AAS	anabolic-androgenic steroid
AAV	adeno-associated virus
ABD	actin-binding domain
AChE	acetylcholinesterase
AChR	acetylcholine receptor
ACTH	adrenocorticotropic hormone
AD	autosomal dominant
ADCNM	autosomal dominant centronuclear myopathy
ADEDMD	autosomal dominant Emery–Dreifuss muscular dystrophy
ADP	adenosine diphosphate
AIRE	autoimmune regulator
ALS	amyotrophic lateral sclerosis
AMC	arthrogryposis multiplex congenita
AMP	adenosine monophosphate
ANCA	antineutrophil cytoplasmic antibody
AR	autosomal recessive
ARCNM	autosomal recessive centronuclear myopathy
AREDMD	autosomal recessive Emery–Dreifuss muscular dystrophy
ATGL	adipose triglyceride lipase
ATP	adenosine triphosphate
ATRA	all-trans-retinoic acid
AVM	autophagic vacuolar myopathies
AVSF	autophagic vacuoles with sarcolemmal features
AZT	azidothymidine
BM	Bethlem myopathy
BMD	Becker muscular dystrophy
bp	base pairs
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CADM	clinically amyopathic dermatomyositis
CCD	cardiac conduction defect, central core disease
CDS	Chanarin–Dorfman syndrome
CFTD	congenital fiber type disproportion
CGH	comparative genomic hybridization
CGL	congenital generalized lipodystrophy
CIM	critical illness myopathy
CIPNM	critical illness polyneuromyopathy
CK	creatine kinase
CMAP	compound muscle action potential
CMD	congenital muscular dystrophy
CMS	congenital myasthenic syndrome
CMT	Charcot–Marie–Tooth disease
CNM	centronuclear myopathy
CNS	central nervous system
CNTF	ciliary neurotropic factor
CNV	copy number variation
COX	cytochrome c oxidase
CPEO	chronic progressive external ophthalmoplegia
CPT	carnitine palmitoyltransferase
CPT2	carnitine palmitoyltransferase II
CRM	core-rod myopathy
CS	cylindrical spirals
CSF	cerebrospinal fluid
CT	computed tomography
CTD	connective tissue diseases
DA	distal arthrogryposis
DG	dystroglycan
DGC	dystrophin glycoprotein complex
DM	myotonic dystrophy/distal myopathy/dermatomyositis
DMAT	distal myopathy with anterior tibial onset
DMD	Duchenne muscular dystrophy
DMRV	distal myopathy with rimmed vacuoles
DTI	diffusion tension imaging
DYS	dystrophin
EACA	epsilon aminocaproic acid
EBS-MD	epidermolysis bullosa simplex with muscular dystrophy
EBS-PA	epidermolysis bullosa simplex with pyloric atresia
E-C	excitation-contraction
ECG	electrocardiogram
ECM	extracellular matrix
EDMD	Emery–Dreifuss muscular dystrophy
EDS	Ehlers–Danlos syndrome

ELISA	enzyme-linked immunosorbent assay
EM	electron microscopy
EMG	electromyography
EOMG	early-onset myasthenia gravis
EPP	endplate potential
ER	endoplasmic reticulum
ERAD	endoplasmic reticulum-associated degradation
ES	embryonic stem
ETF	electron transfer flavoprotein
ETFDH	electron transfer flavoprotein dehydrogenase
FADS	fetal akinesia deformation sequence
FCMD	Fukuyama muscular dystrophy
FSHD	facioscapulohumeral dystrophy
FTD	frontotemporal dementia
FTLD	frontotemporal lobar degeneration
GBS	Guillain–Barré syndrome
GGT	γ-glutamyltransferase
GH	growth hormone
GNE	UDP-*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase
GSD	glycogen storage disease
HCK	hyperCKemia
HCM	hypertrophic cardiomyopathy
H&E	hematoxylin and eosin
HIBM	hereditary inclusion body myopathy
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HMERF	hereditary myopathy with early-onset respiratory failure
HMGCR	3-hydroxy-3-methylglutaryl-coenzyme A reductase
HMSN	hereditary motor and sensory neuropathy
HTLV	human T lymphotropic virus
HyperPP	hyperkalemic periodic paralysis
HypoPP	hypokalemic periodic paralysis
IBM	inclusion body myositis
IBMPFD	inclusion body myopathy with Paget disease of bone and frontotemporal dementia
ICD	implantable cardioverter defibrillator
IF	intermediate filament
IFN	interferon
Ig	immunoglobulin
IGF	insulin-like growth factor
IIM	idiopathic inflammatory myopathy
IL	interleukin
ILD	interstitial lung disease
IMNM	immune-mediated necrotizing myopathy
INI	intranuclear inclusion
ISN	International Society of Neuropathology
IVCT	*in vitro* contracture test
JDM	juvenile dermatomyositis
kb	kilobase
KSS	Kearns–Sayre syndrome
LAMP	lysosome-associated membrane protein
LCHAD	long-chain 3-hydroxyacyl-CoA dehydrogenase
L-CMD	*LMNA*-related congenital muscular dystrophy
LDH	lactate dehydrogenase
LEMS	Lambert–Eaton myasthenic syndrome
LGMD	limb-girdle muscular dystrophy
LHON	Leber hereditary optic neuropathy
LPL	lipoprotein lipase
LQTS	long QT syndrome
LSM	lipid storage myopathy
MAA	myositis-associated antibody
MAC	membrane attack complex
MAD	myoadenylate deaminase
MADD	myoadenylate deaminase deficiency/multiple acyl-coenzyme A dehydrogenase deficiency
MB-DRM	desmin-related myopathy with Mallory body-like inclusions
MC	myotonia congenita
MCT	medium-chain triglyceride
MCTD	mixed connective tissue disease
MD	muscular dystrophy
MDC1C	muscular dystrophy – congenital type 1C
MEB	muscle–eye–brain disease
MELAS	mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke
MEPP	miniature endplate potential
MFM	myofibrillar myopathy
MG	myasthenia gravis
MHC	major histocompatibility complex
MHCd	myosin heavy chain, developmental
MHS	malignant hyperthermia susceptibility
MLPA	multiplex ligation probe amplification
MM	Miyoshi myopathy
MmD	multi-minicore disease
MMF	macrophagic myofasciitis
MND	motor neuron disease
MRF	muscle regulatory factor
MRI	magnetic resonance imaging
MSA	myositis-specific antibody
MSS	Marinesco–Sjögren syndrome
MTP	mitochondrial trifunctional protein
MuRF1	muscle RING-finger 1
MuSK	muscle-specific kinase
MyHC	myosin heavy chain
NADH-TR	reduced nicotinamide adenosine dinucleotide tetrazolium reductase
NARP	neuropathy, ataxia, and retinitis pigmentosa
NBT	nitroblue tetrazolium
NCAM	neural cell adhesion molecule
NGS	next-generation sequencing
NLSD	neutral lipid storage disease
NM	nemaline myopathy
NMJ	neuromuscular junction
nNOS	neuronal nitric oxide synthase
OM	overlap myositis

OMIM	*Online Mendelian Inheritance in Man*
OPMD	oculopharyngeal muscular dystrophy
ORF	open reading frame
ORO	oil red O
OXPHOS	oxidative phosphorylation
PAM	potassium-aggravated myotonia
PAS	periodic acid–Schiff
PC	paramyotonia congenita
PCD	primary carnitine deficiency
PCR	polymerase chain reaction
PDB	Paget disease of bone
PEO	progressive external ophthalmoplegia
PFK	phosphofructokinase
PFKD	phosphofructokinase deficiency
PGAM	phosphoglycerate mutase
PGK	phosphoglycerate
PGM	phosphoglucomutase
PHK	phosphorylase b kinase
PM	polymyositis
PPAR	peroxisome proliferator-activated receptor
PRD	plectin repeat domain
PTRF	polymerase I and transcript release factor
RA	rheumatoid arthritis
RBM	reducing body myopathy
RF	rheumatoid factor
RFLP	restriction fragment length polymorphism
RMD	rippling muscle disease
RNS	repeat nerve stimulation
ROS	reactive oxygen species
RRF	ragged red fiber
RSMD	rigid spine muscular dystrophy
RSS	rigid spine syndrome
SCARMD	severe childhood autosomal recessive muscular dystrophy
SDH	succinate dehydrogenase
SEPN1-RM	SEPN1-related myopathy
SERCA	sarcoplasmic endoplasmic reticulum ATPase
SFEMG	single-fiber electromyography
SG	sarcoglycan
sIBM	sporadic inclusion body myositis
SIDS	sudden infant death syndrome
SLE	systemic lupus erythematosus
SMA	spinal muscular atrophy
SMARD1	spinal muscular atrophy with early respiratory insufficiency
SNP	single nucleotide polymorphism
SR	sarcoplasmic reticulum
SRP	signal recognition particle
SS	Sjögren syndrome
SSc	systemic sclerosis
STIR	short tau inversion recovery
STM	sarcotubular myopathy
TC	terminal cisternae
TG	triglyceride
TGF	transforming growth factor
TMD	tibial muscular dystrophy
TNF	tumor necrosis factor
TSP	thrombospondin
TTS	transverse tubular system
TTX	tetrodotoxin toxin
UCMD	Ullrich congenital muscular dystrophy
UPS	ubiquitin-proteasome system
US	ultrasonography
UTR	untranslated region
VCP	valosin-containing protein
VCPDM	vocal cord and pharyngeal weakness and distal myopathy
VLCAD	very long-chain acylcoenzyme A dehydrogenase
WB	Western blotting
XMEA	X-linked myopathy with excessive autophagy

1 Introduction to Muscle Disease: Pathology and Genetics

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Introduction

There is a very wide variety of disorders that result in muscle weakness, pain, and wasting. The causes of muscle disease range from disruption of the nerve supply and destruction of segments of muscle fibers to interference with the function of individual enzymes or proteins within fibers that characterizes genetic disorders of muscle. Appropriate management and treatment of muscle disease entail close collaboration between clinicians, pathologists, and geneticists, although the balance of involvement of the three groups may vary depending upon the nature of the disease. In adults, muscle diseases are often due to denervation or inflammation as in polymyositis, dermatomyositis, and inclusion body myositis, or to toxic and drug-related myopathies and the effects of aging. However, there is also a growing number of recognized inherited muscle disorders of adult onset. The picture is rather different in children, in whom genetic disorders predominate. During the last two decades, there has been an explosion of research into genetic disorders of muscle and this has changed the way in which clinicians and researchers view muscle disease and challenged the traditional classification of muscle disease.

The aim of this book is to review the whole range of muscle disease using the motor unit and the subcellular components of the muscle fiber to guide the reader through the many different disorders. The concept behind the book is that clinicians, pathologists, and geneticists require an understanding of each other's disciplines to communicate effectively in the quest for diagnosis and appropriate management and treatment of the patient. In some cases, the diagnosis may be obvious from the clinical presentation and from relatively noninvasive investigations such as electromyography (EMG), magnetic resonance imaging (MRI), and measurements of enzymes such as creatine kinase in the blood. Other cases of muscle disease require muscle biopsy to confirm, pathologically, the presence of denervation, an inflammatory disorder or a reaction to a drug. In a growing number of cases, a muscle biopsy is required to identify the presence of abnormal structures and/or abnormalities in protein expression which, when correlated with clinical features, can aid the identification of a gene defect. This last pathway to diagnosis is often complicated as a defect in one gene may result in a spectrum of phenotypes, or in different phenotypes and pathologies that may overlap with more than one disorder. On the other hand, defects in several different genes may produce similar clinical phenotypes and pathologies. It is the role of this book to set out the pathology and genetics of muscle disease in such a manner that it will guide clinicians, pathologists, and geneticists through the complicated maze of our current understanding of muscle disorders.

Structure of the book

The book is divided into 17 sections, starting with general chapters on clinical features, pathology, and genetics. These are followed by sections related to disorders of nerve supply and genetic disorders of specific subcellular structures in muscle fibers. The book concludes with all-important sections on the inflammatory, toxic, and aging disorders of muscle that often predominate in adults.

Section 1

This section contains three chapters devoted to the general aspects of clinical muscle disease (Chapter 2), to an approach to muscle pathology (Chapter 3) and to the genetics of muscle disorders

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(Chapter 4). In this section, the three chapters set the scene for interpreting the rest of the book by covering the salient clinical features, the role of investigations, such as muscle imaging and serum enzyme levels; by outlining the techniques and pathological features used in assessing muscle biopsies; and by discussing the development and limitations of genetic techniques in the diagnosis of muscle disease.

In subsequent sections, the chapters are laid out in a standard pattern, where feasible, starting with a definition of the disorder and a list of major synonyms. Incidence of the disorder with sex, age, and geographical distribution follow and there is a short account of the clinical features and investigations that are characteristic of the particular disease. A description of the pathology, that may include histopathology, histochemistry, immunohistochemistry, immunoblotting, electron microscopy, and immunological investigations where relevant, is succeeded by an account of the genetics and differential diagnosis where possible. Each chapter ends with a review of animal models and an insight into future perspectives.

Sections 2–17 relate to Figure 1.1. In this diagram, a muscle fiber is depicted with its nerve supply and motor endplate. Components at the surface of the muscle fiber and within the fiber itself are labeled with numbers that refer to the sections of the book dealing with disorders that involve those particular organelles and structures.

Section 2: Neurogenic Muscle Pathology (Chapter 5)

Normal innervation is essential and paramount for the functioning of a muscle fiber. This section covers the major effects on muscle of defects in motor neurons of the spinal cord and of the peripheral nerve axons, many of which are inherited. A subsequent book in the present series will cover these disorders in greater detail. Atrophy of muscle fibers is common to neurogenic disorders of muscle. Early atrophic muscle fibers may be diffusely distributed but later the pathology is characterized by grouping of atrophic fibers. Muscle fibers are reinnervated by surviving axons and by collateral sprouting of axons so that the normal checkerboard pattern of fiber types is disrupted and all fiber types may show grouping.

Section 3: Diseases of Neuromuscular Transmission (Chapters 6 and 7)

Depolarization of muscle fibers that leads to contraction requires not only a fully functional neuron and axon but also a functioning neuromuscular junction. The neuromuscular junction consists of a presynaptic part (the peripheral nervous system) and a postsynaptic part (the muscle fiber) where junctional folds form the subneural apparatus. Diseases of the neuromuscular junction or of neuromuscular transmission are referred to as "myasthenic syndromes" and may affect the presynaptic or postsynaptic compartment. Myasthenic conditions may be acquired, i.e. myasthenia gravis and Eaton–Lambert syndrome, both of autoimmune origin (Chapter 6), or they may be hereditary disorders (so-called congenital myasthenic syndromes) that result from defects in genes encoding proteins localized or enhanced at the neuromuscular junction (Chapter 7). Both disease types affect the threshold of functional postsynaptic acetylcholine receptors and the structure of the junctional folds of the motor endplate.

Section 4: Sarcolemma: Muscular Dystrophies and Related Disorders (Chapters 8–11)

The sarcolemma consists of the outer basement membrane and basal lamina, the plasma membrane (a protein and lipid bilayer), and its associated cytoskeleton. Defects in several proteins of the layers of the sarcolemma cause muscular dystrophies and related disorders (Chapters 8–10). Dystrophin was the first defective protein to be identified in a neuromuscular disorder and this paved the way for the explosion in understanding the molecular basis of muscle diseases. The large dystrophin molecule in the fiber cytoskeleton is connected to a complex of cell membrane proteins that link it to the basal lamina. Defects in this complex and in the extracellular matrix result in a number of disorders, including Duchenne, Becker, limb-girdle and congenital muscular dystrophies, and are associated with varying degrees of destruction and regeneration of muscle fibers, fiber hypertrophy, and fibrosis of the endomysium; all are typical features of a muscular dystrophy but may vary in their severity (Chapters 8 and 9). Other sarcolemmal proteins that are not components of this complex (but may bind to some components) are also associated with other forms of muscular dystrophy (Chapter 10), in which disorders of sarcolemmal ion channels result in disturbances of ionic concentrations that affect muscle contraction and relaxation (Chapter 11).

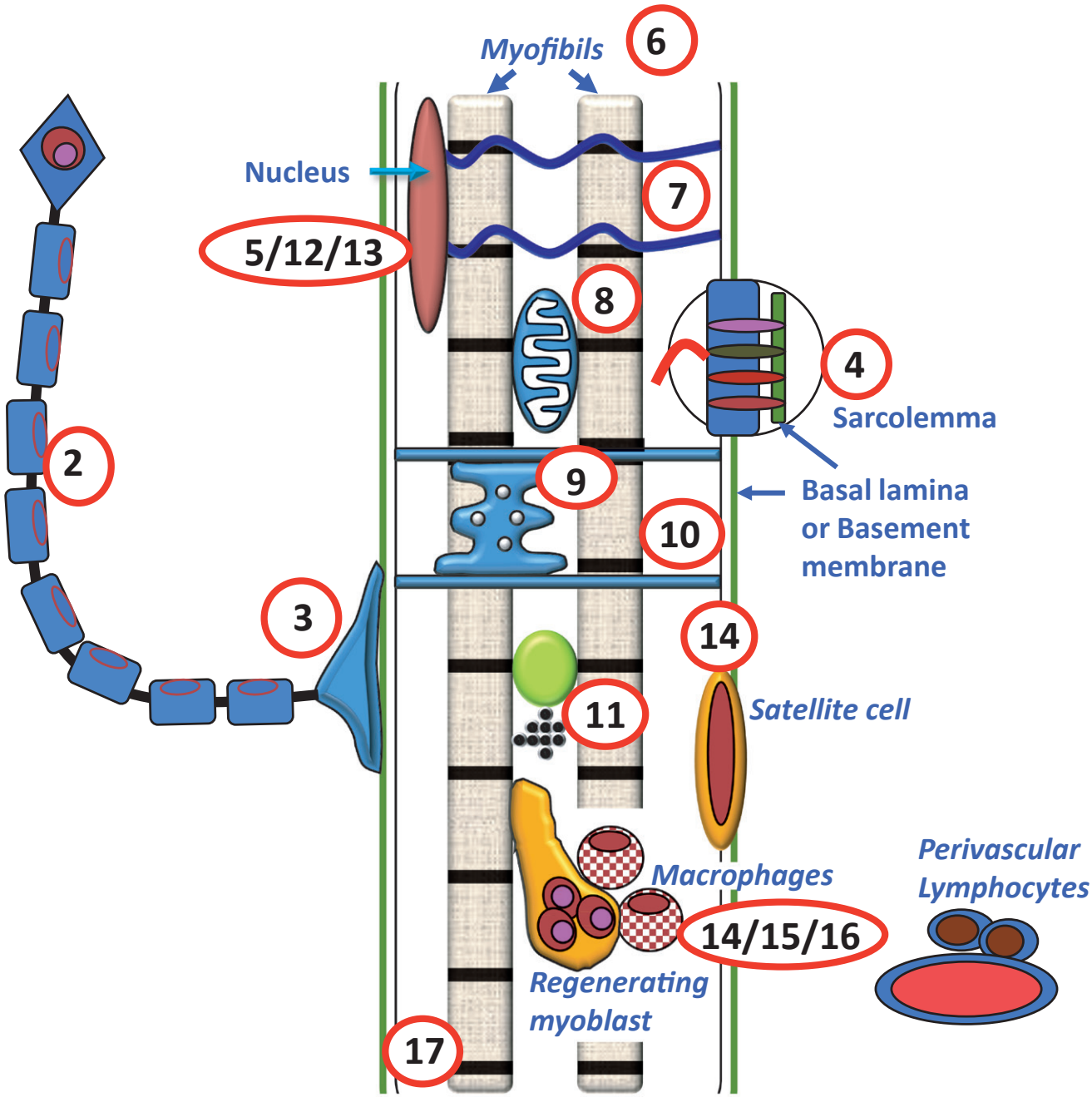
Section 5: Disorders of Nuclear Proteins and Nuclear Positioning (Chapters 12 and 13)

The nuclear envelope has a specialized complex of proteins that interacts with the nuclear matrix. Defects in these proteins are associated with several phenotypes with overlapping symptoms (Chapter 12). Muscle fibers are multinucleated syncytial cells and nuclei in normal muscle fibers reside beneath the sarcolemma. Nuclei displaced from this normal position are a common feature of pathological muscle which is particularly prominent in some disorders, including those caused by defects in genes encoding proteins of the nuclear envelope. Nuclei in the center of fibers are the pathological hallmark of disorders collectively known as centronuclear myopathies (Chapter 13); interactions between the proteins responsible for these disorders may explain the common pathological feature. Some of the same proteins may also have a role in other disorders (see Chapter 30).

Section 6: Myofibrils: Early- and Late-Onset Disorders (Chapters 14–19)

Proteins of the sarcomere are essential for muscle contraction and defects in several of the proteins result in a variety of disorders of early (congenital myopathies) or late onset. Defects in thin filament proteins are associated with the presence of a particular

Organisational Plan:
Muscle Disease: Pathology and Genetics



Section	Description	Section	Description
1	General Introduction – (not in diagram)	10	Cytoplasmic proteins
2	Neurogenic muscle disease	11	Metabolic and storage disorders: *glycogen and lipids*
3	Neuromuscular transmission: *Myasthenia gravis etc*	12	Muscle diseases with DNA expansions
4	Sarcolemma: *Duchenne muscular dystrophy and related disorders*	13	Facioscapulohumeral dystrophy
5	Nuclear proteins and nuclear positioning	14	Inflammatory myopathies
6	Myofibrils	15	Toxic myopathies
7	Intermediate filaments and associated proteins	16	Ageing and systemic disease
8	Mitochondria	17	Rare structural abnormalities
9	Sarcoplasmic reticulum and T-tubules		

Figure 1.1 The numbers in the diagram refer to the sections in the table and in the book.

structural feature such as nemaline rods (Chapters 14 and 15), and sometimes the accumulation of a protein such as actin (Chapter 14) or myosin (Chapter 16). The congenital myopathies, in particular, highlight the overlap of pathological and genetic defects. Defects in more than one gene may result in a similar pathology, whereas defects in the same gene may result in more than one pathology even in the same muscle sample. In addition, the typical structural feature associated with a defective gene, such as rods, may not be present and then careful clinical assessment and imaging are essential (Chapter 15). Defects in proteins of the Z-disk (such as myotilin, telethonin, ZASP, filamin, BAG3) are also associated with a variable phenotype in disorders collectively termed myofibrillar myopathies. These are often of adult onset and may show similar characteristic pathological features, despite the involvement of different genes (Chapter 17), emphasizing the difficulty of differential diagnosis. Some, however, are of childhood onset and have a severe, rapid progression (Chapters 17 and 19). Titin is a giant protein that stretches from the Z-disk to the M-line of the sarcomere and defects in certain domains are associated with a variety of phenotypes (Chapter 18). Detection of mutations of both titin and nebulin is hampered by their very large number of coding exons (363 and 183 respectively) and by alternative splicing that leads to multiple isoforms. Advances in molecular techniques, such as next-generation sequencing (see Chapter 4) will undoubtedly aid detection of genetic variations in these genes. Application of the technique of laser capture coupled with mass spectrometry led to the identification of FHL1 as the defective protein responsible for the presence of reducing bodies (Chapter 19), and the gene is now known to be associated with a wide spectrum of phenotypes.

Section 7: Disorders Associated with Intermediate Filaments (Chapters 20 and 21)

This is a family of proteins of the cytoskeleton, intermediate in size (10 nm) between thin actin filaments (~7 nm) and microtubules (25 nm). Lamin A/C is an intermediate filament of the nuclear membrane (see Chapter 12). Desmin (Chapter 20) is the muscle-specific intermediate filament that is highly expressed during development of muscle fibers and together with the giant protein plectin (Chapter 21), links the myofibrillar bundles to each other, to other organelles, and to the sarcolemma. Both desmin and plectin are of pathological significance in muscle and aggregation of desmin is an important primary and secondary pathological marker, the hallmark of which is accumulation of granulofilamentous material. Defects in desmin may also cause cardiomyopathy in common with defects in other sarcomeric proteins such as myosin; defects in plectin can also cause a myasthenic condition (see Chapter 9).

Section 8: Mitochondria (Chapter 22)

Mitochondria are abundant in muscle fibers and essential for the production of adenosine triphosphate (ATP). They are located between the myofibrils (Figure 1.1) and in clusters beneath the plasma membrane. Pathology of mitochondria may be expressed by an increase in their number, alterations in size and distribution, abnormal structure of cristae, or by the presence of inclusions. Identification of a mitochondrial defect may require a combination of techniques including histology (presence of ragged red fibers with abundant structurally abnormal mitochondria), enzyme histochemistry (presence of fibers deficient in cytochrome c oxidase), and electron microscopy (visualization of structurally abnormal cristae or inclusions). Pathological studies may reveal no identifiable defect, in which case biochemistry of respiratory chain enzymes and molecular analysis of mitochondrial and/or genomic nucleic acids are very important. Mitochondrial changes can also be associated with aging and as a secondary feature in disorders such as inclusion body myositis (see Chapter 33).

Section 9: Sarcoplasmic Reticulum and T-tubules (Chapter 23)

Sarcoplasmic reticulum and T-tubules play an essential role in excitation and contraction and in the movement of ions, particularly calcium, in response to depolarization of the muscle fiber membrane by a nerve impulse. Defects in the *RYR1* gene are associated with a wide spectrum of clinical phenotypes; the histochemical identification of core lesions, devoid of oxidative enzyme activity, led to the definition of a congenital myopathy, central core disease. The identification of molecular defects in the *RYR1* gene has broadened the appreciation of clinical and pathological features and the overlap with other disorders. Defects in other genes encoding proteins of the sarcoplasmic reticulum and T-tubules are relatively rare causes of muscle disease but highlight the interaction between organelles within the muscle fiber.

Section 10: Cytoplasmic Proteins (Chapters 24–27)

Cytoplasmic proteins are very diverse. They comprise enzymes such as calpain-3, GNE, chaperone proteins, such as SIL1 and αB-crystallin, Kelch proteins and proteins of autophagy, e.g. LAMP2, VMA21, VCP, and TRIM32. The diseases are accordingly diverse by nature; for example, a muscular dystrophy (LGMD2A) is caused by deficiency of calpain-3 and inclusion body myopathy is due to mutations in the *GNE* gene. Other disorders in this group include vacuolar myopathies, such as Danon disease and XMEA or sarcotubular myopathy, the Marinesco–Sjögren syndrome, αB-crystallinopathy, and nemaline myopathy type 6. The function and role of several of these proteins are not fully understood and secondary reductions can be a consequence of defects in various proteins with which they interact. For example, calpain-3 may be reduced when dysferlin, caveolin-3 or titin is affected by gene mutations.

Section 11: Metabolic and Storage Disorders (Chapters 28 and 29)

Glycogen and lipid are the essential energy stores of muscle fibers so defects affecting their metabolism have major effects on muscle function. Glycogen is spread across the entire muscle fiber and in normal muscle is seen as granules that can be stained with various

techniques (see Chapter 3). Defects in various parts of the glycolytic pathway result either in storage of glycogen or, more rarely, in abnormal synthesis of glycogen. The major glycogen storage diseases can present in childhood or in adults, and are due to deficient breakdown of glycogen; some of the defective enzymes can be recognized by enzyme histochemistry (Chapter 28). Disorders of lipid metabolism are genetically heterogeneous (Chapter 29) and lipid droplets may accumulate within muscle fibers but this is often not the case, particularly in disorders of adult onset; in these cases biochemical techniques are required to identify the defect.

Section 12: Muscle Diseases with DNA Expansions (Chapters 30 and 31)

Most mutations that cause disease affect the coding reading frame but some muscle disorders result from an unstable expansion of a repeat sequence (see Chapter 4). Two forms of myotonic dystrophy (DM1 and DM2) are caused by an increase in the number of repeats on two different genes (Chapter 30), and oculopharyngeal muscular dystrophy by expansion on another gene (Chapter 31). These disorders have several clinical features in common, in particular muscle myotonia, and the pathogenesis is thought to relate to the binding of proteins such as musclebind that leads to missplicing of several proteins in multiple tissues. Molecular techniques for detecting these disorders are highly reliable so muscle pathology now has a less important role in diagnosis, particularly in DM1, one of the most common inherited disorders of muscle. However, clinical features of DM2 may be less obvious and muscle pathology is then useful.

Section 13: Facioscapulohumeral Dystrophy (Chapter 32)

Facioscapulohumeral dystrophy (FSHD) also results from an unusual molecular event which is contraction of D4Z4 repeats at 4q35, and is associated with a specific haplotype. How these missing repeats produce clinical weakness and muscle pathology is unknown. The pathology of FSHD is nonspecific, although myopathic and may be associated with inflammatory infiltrates or with lobulated muscle fibers. There is no specific immunohistochemical marker for FSHD and muscle biopsies are now performed less often.

The last sections of the book (14–17) cover acquired muscle diseases, some of which are amongst the more common muscle disorders.

Section 14: Inflammatory Myopathies (Chapters 33–36)

There are several different forms of inflammatory myopathy in which the most characteristic feature is the presence of inflammatory cells (Chapters 33–35). The underlying pathogenesis of these disorders is variable and includes toxins, bacteria, and viruses (Chapter 36) and autoimmune processes. Differential diagnosis is not always straightforward and muscle pathology has a role in identifying the types and distribution of cells present; however, inflammatory cells and typical pathological markers may not be present in all muscle samples.

Section 15: Toxic Myopathies (Chapter 37)

There is a wide spectrum of toxic agents that affect muscle and produce clinical symptoms and a variety of pathological changes. An increasing number of such agents are commonly prescribed drugs, such as statins that may result in a necrotizing myopathy, steroids that produce type 2 muscle fiber atrophy, and drugs that affect lysosomal function (such as chloroquine and amiodarone) and result in the storage of lipids within lysosomes. The common denominator in this chapter is the exogenous compounds that damage skeletal muscle.

Section 16: Aging and Systemic Disease (Chapter 38)

This chapter addresses the wide variety of factors that affect skeletal muscle during aging and characterizes the resulting myopathology. Neuromuscular disorders associated with cancer, vitamin deficiencies, endocrine disorders, and amyloidosis (most often of the AL or immunological type) are some of the conditions reviewed that emphasize the diverse myopathology associated with aging.

Section 17: Rare Structural Abnormalities (Chapter 39)

Many structural defects have been identified in muscle biopsies over the years, some of which have given their name to a disorder; they are discussed in this chapter. A similar chapter was included in the previous edition of this book and the molecular cause of some of the disorders has been elucidated, but it is uncertain if others are genetic entities, as many are isolated cases and only a few rare cases have been identified. The occurrence of familial cases with unusual structures, however, suggests an underlying molecular cause in some. Wider application of techniques such as laser capture and mass spectrometry may lead to a better understanding of these structures.

Conclusion

All authors have attempted to give a comprehensive account of the pathology and genetics of muscle disease but new discoveries are published so rapidly that it is not possible to include all the latest advances. The different chapters concentrate on the concepts of the various muscle disorders in the hope that readers will become well equipped to download recent advances from websites such as http://neuromuscular.wustl.edu/ and Online Mendelian Inheritance in Man (OMIM, www.ncbi.nlm.nih.gov/omim) and from searches of the scientific literature.

2 Clinical Features of Muscle Disease

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Introduction

Most neuromuscular diseases are rare, in particular the inherited disorders, whilst diabetic and toxic polyneuropathies are frequently occurring acquired diseases. Although the number of patients with hereditary neuromuscular disease may be small (approximately 1% of the population), the disease burden is often severe in most disorders. There is a wide variety of neuromuscular diseases that affect various sites of origin, either genetic or acquired diseases of the motor neuron, spinal root or plexus, peripheral nerve, neuromuscular junction or components of the skeletal muscle fiber (Box 2.1; see also Figure 1.1). Diagnosis of neuromuscular diseases has often been considered difficult but in the majority of the cases, careful clinical examination and routine laboratory evaluations can indicate a particular neuromuscular disease. It is sometimes more difficult, however, to reach a specific genetic diagnosis of a neuromuscular disease, and this often requires careful correlation of all data on a patient. The development of new techniques for the investigation of muscle biopsies, genetic testing, muscle imaging, and metabolic studies are providing a faster and more precise diagnosis of a specific neuromuscular disease and broadening our understanding of disease entities.

The clinical semiology, i.e. the careful gathering and interpretation of data from taking a history and examining patients, is the cornerstone of the diagnosis. The identification of specific symptoms and signs helps to localize the disease to the motor neuron or anterior horn cell, spinal roots or plexus, peripheral nerves, motor endplates or skeletal muscle. In addition. ancillary investigations, biochemical tests, electromyography, muscle imaging. and evaluation of a muscle biopsy can be an adjunct to the history and clinical examination.

The correlation of clinical features with muscle pathology is emphasized throughout this book but for a few conditions. the clinical clues are well established and molecular analysis is now very reliable. This usually obviates the need for a muscle biopsy, which is now rarely performed in some conditions. The muscle pathology associated with these disorders often contributes little additional diagnostic information. In particular, molecular analysis is now the test of choice for the diagnosis of spinal muscular atrophies (SMA), myotonic muscular dystrophy type 1 and 2 (DM1 and 2) and facioscapulohumeral muscular dystrophy (FSHD). In addition, for some conditions there is no specific muscle pathological marker, such as disorders associated with mutations in the gene encoding lamin A/C and limb-girdle muscular dystrophy (LGMD) due to mutations in the gene encoding anoctamin 5 (ANO5), thus gene analysis, directed by clinical examination, serum creatine kinase activity (CK) assessment and muscle imaging, may be the only way to accurately reach the diagnosis. Similarly, muscle pathology may be absent or minimal, or nonspecific in myasthenic syndromes or some metabolic conditions, where the combination of careful clinical, serological, and electrophysiological studies often provides the diagnosis. Clinical features and symptoms, however, provide useful clues that direct the diagnosis.

Clinical history and examination

The main reasons for suspecting a neuromuscular disorder are muscle weakness, sensory disturbances, muscle stiffness, muscle cramps, muscle ache or discomfort (especially during or immediately following exercise), exercise intolerance or decreased stamina (Box 2.2). These may be apparent early in the development of a child or cause a patient to seek help from a general

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Box 2.1 Summary of hereditary and acquired neuromuscular disorders

Diseases of the motor neuron/anterior horn cell

Hereditary
- Motor neuron disorders (hereditary in 5–10%)
- Proximal spinal muscular atrophies types I–IV
- Distal spinal muscular atrophies
- Bulbospinal muscular atrophy or Kennedy disease
- Scapuloperoneal neuronopathy

Acquired
- Segmental or focal spinal muscular atrophies
- Postpolio syndrome

Diseases involving the spinal roots and the plexus

Acquired
- Plexus brachialis or lumbosacralis neuropathy (rarely hereditary)
- Multifocal demyelinating (Lewis–Sumner) neuropathy

Peripheral nerve disorders

Hereditary
- Polyneuropathy (Charcot–Marie–Tooth disease)
- Hereditary neuropathy with pressure palsies
- Familial amyloid neuropathy

Acquired
- Immune-mediated neuropathies (multifocal motor neuropathy, chronic immune-mediated demyelinating neuropathy, Guillain–Barré syndrome)
- Vasculitic neuropathy
- Paraproteinemic neuropathy

Disorders affecting the neuromuscular junction

Hereditary
- Congenital myasthenias

Acquired
- Myasthenia gravis
- Lambert–Eaton syndrome

Myopathies

Hereditary
- Muscular dystrophies
  - Duchenne and Becker muscular dystrophies
  - Limb-girdle muscular dystrophies including Emery–Dreifuss muscular dystrophies
  - Facioscapulohumeral dystrophy
  - Oculopharyngeal muscular dystrophy
  - Bethlem/Ullrich myopathy
  - Distal myopathies
- Myotonic syndromes
  - Myotonic dystrophies
  - Myotonia congenita (Thomsen, Becker)
  - Paramyotonia congenita
- Other ion channel disorders
  - Hyperkalemic periodic paralysis
  - Hypokalemic periodic paralysis
- Myofibrillar myopathies
- Metabolic myopathies
  - Disorders of lipid metabolism
  - Glycogen storage disorders
    Acid maltase deficiency, Pompe disease
    McArdle disease and other enzyme deficiencies
    Danon disease
  - Mitochondrial myopathy
- Congenital myopathies
  - Central and multicore myopathy
  - Nemaline myopathies
  - Centronuclear myopathies
- Myosin storage and myosin-related disease

Acquired
- Inflammatory myopathies
  - Polymyositis
  - Dermatomyositis
  - Inclusion body myositis
  - Nonspecific or overlap myositis
  - Necrotizing autoimmune myopathy
  - Macrophagic myofasciitis
  - Focal myositis
  - Myositis associated with sarcoidosis
  - Myotoxic medication
- Myopathy with systemic features
  - Myoglobinuria (metabolic, inherited disease, drugs, medication)
  - Amyloid myopathy
  - Endocrine myopathy
  - Critical illness polyneuromyopathy
- Axial myopathy (dropped head, bent spine syndrome)

practitioner later in life. Incidental elevation of CK activity may indicate an underlying skeletal muscle disease and requires investigation. Diagnosis is always based on a detailed account of the clinical and family histories, the clinical examination, and correlation with data from all tests.

A detailed family history is essential and may indicate, or exclude, the mode of inheritance of a disorder. For example, if other members of the family are similarly affected, it may indicate if the disorder is inherited in a recessive, dominant, autosomal or X-linked manner (see Chapter 4). Many patients, however, present as sporadic cases and consanguinity in a family can complicate determination of the mode of inheritance and raise the possibility of digenic conditions. In addition, factors such as multiple miscarriages can be a useful indicator of acquired myasthenic

Box 2.2 General assessment of neuromuscular disorders

History

- Age of onset of symptoms
- Age developmental milestones achieved
- Maximal functional abilities reached (i.e. sitting, walking)
- Progression of weakness
- Fatigue/decreased stamina/exercise intolerance
- Muscle pain or muscle discomfort (on exertion)
- Cramps on exertion

Examination

Distribution of muscle weakness:
- Presence of ptosis and ophthalmoplegia
- Presence of facial ('facies myopathica') and bulbar weakness
- Presence of limb-girdle muscle weakness
- Presence of distal muscle weakness (legs and arms, flexors or extensors)
- Presence of scapular or scapuloperoneal muscle weakness
- Presence of generalized muscle weakness
- Presence of weakness of neck muscles (flexors or extensor)
- Involvement of respiratory muscles (sitting and supine)

Distribution of muscle wasting or hypertrophy
Presence of hypotonia associated with weakness (hypotonia alone is nonspecific)
Presence of myotonia, rippling muscles or fasciculations
Ligamentous laxity
Skeletal involvement:
- Contractures
- Hip dislocation, patellar dislocation
- Spinal rigidity
- Scoliosis

Central nervous system involvement:
- Mental retardation
- Epilepsy
- Dementia
- Structural brain changes on MRI (lissencephaly, hydrocephalus, atrophy)
- White matter changes on brain MRI

Involvement of eye (retinitis pigmentosa, optic atrophy, cataract or other anterior or posterior anomalies)
Sensorineural deafness
Skin involvement (keloid, blistering, lipodystrophy, erythema, Gottron's papules or sign)
Cardiac involvement (hypertrophic or dilated cardiomyopathy, dysrhythmia)

conditions and some severe congenital myopathies. In specific cases, one should ask to examine family members as there can be considerable intrafamilial variability (e.g. FSHD, Charcot–Marie–Tooth disease [CMT]).

It is important in children to differentiate muscle weakness from hypotonia. Children with chromosomal and neurometabolic disorders can have marked central hypotonia that resembles the weakness with hypotonia observed in children with neuromuscular disorders. Typical examples are Prader–Willi syndrome, a chromosomal disorder, and Zellweger syndrome, a peroxisomal disorder in which affected children are profoundly hypotonic and often considered weak. Similarly, in syndromes with joint hypermobility, such as Ehlers–Danlos syndrome, there can be a confusing combination of extreme hypotonia and delayed motor milestones. There are nevertheless conditions in which features of central nervous system involvement, i.e. central hypotonia and skeletal muscle involvement, coexist (such as mitochondrial diseases), and rare forms in which typical Ehlers–Danlos features coexist with a myopathy, such as the recently identified form due to *FKPB14* mutations.

The clinical assessment of a patient with neuromuscular disease has to consider several diagnostic issues such as time of onset, distribution of weakness, progression of weakness, relation to exercise and involvement of other tissues and organs such as skin, eyes, heart, joints, and brain [1] (see Box 2.2). The history should include questions on the use of medication, such as statins or other drugs, as these may aggravate a pre-existing myopathy or unmask a previously undiagnosed neuropathy or myopathy. It is important to establish the time of onset of the disease and to get an indication of the rate of progression, whether it is stable, slowly or rapidly progressive, variable at different times of the day or in relation to cold (as in some neuromuscular junction or ion channel disorders), or gradually improving. All too often, the onset of symptoms dates back further than the patient or the family initially realize and a prompt may be needed such as "Could you climb the stairs without any problem 5 years ago?" or "Were you able to run as a child?" In addition, it is important to establish if onset was acute, as in nerve entrapment neuropathies, subacute as in dermatomyositis, or slowly progressive such as in CMT, ANO5 LGMD, or some late-onset myopathies.

Distribution of weakness

The clinical examination is the next step in the diagnostic process. Not only should one carefully look for signs based on the clinical history but a patient should be examined from head to toe, including a full neurological examination, inspection for atrophy or muscle hypertrophy, as well as for contractures or hyperlaxity of the joints, and the involvement of other tissues and organs. Muscle strength is graded on the Medical Research Council Scale [2] and functional tests may be used such as asking the patient to get up from a squatting position (Gowers' phenomenon), stand on one leg (Trendelenburg sign), climb stairs, hop, walk on tiptoe and heels, or raise the arms sideways or forward (scapulae alatae). Validated functional tests such as the 6-min walk test are suitable for follow-up of patients with neuromuscular diseases [3].

Individual diseases in relation to components of the motor unit are discussed in detail in subsequent chapters of this book. The objective of this chapter is to focus on the most common clinical signs that aid diagnosis and those important for differential diagnosis.

Different patterns of muscle weakness have traditionally helped to distinguish different types of neuromuscular disorders [4]. Muscle weakness can be generalized (as in several congenital myopathies) or it can affect predominantly the proximal limb muscles (e.g. in Duchenne muscular dystrophy [DMD], LGMDs, DM2, SMA types II, III, and IV, acid maltase deficiency, and poly- and dermatomyositis), the distal limb muscles (e.g. in peripheral neuropathies, distal variants of SMA and distal forms of muscular dystrophies, DM1, and distal myopathies), the scapulohumeral and facial muscles (in FSHD), the humeroperoneal muscles (in Emery–Dreifuss syndromes), the extraocular muscles and the levator palpebrae (in mitochondrial disorders, oculopharyngeal muscular dystrophy [OPMD], myasthenia and some congenital myopathies), and the axial and respiratory muscles, e.g. in some forms of muscular dystrophy, the allelic conditions multi-minicore disease and rigid spine muscular dystrophy type 1 (RSMD1) and metabolic conditions such as acid maltase deficiency and hereditary myopathy with early respiratory involvement (HMERF) caused by mutations in the A band domain of the titin gene, and bulbar weakness, i.e. dysphagia and dysarthria (in myotonic dystrophy).

Chronic progressive external ophthalmoplegia and ptosis

Chronic progressive external ophthalmoplegia (CPEO) is characterized by weakness of the external ocular muscles. As progression is slow, patients do not usually complain of double vision. Ptosis, which can be asymmetrical in some disorders, is often not recognized by the patient but by family or friends. It can be helpful to ask the patient to bring pictures to identify the onset of the ptosis. There are numerous neuromuscular causes of CPEO, including mitochondrial myopathy, OPMD, myasthenic conditions, congenital myopathies, the disorder caused by mutations in the *MYH2* gene encoding myosin 2A, DM1, and acid maltase deficiency. In OPMD and classic DM1, ptosis is usually found but extraocular muscle weakness is often not prominent. In cases in which there is unilateral ptosis and extraocular weakness, imaging may help to exclude an aneurysm of the carotid artery at the level of the sinus cavernosus [5].

Facial weakness

Weakness of the facial musculature is seldom the reason why a patient asks for referral, unless it has an acute onset. Again, the family may notice that the eyes are not entirely closed during sleep. Asking for the ability to whistle, blow a balloon or drink through a straw can often trace the onset of the weakness. If the facial weakness is subtle (Figure 2.1) and symmetrical, which is usually the case in myopathies, it can be hard to detect. However, the facial appearance of a patient with FSHD or DM is characteristic and the experienced neuromyologist is able to diagnose these patients when seeing them in the waiting room. Facial weakness is one of the hallmarks of FSHD and can be asymmetrical and hardly detectable, except when the patient is asked to whistle. Many congenital myopathies are also associated with facial weakness, sometimes very severely in autosomal recessive *RYR1*-related myopathies.

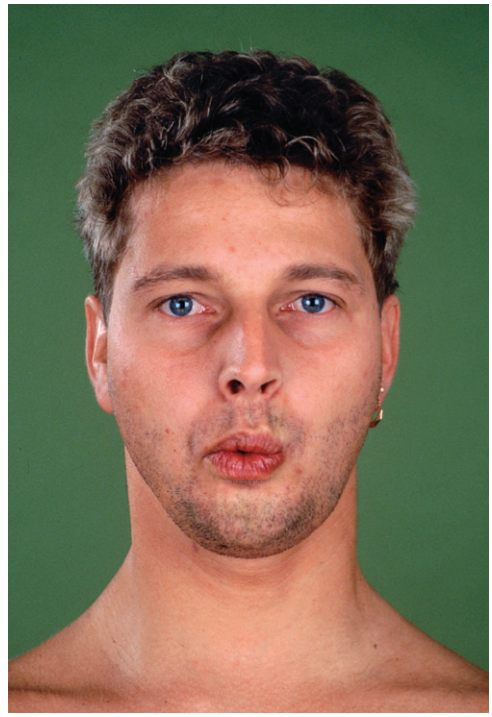

Figure 2.1 Facioscapulohumeral dystrophy. Discrete facial weakness: the left upper part of the mouth does not move properly when the patient whistles. Reproduced from Hijdra A, Koudstaal PJ, Roos RAC (eds). *Neurologie*, 4th revised edition, with permission from Elsevier.

Bulbar weakness

Dysfunction of bulbar muscles can result in dysarthria and dysphagia. Dysphagia can be found in various inherited and acquired myopathies, e.g. DM, OPMD, mitochondrial myopathies, inflammatory myopathies, acid maltase deficiency and other disorders including myasthenia gravis, motor neuron disease, and X-linked bulbospinal muscular atrophy (Kennedy disease). Brown–Vialetto–Van Laere syndrome and Fazio–Londe disease, which were considered to be motor neuron disorders, have recently been found to be of metabolic nature caused by mutations in the SLC5sA3 (formerly *C20orf54*) gene encoding for riboflavin transporter 2. These overlapping disorders present with bulbar paralysis associated in the former with sensorineural deafness. If there is onset in infancy, there is usually hypotonia and respiratory insufficiency leading to early death. The same list of diseases can also cause dysarthria, although this feature is rare in inflammatory myopathies.

Limb-girdle weakness

Symmetrical (occasionally asymmetrical) limb-girdle weakness involves the proximal muscles of the upper and lower limbs. Patients with a limb-girdle distribution of muscle weakness cannot rise from a squatting position without help of the arms or climb stairs without holding a rail. On examination, they show a Gowers' sign (using the upper legs to give support when getting

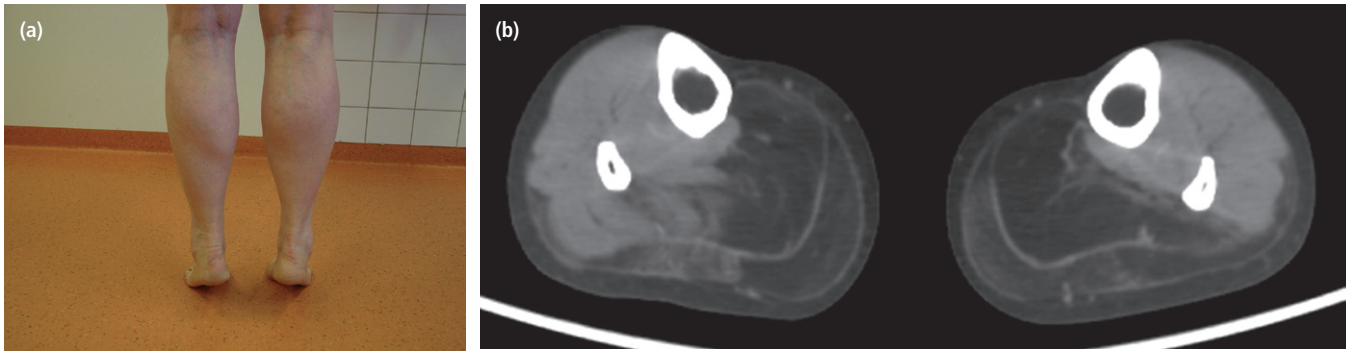

Figure 2.2 Distal myopathy caused by mutations in the gene encoding anoctamin 5. **(a)** The patient is not able to stand fully on tiptoe on the left side. The left calf is smaller compared to the right side. **(b)** CT scan shows fatty replacement of the calf muscles of both legs, left slightly more than right.

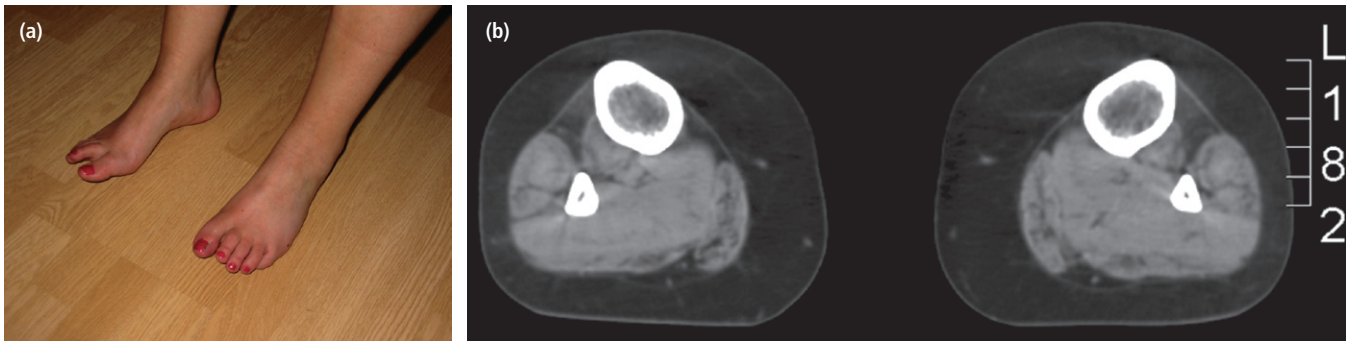

Figure 2.3 Laing early-onset distal myopathy. **(a)** Inability to lift the feet, hanging big toe on the right side. **(b)** CT scan of the lower legs showing fatty replacement of the foot and toe extensors, and to a lesser extent of the gastrocnemius muscles.

up from a sitting position) and a waddling gait. Usually these patients complain less about weakness of the shoulder girdle and upper arm muscles unless specifically asked for (e.g. brushing hair, getting objects off a high shelf). Winging of the scapulae is commonly associated with limb-girdle weakness. There are many myopathies which manifest with a limb-girdle distribution of muscle weakness, including Duchenne and Becker MD (BMD), all LGMDs by definition [6], metabolic disorders, myofibrillar myopathies, DM2, acid maltase deficiency, some forms of congenital myopathy, and also some forms of spinal muscular atrophy (SMA types III and IV). Acquired myopathies which manifest with proximal muscle weakness are poly- and dermatomyositis, hypothyroidism (these patients have a high CK), and steroid myopathy.

Distal muscle weakness

Weakness of the lower legs or hands and forearms is typically found in patients with neuropathies. Weakness of the flexors (of the wrists) and hands is also a feature of inclusion body myositis. In addition, there is an expanding number of distal myopathies with variable age of onset including Welander myopathy (caused by a mutated RNA binding protein), hereditary inclusion body myopathy (caused by *GNE* mutations), myopathies associated with defects in the genes encoding dysferlin, anoctamin 5, nebulin, slow myosin and titin, and myofibrillar myopathies. A helpful algorithm to guide molecular genetic testing of distal myopathies has recently been described, based on the presence or absence of rimmed vacuoles and the distribution of weakness [7] (Figures 2.2, 2.3).

Scapuloperoneal syndrome including scapula alata [8]

Scapula alata is Latin for winging of the shoulder blade. This may result from weakness of the serratus anterior, rhomboid muscle or the lower part of the trapezius muscle. A scapula alata is usually not a complaint of the patient but family or friends notice the abnormal configuration which becomes more apparent if the patient extends the arms forwards or sidewards. A scapula alata is a hallmark of FSHD and can be asymmetrically present (Figure 2.4). Symmetrical winging of the scapulae can also be present in acid maltase deficiency, in cases of BMD and LGMD2L (*ANO5*), and is common in LGMD2A (calpainopathy) and to a variable degree in other limb-girdle syndromes. Scapula alata is also conspicuously present in diseases which manifest with weakness of the scapular region and the peroneal muscles, such as Emery–Dreifuss syndromes caused by mutations in the genes encoding *emerin* and *lamin A/C*, myosin-related myopathy (caused by mutations in the *MYH7* gene), and Kaeser syndrome due to desmin gene mutations.

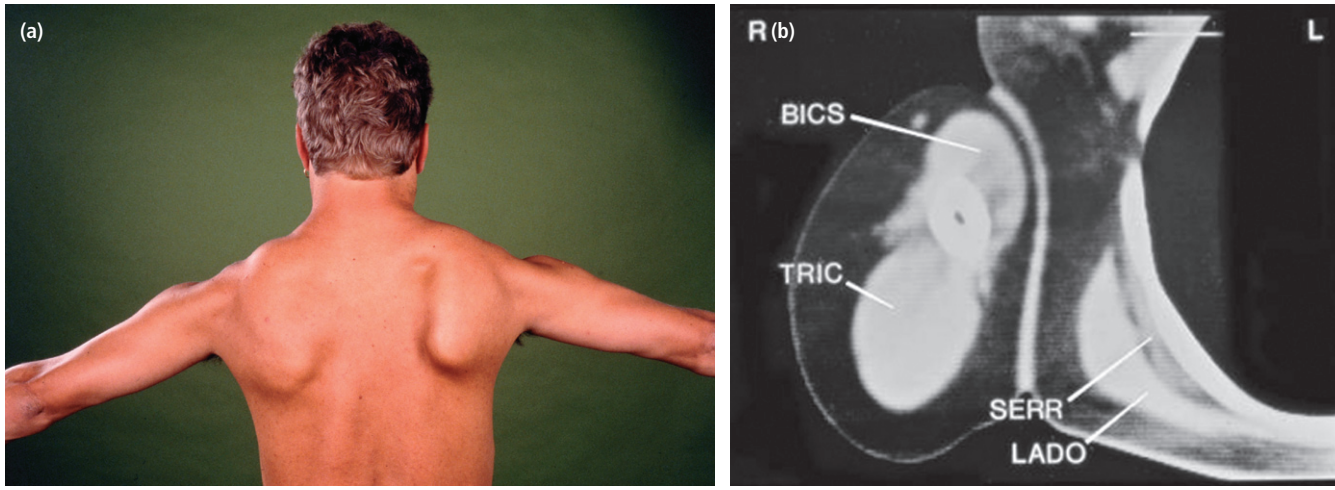

Figure 2.4 Facioscapulohumeral dystrophy. **(a)** Winging of the scapulae when the patient lifts his arms, right more than left. **(b)** CT scan reveals preferential involvement of the right serratus anterior muscle. BICS, biceps; LADO, latissimus dorsi; SERR, serratus anterior;TRIC, triceps.

Dropped head or bent spine syndrome (axial myopathy)

Idiopathic axial myopathy is a rare neuromuscular disorder, presenting in middle age or later, and characterized by selective involvement of the paraspinal muscles at the thoracic and cervical level, leading to a bent spine (camptocormia) and dropped head [9]. The first symptoms are difficulty in keeping the trunk and/or head in an upright position, which improves when the patient is in a supine position (Figure 2.5). Diagnosis can only be made if other disorders manifesting with isolated involvement of the paraspinal musculature, including myasthenia gravis, motor neuron disease, and idiopathic inflammatory myopathies, have been excluded. Patients with acid maltase deficiency can also have weakness of paraspinal and abdominal muscles. Dropped head has also been described in congenital myopathies due to *LMNA* and *SEPN1* gene mutations, in primary amyloidosis, and during treatment with MEK inhibitors in solid tumors. Neck flexor weakness is often seen in myopathies with a limb-girdle pattern of muscle weakness.

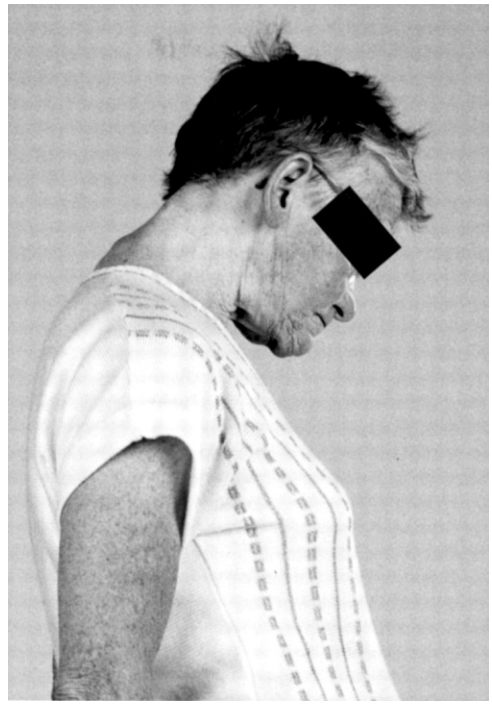

Figure 2.5 Dropped head. Reproduced from Oerlemans WG, de Visser M. J Neurol Neurosurg Psychiatry 1998;65:258–9, with permission from BMJ.

Muscle wasting or enlargement

Differential muscle wasting and enlargement of muscles are also useful indicators of an underlying neuromuscular disorder. Several childhood forms of muscular dystrophy, such as DMD, BMD, some forms of LGMD such as the sarcoglycanopathies, LGMD1C, LGMD2I and 2L, are associated with significant calf muscle enlargement. Muscle hypertrophy, especially of the leg muscles, also characterizes some of the congenital forms of muscular dystrophy, and the milder allelic LGMD variants related to abnormal glycosylation of α-dystroglycan. In some conditions, such as DMD, BMD, acid maltase deficiency, LGMD2I and MDC1C, and amyloid myopathy, hypertrophy may also affect the tongue. Muscle enlargement is often referred to as a "pseudo-hypertrophy" because the hypertrophy reflects an increase in fibrous and fatty tissues, rather than hypertrophy of muscle fibers. However, a true hypertrophic component is present in the initial phases of several conditions. Muscle imaging is very helpful in showing the difference between true and pseudo-hypertrophy (Figure 2.6). True hypertrophy can also occur with overusage in myotonia congenita (Becker disease), Schwartz–Jampel syndrome,

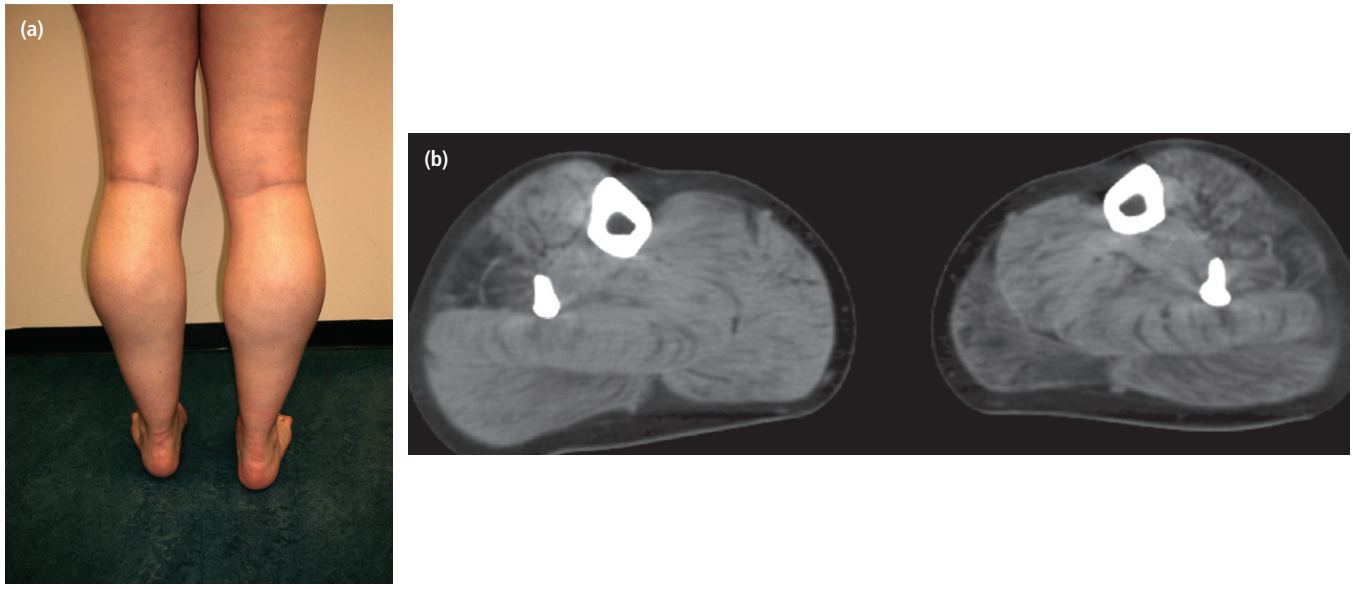

Figure 2.6 Duchenne muscular dystrophy carrier. **(a)** Hypertrophic calves. **(b)** CT shows fatty replacement of the calf muscles by fat, left more than right (pseudo-hypertrophy).

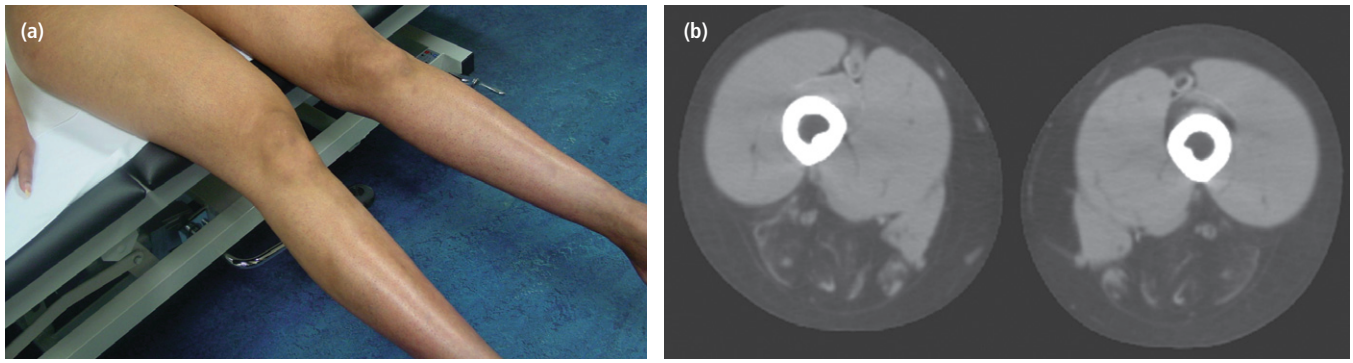

Figure 2.7 GNE-myopathy. **(a)** The patient is able to extend her legs due to relative preservation of the quadriceps muscles. **(b)** CT scan shows striking fatty replacement of the posterior thigh muscles by fat and sparing of the quadriceps muscles except for the rectus femoris muscles.

DM2, and rippling muscle disease. Calf hypertrophy can also occasionally occur in association with a radiculopathy. Focal enlargement, often painful, may be observed in focal myositis, juvenile dermatomyositis, and sarcoidosis.

Differential wasting of muscles can be seen in the biceps muscle in Emery–Dreifuss syndromes and FSHD and thinning of distal lower leg muscles can often be found in cases with distal weakness such as forms of CMT and UDP-*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase (GNE)-myopathy which also shows a striking sparing of the quadriceps (Figure 2.7). Atrophy caused by long-standing functional denervation of the neuromuscular junction that is blocked and destroyed by antibodies can be a residual feature of myasthenia gravis in remission and in anti-MuSK myasthenia. In the latter the tongue is frequently affected.

Rhabdomyolysis/myoglobinuria

Rhabdomyolysis is a rare, potentially dangerous syndrome resulting from necrosis of skeletal muscle fibers and subsequent release of intracellular contents, including myoglobin, into the circulatory system. An isolated attack of rhabdomyolysis can have various causes, e.g. alcohol and drug abuse (mainly opiates, amphetamines, and cocaine), medication including antipsychotics and statins, viruses, trauma, and seizures.

Recurrent episodes and/or a family history of rhabdomyolysis is more likely to be caused by an underlying genetic defect [10].