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Oxford Textbook of Neuromuscular Disorders

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Edited by
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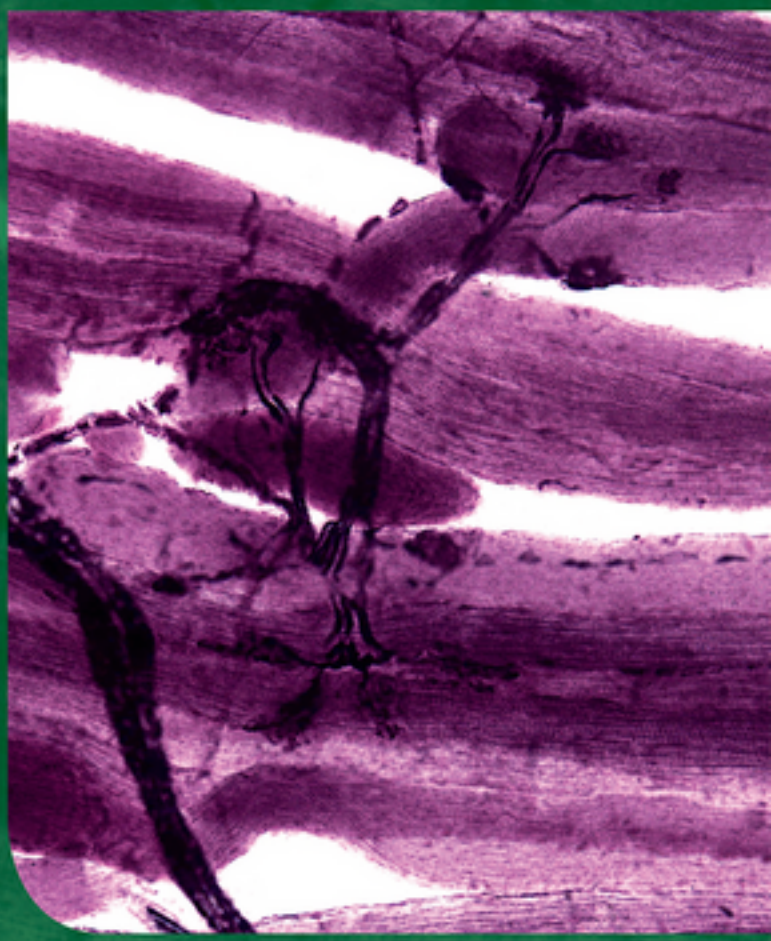

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Oxford Textbook of Neuromuscular Disorders

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Preface

There is a view that the traditional medical textbook is dead—replaced by immediate accessibility to the latest literature and the availability of cheap electronic mobile devices to enable the reading or presentation of data in, literally, any environment. It is undoubtedly wonderful to be able to view the latest paper or systematic review on the management of, say, Churg–Strauss vasculitic neuropathy in a matter of milliseconds, but only if that is the correct diagnosis. The ready accessibility of the primary literature is a boon to the specialist, but it is a potential minefield for the tyro.

We firmly believe that there is still a role for the textbook, but its aspirations need to be clearly defined and understood. This volume on neuromuscular disorders is not primarily intended for neuromuscular specialists. However, given the ultra-specialization that sometimes exists, we hope they may still find it helpful to have a comprehensive summary from an expert in a parallel field. Although individual chapters cover specific disorders in detail, there is an overarching aim, reflected particularly in the first three chapters, to help the novice navigate the pathway from first seeing the patient, to establishing the correct diagnosis, and optimal management.

We have been honoured to be able to assemble many of the opinion leaders from the various specialist fields of neuromuscular disorders. Throughout the volume the reader will benefit from their pearls of wisdom (as we did), many of which are never aired in formal scientific papers.

We hope that you will enjoy reading this book as much as we have enjoyed working with our friends and colleagues internationally to bring it to you. We warmly extend our thanks to the contributors, and to Oxford University Press for making the venture possible.

Contents

Abbreviations

AAV	ANCA-associated vasculitis/ adeno-associated virus
ABC	ATP-binding cassette
ABD	actin-binding domain
ABG	arterial blood gases
ACE	angiotensin-converting enzyme
ACh	acetylcholine
AChE	acetylcholinesterase
AChR	acetylcholine receptors
A-CIDP	CIDP with acute onset
ACTH	adrenocorticotropic hormone
AD	autosomal dominant
ADA	American Diabetes Association
ADG	α-dystroglycan
ADM	abductor digiti minimi
ADQB	abductor digiti quinti brevis
AFO	ankle–foot orthosis
AGEs	advanced glycation endproducts
AIDP	acute inflammatory demyelinating polyneuropathy
AIMG	autoimmune myasthenia gravis
AIN	anterior interosseous nerve
AKI	acute kidney injury
ALD	adrenoleucodystrophy
ALS	amyotrophic lateral sclerosis
ALT	alanine aminotransferase
ALSFRS	ALS Functional Rating Scale
AMAN	acute motor axonal neuropathy
AMC	arthrogryposis multiplex congenita
AMCBN	acute motor conduction block neuropathy
AMN	adrenomyeloneuropathy
AMSAN	acute motor and sensory axonal neuropathy
ANA	antinuclear antibody
ANCA	antineutrophil cytoplasmic antibody
AON	antisense oligonucleotide
APB	abductor pollicis brevis
APL	abductor pollicis longus
AR	autosomal recessive/androgen receptor/aldose reductase
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
ARS	aminoacyl-tRNA synthetase
AST	aspartate aminotransferase
ATGL	adipose triglyceride lipase
BiPAP	bilevel positive airway pressure
BM	Bethlem myopathy
BMD	Becker muscular dystrophy
bpm	beats per minute
BVVL	Brown–Vialetto–Van Laere [syndrome]
CADM	clinically amyopathic dermatomyositis
CAN	cardiac autonomic neuropathy
c-ANCA	cytoplasmic ANCA
CANOMAD	chronic ataxic neuropathy, ophthalmoplegia, monoclonal protein, cold agglutinins, and disialosyl antibodies
CASQ	calsequestrin
CB	conduction block
CBC	complete blood cell count
CCD	central core disease
CFTD	congenital fibre-type disproportion
CGH	comparative genomic hybridization
ChAT	choline acetyltransferase
CHN	congenital hypomyelinating neuropathies
CI	confidence interval
CIAP	chronic idiopathic axonal polyneuropathy
CIDP	chronic inflammatory demyelinating polyneuropathy
CIM	critical Illness myopathy
CIP	critical illness polyneuropathy
CIPA	congenital insensitivity to pain and anhidrosis
CK	creatine kinase
ClC-1	muscle-specific chloride channel 1
CMAP	compound muscle action potential
CMD	congenital muscular dystrophy
CMS	congenital myasthenic syndromes
CMT	Charcot–Marie–Tooth [disease]
CNM	centronuclear myopathy
CNS	central nervous system
ColQ	collagen-Q
CoQ_{10}	coenzyme Q10
COX	cytochrome *c* oxidase
COX-2	cyclooxygenase-2
CPAP	continuous positive airway pressure
CPEO	chronic progressive external ophthalmoplegia
CPK	creatine phosphokinase
CPN	common peroneal neuropathy/common peroneal nerve
CPT	carnitine palmitoyltransferase
CSF	cerebrospinal fluid
CSS	Churg–Strauss syndrome

CTD	connective tissue disorder
CTS	carpal tunnel syndrome
CV	conduction velocity
CYC	cyclophosphamide
DADS	distal acquired demyelinating symmetric polyneuropathy
DAG	diacylglycerol
3,4-DAP	3,4-diaminopyridine
DELTA-P	Dutch–English LEMS Tumor Association Prediction [score]
DEXA	dual-energy x ray absorptiometry
DG	dystroglycan
DGC	dystrophin–glycoprotein complex
DHA	docosahexaenoic acid
DHEA	dehydroepiandrosterone
dHMN	distal hereditary motor neuropathy
DLRPN	diabetic lumbosacral radiculoplexus neuropathy
DM	diabetes mellitus/dermatomyositis
DM1/DM2	myotonic dystrophy Type 1/Type 2
DMD	Duchenne muscular dystrophy
DML	distal motor latency
DPA	D-penicillamine
DRPN	diabetic radiculoplexus neuropathy
DSD	Dejerine–Sottas disease
dSL	desoxysphingolipid
dSMA	distal spinal muscular atrophy
DSPN	diabetic sensorimotor polyneuropathy
EAST	Elevated Arm Stress Test
ECG	electrocardiography/electrocardiogram
ECM	extracellular matrix
ECRB	extensor carpi radialis brevis
ECRL	extensor carpi radialis longus
ECU	extensor carpi ulnaris
EDB	extensor digitorum brevis
EDL	extensor digitorum longus
EDM	extensor digiti minimi
EDMD	Emery–Dreifuss muscular dystrophy
EDS	excessive daytime sleepiness
EEG	electroencephalogram
EFNS/PNS	European Federation of Neurological Societies/ Peripheral Nerve Society
EGRIS	Erasmus GBS Respiratory Insufficiency Scale
EHL	extensor hallucis longus
EIM	electrical impedance myography
ELISA	enzyme-linked immunosorbent assay
EMG	electromyogram/electromyography
ENMC	European Neuromuscular Centre
EOM	extraocular muscles
EPB	extensor pollicis brevis
EPL	Extensor pollicis longus
EPP	endplate potential
EPS	electrophysiological studies
ER	endoplasmic reticulum
ERT	enzyme replacement therapy
ESR	erythrocyte sedimentation rate
ETF	electron transfer flavoprotein
ETFDH	electron transfer flavoprotein dehydrogenase
FAD	flavin adenine dinucleotide
FADS	fetal akinesia deformation sequence
FAO	fatty acid oxidation
FAP	familial amyloid polyneuropathy
FCMD	Fukuyama congenital muscular dystrophy
FCR	flexor carpi radialis
FCU	flexor carpi ulnaris
FD	Fabry disease
FDB	flexor digitorum brevis
FDG	fluorodeoxyglucose
FDI	first dorsal interosseous
FDL	flexor digitorum longus
FDM	flexor digiti minimi
FDP	flexor digitorum profundus
FDS	flexor digitorum superficialis
FEV	forced expiratory volume
FFA	free fatty acid
FGF	fibroblast growth factor
FHB	flexor hallucis brevis
FHL	flexor hallucis longus
FOSMN	facial-onset sensory and motor neuropathy
FPB	flexor pollicis brevis
FPL	flexor pollicis longus
FRAFO	floor reaction ankle–foot orthosis
FSH	facioscapulohumeral
FSHD	facioscapulohumeral (muscular) dystrophy
FTD	frontotemporal dementia
FUS	fused-in-sarcoma
FVC	forced vital capacity
GAA	α-1,4-glucosidase
Gb3	globotriaosylceramide
GBS	Guillain–Barré syndrome
GDE	glycogen debranching enzyme
GGT	gamma-glutamyl transferase
GH	growth hormone
GHRH	growth hormone releasing hormone
GNE	UDP-*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase
GSD	glycogen storage disease
GT	Gomori trichrome [stain]
HAART	highly active antiretroviral therapy
HDAC	histone deacetylase
H&E	haematoxylin and eosin
HGA	hereditary gelsolin amyloidosis
HIBM	hereditary inclusion body myopathy
HIV	human immunodeficiency virus
HKPP	hypokalaemic periodic paralysis
HMGCR	3-hydroxy-3-methylglutaryl-coenzyme A reductase
HMSN	hereditary motor and sensory neuropathies
HNA	hereditary neuralgic amyotrophy
HNPP	hereditary neuropathy with liability to pressure palsies
HRV	heart rate variability
HSAN	hereditary sensory and autonomic neuropathy
HSN	hereditary sensory neuropathy
HSP	hereditary spastic paraplegia/Henoch–Schönlein purpura
HTLV-1	human T-lymphotropic virus type 1
IB	immunoblot
IBM	inclusion body myositis

IC	immune complex
ICD	implantable cardioverter defibrillator
ICU	intensive care unit
ICU-AW	ICU-acquired weakness
IDMC	International Myotonic Dystrophy Consortium
IENF	intra-epidermal nerve fibre
IF	immunofluorescent
Ig	immunoglobulin
IGF-1	insulin-like growth-factor-1
IGT	impaired glucose tolerance
IHC	immunohistochemical
IIM	idiopathic inflammatory myopathy
ILD	Interstitial lung disease
INA	idiopathic neuralgic amyotrophy
INEM	isolated neck extensor myopathy
INFα	interferon-α
INM	inner nuclear membrane
iNOS	inducible nitric oxide synthase
IPV	inactivated polio vaccine
IRIS	immune restoration inflammatory response
IVF	*in vitro* fertilization
IVIg	intravenous immunoglobulin
KAFO	knee–ankle–foot orthosis
L	litre
LCHAD	long chain 3-hydroxy/acyl-CoA dehydrogenase
LDH	lactate dehydrogenase
LDM	Laing distal myopathy
LEMS	Lambert–Eaton myasthenic syndrome
LFCN	lateral femoral cutaneous nerve
LGMD	limb-girdle muscular dystrophy
LH	luteinizing hormone
LHON	Leber hereditary optic neuropathy
LMN	lower motor neuron
LOS	lipo-oligosaccharide
LRP4	low-density lipoprotein receptor-related protein 4
LRPN	lumbosacral radiculoplexus neuropathy
LSDs	lysosomal storage disorders
MAC	membrane attack complex
MADD	multiple acyl-CoA dehydrogenase deficiency
MADSAM	multifocal acquired demyelinating sensory and motor neuropathy
MAG	myelin-associated glycoprotein
MB-DRM	desmin-related myopathy with Mallory body-like inclusions
MCAD	medium chain acyl-CoA dehydrogenase
MCT	medium-chain triglyceride
MCTD	mixed connective tissue disorder
MCV	mean corpuscular volume
MDC	Muscular Dystrophy Campaign
MDC1A	merosin-deficient congenital muscular dystrophy Type 1A
MDDG	muscular dystrophy–dystroglycanopathy
MDNS	Michigan Diabetic Neuropathy Scale
MDSG	Myotonic Dystrophy Support Group
MEB	muscle-eye-brain disease
mEGOS	modified Erasmus Guillain–Barré Outcome Score
MELAS	mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes
MEMSA	myoclonic epilepsy, myopathy, sensory ataxia
MEPP	miniature endplate potential
MERRF	myoclonic epilepsy with ragged-red fibres
MFM	myofibrillar myopathy
MFS	Miller Fisher syndrome
MG	myasthenia gravis
MGFA	Myasthenia Gravis Foundation of America
MGUS	monoclonal gammopathy of undetermined significance
MGUSP	MGUS polyneuropathy
MH	malignant hyperthermia
MHC	major histocompatibility complex
MIRAS	mitochondrial recessive ataxia syndrome
MLPA	multiplex ligation-dependent probe amplification
MM	multiple mononeuropathy/Miyoshi myopathy
MmD	multiminicore disease
MMN	multifocal motor neuropathy
mNCV	motor nerve conduction velocity
MND	motor neuron disease
MNGIE	mitochondrial neurogastrointestinal encephalopathy
MNSI	Michigan Neuropathy Screening Instrument
MPA	microscopic polyangiitis
MPO	myeloperoxidase
MPZ	myelin protein zero
MRC	Medical Research Council
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MSA	myositis-specific autoantibody
MSM	myosin storage myopathy
mtDNA	mitochondrial DNA
MTP	mitochondrial trifunctional protein
MUGA	multigated cardiac radionuclide ventriculography
MUNE	motor unit number estimation
MuSK	muscle-specific kinase
NA	neuralgic amyotrophy
NADH-TR	nicotinamide adenine dinucleotide tetrazolium reductase
NAM	necrotizing autoimmune myopathy
NARP	neurogenic muscle weakness, ataxia, and retinitis pigmentosa
NCS	nerve conduction studies
NCV	nerve conduction velocity
NDS	Neuropathy Disability Score
NEM	nemaline myopathy
NF-1	neurofibromatosis type 1
NFTs	neurofibrillary tangles
NGF	nerve growth factor
NGS	next-generation sequencing
NIS	Neuropathy Impairment Score
NIV	non-invasive ventilation
NLDSI	neutral lipid storage disease with ichthyosis
NMDA	*N*-methyl-D-aspartate
NMJ	neuromuscular junction
^n NOS	neuronal nitric oxide synthase
NSP	Neuropathy Symptom Profile
NSVN	non-systemic vasculitic neuropathy
NT3	neurotrophin 3
OCTN2	sodium-dependent carnitine transporter
ODM	opponens digiti minimi

2OME	2′*O*-methyl phosphothiorate
OMG	ocular myasthenia gravis
OMIM	Online Mendelian Inheritance in Man
ONM	outer nuclear membrane
OPV	oral [live attenuated] polio vaccine
ORF	open reading frame
OT	occupational therapy
PAN	polyarteritis nodosa
p-ANCA	perinuclear ANCA
PARP	poly(ADP-ribose) polymerase
PBG	porphobilinogen
PbP	progressive bulbar palsy
PCD	primary carnitine deficiency
PCR	polymerase chain reaction
PE	plasma exchange
PEEP	positive end-expiratory pressure
PEG	percutaneous endoscopic gastrostomy
PEO	progressive external ophthalmoplegia
PET	positron emission tomography
PFKD	phosphofructokinase deficiency
PFS	pulmonary function score
PGD	preimplantation genetic diagnosis
PGK	phosphoglycerate kinase
PGAM	phosphoglycerate mutase
PGM	phosphoglucomutase
PHK	phosphorylase b kinase
PHYH	phytanoyl CoA hydroxylase
PIN	posterior interosseous nerve
PIRCS	percussion-induced rapid contractures
PKC	protein kinase C
PLP	pyridoxal-5′-phosphate
PLS	primary lateral sclerosis
PM	polymyositis
PMA	progressive muscular atrophy
PME	progressive myoclonic epilepsy
PMO	phosphorodiamidate morpholino oligomer
PNH	peripheral nerve hyperexcitability
PNHD	peripheral nerve hyperexcitability disorder
PNPLA2	pastatin-like phospholipase domain-containing protein 2
PNS	peripheral nervous system
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes
polyA	polyadenylation
PROMM	proximal myotonic myopathy
PQ	pronator quadratus
PR3	proteinase 3
PT	pronator teres
PTH	parathyroid hormone
QMG	Quantitative Myasthenia Gravis [test]
QSART	quantitative sudomotor axon reflex testing
RA	rheumatoid arthritis
RCE	respiratory chain enzyme
RCS	Rosenberg–Chutorian syndrome
RCT	randomized controlled trial
RF	respiratory failure
RIG	radiologically inserted gastrostomy
RNS	repetitive nerve stimulation
ROS	reactive oxygen species
RRFs	ragged red fibres
RSMD	rigid spine muscular dystrophy
RyR	ryanodine receptor
SANDO	sensory ataxia, neuropathy, dysarthria, ophthalmoplegia
SAP	sensory action potential
SBMA	spinal and bulbar muscular atrophy
SCAE	spinocerebellar ataxia with epilepsy
SCAIP	single-condition amplification/internal primer
SCIg	subcutaneous immunoglobulin
SCLC	small cell lung cancer
SDH	succinate dehydrogenase
SFEMG	single-fibre electromyography
SFN	small fibre neuropathy
SGC	sarcoglycan complex
SHA	strategic health authority
sIBM	sporadic inclusion body myositis
SIMV	synchronized intermittent mandatory ventilation
SIRS	systemic inflammation response syndrome
SLE	systemic lupus erythematosus
SMA	spinal muscular atrophy/smooth muscle antibody
SMARD	spinal muscular atrophy with respiratory distress
SNAP	sensory nerve action potential
SNARE	soluble NSF attachment protein receptor
SNP	single nucleotide polymorphism
snRNP	small nuclear ribonucleoprotein
SPMA	scapuloperoneal muscular atrophy
SPT	serine palmitoyltransferase
SRP	signal recognition particle
SSRI	selective serotonin reuptake inhibitor
STIR	short TI inversion recovery
T3	triiodothyronine
T4	thyroxine
TAG	triacylglycerol
TD	temporal dispersion
TDP-43	TAR (transactive response) DNA-binding protein
TGFβ	transforming growth factor β
TL	terminal latency
TMD	tibial muscular dystrophy
TMS	transcranial magnetic stimulation
TNF	tumour necrosis factor
TNM	transient neonatal myasthenia
TOS	thoracic outlet syndrome
TPMT	thiopurine methyltransferase
TPP	thyrotoxic periodic paralysis
TSH	thyroid-stimulating hormone
TTR	transthyretin
TTS	tarsal tunnel syndrome
UCMD	Ullrich congenital muscular dystrophy
UENS	Utah Early Neuropathy Scale
UMN	upper motor neuron
UTR	untranslated region
VAPP	vaccine-associated paralytic poliomyelitis
VCP	valosin-containing protein
VCPDM	vocal cord and pharyngeal distal myopathy
VGCC	voltage-gated calcium channel
VGKC	voltage-gated potassium channel
VGSC	voltage-gated sodium channel

VDP	vaccine-derived poliomyelitis
VEGF	vascular endothelial growth factor
VF	ventricular fibrillation
VLCAD	very long chain acyl-CoA dehydrogenase
VLCFA	very long chain fatty acid
VT	ventricular tachycardia
WDM	Welander distal myopathy
WG	Wegener granulomatosis
WHO	World Health Organization
WWS	Walker–Warburg syndrome
XLDC	X-linked dilated cardiomyopathy
XMPMA	X-linked myopathy with postural muscle atrophy

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SECTION 1

Approach to the Patient

CHAPTER 1

Eliciting the history

David Hilton-Jones and Martin R. Turner

Introduction

With the introduction of non-invasive neuroimaging, many non-specialists assumed there would be a move away from detailed history-taking and the methodical (some might say obsessive) clinical examination considered characteristic of the neurologist. All that would be needed was the ability to complete an imaging request form and the solution would soon be forthcoming. It rapidly became apparent that the new technology created almost as many problems as it solved, revealing incidental 'abnormalities' of uncertain significance begetting potentially hazardous further assessment, sometimes incorrect diagnoses, and filling neurology clinics with the 'worried well'.

Many neuromuscular disorders, and the majority that require long-term follow-up, have a genetic basis. Diagnosis, previously based solely on a detailed clinical assessment of phenotype, has more recently led to the ability to identify causative genes through linkage studies and whole-genome or exome sequencing in cohorts of patients with specific features. Clinical appraisal thus leads to a 'gene shortlist', and targeted DNA testing can be undertaken. Molecular biologists promise a holy grail of a DNA 'chip' which will detect all of the known 'neuromuscular genes' and allow a genetic diagnosis within hours of phlebotomy, with the expectation (once again) of obviating the need for rigorous clinical assessment. However, the issue of interpretation of sequence variants of unknown significance, the fact that only a small number of genes are being assessed, and the possibility of mutations in two or more genes related to neuromuscular disease having additive effects ('double trouble') suggest that accurate clinical appraisal remains paramount. The practise of medicine relies on Bayesian logic, in which the clinical assessment leads to an appropriate differential diagnosis that may (or may not) be refined by appropriate investigation.

The first three chapters of this book are intended to hone the skills of clinicians who do not have regular exposure to neuromuscular disorders. This chapter deals with taking the history, with an emphasis on eliciting and interpreting the relevant symptoms. Chapter 2 is devoted entirely to genetic considerations, the importance of the family history, and potential pitfalls for the unwary. Chapter 3 deals with the physical examination. Despite the important distinction between symptoms and signs in medicine there is of course an overlap—the history may suggest a particular pattern of weakness, and examination may confirm, refute, or extend that observation.

The presenting complaint and related features

There are relatively few ways in which the peripheral nervous system can react to disease, and the presenting symptom is likely to relate to one of the following: weakness, fatigue, sensory disturbance, autonomic dysfunction, pain, stiffness and muscle hyperactivity, muscle wasting or enlargement, or myoglobinuria.

Detailed questioning of the patient is intended to elicit the often subtle variations on a theme that will aid precise diagnosis. Sometimes, the history alone will strongly suggest a specific diagnosis. More often, the history will lead to a relatively short differential diagnosis which examination will help to shorten further. Then, specifically directed investigation will confirm the diagnosis.

Weakness

Weakness is the most common presenting symptom for neuromuscular disorders. In peripheral neuropathies it is frequently accompanied by some form of sensory disturbance, whereas in motor neuronopathies, neuromuscular junction disorders, and myopathies, 'true' sensory disturbance (see section Sensory disturbance) is notably absent. With respect to weakness the history should determine: age of onset/duration, rate of progression, constancy or variability, and distribution.

Patients do not always use the word 'weakness' to describe what a neurologist understands the word to mean. Common synonyms include 'heaviness' (e.g. 'heavy head' for neck weakness), 'deadness', 'aching', and even 'numbness' in the absence of any sensory change. Conversely, they may use the word 'weakness' to describe restriction of movement due to pain or mechanical dysfunction, and occasionally for sensory dysfunction that is otherwise difficult to describe.

Age of onset is highly important in that it may immediately limit the differential diagnosis. The symptoms of Duchenne muscular dystrophy never appear for the first time after the age of 5 years, whereas oculopharyngeal dystrophy and inclusion body myositis (IBM) do not present before middle age. On the other hand, many neuromuscular diseases can present at any age.

The rate of progression must be determined, and whether the weakness is constant or variable. Marked variability, with evidence of fatigability, is characteristic of myasthenic neuromuscular transmission disorders, and episodic weakness of periodic paralysis. However, many patients with amyotrophic lateral sclerosis (ALS) report diurnal variation to their weakness, so this should not be interpreted in isolation.

The specific distribution of the weakness is of the utmost importance with respect to diagnosing both neurogenic and myopathic disorders. Although physical examination may be more discriminating than the history, the latter still provides important clues. Asymmetry is a feature of focal peripheral neuropathies, ALS, multifocal motor neuropathy with conduction block, and

mononeuropathy multiplex (although the latter may mimic a symmetrical polyneuropathy). Acquired polyneuropathy and inherited neuropathies are usually associated with symmetrical weakness, an exception being hereditary neuropathy with a liability to pressure palsies. Symmetry is the norm in most myopathies, but frequent exceptions include facioscapulohumeral dystrophy and IBM.

A major simplification is that myopathic disorders tend to present with proximal weakness whereas neurogenic disorders present with distal weakness. Indeed, most acquired myopathies (e.g. dermatomyositis, polymyositis, endocrine myopathies) are characterized by weakness of the muscles of the pelvis and shoulder girdle, and most neuropathies (e.g. diabetic and nutritional neuropathies, hereditary motor and sensory neuropathies) by distal (lower limb) weakness. Notable exceptions, however, include:

- distal weakness (of the hands) in two of the more common myopathies (myotonic dystrophy and IBM) and the much rarer distal myopathies (e.g. desminopathy and myotilinopathy);
- proximal weakness in acquired demyelinating neuropathies (e.g. chronic inflammatory demyelinating polyradiculoneuropathy) and the common (*SMN*-related) forms of spinal muscular atrophy.

Muscular dystrophies are often characterized by highly selective muscle involvement, which in itself may be diagnostic. In facioscapulohumeral dystrophy there is weakness of the scapular fixator muscles, and possibly biceps and triceps, whereas the deltoid is normal. In acquired myopathies, such as polymyositis, there is weakness of all of the shoulder girdle muscles. Focal peripheral neuropathies are associated with highly selective muscle involvement and, often, well-defined patterns of sensory loss.

Extraocular muscle weakness typically presents with diplopia, but in some chronic disorders it is absent, even in the presence of marked restriction of eye movements. Symptomatically the latter may be evidenced by patients having to turn their head to change their direction of gaze. Ptosis is usually commented upon because of the cosmetic appearance, and less commonly because it obscures vision. *Variable* diplopia and ptosis are highly suggestive of myasthenia. Across the range of neuromuscular disorders, involvement of the extraocular muscles is relatively uncommon and therefore highly discriminatory when present (Table 1.1).

Table 1.1 Neuromuscular disorders associated with extraocular muscle (EOM) involvement

Neuromuscular junction disorders
Myasthenia gravis (EOM involvement common)
Congenital myasthenic syndromes:
• Acetylcholine receptor subunit mutations (EOM involvement common)
• DOK7 mutations (typically limb-girdle weakness without EOM involvement)
• Rapsyn mutations (non-paralytic strabismus)
Lambert–Eaton syndrome (EOM rare)
Botulism (EOM involvement common + pupillary involvement)
Mitochondrial cytopathy
Chronic progressive external ophthalmoplegia (CPEO)
Oculopharyngeal muscular dystrophy
Mainly ptosis
Congenital myopathies
For example ryanodine [*RYR1*] and dynamin2 [*DNM2*] mutations
Thyroid ophthalmopathy
CANOMAD syndrome

CANOMAD, chronic ataxic neuropathy, ophthalmoplegia, M-protein, agglutination disialosyl antibodies.

Weakness of neck flexion presents as difficulty in lifting the head off a pillow. It is common in the inflammatory myopathies and myotonic dystrophy. Weakness of the neck extensors causes the head to fall forwards ('dropped head syndrome') and is seen in myasthenia (typically in older men rather than younger patients of either sex), ALS, and sometimes idiopathically in isolation (isolated neck extensor myopathy, INEM). It should never be attributed to cervical spine spondylosis, although this is frequently coincident. Patients with neck weakness complain of problems when they travel as passengers in a vehicle because their head lolls in response to movement. Those with myasthenia may say that they have to support their head by placing a hand on their chin.

Weakness of the shoulder girdle causes difficulty with activities performed above shoulder height, such as grooming and hair washing, reaching up to a shelf, and putting on a shirt or pullover. Peri-scapular weakness causes scapular winging, which is often first noticed by others. It is characteristic of facioscapulohumeral muscular dystrophy but is also seen in other dystrophies. Unilateral scapular winging may be seen in facioscapulohumeral dystrophy, neuralgic amyotrophy, and with isolated long thoracic nerve palsy (where there may be a history of trauma, e.g. seat-belt injury, or secondary to prolonged compression under anaesthetic during surgery).

Weakness around the pelvic girdle is probably the most common presentation of myopathy. The typical initial complaint is difficulty in either running or climbing stairs. As the weakness progresses there is difficulty in getting up from a squatting position, then from a low chair, and finally problems with walking, initially going up a slope and then on the flat. Preferential weakness of quadriceps (as opposed to weakness of the pelvic muscles), as is seen in IBM or with femoral neuropathy, characteristically presents with falls due to an inability to lock the knee in extension. In IBM and ALS, both of which typically develop in late middle age, the problem is often initially attributed to degenerative disease of the hip or knee, with a consequent delay in diagnosis.

Distal weakness in the upper limbs takes three main forms. Weakness of grip, in the absence of significant weakness of the small hand muscles, is highly characteristic of myotonic dystrophy and IBM. Weakness of the small hand muscles, with little or no weakness of the long finger flexors and extensors, impairs dexterity and is seen in focal and generalized peripheral neuropathies. Weakness of finger extension ('finger drop') can be seen in myasthenia gravis, slow-channel myasthenic syndrome, Laing distal myopathy (*MYH7* mutation), *GNE* mutations (hereditary inclusion body myopathy, quadriceps-sparing myopathy), multifocal motor neuropathy with conduction block, and radial nerve palsy (with wrist drop).

The most common presenting symptom of distal lower limb weakness is foot drop, due to weakness of tibialis anterior, with patients complaining of tripping and catching their toes on the ground (this may be visible to the keen-eyed clinician as a scuff

mark on one shoe). Severe acquired or inherited peripheral neuropathies may eventually lead to the loss of all movements around the ankle. Much less common is presentation with weakness of gastrocnemius, causing difficulty in pushing off when walking; this is characteristic of Miyoshi myopathy.

The presenting symptoms of ventilatory muscle weakness will depend in part on the patient's general mobility. Rare presentations in otherwise active individuals can include the inability to descend into water above the level of the diaphragm without feeling acutely breathless. In many myopathies ventilatory muscle weakness is a late feature of the disease and does not present until long after the patient has become completely wheelchair dependent. As a result of their relatively minimal exertions, breathlessness is therefore not a common complaint. Rather, the presentation relates to nocturnal hypoventilation with sleep fragmentation. Patients frequently erroneously attribute sleep fragmentation as due to 'waking to urinate', while in reality this is just a natural consequence of waking for whatever primary reason. Other symptoms of nocturnal hypoventilation include waking feeling groggy, which may be accompanied by headache, and excessive daytime sleepiness. In Duchenne muscular dystrophy common additional complaints include fear of going to sleep and anorexia (eating further inhibits ventilation). In a few conditions (e.g. acid maltase deficiency, limb-girdle muscular dystrophy Type 2I, rigid spine syndromes) ventilatory muscle weakness is an early feature of a generalized neuromuscular disorder. Patients are more likely to note breathlessness and orthopnoea. In any patient with moderately impaired ventilatory function there may be a history of delayed recovery from anaesthesia or ventilatory failure precipitated by chest infection. Ventilatory failure, usually in association with marked generalized weakness, is a feature of myasthenia gravis and acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome).

Progressive dysphagia due to neuromuscular disease is frequently erroneously referred by primary-care physicians to stroke or otolaryngology clinics. It is not an uncommon presentation of myasthenia, but in the absence of ptosis and with dysarthria preceding the dysphagia it is much more likely to be ALS. This is important as the electromyogram (EMG) may appear normal, even in the tongue, and a small number of people with ALS may have incidental acetylcholine receptor antibodies. The presence of pseudobulbar affect (which the patient recognizes as an exaggerated, often explosive, emotional response to minor stimuli) in this context is probably pathognomonic. Other neuromuscular diagnostic considerations for dysphagia include IBM and oculopharyngeal dystrophy.

Fatigue

Few words in the neuromuscular field cause more confusion and miscommunication between patients and doctors than 'fatigue'. Arguably, doctors would like to restrict the word to true physiological fatigue but patients used it in a far broader, less specific, sense. True fatigue, with reduced strength on attempted sustained effort, both as a symptom and a sign, is almost pathognomonic of myasthenic disorders. In its more general sense, the perception of tiring during attempted activity, or increased effort to achieve a particular end, it is highly non-specific and seen in virtually any disorder causing weakness, whether peripheral neuromuscular or more central (e.g. multiple sclerosis). A sense of fatigue, often profound, without demonstrable weakness or neurophysiological abnormality, is a major feature of chronic fatigue syndrome and related conditions.

Sensory disturbance

As noted in the section Weakness, patients may complain of sensory disturbance when in fact they have predominantly motor dysfunction. A common example is the patient with idiopathic facial (Bell's) palsy who complains of facial numbness—it is best understood as a cortical misperception. True sensory disturbance due to peripheral nerve disease may present as loss of sensation (numbness), abnormally heightened sensation (hyperalgesia and allodynia), or abnormal sensations (dysaesthesia). Focal peripheral nerve lesions, including mononeuropathy multiplex, cause localized areas of sensory disturbance, commensurate with the area of supply of the relevant nerve. Most inherited neuropathies and acquired length-dependent neuropathies cause distal sensory symptoms ('glove and stocking'). As with weakness, age of onset and the time course of progression provide vital diagnostic clues.

Autonomic dysfunction

Symptoms of autonomic dysfunction include postural hypotension, altered sweating, erectile dysfunction, sphincter dysfunction, constipation, and diarrhoea. They may be the presenting symptom of a primary autonomic neuropathy, or be additional features, elucidated from the history, in acquired and inherited sensorimotor polyneuropathies (diabetes most commonly) and in Lambert–Eaton syndrome.

Pain

With respect to neuropathies, the perception of pain may overlap with complaints about sensory disturbance. A number of generalized neuropathies may be painful, notably diabetic neuropathy and idiopathic small-fibre neuropathies. Focal neuropathies such as carpal tunnel syndrome are often associated with pain (which may be reported by the patient as extending proximally in the forearm), and post-herpetic neuralgia is common. The common inherited neuropathies are generally considered to be painless, but many patients with Charcot–Marie–Tooth disease complain of pain, although it is often difficult to determine its precise nature.

Although muscle pain is a very common symptom, it can only infrequently be attributed directly to primary muscle disease. Two critical discriminants are whether the pain is localized or generalized, and whether it is constant or episodic. If episodic, then it is important to establish if it is triggered by any specific circumstance, such as exercise. Generalized continuous muscle pain, with an essentially normal clinical examination, normal serum creatine kinase, negative inflammatory markers, and normal EMG, is a common clinical problem. Causes include chronic fatigue syndrome and arbitrarily defined chronic pain syndromes such as fibromyalgia. Referred pain from orthopaedic and rheumatological disorders is usually localized, and is common. Knee, hip, and back pain, in varying combinations, are almost universal in any neuromuscular disorder that causes lower body weakness and abnormality of gait. The simple assumption is that the abnormal posture and gait place abnormal stresses and strains on joints, ligaments, and associated structures. Patients with facioscapulohumeral dystrophy seem particularly prone to fairly widespread pain, and certainly their lumbar lordosis is frequently a major source of back pain.

Table 1.2 Disorders associated with generalized muscle pain*

Acute myositis (e.g. dermatomyositis)
Infections • Viral (e.g. coxsackie) • Toxoplasmosis
Drug induced (see Table 1.5) • Steroid withdrawal • Metabolic disorders • Hypothyroidism
Metabolic bone disease (osteomalacia)
CPT deficiency
Polymyalgia rheumatica
Parkinson's disease
Kennedy syndrome
Porphyria

CPT, carnitine palmitoyltransferase.
*May be generalized, but mostly proximal limbs.

Tables 1.2–1.4 list specific disorders that can be associated with generalized pain (Table 1.2), localized pain (Table 1.3), and exercise-induced pain (Table 1.4). Drugs that may cause muscle pain are shown in Table 1.5. Exercise-induced pain is a classical feature of metabolic myopathies, with glycogenoses (e.g. McArdle's disease) typically presenting with pain early in exercise and disorders of fatty acid metabolism (e.g. carnitine palmitoyltransferase deficiency) with pain on sustained exertion. An important catch is dystrophin-related disorders. Both Duchenne and Becker muscular dystrophies may present with exercise-induced calf pain, mimicking a glycogenosis, but later develop weakness. Some dystrophin mutations, and other dystrophy-related genes (e.g. *ANO5*) may cause exercise-induced pain without weakness, and this is sometimes referred to as a pseudo-metabolic presentation.

Table 1.3 Disorders associated with localized muscle pain

Neuralgic amyotrophy
Focal neuropathies
Infections • Bacterial (pyomyositis) • Parasitic
Inflammation • Sarcoidosis
Acute alcoholic myopathy
Metabolic myopathies
Tumours (primary muscle tumours, infiltration from other tumours)
Secondary to local joint/rheumatological problems
Compartment syndromes

Table 1.4 Causes of exercise-induced pain

Intermittent claudication
Muscular dystrophies • Duchenne • Becker • Anoctamin 5 (limb-girdle dystrophy Type 2L)
Metabolic myopathies • Glycogenoses (e.g. McArdle's disease) • Disorders of lipid metabolism (e.g. CPT deficiency) • Mitochondrial cytopathies • Brody's syndrome
Dermatomyositis

CPT, carnitine palmitoyltransferase.

Stiffness and muscle hyper-excitability

The terms contracture, cramp, and spasm are misunderstood by patients and doctors alike. Contracture may mean one of two things. Permanent muscle shortening due to fibrosis is an inevitable late sequela of numerous neuromuscular disorders associated with marked weakness and muscle atrophy. Typical examples are fixed flexion contractures at the hips, knees, and elbows. These contractures are in themselves painless, but may contribute to discomfort because of difficulty with positioning. They are rarely a presenting symptom. In some muscle disorders contractures develop as an early feature, when there is little muscle weakness and generally good mobility. The commonest include Emery–Dreifuss syndrome, which is genetically heterogeneous, with early contractures affecting the neck (limiting flexion), elbows and ankles (Achilles tendon tightening), Bethlem myopathy, and the various forms of rigid spine syndrome. The second meaning of contracture is a transient, painful shortening of a muscle due to failure of relaxation,

Table 1.5 Drugs causing muscle pain (not a complete list—see also Chapter 33)

Statins
Amiodarone
Cimetidine
Clofibrate
Emetine
Gemfibrozil
Heroin
Beta blockers
Nifedipine
D-Penicillamine
Procainamide
Vincristine
Zidovudine

and overlaps with the term cramp used by patients. EMG would be silent, and it is due to failure of relaxation secondary to metabolic factors that impair calcium reuptake and thus the end of the contraction process. The commonest example is that seen in McArdle's disease, where it is precipitated by exercise.

Cramps (which may be referred to as spasms by patients) are due to peripheral nerve hyper-excitability and consist of brief painful contracture most commonly affecting gastrocnemius. EMG would show high-frequency motor unit discharges. In the more widespread cramping syndromes (see Chapter 21) cramps may affect the feet, hands, proximal limb and trunk muscles, and axial muscles, and can also be associated with muscle twitching and rippling. The latter is due to peripheral nerve hyper-excitability and must be distinguished from rippling muscle due to caveolin mutations and autoimmune rippling muscle disease, in which the rippling is electrically silent.

Myotonia is due to repetitive depolarization of the muscle fibre membrane and is perceived by the patient as muscle stiffness. Grip myotonia means that after squeezing something tightly there is difficulty in opening the hand (e.g. wringing out a cloth, releasing anything held tightly, releasing after a hand-shake). The most common association is with myotonic dystrophy. In the very much less common myotonia congenita, proximal muscle myotonia causes stiffness when first trying to move after sitting or standing still, and an attempt to move quickly may cause a fall.

Fasciculation, often with frequent cramps, may be the presenting symptom of ALS, and of the much rarer Kennedy disease. It is also a feature of multifocal motor neuropathy and chronic inflammatory demyelinating polyradiculoneuropathy. In ALS, fasciculations are surprisingly rare as the first reported symptom, frequently going unnoticed by the patient until they are pointed out. Benign fasciculation is, by definition, the principal symptom reported and is without weakness. It is a diagnosis of exclusion in those with no abnormality on examination, and does not require EMG to be certain. Benign fasciculations have generally been present in an individual for many years (rather than the more sinister explosive fasciculations of recent onset), but do not have to be confined to the calf muscles. For practical purposes it includes the commonly seen twitching of the peri-orbital muscles, sometimes also referred to as myokymia.

Muscle wasting or muscle enlargement

Muscle wasting or muscle enlargement are rare presenting symptoms. Wasting tends to be a late feature of myopathies, and so presentation is more likely to be with weakness. By contrast, in neurogenic disorders, wasting may be the presenting symptom. Examples include the patient noticing wasting of the dorsal interossei in ulnar neuropathy, and wasting of the first dorsal interosseous and thenar eminence with relative preservation of the medial hand muscles in ALS (the so-called split hand). Progressive and bilateral wasting of the tongue, typically the lateral borders, and especially with visible fasciculations, is essentially pathognomonic for ALS. Focal muscle wasting due to radiculopathy in either the cervical or lumbar regions is rare, e.g. calf atrophy with a S1 lesion where the patient notices that a boot on that side is loose-fitting.

Muscle hypertrophy, other than in response to physical training, is uncommon and is rarely a presenting symptom. Generalized muscle hypertrophy may be a feature of myotonia congenita, caveolin mutations (often associated with rippling muscles), and primary amyloidosis (typically also with tongue enlargement). More restricted hypertrophy may be seen in dystrophinopathies (calves, quadriceps, and less commonly deltoid, but rarely more generalized) and limb-girdle dystrophies (often the quadriceps appears wasted in some parts and hypertrophic in others). Tongue hypertrophy may be seen in Duchenne muscular dystrophy and limb-girdle muscular dystrophy Type 2I. Focal muscle hypertrophy may be seen with local infection (abscess, cysticercosis) or tumour, but is also seen rarely in response to peripheral nerve or nerve root irritation (e.g. calf hypertrophy with S1 radiculopathy).

Myoglobinuria

Extensive breakdown of muscle fibres (rhabdomyolysis), with disruption of the plasma membrane, leads to the release of cytoplasmic contents into the circulation, evidenced by a marked increase in the serum creatine kinase level and myoglobinaemia (not routinely estimated). Excretion of myoglobin into the urine gives rise to myoglobinuria, which the patient reports as the passage of very dark or apparently blood-stained urine (importantly, cross-reactive with the blood detection region of many routine urinalysis sticks). It carries with it the risk of acute tubular necrosis/renal failure. There are numerous causes of myoglobinuria (Table 1.6).

Table 1.6 Causes of myoglobinuria

Metabolic myopathies:
• Glycogenoses (e.g. McArdle's disease)
• Disorders of lipid metabolism (e.g. CPT deficiency)
• Malignant hyperthermia
• Neuroleptic malignant syndrome
Muscular dystrophies:
• Duchenne
• Becker
• Limb-girdle (rare)
Acquired myopathies:
• Myositis
• Infections (viral or bacterial)
Ischaemia and trauma:
• Crush injury
• Status epilepticus
• Electric shock
Drugs and toxins:
• Opiates
• Alcohol
• Statins
• Snake venom
• Bacterial toxins
Others:
• Heat stroke
• Idiopathic
• Extreme exercise in normal individuals

CPT, carnitine palmitoyltransferase.

Systems review

A detailed systems review is required and fulfils several purposes:

1. If the diagnosis is not evident from the foregoing assessment then such a review may point to an underlying cause for the neuromuscular disorder. Examples include features of hormonal dysfunction establishing a diagnosis of endocrine myopathy, haemoptysis from small cell lung cancer presenting with Lambert–Eaton syndrome, cutaneous features suggesting dermatomyositis, or psychiatric or bowel symptoms associated with porphyritic neuropathy.
2. Evidence of multisystem involvement in conditions such as mitochondrial cytopathy (e.g. heart, liver, bowel, skin, central nervous system) or myotonic dystrophy (e.g. cataracts, excessive daytime sleepiness, heart, bowel) may be found.
3. Problems that may complicate management of the neuromuscular disorder can be identified. For example, in a patient with an inflammatory myopathy steroids may be problematic against a background history of diabetes, obesity, hypertension, cataracts, osteoporosis, or affective disorder.

The systematic enquiry thus needs to be thorough and must also be considered alongside the patient's past medical, social, and medication history. The potential links between systemic disease and the presenting neuromuscular complaint are limitless. Associations will be considered further in the chapters dealing with specific disease areas.

Past medical history

The potential relevance of the past medical history to the presenting neuromuscular complaint is largely as discussed in the section The presenting complaint and related features. Identifying a pre-existing condition that is known to be associated with neuromuscular disease may provide answers, but is also subject to false associations. A past history of alcoholism does not prove that that is the cause of the presenting neuropathy, nor does a history of malignancy necessarily mean one is dealing with a paraneoplastic disorder.

Drug and social history

As discussed in detail in Chapter 35, and in other chapters relating to specific forms of neuropathy and myopathy, drugs (therapeutic and recreational) and toxins are a common cause of neuromuscular disorders. The history will readily elicit details of therapeutic drug usage, but more specific enquiry is needed to identify drug and substance abuse, and the possibility of exposure to toxins within the workplace or home environment. Traditional, herbal, or complementary therapies and dietary products, which neither the patient nor the physician may consider important, are in fact a significant potential source of toxicity (e.g. L-tryptophan and eosinophilia–myalgia syndrome) and potential interactions with therapeutic drugs (e.g. grapefruit juice causing drug toxicity by blocking intestinal cytochrome P-450 3A4 and the increased risk of rhabdomyolysis from statins).

Alcohol is an important and ubiquitous neuro- and myotoxin and patient-reported levels of consumption is notoriously unreliable.

Family history

This is so important that the whole of Chapter 2 is devoted to genetic considerations.

CHAPTER 2

Genetic considerations

David Hilton-Jones and Martin R. Turner

Introduction

Many neuromuscular disorders have a specific genetic basis; that is, they are linked to mutation within a single gene. Even those considered to be acquired may be the consequence of as yet poorly understood polygenic factors that predispose the individual to the disorder, possibly triggered by environmental factors [e.g. myasthenia gravis, in inclusion body myositis (IBM), idiopathic inflammatory myopathies, motor neuron disorders, polyneuropathies]. The genetic basis of virtually all of the more common neuromuscular disorders, and indeed of many vanishingly rare disorders, is now known and information is available from many readily accessible on-line databases (e.g. <http://www.musclegenetable.fr>, supported by the World Muscle Society). In some instances, especially for rarer disorders, there is a frustrating lag between a specific gene being identified by researchers and the availability of routine testing in the clinical arena. For some diseases associated with multi-exonic genes and no common mutations, analysis may be extremely time-consuming and costly, limiting routine availability. However, it is likely that in the very near future DNA chips and new-generation sequencing technology will advance to allow relatively cheap and simultaneous analysis of many neuromuscular disease-related genes. Advantageous though this will undoubtedly be, it will also generate in a few patients difficulties with the interpretation of variants of uncertain significance.

Specific aspects of the genetic and molecular features of individual disorders will be discussed throughout this book, but the present chapter will address some general issues that need to be considered when dealing with neuromuscular disorders that might have a genetic basis. It assumes that readers are familiar with the principles of autosomal, sex-linked, and mitochondrial inheritance. Specific issues that commonly arise in clinical practice relating to each of these are noted in Table 2.1 and discussed in more detail in the section Issues relating to specific inheritance patterns.

Relationships between genes and diseases—heterogeneity

It would simplify matters greatly if mutations in one gene always caused a specific disorder, and if a characteristic inherited clinical disorder was only associated with mutations in one specific gene. It has long been recognized that that is not the case, and neuromuscular disorders provide numerous examples of both genetic and phenotypic heterogeneity.

Genetic heterogeneity

This describes the situation of a common phenotype which can be caused either by different mutations within the same gene locus (allelic heterogeneity) or by mutations in completely different gene loci (locus heterogeneity).

Allelic heterogeneity is common in all forms of autosomal inheritance. Some mutations are relatively common, and even traceable to a single founder. Screening tests can be devised to look for these specific common mutations. However, in many diseases, for example ryanodine receptor-associated disorders, collagen VI-related disorders, and motor neuron disease (MND) linked to superoxide dismutase-1, many different mutations at the same allele are recognized. Diagnosis may then require sequencing of the whole gene, which is currently time-consuming and expensive. Different mutations within the same gene, e.g. the chloride channel gene in myotonia congenita, may behave in either a recessive or a dominant fashion.

Locus heterogeneity is perhaps best reflected in two major groups of neuromuscular disorders, namely Charcot–Marie–Tooth (CMT) disease and limb-girdle muscular dystrophy (LGMD). Numerous different genes, relating to nerve and muscle proteins respectively, give rise to essentially the same, highly characteristic, phenotype. In both disorders one may see examples of autosomal dominant and autosomal recessive inheritance, and, in the case of CMT disease, X-linked inheritance. Identifying the specific mechanism for an affected individual is essential for genetic counselling for the patient and wider family

Phenotypic heterogeneity

This term is, arguably, less precise than genetic heterogeneity, and encompasses a range of factors. In essence it refers to the fact that mutations in one gene may produce more than one phenotype. Related issues, discussed in the section Issues relating to specific inheritance patterns when considering autosomal dominant inheritance, include penetrance, expressivity, pleiotropy, and anticipation.

It is not surprising that mutations in different parts of the same gene may have different phenotypic consequences relating to different functional domains within the protein being coded for. Depending on the site and type of mutation, mutations in the lamin A/C gene (*LMNA*) can produce a diverse range of often overlapping phenotypes, including Emery–Dreifuss syndrome, LGMD, cardiomyopathy, CMT disease, lipodystrophy, and progeria. Mutations in one region of the *MYH7* gene cause early onset distal myopathy, and in another cardiomyopathy.

What is more surprising is that the same mutation may produce different phenotypes in different individuals, even within the same family. Thus, certain mutations of the caveolin gene (*CAV3*) can produce either LGMD, distal myopathy, isolated hyperCKaemia, or rippling muscle disease.

Mutations in the dystrophin gene (*DMD*), depending upon their site and whether or not the reading frame is disrupted, may cause Duchenne or Becker muscular dystrophy, isolated cardiomyopathy, or a cramp/myalgia syndrome.

Issues relating to specific inheritance patterns

As indicated in Table 2.1, despite the relative simplicity of the general rules there are a number of potential catches relating to each pattern of inheritance.

Autosomal dominant inheritance

In general, those with an autosomal dominant disorder will have inherited the condition from one or other parent and will themselves have a 50% chance of passing the condition on to each of their offspring, all independent of the sex of the individual. The family history is thus likely to be highly informative. Catches to be aware of include the following:

- Non-paternity: rates vary widely according to the population studied (1–10%, and even higher in some). Estimates are much higher for studies where disputed parentage was the reason for testing.
- New mutations: neither parent has the mutation but it arises in meiosis giving rise to the affected offspring, who may then transmit it to the next generation. In some disorders this is quite common [e.g. facioscapulohumeral (FSH) muscular dystrophy]. This will not necessarily cause difficulty if the phenotype is as characteristic as FSH muscular dystrophy, and DNA analysis is readily available. However, if the phenotype is one associated with genetic heterogeneity, such as LGMD, then it may not be immediately apparent whether the individual has a dominant disorder due to a new mutation or has an autosomal recessive disorder, and DNA-based diagnosis may not be readily available. This presents major difficulty with genetic counselling.
- Germline (gonadal) mosaicism: this is sufficiently common to be problematic in everyday clinical practice and, as with non-paternity and new mutations, is also relevant to X-linked disorders (and, extremely rarely, recessive conditions as well). In this situation an individual has two populations of cells in their gonads, one normal (as in the rest of their body) and the other carrying the mutation. The individual is clinically unaffected and standard (blood and any tissue other than gonad) DNA testing would be normal. However, a fetus arising from the mutated cell line would be affected, and of course then be at risk of passing on the abnormality to future generations in standard Mendelian fashion. It is not easily possible to distinguish between a new mutation and germline mosaicism as the cause of a 'normal' individual having a child with an autosomal dominant disorder, but the distinction is hugely important in terms of advising about recurrence risk. In the case of a new mutation the recurrence risk is essentially zero. With germline mosaicism the risk depends largely on the proportion of germline cells with the mutation, and that is impossible to measure. For a few more common diseases risk estimates are available.
- Penetrance: not everybody carrying a dominant mutation develops clinical symptoms. In those who do not the mutation is said to be non-penetrant. When considering penetrance, age must be taken into account. The expression of many diseases is age dependent. For those who do not present before middle age, penetrance may appear to be near zero at age 20 years but may be 100% by 80 years.
- Expressivity: this is often confused with penetrance, but rather than indicating whether or not there is clinical expression of the mutation it describes quantitative and qualitative manifestations of that expression in an individual in whom the disorder is penetrant. It covers the relative severity of expression, and is also often related to that to the age of onset of symptoms. It also covers variation in the different phenotypic features that might be associated with the condition. Both penetrance and expressivity need to be considered alongside pleiotropy and anticipation discussed next.
- Pleiotropy: this term describes multiple phenotypic traits arising from a mutation in one gene, because that gene product is used by different cell types, or is involved in signalling pathways affecting various targets. An example already alluded to is *LMNA* mutations.
- Anticipation: this describes the earlier age of onset of symptoms in subsequent generations. It is best understood in relation to unstable trinucleotide-repeat expansion disorders, most strikingly exemplified by myotonic dystrophy Type 1 (DM1). In addition to earlier age of onset in subsequent generations it is often blandly stated that the severity of symptoms also increases, but in DM1 that hides a more complex picture. Not only is the age of onset earlier, but the pattern of symptomatology changes strikingly, discussed in detail in Chapter 25. In brief summary, in a three-generation family one might see a grandparent who is of normal intellect and develops cataracts at a slightly earlier age than average, but is otherwise asymptomatic. The daughter develops distal weakness and myotonia in adolescence/early adulthood, and may have an IQ in the normal range or slightly reduced. She then has a child with congenital disease, who is hypotonic at birth, has transient feeding and breathing difficulties, dysmorphic facial features, and subsequent learning difficulties that prevent independent existence.

Table 2.1 Some issues relating to different inheritance modes

Autosomal dominant	New mutations
	Germ-line mosaicism
	Penetrance
	Expressivity
	Pleiotropy
	Anticipation
Autosomal recessive	Many cases appear 'sporadic'
	Pleiotropy
	Pseudodominant inheritance
X-linked	Manifesting carriers/dominant expression
	New mutations
Mitochondrial	Non-transmission of the 'common deletion'
	Many 'mitochondrial' disorders are autosomally inherited

Autosomal recessive inheritance

Most individuals with an autosomal recessive disorder have no family history of the condition and thus appear to be sporadic. This manifestation is sometimes referred to as 'horizontal inheritance' as a family tree shows affected members in a horizontal line, with vertical family members (parents and subsequent generations) being unaffected. This is in contrast to the 'vertical inheritance' pattern of dominant disease with parent-to-child transmission.

Penetrance and expressivity are generally considered only to be features of autosomal dominant disease. Although as a general rule recessive disorders tend to have an earlier onset than dominant disorders, there are many exceptions. Another generalization, again with exceptions, is that recessive phenotypes tend to show less variability than dominant ones.

Pseudodominant inheritance describes the apparent 'vertical transmission' of a disorder that is autosomal recessive in nature. McArdle's disease is an autosomal recessive disorder, and thus affected individuals have two mutated alleles and carriers of one mutated allele are asymptomatic. If an affected individual has offspring with an asymptomatic partner who happens to have one mutated allele, then each child has a 50% risk of developing McArdle's disease and the family tree suggests dominant inheritance (Fig. 2.1). Consanguinity of course greatly increases the likelihood of seeing pseudodominant inheritance, so the ethnic background and traditions of the parents need to be considered.

X-linked inheritance

Mutations on the X chromosome, as on an autosome, may behave in recessive or dominant fashion, but the distinction between the two becomes a little blurred due to a variety of factors.

Dominant X-linked disorders are relatively rare but in the neuromuscular field include *FHL1* mutations which can cause a range of phenotypes including scapuloperoneal syndrome, X-linked myopathy with postural muscle atrophy, and reducing body myopathy. As with any dominant disorder, penetrance and expressivity can vary. Despite being dominant, severity tends to be greater in males. Similarly, CMT disease type 1X is inherited as an X-linked dominant trait but almost invariably females are less affected, both clinically and electrophysiologically, than males. Indeed, some females show no clinical features, indicating low penetrance.

The X-chromosome mutations causing Duchenne and Becker muscular dystrophy are considered to be recessive, which classical teaching suggests should mean that females are asymptomatic carriers and only hemizygous males are affected (cf. haemophilia). However, up to 10% of female carriers may show mild skeletal muscle involvement (most commonly calf hypertrophy, less commonly proximal weakness which very rarely is severe) and are referred to as manifesting carriers. A small number of female carriers may develop cardiomyopathy with or without evidence of skeletal muscle involvement. These 'exceptions' have been attributed to skewed inactivation (or lyonization) of the X chromosome. If there is preferential inactivation of the chromosome carrying the normal gene, then the effects of the mutated gene on the other allele become apparent, but the evidence for this remains inconclusive and other factors may be relevant. Other rare causes of females manifesting disease include the female inheriting two affected X-chromosomes (with a new mutation on one being possible), Turner's syndrome (XO), and X–autosome translocation.

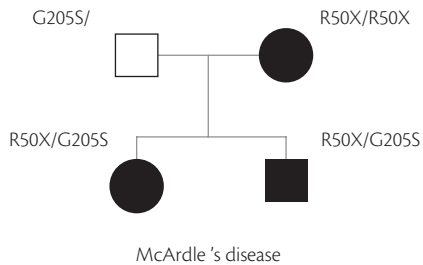

Fig. 2.1 Pseudodominant inheritance. The affected mother (black circle) is homozygous for the most common mutation associated with McArdle's disease. Her asymptomatic partner (open square) carries another recognized mutation on one allele, whereas the other allele is normal. Each child is a compound heterozygote for the two mutations.

As with autosomal recessive disorders, many affected individuals are seen with no family history, or an affected male sibling (apparent 'horizontal transmission'). One explanation for the apparent absent family history is that in preceding generations the mutation may only have been carried by 'asymptomatic' females. Sometimes the family history has simply not been taken back far enough, and more detailed enquiry will reveal, for example in the case of Duchenne muscular dystrophy, death of an adolescent male several generations ago without the family being aware of the precise diagnosis. For Duchenne and Becker muscular dystrophies, the greatest catches are new mutations and germline mosaicism (both discussed in the section Autosomal dominant inheritance). New mutations are responsible for about one-third of cases. Germline mosaicism is less common, but presents particular difficulties for counselling about recurrence risk.

Mitochondrial inheritance

'Mitochondrial myopathy' was first defined by the demonstration of accumulations of structurally abnormal mitochondria in muscle biopsy specimens. It was then shown that respiratory chain function was impaired in some (e.g. complex 1 or complex 4 deficiencies). Subsequently abnormalities of mitochondrial DNA (mtDNA) were identified, initially deletion of a large section of the circular mtDNA molecule (the so-called common deletion), and later point mutations within mtDNA. The clinical diversity of mitochondrial disorders rapidly became evident, leading to the preferred term 'mitochondrial *cyto*pathy' as in many mitochondrial disorders there is no evidence of muscle involvement. mtDNA is maternally inherited and encodes for only a small number of mitochondrial (respiratory chain) proteins, the rest being autosomal in origin. Thus, mitochondrial cytopathy does not necessarily imply maternal inheritance, and indeed the majority of mitochondrial disorders are either sporadic, and not inherited (e.g. the 'common' deletion of mtDNA, causing late-onset chronic progressive external ophthalmoplegia), or are the result of a dominant or recessive autosomal mutations and behave as already described. A precise molecular diagnosis is clearly essential for correct genetic counselling, which is particularly difficult for maternally inherited mtDNA point mutations, as discussed in detail in Chapter 32.

Family history

Little encouragement is needed to take a detailed family history if the patient spontaneously volunteers information about other

affected family members, or the patient's clinical history and examination clearly indicate a genetic neuromuscular disorder. In the absence of such clues, a cursory family history may miss potentially relevant information. Most acquired neuromuscular disorders are sporadic, and thus there will indeed be no relevant family history, but inheritable disorders frequently occur in an isolated individual. Family histories may be misleading or incomplete. Not infrequently, the clue to a genetic disorder may only come after further clinical and laboratory assessment (e.g. finding neurophysiological evidence of a demyelinating neuropathy in a patient initially thought to have an acquired peripheral neuropathy—the correct diagnosis being autosomal dominant CMT disease with incomplete penetrance). One then has to return to the family history. The patient may have inadequate knowledge about their family, and other family members may need to be interviewed. The history-taking may need to be extended to physical assessment of other, apparently unaffected, family members, thus overlapping with issues discussed in the section Genetic counselling later.

It is worth noting that many highly educated individuals will not understand the concept of a condition that 'runs in the family'. Neither should questioning be limited to 'has anybody else in the family had the same problems'; more directed enquiry should be made, such as the use of walking aids, mobility problems, 'undiagnosed' problems leading to disability, and details of potentially erroneous diagnoses such as 'arthritis' as a cause of walking impairment, etc. Recently, an autosomal dominant intronic hexanucleotide repeat expansion in *C9orf72* has been associated with cases of MND (also known as amyotrophic lateral sclerosis, ALS) and frontotemporal dementia (FTD) occurring in members of the same family. MND was often historically termed 'creeping paralysis', and may be labelled erroneously as MS or stroke (in the case of the elderly with bulbar onset). FTD may be considered generically as 'Alzheimer's' or even as simply eccentric behaviour. Such factors have undoubtedly led to cases of MND being labelled erroneously as sporadic.

As emphasized in Chapter 1, many inherited neuromuscular disorders have multisystemic manifestations, and many acquired disorders are secondary to an underlying disorder, so the family history needs to extend beyond neurological problems. Examples of relevant 'general medical' associations are too legion to list, but one example, shown in the section Illustrative family histories, might be a mitochondrial disorder presenting as a myopathy in one individual but as deafness, cardiomyopathy, or diabetes in other family members.

Consanguinity substantially increases the risk of autosomal recessive disorders. This is recognized as being common in certain ethnic and religious groups but may be overlooked in populations in whom consanguineous relationships are rare. The question needs to be asked despite any discomfort that may arise. A related issue is having knowledge of the frequency of particular disorders in the local population as some show considerable regional variability. A classic example relating to ancestral issues is the high prevalence of myotonic dystrophy type 1 in Quebec, Canada.

Taking an adequate family history requires time and patience and may need to be undertaken in more detail at a later date than the initial clinic assessment. Depending upon the experience of the clinician, help may need to be sought from a geneticist or genetics nurse specialist, both of whom may have a subsequent role in genetic counselling.

The next subsection (Illustrative family histories) gives some examples of 'diagnostic', 'missing', 'inadequate', and 'misleading' family histories, all based on real-life examples.

Illustrative family histories

With dominant disorders in particular the family history is often straightforward and highly informative. FSH muscular dystrophy is inherited in an autosomal dominant fashion and is associated with a deletion in the D4Z4 repeat sequence in the telomeric region of chromosome 4. Figure 2.2 illustrates a family in which the patient presented with typical features of FSH muscular dystrophy. His mother and maternal grandfather were known to have had the condition, and his mother had been shown to have the relevant mutation. Arguably, the patient does not require DNA confirmation of the diagnosis.

In the family shown in Fig. 2.3(a) the patient presented with unilateral scapular winging, a well-recognized presentation of FSH muscular dystrophy, and the diagnosis was confirmed at a molecular level. However, neither parent was known to be affected by the condition. There are five possible explanations for what is a common scenario:

1. One parent may be found on examination to have features of the condition but was either not aware of any symptoms or chose to ignore/deny them.
2. One parent carries the mutation but it is non-penetrant and they have no signs of the condition.
3. One parent is a germline mosaic.
4. There has been a new mutation.
5. Non-paternity (Fig. 2.3b).

A patient presented with features consistent with Duchenne muscular dystrophy (Fig. 2.4a) but enquiry back to his grandparents revealed no family history of the condition. Taking the history back (Fig. 2.4b) further identified a male predecessor who died during the Second World War at the age of 16 years from a muscle-wasting condition, without any more detail being available (a common scenario). The patient was shown to have a dystrophin mutation and his mother to carry the mutation. The presumption

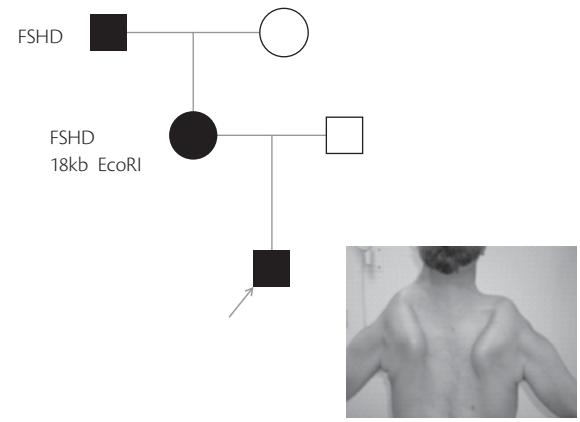

Fig. 2.2 'Diagnostic' family history. The patient presented with typical features of facioscapulohumeral muscular dystrophy. His mother (black circle) and maternal grandfather (top black square) were known to have had the condition, and his mother had had confirmatory DNA analysis.

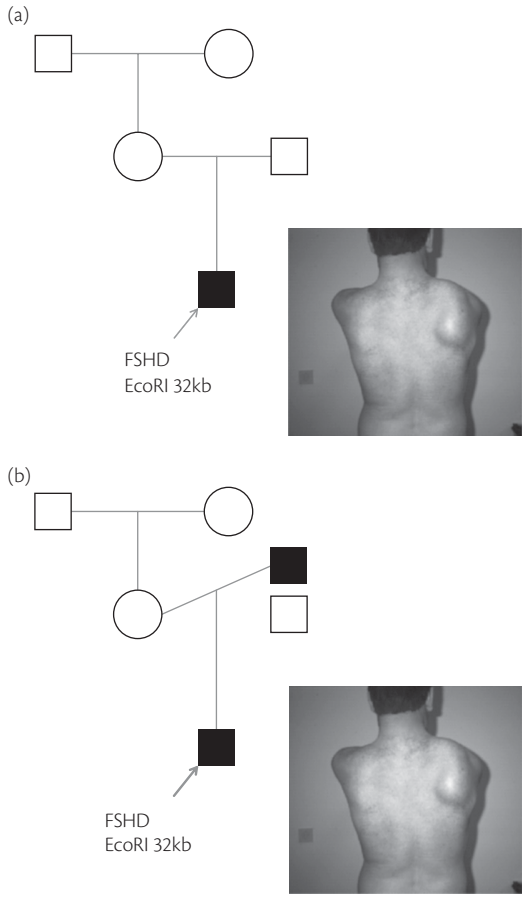

Fig. 2.3 'Missing' family history. The patient presented with unilateral scapular winging (a common presenting feature in milder cases of facioscapulohumeral muscular dystrophy, FSHD) and DNA analysis confirmed the diagnosis. See text for discussion of paternity.

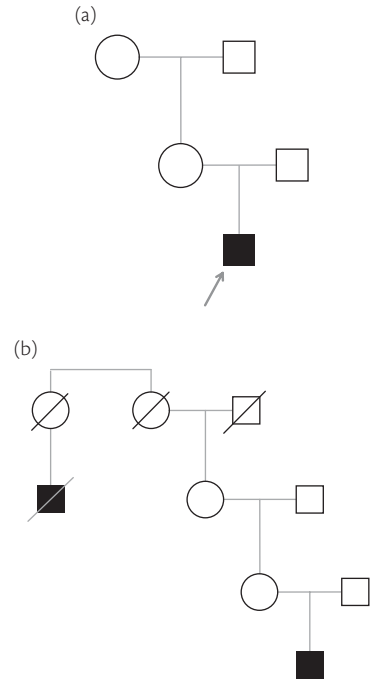

Fig. 2.4 'Inadequate' family history. (a) A male presented with early childhood onset weakness and became wheelchair dependent early in the second decade. (b) Initial family history was 'negative' for neuromuscular disease, but became positive on more detailed enquiry.

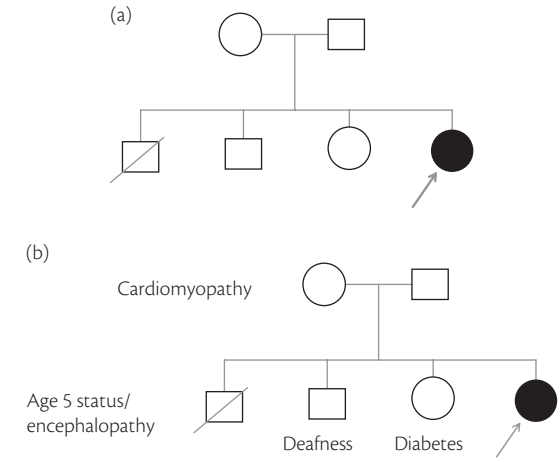

Fig. 2.5 'Inadequate' family history. (a) Enquiry into the family history must go beyond questions about neuromuscular problems, as shown by this family with a maternally inherited mitochondrial cytopathy (b).

is that his ancestor also had Duchenne muscular dystrophy with intervening female carriers.

Particularly in conditions associated with multisystemic involvement, specific enquiry must be made about non-muscular manifestations. This is exemplified by a family with a maternally inherited mtDNA mutation in whom initial enquiry about muscle problems revealed no relevant family history (Fig. 2.5a), but more detailed enquiry revealed an extensive history of related clinical expression (Fig. 2.5b).

Finally, one must be wary of being misled by the family history. In the family shown in Fig. 2.6, three generations were known to be affected by FSH muscular dystrophy, with DNA confirmation of the diagnosis. In addition, patient III.1 presented with features of myotonia congenita and was shown to be a compound heterozygote for *CLCN1* chloride channel mutations, confirming a diagnosis of autosomal recessive myotonia congenita. At the age of 21 years, patient III.2 presented complaining of weakness and muscle stiffness. She realized that she had a 50% risk of inheriting the FSH mutation, and a 25% risk of developing myotonia congenita, and

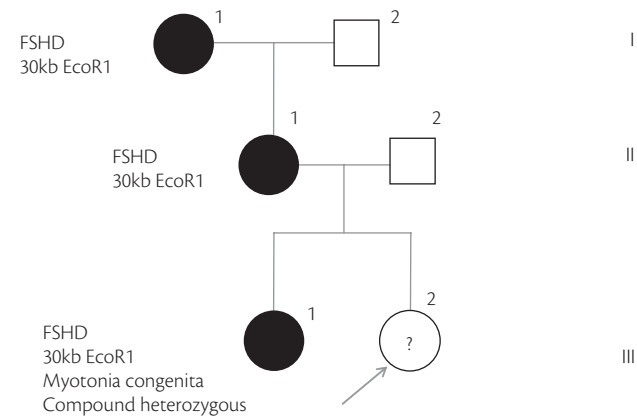

Fig. 2.6 'Misleading' family history. Three generations had clinical features of facioscapulohumeral muscular dystrophy (FSHD) with molecular confirmation of the diagnosis. One member, III.1, in addition had features of myotonia congenita and was shown to have compound heterozygous mutations affecting the chloride channel gene, *CLCN1*, indicating recessive inheritance. Her sibling, III.2, presented at the age of 20 years complaining of muscle stiffness and weakness.

believed that she had been twice unlucky. However, examination showed no abnormality, and DNA testing showed that she had not inherited the FSH mutation and was a carrier for only one of the two myotonia congenita mutations.

The last example relates to another common clinical problem, whereby parents knowing that their children have a risk of inheriting a neuromuscular disorder may perceive problems that do not exist. For example, knowledge of a family history of CMT disease may lead to parental anxiety that every trip and fall in the school playground heralds the onset. Another common example is concern that normal scapular prominence in a relatively thin child is the first evidence of FSH muscular dystrophy. These issues are highly relevant when considering genetic counselling issues.

Genetic counselling

In brief, genetic counselling refers to the process of informing individuals about genetic risks and, by extrapolation, advising them about reproductive options. Although potentially complex in the minutiae, the major issues relevant to neuromuscular disorders are summarized in Table 2.2. Genetic counselling should ideally be provided by a clinician who not only has the requisite genetic knowledge but also has widespread experience in the diagnosis and management of neuromuscular disorders, both genetic and acquired. This might be a geneticist who has subspecialized in the field of neuromuscular disorders, or a paediatric or adult neuromuscular specialist who has undertaken appropriate genetic training. In many centres the goal is achieved through collaboration between the relevant clinical service responsible for diagnosis and management, and the department of genetics.

A common clinical problem is an individual who comes from a family known to have a specific neuromuscular disorder and who wishes to know their risk of developing the 'familial condition'. If the mode of inheritance of that condition is known (e.g. dominant, recessive, X-linked, mitochondrial) then it is a simple paper exercise to determine the specific risk of that individual having inherited the relevant mutation(s). And even simpler in principle, if the specific mutation is known, DNA analysis can determine, essentially with 100% accuracy, whether or not that individual has inherited the mutation. In practice however, the question of whether they will develop the familial condition is far more complex.

Table 2.2 Issues relating to genetic counselling

Informing individuals of genetic risks:
• The risk to an individual who has a family history of genetic disease
• The risk of a parent with a genetic disorder having an affected child
• The recurrence risk in subsequent pregnancies if a child has been born with a genetic disorder
Reproductive options:
• Sperm or egg donation
• Pre-implantation genetic diagnosis
• Prenatal diagnosis (e.g. by chorionic villus sampling)

As discussed in the section Illustrative family histories, carrying a mutation does not necessarily mean that an individual will express it, or if they do how severe it will be (including the age of onset) or which organ system(s) it will involve. Counselling of the individual must take into account all of these considerations. Adequate counselling can only be given if the counsellor has intimate knowledge of the condition and all of its potential manifestations.

One special issue relates to the testing of the children of a parent with an inheritable neuromuscular disorder. If the condition was known about prior to conception, then appropriate counselling should have been given beforehand and reproductive options discussed. However, a common scenario is that a parent is diagnosed with such a condition after they have already conceived. Considering the simplest example of an autosomal dominant disorder they will realize that each child has a 50% risk of having inherited the mutation and may enquire about testing. As a general principle, testing asymptomatic children (who, by definition, cannot provide informed consent) is *not* indicated unless a specific therapeutic intervention is available, or knowledge of the mutation might directly affect overall management. If the child develops symptoms or signs that might be attributable to the mutation, then testing may be indicated, but otherwise the general principle is to counsel the child to enable to make their own decision about pre-symptomatic testing once they have reached the age of consent. The parental anxiety is readily understandable. Counselling should help them deal with those anxieties and should include advice to be open in discussions with their children as they mature and might ask questions about their parent's health issues. No rule is absolutely rigid, and the relationship between the patient and clinician over the years should allow constant review of relevant genetic issues.

For all patterns of inheritance, after the birth of an affected child a major issue is the risk of recurrence in subsequent pregnancies. Where the mutation is known, this gives rise to the possibility of prenatal diagnosis in future pregnancies, or pre-implantation genetic diagnosis. Other options, even when the mutation is not known, include egg or sperm donation.

Individual disorders are associated with specific genetic counselling issues, which will be addressed in more detail in the relevant chapters. Myotonic dystrophy presents a number of issues relating to anticipation, and the disease tends to manifest itself in different ways in different generations. It is one of the few neuromuscular disorders where there are good grounds to actively seek out asymptomatic family members to offer genetic testing. An important potentially preventable situation is an asymptomatic mother giving birth to a child with the severe congenital form of the condition.

The principles of genetic counselling seem inherently simple, but the practice is complex and a rashly sent test has the potential to cause irreparable and far-reaching emotional harm. All counselling, by definition, is non-directional. There are enormous sensitivities relating to specific religious and cultural issues. Clinical assessment and DNA testing take place against the background of informed consent, and that is inherently dependent upon provision of the right information, presented in an appropriate fashion.

CHAPTER 3

Examination

David Hilton-Jones and Martin R. Turner

Introduction

Despite the traditional concept of distinguishing rigidly between symptoms and signs, in reality there is substantial overlap, which will have been readily evident from the discussion in Chapter 1. For example, careful elucidation of the history will give a strong indication of the distribution of weakness, which is so critical in establishing the differential diagnosis, and then examination will further refine that distribution. Not infrequently, an observation on examination may lead to further questioning of the patient to elucidate additional features of the symptomatology. Contrary to the established dogma of 'history first, and then examination', the reality is that examination comes first—as one watches the patient walking from the waiting room into the clinic, and observes the patient whilst he or she is relating their history.

Those reading this book will be familiar with the general approach to physical examination, and the purpose of this chapter is to offer some focused observations in relation to neuromuscular disorders.

General examination

The purpose of the general physical examination is to determine whether:

1. There is evidence of a primary general medical disorder that might cause secondary neuromuscular problems. For example:
   (a) endocrinopathy such as hypothyroidism [causing proximal myopathy, or focal neuropathy (carpal tunnel syndrome)] or Cushing's syndrome (proximal myopathy),
   (b) malignancy causing paraneoplastic neuromuscular disorder.
2. There are systemic features associated with a primary neuromuscular disorder. For example:
   (a) myotonic dystrophy—cataracts, hair loss, irregular pulse, pilomatrixomata,
   (b) mitochondrial cytopathy—skin (lipomatosis), pigmentary retinopathy, cardiomyopathy, irregular pulse, movement disorder,
   (c) an association with cardiac arrhythmia and/or cardiomyopathy.
3. There are 'general' medical problems that may complicate a primary neuromuscular disorder or its management. For example:
   (a) rheumatological/orthopaedic problems that will further exacerbate mobility and posture issues relating to a primary neuromuscular disorder (e.g. hip and knee arthritis exacerbating problems relating to quadriceps weakness in inclusion body myositis, or further impairing mobility in hereditary neuropathies),
   (b) cardiorespiratory problems (e.g. asthma, chronic obstructive pulmonary disease, ischaemic heart disease/cardiomyopathy) that may exacerbate ventilatory muscle insufficiency and cardiac problems directly related to the primary neuromuscular disorder.

The findings on general physical examination, or the identification of a primary neurological disorder that is known to be associated with multisystemic features, may require more detailed specialist investigations. Amongst the most common are cardiorespiratory studies. Electrocardiography (ECG) should be an integral part of the initial assessment if a disorder known to affect the heart is suspected (e.g. myotonic dystrophy, laminopathy, dystrophinopathy) and in any patient with an as yet unidentified generalized neuromuscular disorder. A resting tachycardia may be a clue to dysautonomia, and bradycardia to hypothyroidism. More detailed cardiac assessment (echocardiography) is needed at initial assessment and on long-term review in those patients with conditions known to be associated with cardiomyopathy (e.g. dystrophinopathies). More detailed respiratory studies (pulmonary function, sleep studies) may be indicated, but initial assessment should include measurement of erect and supine forced vital capacity in those conditions known to be associated with ventilatory muscle weakness [e.g. Guillain–Barré syndrome, motor neuron disease (MND), myasthenia gravis, and acid maltase deficiency].

Motor examination

Inspection and palpation of muscle and nerves

Adequate physical observation in the setting of neuromuscular symptoms requires the patient to be undressed to their underwear. The distribution of any atrophy or hypertrophy should be noted, together with any spontaneous involuntary movements (e.g. fasciculation, rippling, twitching, myokymia). Fasciculations in MND may be sparse, and are most often missed over the shoulder region and back. Facial fasciculation (especially of the chin) is particularly prominent in Kennedy disease. Tongue fasciculations are best observed with the tongue relaxed. Forced protrusion leads to false positive assignation. In the setting of bilateral tongue wasting and dysarthria, tongue fasciculations are highly suspicious for MND.

Peripheral nerve hypertrophy is seen, or rather felt, in some demyelinating polyneuropathies (including the most common form of hereditary motor and sensory neuropathy, Type 1A), leprosy, and neurofibromatosis. However, it is inconsistent, and there is often not a clear distinction from normality.

Muscle palpation may help detect subtle atrophy. Various textures described in different clinical settings include hardness, 'woody

feeling', 'doughy feeling', and 'fibrotic', but we have not found such assessment contributory.

An assessment of limb tone is vital in establishing a central component to a neuromuscular disorder, e.g. amyotrophic lateral sclerosis (ALS). This may range from a subtle 'catch' in forced supination of the forearm, to sustained clonus of the ankle and even patella. Passive movement of joints and the spine are required to identify contractures (see Chapter 1). Common sites include the neck and spine (as in rigid spine syndromes), elbows, finger flexors (e.g. Bethlem myopathy), hips, knees, and ankles.

Strength assessment

Whilst the term *strength assessment* is obviously readily applicable to axial and limb muscles, it is not so appropriate for evaluation of the extraocular or ventilatory muscles. Even when considering limb muscles, in the clinical setting it is often most helpful to think in terms of functional ability than ascribing a numerical value.

Cranio-cervical muscles

With the notable exceptions of myasthenia gravis and myotonic dystrophy, extraocular muscle involvement is uncommon in neuromuscular disorders, but when present is very useful in shortening the differential diagnosis (see Table 3.1). Assessment for ptosis and of the eye movements should be made even in the absence of suggestive symptoms.

Ptosis may be subtle, and is equally a frequent false positive sign. When ptosis is marked the patient may tilt their head back to enable them to see ahead. There may be persistent over-activity of the frontalis muscle to try to compensate (Fig. 3.1). Ptosis is often asymmetric. This is the norm in myasthenia gravis, but even in conditions such as oculopharyngeal muscular dystrophy there may be striking asymmetry. Fatigability, seen as the eyelid progressively drooping either spontaneously or on attempted sustained up-gaze, is virtually pathognomonic of myasthenia gravis.

Weakness of any of the six muscles moving each globe typically presents with diplopia. There may be obvious underactivity of one or more muscles when testing eye movements, but minor weakness causing diplopia may not be readily visible and requires cover testing to determine the muscle(s) involved. A striking feature of mitochondrial chronic progressive external ophthalmoplegia (CPEO) is that diplopia is uncommon, despite often gross restriction of eye movements and sometimes with very evident divergence of the ocular axes (Fig. 3.2).

Fig. 3.1 Myasthenia gravis. Ptosis/frontalis over-activity. Asymmetry.

Temporalis muscle atrophy is often striking in myotonic dystrophy and contributes to the characteristic facies (Fig. 3.3). Weakness of the masseter and temporalis is often seen as part of the bulbar weakness in myasthenia gravis.

Mild unilateral weakness of the facial muscles is usually very obvious because of the asymmetry on movement. Conversely, even marked bilaterally symmetric facial weakness may not be obvious and is frequently missed. The first impression of facial weakness may be suspected from the failure of the patient's face to respond to the normal pleasantries exchanged at the start of a consultation, or as they give their history. Arguably, the best sign is the failure to completely bury the eyelashes on attempted forceful closure (Fig. 3.4), and there is no additional information to be gained from attempting forced eye opening. Not all incomplete burying of the eyelashes indicates weakness—those with contact lenses and those with lashings of mascara may be reluctant to attempt the manoeuvre! Weakness of lip closure may be suggested during speech, and can be demonstrated by failure to keep the lips closed when 'blowing up the cheeks' or when the examiner tries to forcibly separate the lips with their thumbs. Patients with facioscapulohumeral muscular dystrophy often have a rather characteristic bulbous appearance to their lips (Fig. 3.5).

The strength of the tongue and soft palate are best assessed by listening to speech (asking the patient to recite a nursery rhyme may be useful), perhaps aided by getting the patient to attempt to produce specific sounds, e.g. saying k and producing a hard g are problematic with palatal weakness, whereas tongue weakness is revealed by difficulty producing d, l, n, and t.

Swallowing can be assessed qualitatively by observation and quantitatively by timing the swallow of a specified amount of water.

Several neuromuscular disorders cause weakness of the neck flexors and extensors (Fig. 3.6), and this often neglected sign can be highly discriminatory in conjunction with other findings. It is often asymptomatic, but marked weakness of flexion causes difficulty lifting and throwing the head forwards in the normal action of sitting up from the supine position (Fig. 3.7). Marked weakness of extension causes the 'dropped head' appearance mentioned in Chapter 1. Weakness of flexion, which may be marked, with normal or only minimal weakness of extension is seen commonly in myasthenia gravis in both sexes and at all ages, myotonic dystrophy, and

Table 3.1 'Minimum' assessments of limb and trunk strength

Neck flexion and extension
Scapular fixation
Shoulder abduction
Elbow flexion and extension
Wrist flexion and extension
Finger flexion, extension, and abduction
Hip flexion and extension
Knee flexion and extension
Ankle dorsiflexion and plantar flexion
Trunk—sitting up from lying supine
Gait

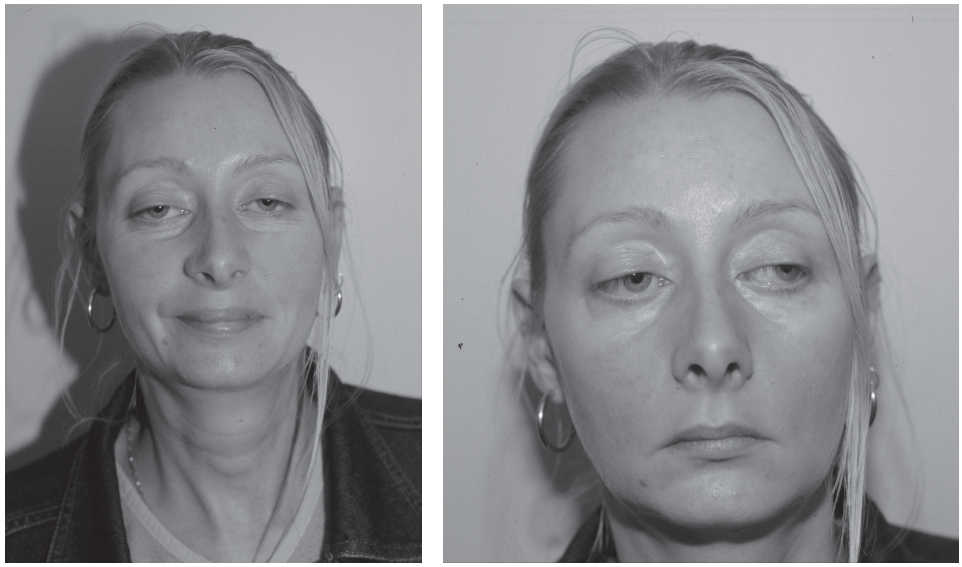

Fig. 3.2 Mitochondrial chronic progressive external ophthalmoplegia.

Fig. 3.3 Myotonic dystrophy facies—wasted temporalis.

Fig. 3.5 Facioscapulohumeral muscular dystrophy—mild facial weakness and bulbous lips.

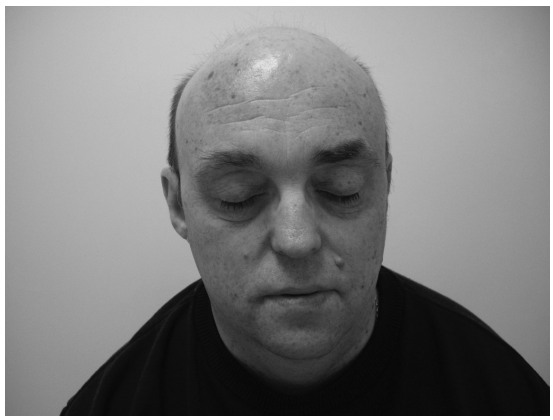

Fig. 3.4 Myotonic dystrophy. Bilateral facial weakness—incomplete burying of the eyelashes.

the idiopathic inflammatory myopathies. Causes of dropped head syndrome include myasthenia gravis in older men, MND, and, rarely, inflammatory myopathies and myotonic dystrophy. Overall, neck weakness is rather uncommon in most dystrophies except in advanced stages.

Axial and limb muscles

Involvement of the axial muscles in the neck has been described (see the section Cranio-cervical muscles). Weakness of the paravertebral muscles is seen in *FHL1* myopathies (XMPMA; X-linked myopathy with postural muscle atrophy), acid maltase deficiency, and ALS. Marked involvement of the lumbar paravertebral muscles in FSH muscular dystrophy leads to an exaggerated lordosis (Fig. 3.8) and is frequently associated with lumbar pain.

All readers will be familiar with assessment of limb muscle strength, but it is appropriate to make some comments concerning which muscles should be assessed, how strength can be

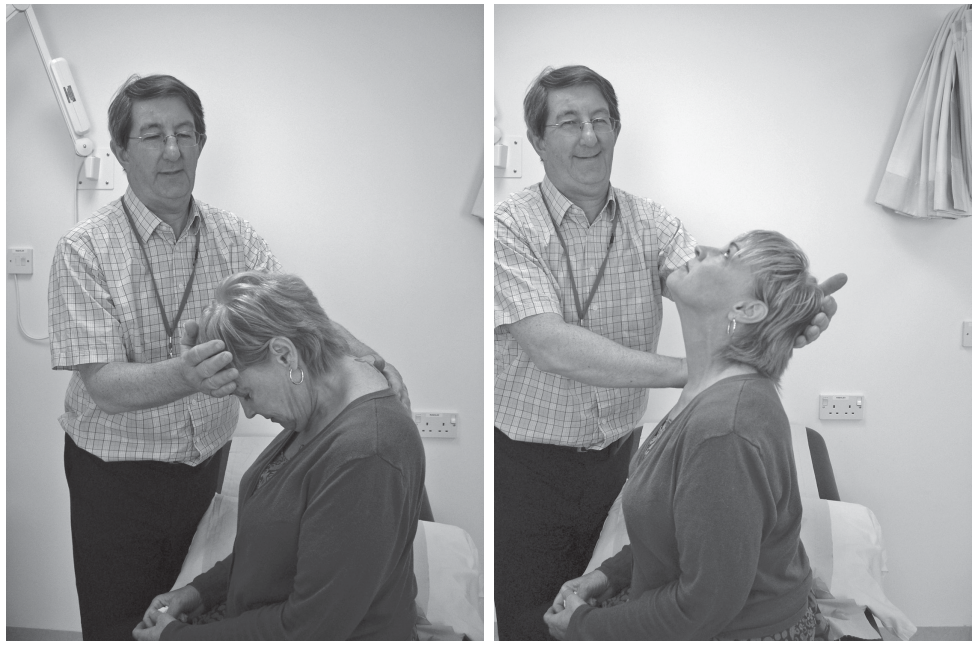

Fig. 3.6 Demonstration of positions for testing neck flexion and extension.

measured and recorded, and the importance of simple functional assessments.

Which muscles?

From the more than 600 skeletal muscles in the human body, the history provides vital clues to the approach that should be taken during examination. A history suggestive of a focal mononeuropathy indicates the need to assess the muscles innervated by that nerve, to confirm one's suspicions but also to look at nearby muscles to show that those innervated by other nerves are unaffected. Symptoms of peripheral neuropathy make distal rather than proximal weakness most likely. A history of generalized weakness may be associated with proximal, distal, or combined weakness, and the examination must look in detail to complement the history to try and identify the exact pattern of weakness which, as stressed in Chapter 1, may greatly shorten the differential diagnosis. As a minimum, the movements listed in Table 3.1 should be assessed in all patients, but the history and preliminary observations on examination will direct further assessments. The finding of a so-called 'pyramidal' pattern of weakness, whereby there is preferential weakness of upper limb extensors and lower limb flexors, offers little discriminatory value for central versus peripheral neuromuscular disorders in reality.

The position of the limb is critical when assessing strength. Most clinicians use the approaches outlined in the classic *Aids to the Examination of the Peripheral Nervous System*, with personal variations learnt from experience.

Recording strength is easy in principle, but proves to be harder in practice. In routine clinical practice most clinicians use the Medical Research Council (MRC) scale, despite its limitations. The problem with the original scale is that grade 4 covers a wide range, encompassing minimal to substantial weakness. To try to deal with this various expansions have been tried (Table 3.2), but then inter- and intra-observer variations become more apparent. On the basis of Rasch analysis it has recently been proposed that the scale should be reduced to only four items. Whilst this may reduce observer variability, it is less useful for noting small changes in strength over

Fig. 3.7 Neck flexion weakness. The patient is trying to get up from the supine position but cannot raise and throw his head forwards (myotonic dystrophy).

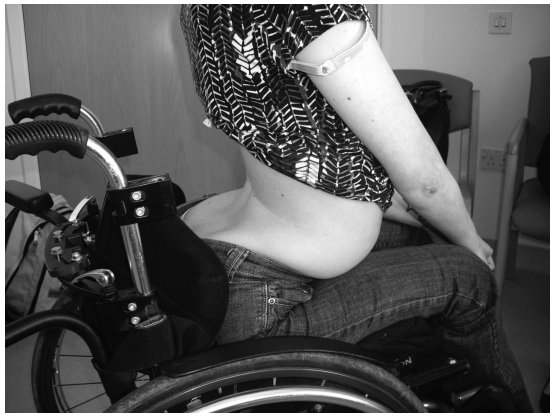

Fig. 3.8 Facioscapulohumeral muscular dystrophy—exaggerated lumbar lordosis due to weakness of the lumbar paravertebral muscles.

time, which may be vital for assessing improvement or deterioration. As noted, in clinical practice it is often more helpful to use quasi-objective functional assessments rather than numbers.

In the research setting MRC scores may be used as well as summed scores from assessing particular groups of muscles, often trying to reflect the particular pattern of muscle weakness associated with a particular disease. In addition to such manual muscle testing, various forms of dynamometry, hand-held or static, are used for quantification. A few diseases have well-validated assessment scales, e.g. the Quantitative Myasthenia Gravis (QMG) test.

A number of simple bedside functional tests provide a powerful tool to record the patient's current status, and readily allow the same clinician or others to note change over time, either deterioration reflecting the natural progression of the disorder or improvement in response to treatment (Table 3.2). For example, a patient with myositis and hip flexion weakness may, when lying supine, be able to raise their leg to get their heel 5 cm off the sheet. A month later they can raise it to 40 cm—a clear demonstration of improvement and yet on both occasions the MRC grade would be recorded as 4. Similarly, being able to rise from a standard height chair without using the arms on one occasion but needing to use the arms a month later suggests deterioration.

Manual dexterity relates to both strength and sensory function. A variety of tests have been devised to quantify such function, of which the most commonly used is the nine-hole peg test. They have some value in routine practice, e.g. monitoring progress in multifocal motor neuropathy with conduction block.

Table 3.2 Functional assessments

Standing up from a standard height chair—whether or not the arms need to be used
Rising from a squat
Timed walk: distance within a specific time (6-min walk), or time to walk a specific distance (10-m test), or timed up and go (TUG)
Lying supine ability to lift the head straight leg lift (heel–sheet distance, time able to maintain) sitting up from lying
Ability to run and hop
Ability to walk on heels and tip-toe
Ability to climb stairs in an 'adult' or 'child' (one step at a time) fashion
Height to which arms can be raised (and time able to maintain)

Ventilatory muscles

Severe weakness is evidenced by orthopnoea, dyspnoea at rest, use of the accessory muscles of ventilation, ability to speak in only short sentences, and, in extremis, cyanosis. Mild weakness may be asymptomatic and easily overlooked, yet important to establish and monitor regularly in rapidly evolving conditions, e.g. Guillain–Barré syndrome and myasthenic crisis. Chronic nocturnal hypoventilation gives rise to excessive daytime sleepiness and waking with a headache and drowsiness. At the bedside the best assessment of ventilatory muscle strength is measurement of the forced vital capacity (FVC). This needs only a simple, relatively cheap, hand-held spirometer. Devices for measuring peak expiratory flow are totally inadequate for assessment of the neuromuscular patient. As a rule of thumb in an adult, a decline in FVC to 1 L necessitates urgent anaesthetic review for possible admission to an intensive care unit, although earlier transfer for rapidly progressing conditions may also be appropriate.

Many neuromuscular disorders specifically affect the diaphragm, leading to two important additional physical signs. Normally inspiration leads to the diaphragm descending and the abdominal wall moving outwards, but with weakness of the diaphragm it is drawn upwards during inspiration and the abdominal wall moves inwards ('abdominal paradox'). More sensitive is a fall in forced FVC on lying supine compared with when erect. Upon lying, the abdominal contents push the weak diaphragm cranially and reduce the FVC. In normal individuals there is some fall, more marked if they are obese. A fall of more than 10% is likely to be significant, and more than 20% certainly is.

Abnormal relaxation and movements

The most common form of delayed muscle relaxation is myotonia. Myotonic dystrophy is the most often encountered cause, and Type 1 is generally much more prevalent than Type 2. Electromyography may demonstrate myotonia when it is not obvious clinically. Cold tends to exacerbate myotonia. The classical textbook finding is of grip myotonia, whereby after shaking the examiner's hand, or forcefully gripping the examiner's fingers, there is delayed relaxation (Fig. 3.9). This may be severe, taking 10 s or more to achieve full relaxation, but it is frequently very mild and easily missed, especially as the 'warm-up' phenomenon means that it tends to lessen on repeated effort. More sensitive is the demonstration of percussion myotonia, whereby a sharp tap with a tendon hammer of the thenar eminence muscles leads to exaggerated contraction and delayed relaxation (Fig. 3.10).

Muscle stiffness and delayed relaxation are features of severe, long-standing hypothyroidism, and in adults are associated with Hoffman syndrome and in children with Kocher–Debré–Semelainge syndrome. Both are now extremely rare.

Brody's syndrome, due to sarcoplasmic reticulum ATPase deficiency, is also extremely rare and is characterized by impaired relaxation after repeated contractions, evidenced by difficulty opening the hand after repetitive finger flexion.

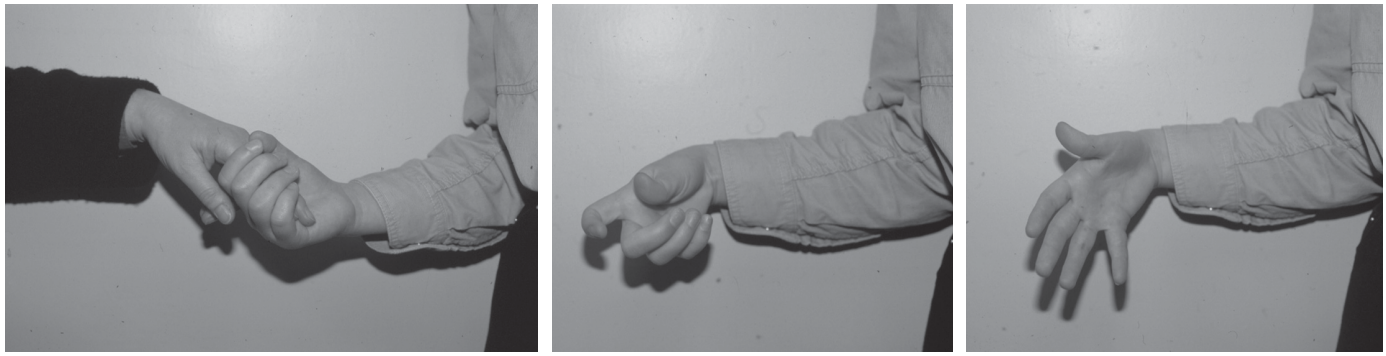

Fig. 3.9 Grip myotonia (myotonic dystrophy).

Rippling muscle describes an extraordinary phenomenon of wave-like contractures traversing a particular muscle. It may occur spontaneously but is often triggered by either stretching or percussion. The movements are electrically silent and their mechanism is not fully understood, but is presumed to relate to disordered membrane function. It was first noted in patients with caveolin mutations, also associated with limb-girdle muscular dystrophy, but is also seen, even more rarely, in association with myasthenia gravis and has an immune basis. Dysfunction of caveolae, membranous lipid rafts associated with various signalling functions, appears to underlie both forms.

Reflexes

As a general rule reflexes are lost late in the course of myopathies, when muscle wasting has become evident, and early in the course of neuropathies, when muscle bulk is still normal, although with some important exceptions. Reflexes are lost, even in clinically apparently unaffected muscles, in Lambert–Eaton syndrome, but may reappear transiently after sustained contraction of the muscle. In acquired demyelinating neuropathies reflexes may be lost over the course of several hours, and preceding weakness. In the common inherited neuropathies (e.g. Charcot–Marie–Tooth disease) generalized areflexia is the norm, but in mild cases may be restricted to the ankle jerks. Curiously, in some patients the ankle jerks are preserved even in the presence of significant distal weakness.

Delayed relaxation of a reflex is characteristically associated with hypothyroidism; although usually considered with respect to the ankle jerk, it is often more impressive with the supinator jerk.

As well as identifying pathologically brisk reflexes in the limbs, demonstration of a brisk jaw or facial jerks in the presence of tongue wasting has important diagnostic value in ALS.

Sensory examination

A distinguished former Oxford Professor of Neurology, Bryan Matthews, advised against 'trying to demonstrate sensory signs in public' (e.g. at a grand round), which appropriately emphasizes the inherent difficulties of sensory testing. With respect to the common sensory modalities of touch, pain, and temperature it is arguable that as much will be gleaned from the patient's description of the distribution and nature of the sensory disturbance as from examination. It is common for a patient with an acquired peripheral neuropathy to describe sensory dysfunction up to the mid-shins, but then be able to distinguish light touch and pin-prick sensation in these regions. Arguably more refined testing techniques may demonstrate a sensory level, but little more is likely to be revealed. Conversely, those with inherited neuropathies may present no sensory symptoms but have readily demonstrable 'stocking' sensory loss.

The history is likely to suggest either a focal peripheral or a generalized peripheral neuropathy, and thus whether examination is directed to look for sensory loss in the distribution of a specific nerve or glove-and-stocking distribution. The history may indirectly suggest disturbance of proprioception or vibration sense, but these are modalities that must be assessed specifically in all suspected neuropathies. In many cases of Charcot–Marie–Tooth disease vibration sense is absent below the knees or ankles, but joint position sense is usually preserved.

Bedside tests of autonomic function are limited in scope and few centres have access to autonomic function laboratories.

Specific tests of autonomic function must be considered where there is suspicion, e.g. diabetic, amyloid, and paraneoplastic autonomic neuropathies, and acutely in Guillain–Barré syndrome where it is a significant cause of mortality. Assessment includes

Fig. 3.10 Percussion myotonia (myotonic dystrophy).

measurement of supine and erect blood pressure and pulse rate, and beat-to-beat variation on ECG. Sudomotor testing, both electrical and physiological, is essentially a specialist laboratory activity, but dysfunction may be readily apparent at a simple observational level.

Conclusion

Whilst history-taking should establish a limited differential diagnosis, examination should then be used to exclude some of those possibilities and add support to others. Each informs the other, and as further information is gleaned it may be appropriate to go back to the history, both personal and family, to tease out further points. Seeing other family members, rather than relying on the observation of others, may be extremely helpful.

Appropriately directed further specialist investigations will be discussed in the context of specific disorders.

SECTION 2

Anterior Horn