Neuromuscular Disease

Case Studies from Queen Square

Hadi Manji
Chris Turner
Matthew R.B. Evans
Editors

Springer

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Dedicated to Prof. P.K. Thomas, Dr John Morgan-Hughes and Prof. Anita Harding.

Professor P.K. Thomas

Dr John Morgan-Hughes

Professor Anita Harding

Foreword I

It is with great pleasure that I went through the *Cases Studies from Queen Square on Neuromuscular Diseases* written by Hadi Manji, Chris Turner, and Matthew RB Evans. The body of knowledge concerning neuromuscular disorders has grown exceptionally rapidly over the past five decades. This book has the unique advantage to combine clinical, electrophysiological, immunologic, genetic, and pathologic information in carefully selected illustrative cases of peripheral neuropathies, neuromuscular junction, and muscle disorders. It is only in highly active neurological centers like Queen Square that one can find the ingredients to achieve this task. The authors have skillfully emphasized the practical management of patients, with selected investigations crucial to diagnosis, and appropriate treatment.

I have been lucky enough to work with one of the co-authors (HM) and had the opportunity to appreciate his sense of humor and expertise. He came to work with me after being recommended by PK Thomas and it was a rewarding collaboration. I am glad to see that he continues to produce the excellent work he used to. This book covers an often neglected field in a manner that will be useful to general neurologists as well as to neurologists in training and internists. The authors have to be congratulated on their achievement.

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Foreword II

Clinical neurology first enticed me as a third year medical student serving as a clinical clerk at the National Hospital, Queen Square. Daily clinical demonstrations with MacDonald Critchley, Russell Brain, Dennis Williams, Chris Earle, William Goody, and others left an indelible impression. Arriving at a clinical diagnosis, I learned, depended largely on the history—occasionally aided by the neurological examination and only occasionally by neurodiagnostic studies. It is a great pleasure to see that today's descendants of the greats of the past take the same pleasure in ferreting out the causes of clinical cases. Editors Manji, Turner, and Evans have assembled an extraordinarily interesting series of neuromuscular cases which can be read quickly and which make an indelible impression with key diagnostic points. The cases lead into succinct presentations of neuropathology, neuroimaging, neuroimmunologic, neuromolecular, and other laboratory data and are buttressed by key references. The very titles of the vignettes draw one into the cases: "A lady with ataxia—an Example of Hickam's dictum"; "When the wind comes back"; and "Rare as rocking horse droppings." I had not planned to read them all but could not help myself. In the past, one might, just possibly, be able to read a neurology textbook through. No more. But here is a book that one can and should read through: senior clinicians just to be certain that they would not miss something (I predict most will), residents and fellows to fill in gaps in their clinical experience, and students to let role model clinicians help shape their own diagnostic acumen. There are not many medical books that are entertaining and highly readable, but here is one that readers will enjoy. The Dedication of the book to the late Professor P.K. Thomas, Dr. John Morgan-Hughes (my senior registrar at Queen Square), and Professor Anita Harding will evoke fond memories to those who knew these icons. They would be proud to have their names introduce the book.

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Preface

Diseases of the neuromuscular system include disorders of the peripheral nerves, muscles, neuromuscular junction, and anterior horn cells. It has been helpful to group these heterogeneous disorders, as they often present with overlapping clinical signs and symptoms, which can present diagnostic challenges to even the most experienced clinician. In an epidemiological study in 1999 (MacDonald et al.), four out of the most common nine neurological disorders involved the neuromuscular system. Conversely, the neuromuscular system has the broadest range of described neurological disorders including many genetically defined neuropathies and myopathies. Neuromuscular disorders have also been at the vanguard of developing new genetic treatments. Ataluren has recently been approved by the European Medicines Agency for a subset of patients with Duchenne muscular dystrophy and is likely to be the first of many new treatments for neuromuscular diseases.

Neuromuscular disorders historically have been seen not only at the periphery of the anatomy of the nervous system but also at the periphery of efforts by clinicians and the central funding bodies. The 2009 All Party Parliamentary Group for Muscular Dystrophy document "Access to Specialist Neuromuscular Care: The Walton Report" highlighted the gap between patient needs and available services for patients with neuromuscular disease in the UK.

This culture was generated by many years of prominence of other neurological subspecialties such as movement disorders, multiple sclerosis, epilepsy, and dementia. At the National Hospital, this prominence was, at least in part, due to the pioneering work of several individuals including Professor David Mardsen (who co-authored the first case series book from Queen Square with Adrian Wills) in the field of movement disorders and Professor Ian MacDonald in multiple sclerosis.

However, times change and from the solid foundations established by Professor PK Thomas (peripheral nerve), Dr. Morgan Hughes (muscle), and Professor Anita Harding (genetics) the study and management of patients with neuromuscular disorders have blossomed at the National Hospital with the establishment in 2008, of the MRC Centre for Neuromuscular Diseases under the leadership of Professor Michael Hanna and Professor Mary Reilly. In 2014, the Neuromuscular Complex Care Centre (NMCCC), the first in the UK, was opened.

We wrote this book to highlight both common and rare neuromuscular cases encountered by the authors to enthuse and educate all levels of neurologists. Additionally, we hope the book demonstrates the vast spectrum of diseases and the exciting future of diagnostics and therapeutics in the field of neuromuscular disorders.

London, UK
December 2015

Hadi Manji
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Abbreviations

3,4-DAP	3,4-Diaminopyridine
ACE	angiotensin converting enzyme
ACh	Acetylcholine
AChR	Acetylcholine receptor
AD	Autosomal dominant
ADHD	Attention deficit hyperactivity disorder
ADM	Abductor digiti minimi
AH	Abductor hallucis
AIDP	Acute inflammatory demyelinating polyradiculoneuropathy
ALS	Amyotrophic lateral sclerosis
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
ANCA	Anti-neutrophil cytoplasmic antibody
APB	Abductor pollicis brevis
AR	Autosomal recessive
ATP7A	ATPase copper transporting alpha
ATS	Anderson-Tawil syndrome
BAG3	BCL2 associated athanogene 3
BICD2	Bicaudal D homolog 2 (Drosophila)
BIN1	Bridging integrator 1
BM	Bethlem myopathy
BMI	Body mass index
BSCL2	Berardinelli-Seip Congenital Lipodystrophy 2 (Seipin)
C9ORF72	Chromosome 9 open reading frame 72
CA 15-3	Cancer antigen 15-3
CACNA1S	Calcium voltage-gated channel subunit alpha1 S
CaEDTA	Calcium disodium EDTA
CANOMAD	Chronic sensory ataxic neuropathy with anti-disialosyl IgM antibodies
CAPN3	Calpain 3
CCP	Cyclic citrullinated peptide

CD4	Cluster of differentiation 4
CEA	Carcinoembryonic antigen
CHAT	Choline acetyltransferase
CHRNE	Cholinergic receptor nicotinic epsilon subunit
CIDP	Chronic inflammatory demyelinating polyneuropathy/ polyradiculoneuropathy
CISP	Chronic immune sensory polyradiculopathy
CK	Creatine kinase
CLCN1	Chloride voltage-gated channel 1
CMAP	Compound muscle action potential
CMS	Congenital myasthenic syndromes
CMT	Charcot-Marie-Tooth disease
CNS	Central nervous system
COL6A1	Collagen type VI alpha 1
COLQ	Collagen-like tail subunit of asymmetric acetylcholinesterase
COX	Cytochrome oxidase
COX/SDH	Cytochrome oxidase/succinate dehydrogenase
CPEO	Chronic progressive external ophthalmoplegia
CPT	Carnitine palmitoyltransferase
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computerised tomography
CV	Conduction velocity
DCTN1	Dynactin subunit 1
DIO	Dorsal interosseous
DM	Myotonic dystrophy
DM	Dermatomyositis
DM1	Myotonic dystrophy Type 1
DM2	Myotonic dystrophy Type 2
DMD	Duchenne muscular dystrophy
DML	Distal motor latency
DMPK	Dystrophia myotonica protein kinase
DMSA	2,3-Dimercaptosuccinic acid
DNA	Deoxyribonucleic acid
DNM1	Dynamin 1
DOK7	Docking protein 7
dsDNA	Double-stranded DNA
DYNC1H1	Dynein cytoplasmic 1 heavy chain 1
ECG	Electrocardiogram
ECHO	Echocardiogram
ECR	Extensor carpi radialis
ECRL	Extensor carpi radialis longus
ECU	Extensor carpi ulnaris
EDB	Extensor digitorum brevis
EDC	Extensor digitorum communis

EDMD	Emery-Dreifuss muscular dystrophy
EDTA	Ethylenediaminetetraacetic acid
EIP	Extensor indicis proprius
ELISA	Enzyme-linked immunosorbent assay
EMG	Electromyography
ENA	Extractable nuclear antigens
ENMC	European Neuromuscular Centre
ER	Exercise-induced rhabdomyolysis
ESR	Erythrocyte sedimentation rate
F3	Finger 3
F5	Finger 5
FAP	Familial amyloid polyneuropathy
FBC	Full blood count
FDG	Fluorodeoxyglucose
FDI/FDIO	First dorsal interosseous
FEV1	Forced expiratory volume in 1 second
FHL1	Four and a half LIM domains 1
FKRP	Fukutin-related protein
FLAIR	Fluid-attenuated inversion recovery
FPL	Flexor pollicis longus
FSHD	Facioscapulohumeral muscular dystrophy
FTD	Frontotemporal dementia
FUS/TLS	Fused in Sarcoma/Translocated in Liposarcoma
FVC	Forced vital capacity
GARS	Glycyl-tRNA synthetase
GCSE	General certificate of secondary education
GD1b	Ganglioside D1b
GLA	Alpha-galactosidase
GM1	Ganglioside M1
H&E	Haematoxylin and eosin
Hb	Hemoglobin
HIV	Human immunodeficiency virus
HMN	Hereditary motor neuropathy
HNA	Hereditary neuralgic amyotrophy
HNPP	Hereditary neuropathy with liability to pressure palsies
HS	Heat stroke
HSAN	Hereditary sensory and autonomic neuropathy
HSAN1	Hereditary sensory and autonomic neuropathy Type 1
HSMN	Hereditary sensory and motor neuropathy
HSN	Hereditary sensory neuropathy
HSP	Heat shock protein
HTLV	Human T-cell lymphotropic virus
IBM	Inclusion body myositis
ICD	Implantable cardioverter defibrillator
IGHMBP2	Immunoglobulin mu binding protein 2

IKBKAP	Inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein
IMNM	Immune-mediated necrotizing myopathy
IS	Internal standard
IVCT	In vitro contracture test
IVIG	Intravenous immunoglobulin
KCNJ2	Potassium voltage-gated channel subfamily J member 2
KSS	Kearns-Sayre syndrome
LEMS	Lambert-Eaton myasthenic syndrome
LFT	Liver function tests
LGMD	Limb girdle muscular dystrophy
LMNA	Lamin A/C
LP	Lumbar puncture
LRP4	Lipoprotein-related protein 4
LVEDD	Left Ventricular End Diastolic Diameter
MAC	Membrane attack complex
MADSAM	Multifocal acquired demyelinating sensory and motor neuropathy
MAG	Myelin-associated glycoprotein
MC	Myotonia congenita
MCV	Mean cell volume
MCV	Motor conduction velocity
MFM	Myofibrillar myopathies
MG	Myasthenia gravis
MH	Malignant hyperthermia
MHC	Major histocompatibility complex
MM	Mononeuropathy/mononeuritis multiplex
MMNCB	Multifocal motor neuropathy with conduction block
MND	Motor neurone disease
MRC	Medical Research Council
MRI	Magnetic resonance imaging
mtDNA	Mitochondrial DNA
MTM1	Myotubularin 1
MUAP	Motor unit action potential
MuSK	Muscle-specific tyrosine kinase
NADH	Nicotinamide adenine dinucleotide
NCV	Nerve conduction velocity
NGF	Nerve growth factor
NIDDM	Noninsulin-dependent diabetes mellitus
NIPPY	Non-invasive positive pressure ventilation
NMDA	N-methyl-D-aspartate
NMJ	Neuromuscular junction
NR	Not recordable
NTRK1	Neurotrophic receptor tyrosine kinase 1
OPV	Oral polio virus

PCR	Polymerase chain reaction
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
PIN	Posterior interosseous nerve
PM	Polymyositis
PMP22	Peripheral myelin protein 22
PNS	Peripheral nervous system
PNST	Peripheral nerve sheath tumour
POEMS	Polyneuropathy, organomegaly, endocrinopathy, M-band protein, skin changes
POLG	Polymerase (DNA) gamma, catalytic subunit
PSA	Prostate-specific antigen
PYGM	Phosphorylase, glycogen, muscle
RAB7	Ras-associated protein RAB7
RAPSN	Receptor associated protein of the synapse
REEP1	Receptor accessory protein 1
RF	Rheumatoid factor
RNA	Ribonucleic acid
RNP	Ribonucleoprotein
RNS	Repetitive nerve stimulation
RYR1	Ryanodine receptor 1
SANDO	Sensory ataxic neuropathy, dysarthria and ophthalmoparesis
SAP	Serum amyloid P
SCL-70	Topoisomerase 1
SCLC	Small cell lung cancer
SCN4A	Sodium voltage-gated channel alpha subunit 4
SE	Surface electrode
SEPT9	Septin 9
SETX	Senataxin
sfEMG	Single fibre EMG
sIBM	Sporadic inclusion body myositis
SLC5A7	Solute carrier family 5 member 7
SMA	Spinal muscular atrophy
SMALED	Spinal muscle atrophy, lower-extremity predominant
SMAX3	Spinal muscular atrophy, distal, X-linked 3
SMN1	Survival of motor neurone 1
SNAP	Sensory nerve action potential
SNARE	Soluble NSF attachment protein receptor
SOD1	Superoxide dismutase type 1
SPTLC	Serine palmitoyltransferase, long-chain
SQSTM1	Sequestosome 1
SRP	Signal recognition particle
SSEPs	Somatosensory evoked potentials
STA	emerin
STIR	Short-tau inversion recovery

TA	Tibialis anterior
TARDBP	TAR DNA-binding protein
TDP43	TAR DNA-binding protein 43
TFT	Thyroid function tests
TPMT	Thiopurine methyltransferase
TSH	Thyroid-stimulating hormone
TTR	Transthyretin
U&E	Urea and electrolytes
UCMD	Ullrich congenital muscular dystrophy
URTI	Upper respiratory tract infection
VAPP	Vaccine-associated paralytic poliomyelitis
VDP	Vaccine-derived poliomyelitis
VEGF	Vascular endothelial growth factor
VGCC	Voltage-gated calcium channel
WAIS-R	Wechsler adult intelligence scale-revised
WBC	White blood cell
WHO	World Health Organisation
WNK1	WNK lysine deficient protein kinase 1
WSM	Widely spaced myelin
XLMTM	X-linked myotubular myopathy
ZNF9	Zinc finger protein 9

Part I
Peripheral Nerve, Neuromuscular Junction and Motor Neuron Disorders

Case 1
A Woman Who Could Not Wear High Heels

Mohamed Mahdi-Rogers, Matilde Laurá, and Mary M. Reilly

History

A 44 year old woman had a history of difficulty walking since childhood. Her motor milestones were delayed and she walked with an abnormal gait. She was unable to run during the first decade of life and was not good at sports at school. She developed high foot arches and had difficulty fitting shoes. She toe walked from age 5 to 8 years. She continued to walk with an abnormal gait and could not wear high heel shoes in her teens. She had surgery to both feet during her teenage years and started using ankle braces in the last 20 years. She sometimes had difficulty with buttons and zips but significant upper limb symptoms only started at age 42.

Her mother had a genetic neuropathy with a similar phenotype. There was no other relevant family history.

Examination

Examination revealed pes cavus with clawed toes (Fig. 1.1) and operation scars. She could stand on her toes but not on her heels. There was Achilles tendon tightening bilaterally.

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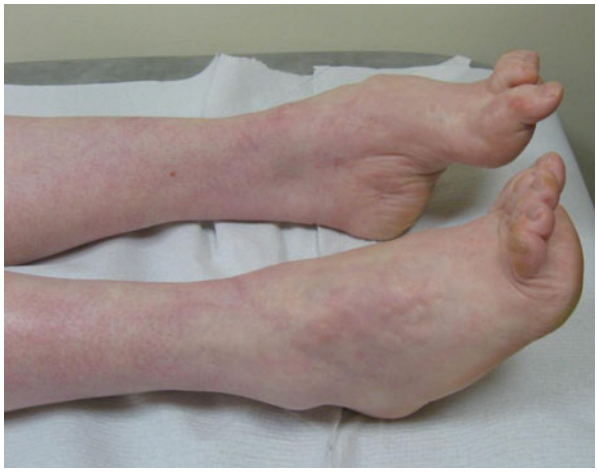

Fig. 1.1 Bilateral distal wasting, pes cavus and clawed toes.

There was wasting of the distal upper limbs particularly the right first DIO and also of the distal lower limbs.

There was mild weakness of the right first DIO and both ADM muscles. The strength in APB and the rest of the upper limb muscles was normal.

In the lower limbs, ankle dorsiflexion was markedly weak bilaterally.

She was areflexic.

Sensation to pin prick was normal except in the right ulnar distribution where it was reduced. Vibration sense was reduced to both ankles. The remainder of the neurological examination was normal.

Investigations

Routine blood tests including glucose, vitamin B12, folate, homocysteine, methylmalonic acid, thyroid function tests and ANA were normal. No paraprotein was detected on serum protein electrophoresis.

Neurophysiology (Tables 1.1 and 1.2)

Table 1.1 Sensory and mixed nerve conduction studies

	Right	Left
	μV	μV
Median (F3-wrist)	Absent	Absent
Ulnar (F5-wrist)	Absent	Absent
Ulnar (Wrist-above elbow)	Absent	Absent

Table 1.2 Motor nerve conduction studies

	Right	Left
Median (SE on APB)		
DML	8.0 ms	8.4 ms
CV (wrist-elbow)	19 m/s	19 m/s
CMAP (wrist)	6.3 mV	6.2 mV
CMAP (elbow)	4.8 mV	6.3 mV
Ulnar (SE on ADM)		
DML	8.5 ms	7.0 ms
CV (palm-wrist)	–	16 m/s
CV (wrist-below elbow)	14 m/s	15 m/s
CV (around elbow)	11 m/s	–
CMAP (palm)	–	5.5 mV
CMAP (wrist)	2.6 mV	4.8 mV
CMAP (below elbow)	2.3 mV	4.5 mV
CMAP (above elbow)	2.5 mV	–

Conclusion
Sensory responses are absent in the upper and lower limbs. Motor conduction velocities are homogenously slow in the upper and lower limbs with prolonged distal motor latencies. Motor responses are reduced or absent in the upper and lower limbs. Additional right ulnar neuropathy - difficult to localise. Needle EMG (not shown) of FDIO was neurogenic on both sides, perhaps more prominent on the right.

Genetic test
1.4 Mb duplication on Chromosome 17p11.2 (the region containing the PMP22 gene).

Diagnosis

Charcot Marie Tooth type 1A (CMT1A) with superadded right ulnar neuropathy.

Discussion

CMT1A is the most likely diagnosis given the clinical presentation and family history; a clinical impression confirmed on genetic testing. Neurophysiology shows uniform slow motor conduction velocities, prolonged distal motor latencies and absent sensory action potentials, all consistent with CMT1A. The isolated numbness detected in the distribution of the right ulnar nerve is not in keeping with CMT. She later developed progressive weakness of right FDIO and was diagnosed with a right ulnar neuropathy. Right hand symptoms improved following right ulnar nerve decompression at the elbow.

There are various clues in the history that suggest that the neuropathy is long-standing and therefore likely to be genetic rather than acquired. Delayed motor milestones, poor performance in sports at school, toe walking and difficulty wearing high heel shoes in her teens are all features that favour a genetic rather than an acquired neuropathy. Examination findings of clawed toes, pes cavus, achilles tendon tightness, distal wasting and weakness are all in keeping with CMT1A. The most sensitive sensory sign in CMT is reduced distal vibration sensation, which is seen in this patient, although individuals with CMT may not have sensory symptoms and sometimes no sensory signs.

CMT1A is the most common form of CMT in most populations, accounting for up to 70 % of all CMT. CMT1A is caused by a duplication on chromosome 17 in the region that carries the PMP22 gene. It has an autosomal dominant pattern of inheritance, but up to 10 % of patients have no family history, indicating that the duplication can occur spontaneously. In a patient with CMT1; if there is a clear family history of autosomal dominant inheritance; if the patient is apparently "sporadic", or if there is definite male-to-male transmission (ruling out X-linked inheritance), the most likely diagnosis is CMT1A.

As seen in this patient, lower limb motor symptoms such as difficulty walking and foot deformity in the first two decades are often the first symptoms experienced by individuals with CMT. Examination typically shows distal muscle atrophy, foot deformity, distal weakness, hyporeflexia and distal sensory loss. CMT patients with severe distal weakness develop a knee bob sign which is caused by ankle plantar flexion weakness with pre-existing weakness of ankle dorsiflexors. This sign, where the knees bob up and down when attempting to stand still, is said to be a reliable marker of ankle plantar flexion weakness. Knee bobbing indicates progression of typical CMT and results in significant functional deterioration for patients.

Neurophysiology in CMT1 typically shows median and ulnar MCVs below 38 m/s with reduced or absent sensory action potentials. Nerve biopsy demonstrates de and re-myelination with onion bulb formation but a biopsy is not needed to make the diagnosis given that genetic testing is now widely available.

CMT1A is a very slowly progressive neuropathy. Patients have normal life spans but frequently need ankle–foot orthoses and occasionally a stick to walk.

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Case 2
Rare as Rocking Horse Droppings

Matthew R.B. Evans, Zane Jaunmuktane, Sebastian Brandner, and Hadi Manji

History

A 25 year old banker from Brazil who had lived in the UK for 5 years, presented with an 18 month history of pain on the plantar aspect of the right foot. Six months later, a similar pain developed in the left foot. She suffered with nocturnal cramps in her feet. More recently, she had developed numbness involving the right foot to the shins associated with sharp stabbing pains. Her sleep was disturbed and walking was uncomfortable. Two months later she developed occasional paraesthesiae in her hands and shooting pains from the elbows radiating down the medial forearms.

Examination

Her gait was antalgic. Romberg's test was positive.

Cranial nerve and upper limb examinations were normal. There was a suggestion that the right superficial radial nerve was thickened on palpation.

In the lower limbs, EDB muscles were absent. Power and knee and ankle jerks were normal. Plantar responses were flexor.

Joint position sense and vibration sense were impaired to the ankles bilaterally. Pin prick sensation was reduced to the mid-shin on the right and to the ankle on the left.

General examination was normal.

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Investigations

Blood tests were normal except a raised ESR of 33 mm/hr (1–20).

Serum protein electrophoresis revealed a polyclonal increase in gamma globulins. No paraprotein was detected.

CSF - white cell count normal, protein normal, oligoclonal bands negative.

Neurophysiology (Tables 2.1 and 2.2)

Table 2.1 Sensory and mixed nerve conduction studies

	Amplitude (μV)	Onset latency (ms)	Peak latency (ms)	Conduction velocity m/s
Right Median (F3-wrist)	8.0	2.5	3.2	50
Right Ulnar (F5-wrist)	7.0	2.1	2.1	52.5
Right Radial	1.3	–	–	40
Left Median	8.0	–	–	50
Left Ulnar	3.5	–	–	45
Left Radial	Absent			
Right Sural (calf-ankle)	Absent			
Right Superf. Peroneal (calf-ankle)	Absent			
Left Sural (calf-ankle)	Absent			
Left Superf. Peroneal (calf-ankle)	Absent			

Table 2.2 Motor nerve conduction studies

	Right	Left
Median (SE on APB)		
DML	2.9 ms	–
CV (wrist-elbow)	58 m/s	–
CMAP (wrist)	4 mV	–
CMAP (elbow)	4 mV	–
F latency	26 ms	–
Right common peroneal (SE on EDB)		
No response to stimuli at ankle or knee		
Right common peroneal (SE on TA)		
DML	3.3 ms	–
CV (fib. neck-ankle)	52 m/s	–
CMAP (fib neck)	3 mV	–
CMAP (pop. fossa)	2.5 mV	–
Posterior tibial (SE on AH)		
DML	3.4 ms	4 ms
CMAP (ankle)	1.3 mV	1.2 mV
F latency	58.5 ms	57.2 ms
Left common peroneal (SE on EDB)		
DML	5.6 ms	–
CV (fib. neck-ankle)	52 m/s	–
CMAP (ankle)	0.6 mV	–
CMAP (fib. neck)	0.5 mV	–
F latency	Absent	–

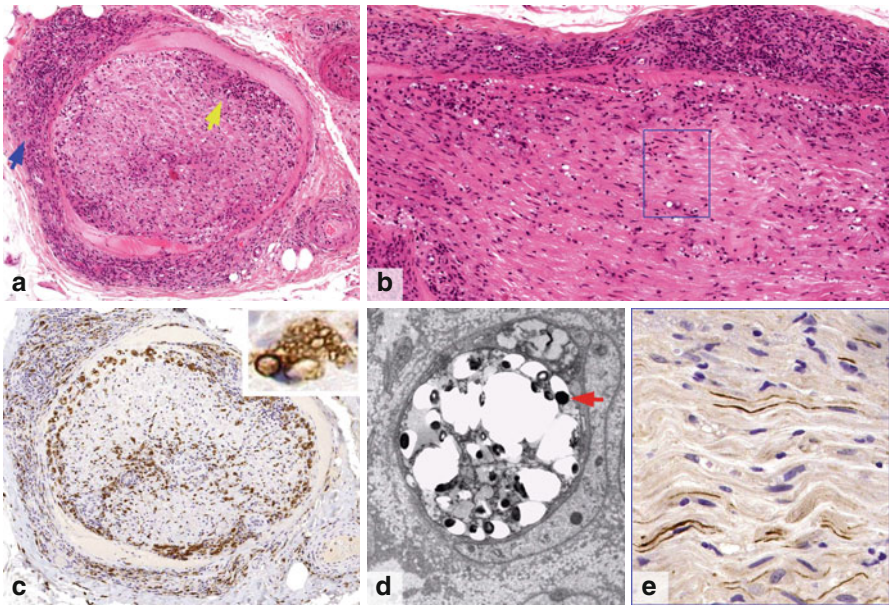

Fig. 2.1 Sural nerve biopsy. Haematoxylin-Eosin stained section shows transversely (**a**) and longitudinally (**b**) oriented nerve fascicle in which there is a prominent perineural (*blue arrowhead* in **a**) and to a lesser extent endoneural (*yellow arrowhead* in **a**) inflammation. The inflammatory infiltrate is composed of a mixed population of T lymphocytes and B lymphocytes (not shown) and frequent CD68 positive macrophages (**c**). Many of the macrophages in the endoneurium have voluminous foamy cytoplasm (*inset* in **c**). Electron microscopy demonstrates numerous *Mycobacterium leprae* bacilli within macrophages (**d**, *red arrowhead* highlights one of the bacilli). Immunostaining for neurofilaments with SMI31 antibody (**e**, *blue square* in **b**) highlights marked loss of fibres across the fascicles. Scale bar: 200 μm in **a** and **c**; 150 μm in **b**; 2 μm in *inset* in **c**; 2 μm in **d** and 30 μm in **e**

Concentric needle EMG (Right TA) – no fibrillations or fasciculations. Moderate excess of polyphasic units of normal or increased duration. Reduced interference pattern on strong contraction.

Conclusion

There is support for a generalised neuropathy but the very abnormal radial responses suggest a multifocal rather than a length-dependent process.

Nerve biopsy – see Fig. 2.1.

Diagnosis

Lepromatous leprosy.

Discussion

The clinical presentation and neurophysiology here suggested a diagnosis of a painful mononeuritis multiplex (MM). This implies an inflammatory or vasculitic process. The differential diagnosis for MM includes vasculitis, hereditary neuropathy with liability to pressure palsies (HNPP) though this is usually painless, infiltration with cancer or lymphoma and sarcoidosis. The clues to leprosy are the fact that the patient is from Brazil and the clinical sign of thickened nerves on palpation. Other causes of thickened nerves include chronic inflammatory demyelinating polyneuropathy (CIDP), CMT1A and HNPP, Refsum's disease, amyloid neuropathy, neoplastic infiltration with tumours and neurofibromatosis.

There are 500,000 new cases of leprosy per year worldwide. 80 % occur in India, Brazil, Nepal, Mozambique and Madagascar. In the UK, 15 new cases are diagnosed each year, usually in patients from the Indian subcontinent.

The incubation period is long – two to five years as in this patient. Hence the diagnosis is delayed in most patients who will have developed established nerve damage at presentation.

The nature of the lesions and the progression of the disease is dependent upon the immune response to the Mycobacterium leprae. The tuberculoid form develops in patients who mount a strong cell mediated immune response. The more infectious form of the disease, lepromatous leprosy, develops in those with a poor immune response. The borderline form shows characteristics of both.

The clinical features of tuberculoid leprosy include anaesthetic hypopigmented or erythematous skin lesions, mononeuropathies (in descending order of frequency) affecting the ulnar nerve, posterior tibial nerve near the medial malleolus and the common peroneal nerve around the fibular head, median nerve, facial nerve, supraorbital nerves and the greater auricular nerve, all of which maybe thickened.

In the more disseminated lepromatous form of the disease, there is skin and nerve infiltration usually in the coolest regions of the body: the ear lobes, face, soles and palms and testicles. The neuropathy is a progressive neuropathy starting in the hands and feet with at times a superimposed mononeuritis multiplex. Hand and feet deformities as well as non-healing trophic ulcers are common. The nasal mucosa is heavily infiltrated with the bacilli and a source of contagious spreading of the disease which usually requires prolonged close contact. Sterility and gynaecomastia in men results from testicular infiltration.

The diagnosis of leprosy is confirmed by skin slit smears, skin or nerve biopsy.

This patient had pure neuritic leprosy which is a form of tuberculoid and borderline leprosy, with no evidence of skin involvement.

Leprosy is eminently treatable with a multidrug regimen of dapsone, rifampicin and clofazamine. Corticosteroids are used to treat the lepra reaction which occurs either spontaneously or in response to treatment. Neurologically these will present with worsening nerve damage and pain.

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Case 3
A Lady with Ataxia – An Example of Hickam's Dictum

Michael P. Lunn

History

A 76 year old lady presented with a rapidly progressive syndrome of sensory dysfunction and unsteadiness.

She had a history of mild diabetes and hypertension.

She initially presented with pain under her right chest and breast. Although there was no associated rash, this was diagnosed as shingles and aciclovir was prescribed.

A few weeks later she reported painful burning feet in a 'shoes' distribution. Over 6 weeks her gait became affected and she became wheelchair bound with unsteadiness. There was no weakness.

A diagnosis of neuropathy was made and she was prescribed amitriptyline. There was intermittent severe burning or fizzing pain in the feet which subsequently became numb. Two months later, over a period of several weeks, she developed incoordination of her arms without weakness or other sensory loss.

On direct questioning she admitted to loss of weight of one stone over 2–3 months. She had an occasional dry mouth.

On the basis of a progressive ataxia and a positive ANA and ENA (positive anti-Ro, negative anti-La) she was diagnosed with Sjögren's Syndrome with 'diabetic pseudoathetosis' and commenced on prednisolone and mycophenolate.

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Examination

She was unable to stand without assistance. The left leg was more ataxic than the right. She was able to stand on toes and heels with support for balance.

The cranial nerves were normal. In the limbs there was normal tone and power but she was areflexic throughout with downgoing plantars.

Proprioception was impaired to the wrists and the hips. Vibration was impaired to the costal margins from the legs. Pin prick was impaired from C6 to C8 in the right hand and in a more length dependent manner in the legs and trunk.

Breast examination was normal. A firm fullness was palpable in the right axilla but no discrete lymphadenopathy was noted. Chest, cardiovascular and abdominal examinations were otherwise normal.

Investigations

Blood tests revealed a positive ENA (+Ro, −La) and ANA (1:1260). The remainder of the inflammatory markers, full blood count and differential, renal and liver function were normal. HbA1c was mildly raised at 6.8 % (<6.5). Anti-neuronal antibodies, antiganglioside antibodies and HIV were all negative. Vitamin B6 113 nmol/L (30-144), B1 99 nmol/L (66-200) and B12 518 pg/ml (191–663) with normal levels of homocysteine and methylmalonic acid.

Neurophysiology (Table 3.1)

Motor nerve conduction studies of median, ulnar, common peroneal and tibial nerves were normal.

Table 3.1 Sensory and mixed nerve conduction studies

	Right		Left	
	μV	m/s	μV	m/s
Radial (forearm-wrist)	4	58	No response	
Median (F2-wrist)	No response		2	47
Median (F3-wrist)	No response		2	45
Median (palm-wrist)	No response		8	39
Ulnar (F5-wrist)	No response		No response	
Ulnar (palm-wrist)	No response		No response	
Sural (calf-ankle)	No response		No response	
Superf. peroneal (calf-ankle)	No response		No response	

Conclusion

There is a severe generalised sensory polyneuropathy or ganglionopathy.

Imaging
A chest X-ray was normal.
A CT chest revealed a confluent soft tissue mass within the right axilla.
A PET scan demonstrated extensive highly FDG-avid tissue within the right axilla and superior chest anterior and posterior to the pleural cavity.

A ***needle biopsy*** was performed which demonstrated a metastatic non-keratinising squamous cell carcinoma.

Diagnosis

Paraneoplastic dorsal root ganglionopathy. Although possible primary sites included lung and head and neck region, no primary source was found.

Treatment

The patient was treated with high dose chemotherapy for a squamous cell carcinoma of unknown primary. After six cycles at re-evaluation she had had complete resolution of the tumour, and was in remission. There was no further progression of the neurological condition although at 9 months there was also no improvement and she remained confined to a wheelchair.

Discussion

A clinical diagnosis of a rapidly progressive sensory neuropathy/neuronopathy was made. Given its rapidity and severity it was strongly suspected that this was paraneoplastic. The differential diagnosis included Sjögren's syndrome (the original diagnosis), lymphoma, vitamin B6 toxicity and an idiopathic sensory neuronopathy

This case is interesting for many of the things that it is not. The lessons to learn are: that shingles *sine herpete is a diagnosis of exclusion* and another cause for the pain should be sought: that neurology is easy to attribute to Sjögren's when an ENA is present, but that the ENA is not specific, and that some diagnoses such as diabetic pseudoathetosis are very unusual.

A paraneoplastic syndrome is a disease or symptom that is the consequence of the presence of cancer in the body, but not directly due to the presence of cancer cells. The diseases are caused by immune factors presumably released by, or in response to a tumour which cause damage to the end tissue and subsequently result in the phenotypic symptoms and signs. The agents causing the damage are presumed to be antibodies, T-cells or other soluble molecules but these are often difficult to demonstrate. A number of well known paraneoplastic antibodies are described (for example anti-Hu, anti-Yo and anti-Ri) that are associated with a group of phenotypically recognisable disorders such as

sensory ganglionopathies, limbic encephalitis and the opsoclonus myoclonus syndrome. They are also associated with a number of underlying tumour types such as small cell cancers, breast and ovarian tumours but neither the antibody nor the tumour types cosegregate with one another. Many of the antibodies first described are to intracellular antigens and mechanisms of pathogenesis remain unexplained; in these the antibody may be an epiphenomenon and the disease mechanism T-cell mediated. Increasing numbers of antibodies to surface antigens and receptors are now being described where the antibody appears to have a direct effect. The first of these was the voltage gated calcium channel antibodies found in Lambert Eaton Myasthenic Syndrome and more recently antibodies to surface channels in the encephalitides associated with antibodies to voltage gated potassium channels, NMDA receptors and glycine receptors.

Paraneoplastic sensory ganglionopathies are rare but severe and disabling consequences of a tumour. They are seldom reversible but early treatment of the tumour may halt the progression of the condition. Typically they are associated with small cell carcinomas of the lung but other tumour types have been described. An association with anti-Hu antibody has also been made. This case is particularly unusual, not because of the absence of a linking antibody but by the association with a squamous cell carcinoma. These are very rarely described but this case is assumed to be linked given the co-temporal presentation, the rapid progression and paraneoplastic course and the arrest of that progression following treatment.

Sjögren's syndrome is a connective tissue disease which may be primary or secondary to another connective tissue disease. The syndrome results in inflammation of exocrine glands resulting in xerophthalmia and xerostomia. The diagnosis is largely clinical and is made by fulfilling four of six criteria which include symptomatic dry membranes, a positive ENA and biopsy proven inflammation in labial glands. Sjögren's syndrome is associated with a sensory ganglionopathy, and has also been described with small fibre neuropathies, myelopathies and sensorimotor peripheral neuropathies. However the association is rare and in the authors experience another diagnosis is frequently found. In this case a diagnosis of Sjögren's syndrome was made on a positive ENA and mild xerostomia (on amitriptyline), resulting in misdiagnosis and a delay in making the correct diagnosis. Furthermore the clinical finding of pseudoathetosis was attributed to a 'diabetic pseudoathetosis'; diabetes does not cause severe enough large fibre loss without severe weakness to cause the deafferentation required to result in pseudoathetosis. Where diabetes and pseudoathetosis coexist it is probably safe to assume they are not causally related.

Hickam's dictum as opposed to Occam's Razor states that a person can have as many diagnoses as he or she pleases – in this case diabetes, possibly Sjögren's syndrome and a squamous cell carcinoma: all unrelated disorders.

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Case 4
A Lady with Tremor Not Due to Parkinson's Disease

Anupam Bhattacharjee and Rahul Phadke

History

A 76 year old lady presented with a bilateral upper limb tremor which had slowly progressed over 15 years. Eight years prior to being assessed she started becoming unsteady and particularly noted she had to hold on to the shower wall when washing her hair and admitted to being more unsteady in the dark. Five years before her assessment she became aware of numbness in her feet which progressed to reach her knees over three years. At this stage she noticed that her feet were "slapping" when walking and she would sometimes trip on pavements. At the time of consultation she complained of developing numbness in her hands with poor grip over the past year

Examination

With her arms outstretched there was a coarse postural tremor. There were no extrapyramidal signs. Her gait was unsteady and broad-based and she needed support.

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Wasting of both first dorsal interossei and tibialis anterior was noted. There was bilateral MRC grade 4 weakness of the first dorsal interosseous, abductor digiti minimi, abductor pollicis brevis and flexor pollicis longus. In the legs, grade 1 weakness of ankle dorsiflexion and plantar flexion was evident.

All deep tendon reflexes were absent except for the right biceps jerk.

In the upper limbs there was normal sensation to pin prick, vibration and proprioception sense, but in the lower limbs pin prick was reduced to the knees, and vibration and joint position sense were impaired to the ankles. Romberg's test was not possible due to severe unsteadiness on standing even with the eyes open.

Investigations

Blood tests - Full blood count, urea and electrolytes, liver function, glucose, autoimmune serology (ANA, ANCA, dsDNA, ENA), ESR and CRP were all normal. Serum protein electrophoresis and immunofixation showed an IgM level of 4.11 g/L (0.4–2.3) and two discrete IgM kappa paraprotein bands.

The Anti-MAG antibody test was positive.

Neurophysiology

There were reduced sensory (SNAP) and compound motor action potential (CMAP) amplitudes in all limbs. Upper limb motor conduction velocities (CV) were between 38 and 45 m/s and in the lower limbs between 28 and 34 m/s. There was no conduction block or temporal dispersion. The right radial nerve demonstrated a distal motor latency (DML) of 7 ms with a CV of 42 m/s.

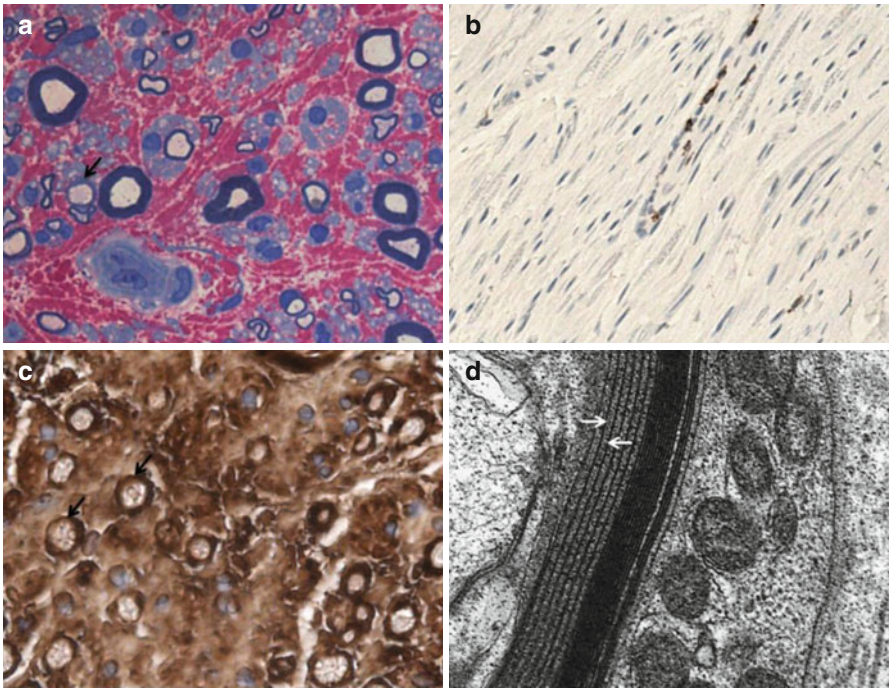

Fig. 4.1 Sural nerve biopsy from a case of IgM κ anti-MAG neuropathy shows moderate depletion of myelinated fibres in the resin section. Scattered thinly myelinated fibres are suggestive of remyelination. One such profile (*arrow*) shows poor staining of the myelin sheath indicating abnormal myelin periodicity (**a**). Sparse CD3+ endoneurial T cells are seen (**b**). Immunostaining for IgM strongly decorates the outer layers of the myelin sheaths of several axons (*arrows*) (**c**). Electron microscopy reveals the characteristic abnormal myelin period called widely spaced myelin resulting from increased separation of the major dense lines (*arrows*) (**d**) (Image courtesy of Zane Jaunmuktane and Sebastian Brandner)

Diagnosis

Anti-myelin-associated glycoprotein (MAG) neuropathy.

Discussion

This patient presents with a long history of very slowly progressive tremor followed by prominent unsteadiness and distal weakness. This is the classic clinical phenotype for anti-MAG neuropathies.

The initial symptoms were of a postural upper limb tremor which is a useful clue that a neuropathy is demyelinating rather than axonal. She also became unsteady prior to developing any common sensory (numbness, paraesthesiae) or motor impairment. If these prior factors were not considered, the progressive (and more commonly seen) sensory-motor neuropathy symptoms she developed would have otherwise appeared length-dependent and therefore axonal.

The prominence of tremor and unsteadiness suggest a demyelinating neuropathy. The major differential diagnosis therefore includes Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). Genetic demyelinating neuropathies also enter the differential although the initial presentation with tremor would be unusual for these.

Demyelinating neuropathies are associated with paraproteins more often than would be predicted by chance alone but a clear causal relationship has not been established. Paraproteins should be checked with both electrophoretic and immunofixative techniques. When a paraprotein is found it is important to exclude an underlying haematological process such as myeloma or Waldenström's Macroglobulinaemia.

Approximately 50 % of patients with peripheral neuropathy and IgM monoclonal gammopathy have IgM (κ light chain) antibodies that bind to MAG. MAG is present in both central and peripheral nerve myelin. Specific anti-MAG antibody testing needs to be done separately and in this case showed a "strong positive" response on the Buhlmann ELISA.

There are typical NCS findings in anti-MAG neuropathy which this case demonstrates. The NCS suggest that, whilst there is some reduction of SNAP and CMAP amplitudes (which suggests axonal loss), the major finding is that the motor CVs are globally reduced thus supporting a demyelinating neuropathy. Additionally, there is a significant prolongation of the DML of the right radial nerve that is significantly out of proportion to the CV of the same nerve. This latter pattern of disproportionate DML prolongation compared to the CV is seen in typical anti-MAG neuropathy.

There are occasions where the clinical presentation of a patient with anti-MAG antibodies may not match the "typical" clinical phenotype that this case illustrates. In these cases, if there is doubt from the clinical phenotype and NCS data, then a sural nerve biopsy could be considered. A representative biopsy is shown (Fig. 4.1). In a nerve biopsy, signs of active demyelination such as myelin breakdown, 'naked' axons and thinly myelinated fibres are more often seen in anti-MAG neuropathy. Active axonal degeneration may be seen. Chronic demyelinating features including onion bulbs, redundant myelin loops and/or abnormally thickened myelin may appear. Positive immunostaining for IgM on the myelin sheaths is highly suggestive of IgM paraproteinaemic neuropathy, although not entirely specific. An increase in myelin periodicity resulting from a lack of apposition of the outer aspects of the Schwann cell membrane results in 'widely spaced myelin' (WSM) appearing as increased spacing between the major dense lines. His abnormality is seen ultrastructurally in 50–90 % of cases of IgM κ paraproteinaemic neuropathy, usually with anti-MAG activity.

Anti-MAG associated neuropathies are particularly resistant to treatment. Standard therapies that have been tried include immune modulation with steroids, intravenous immunoglobulin, and cyclophosphamide amongst others. There is also some evidence for the use of the anti-B cell therapy rituximab though there are conflicting reports on the efficacy of this drug.

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Case 5
A Makeup Artist with Crohn's Disease

Sonia Gandhi and Hadi Manji

History

A 36 year old right handed woman presented with gradual onset weakness affecting the right hand. She described difficulty in working as a make-up artist, gripping pens, writing, and using a spray. There was no associated pain, numbness or paraesthesia. There were no neurological symptoms affecting the face or any other limbs.

She had been diagnosed with Crohn's disease at the age of 31. The Crohn's disease was managed initially using azathioprine, mesalazine and methotrexate, all of which were not tolerated or ineffective. She was commenced on infliximab 6 months prior to her presentation and had received five doses in total. She also had a history of hypothyroidism, iron deficiency anaemia, vitamin B12 and folate deficiency (secondary to Crohn's disease).

Her medications included folic acid, vitamin B12 replacement therapy, levothyroxine 50 ug daily, and omeprazole 10 mg daily.

There was no significant family history.

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Examination

Neurological examination revealed weakness with MRC grade 4/5 of the following right upper limb muscles: flexor carpi radialis, flexor digitorum superficialis, flexor digitorum profundus 1 and 2, flexor pollicis longus, abductor policis brevis, opponents pollicis. There was no muscle wasting or fasciculation. Sensory testing was normal. Reflexes were intact and symmetrical. The remainder of the cranial nerves, left upper limb and both lower limbs were unremarkable. General examination was normal.

Investigations

Blood tests including full blood count, renal and liver function, thyroid function, vitamin B12 and folate, glucose, ANA, ANCA, ENA, immunoglobulins, paraprotein levels were normal or negative. ESR was raised at 102 mm/h (1-20). Anti-GM1 antibody was negative.

Neurophysiology (Tables 5.1 and 5.2)

Table 5.1 Sensory nerve conduction studies

	Right		Left	
	μV	m/s	μV	m/s
Radial (forearm-wrist)	85	66	–	–
Median (F2-wrist)	22	54	32	58
Median (F3-wrist)	29	53	–	–
Ulnar (F5-wrist)	16	57	–	–
Lateral cutaneous (elbow-forearm)	8	61	–	–

Table 5.2 Motor nerve conduction studies

	Right	Left
Median (SE on APB)		
DML	3.2 ms	3.1 ms
TLI	0.39	–
CV (wrist-elbow)	56 m/s	59 m/s
CV (elbow-axilla)	48 m/s	66 m/s
CV (axilla-Erb's)	72 m/s	–
CMAP (wrist)	16.4 mV	13.2 mV
CMAP (elbow)	16.3 mV	13.3 mV
CMAP (axilla)	3.1 mV	13.3 mV
CMAP (Erb's)	3.1 mV	–
Minimal F-wave latency (wrist)	Unreliable	25.0 ms

Conclusion

Neurophysiology demonstrated striking motor conduction block in the right median nerve just proximal to the elbow, affecting the main trunk of the median nerve (APB showed conduction block) as well as the anterior interosseous nerve (FPL showed conduction block). Median somatosensory evoked potentials were normal suggesting intact large sensory fibre conduction in the region of the conduction block. The nerve excitability test of the median nerve at the wrist showed an unusual pattern with a so-called "fanning-in" of the hyperpolarizing electrotonus and a prolonged refractoriness. These results were consistent with a conduction block type picture of some axons at the wrist. There was no abnormality affecting the sensory or motor nerves of the left upper limb or lower limbs.

MRI of the right elbow in the region of the conduction block demonstrated hyperintensity of the median nerve on T2 with subtle enhancement of the median nerve, suggestive of inflammatory change.

Diagnosis

Multifocal motor neuropathy with conduction block secondary to infliximab treatment.

Treatment

The infliximab was discontinued at the time of presentation. The patient made a full recovery over a period of 4 months. Neurological examination returned to normal within a year. Repeat neurophysiology 8 months after onset also confirmed complete resolution of conduction block in the right median nerve and normal EMG of the relevant innervated muscles.

Discussion

Anti-TNF alpha therapy has been a major advance in the treatment of rheumatoid arthritis and inflammatory bowel disease. Since its widespread use, a spectrum of neurological disease has been reported in association with anti-TNF alpha therapy.

This includes CNS inflammatory demyelinating disorders such as transverse myelitis, optic neuritis and multiple sclerosis. Peripheral nerve disorders such as Guillain Barre syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, small fibre polyneuropathy, and multifocal motor neuropathy with conduction block (MMNCB) have all been anecdotally reported. The temporal association of symptom onset with anti-TNF alpha treatment, and the resurgence of symptoms on repeat challenge with anti-TNF alpha treatment in a small number of reports, has

strongly suggested a causal association between these agents and demyelinating disorders.

However these reports are confounded by the fact that many of the diseases treated with anti-TNF alpha agents are associated with neurological syndromes such as polyneuropathy, and that some of the neurological syndromes (such as MS) have a relapsing remitting course that persists despite discontinuation of anti-TNF alpha treatment.

One of the largest literature reviews of 151 cases of new onset neurological syndromes associated with anti-TNF alpha therapy (Solomon et al. 2011) describes 64 CNS disorders, 18 cases of isolated optic neuritis, and 69 cases of neuromuscular syndromes. Of the CNS syndromes, the majority (62 %) were exposed to etanercept (anti-TNF alpha receptor antagonist). Of the PNS syndromes, the majority (67 %) occurred on exposure to infliximab, and within 6 months of treatment (66 %). Neurophysiology was abnormal, with the commonest diagnosis being GBS, followed by MMNCB in 12 % of cases. Approximately half the cases were treated with IVIG alone or with other immunosuppressants. For the PNS syndromes, the outcome data at 1 year showed resolution in 37 %, partial improvement or stabilisation in 53 %, and a relapsing-remitting course in 10 %.

MMNCB is an asymmetric motor neuropathy that develops over months to years. It is diagnosed on the basis of multifocal partial motor conduction block on neurophysiology, and can be associated with anti-GM1 antibodies in half of cases. Barber et al. (2010) report a case of MMNCB induced by infliximab and describe six other similar cases in the literature.

Taking these seven cases together with our case, we describe here the characteristics of MMNCB secondary to infliximab (based on eight reported cases). The mean age of the patients was 43 years (range 34–60), with five males and three females affected. The underlying diagnoses included rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, hidradenitis suppurativa, and polyarthritis and cryoglubulinaemia with chronic hepatitis C. The mean duration of infliximab treatment was 5.5 months (range 4–10 months, where documented).

The diagnosis of MMNCB was confirmed by neurophysiology in all cases. Anti-GM1 antibodies were positive in three of the cases tested.

Treatment and follow up was reported in seven cases. Infliximab was discontinued in all cases. In two cases there was spontaneous resolution of symptoms. IVIG was used in five cases, and plasma exchange was required in one case. In all seven cases of MMNCB induced by infliximab, there was complete recovery.

In summary, both central and peripheral demyelinating complications can occur during anti-TNF therapy. The evidence suggests that in susceptible individuals (due to their autoimmune diathesis), anti-TNF agents are responsible for triggering inflammation in the nervous system, and that once present, there is a small but significant rate of recurrent disease. The appearance of a new inflammatory demyelinating disorder in the context of anti-TNF alpha therapy should therefore prompt discontinuation of the agent. Overall it appears that the PNS syndromes induced by infliximab carry a better prognosis for recovery, especially in the case of MMNCB.

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Case 6
Not a Laughing Matter

Michael P. Lunn

History

A 27 year old man presented with a progressive flaccid areflexic quadriparesis which had progressed over days. He complained that for the previous few weeks he had had some weakness in his arms and legs. He had a long history of self harm, depression, a number of overdoses and suicide attempts. He drank minimal alcohol and denied any regular medications. He claimed to have anaphylactic allergies to paracetamol, penicillin, pepper, sugar and a number of other medicinal and non-medicinal substances. Of note was that he had presented a number of times in the recent past to the accident and emergency department with recurrent patella dislocations which were relocated with inhaled anaesthesia because of his allergies to a number of analgesic agents.

Examination

On admission, cranial nerve examination was normal.

There was proximal and distal weakness of the lower more than the upper limbs. He was areflexic.

Sensory testing revealed loss of pinprick to the elbow in the upper limbs and a loss to the inguinal crease in the lower limbs. Large fibre sensation (joint position and vibration sensation) was impaired to the toes.

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Investigations

The abnormal tests were a raised gamma GT, a vitamin B12 of 81 pg/ml (191–663) with a normal folate. The vitamin B12 was rapidly corrected and remeasured 4 days later at which stage homocysteine was normal at 8umol/L (5–15).

CSF was normal with 2 WBC/mm^3 and a normal protein of 0.33 g/L (0.25–0.4).

Neurophysiology (Tables 6.1 and 6.2).

Table 6.1 Sensory and mixed nerve conduction studies

	Left			
	Amplitude (μV)	Onset latency (m/s)	Peak latency (ms)	Conduction velocity (m/s)
Median	5.0	3.0	3.6	41
Ulnar	3.0	2.6	3.5	41
Radial	16	1.5	2.2	55
Sural	No response			

Table 6.2 Motor nerve conduction studies

	Right
Median (SE on APB)	
DML	4.3 ms
CV (wrist-elbow)	38 m/s
CV (elbow-axilla)	48 m/s
CMAP (wrist)	6.3 mV
CMAP (axilla)	6.3 mV
Minimal F-wave latency (wrist)	50.2 ms
Ulnar (SE on ADM)	
DML	3.2 ms
CV (wrist – below elbow)	41 m/s
CV (wrist – above elbow)	40 m/s
MAP (wrist)	9.1 mV
Minimal F-wave latency	39.4 ms

Concentric needle EMG
Right vastus medialis – occasional fibrillations. No motor units seen under voluntary control.
Right tibialis anterior – profuse fibrillations and positive sharp waves. No motor units seen under voluntary control.
Right gastrocnemius (medial head) – frequent fibrillations and positive sharp waves. No motor units seen under voluntary control.

Conclusion – demyelinating neuropathy with sensory and motor, proximal and distal involvement.

Further Course

IVIG was given at a dose of 2 g/kg over five days with some improvement in power such that he was able to mobilise with a frame.

He was discharged but medications were not continued and he experienced a rapid decline in function with no response to IVIG or prednisolone about 9 months later and he was readmitted. At this stage he had a profound flaccid paraplegia and was unable to stand. There was profound loss of all sensory modalities to the waist.

Repeat neurophysiology had improved but there was evidence of central conduction delay on evoked potential studies from the upper limbs (lower limb responses were poorly formed). A ***sural nerve biopsy*** showed no evidence of demyelination but revealed axonal loss and vascular occlusion (see Fig. 6.1). ***Repeat blood tests*** demonstrated a vitamin B12 of 108 pg/ml (191–663) and a homocysteine of 115 umol/L (5–15) as well as a methylmalonic acid of 1.18 umol/L (<0.29)

Diagnosis

Subacute combined degeneration of the cord with peripheral neuropathy.

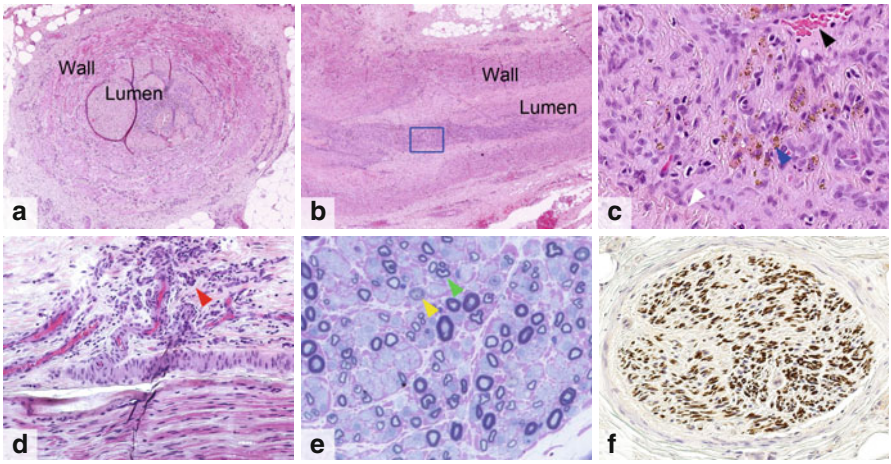

Fig. 6.1 Morphological appearances of large adjacent artery and sural nerve biopsy. Large artery (**a–c**): Haematoxylin-Eosin (H&E) stained sections shows transversely (**a**) and longitudinally (**b**) oriented fragment of a large artery the lumen of which is obliterated by dense fibrous tissue and fibroblasts. Higher power (**c**, *Blue Square* in **b**) highlights reactive fibroblast proliferation, frequent haemosiderin-laden macrophages (*blue arrow*), minimal recanalization (*black arrow*) within the lumen and fragmentation of the internal elastic lamina (*white arrow*). Sural nerve (**d–f**): H&E stained section (**d**) shows neovascularization in the epineurium (*red arrow*). Semi-thin resin section stained with MBA-BF (**e**) shows a nerve fascicle with moderate loss of large myelinated fibres, occasional actively degenerating axonal profiles (*yellow arrow*) and regeneration clusters (*green arrow*). Immunostaining for neurofilaments with SMI31 antibody reveals a nerve fascicle well populated by axons, indicating better preservation of unmyelinated fibres (**f**). Scale bar: 200 μm in **a** and **b**, 50 μm in **c**, 30 μm in **e** and 80 μm in **d** and **f** (Image courtesy of Zane Jaunmuktane and Sebastian Brandner)

Discussion

The patient was dislocating his own patella using physical force in order to access healthcare services and obtain nitrous oxide anaesthesia. He was also abusing nitrous oxide at home with a homemade inhalation system to achieve short-lasting 'highs'. Nitrous oxide completely inhibits the B12 metabolism pathway by inactivating the cobalamin form of B12 by oxidation. This results in neuropathy, myelopathy and sometimes an encephalopathy. Unfortunately despite being appropriately treated and a full explanation of the cause of his problems and clear instructions not to ever expose himself to nitrous oxide again, he continued to present to multiple accident departments across the UK demanding nitrous oxide anaesthesia.

Recovery can be very slow and is often poor or incomplete. Chronic nitrous oxide poisoning is usually from recreational use of this sort. Poisoning may occur however in patients who are significantly deficient in B12 even with a single exposure to the chemical for anaesthesia (now seldom used).

The changes on the nerve biopsy are probably the result of the vitamin B12 deficiency and have been recognised for a long time. Hamilton and Nixon (1921) demonstrated that the more thickly myelinated fibres were vulnerable to B12 deficiency. 'The histological picture …[is of]..continuous damage to the myelin sheaths though there was no axonal degeneration….. Peripheral nervous system avitaminosis B12 is confined to lesions of the myelinated sheaths but is too trifling to be noticed behind the funicular symptoms'. Subsequently a number of other case reports and series describe what is now an almost forgotten condition. No one has proven the exact pathological reasoning but highly raised homocysteine is associated with vessel occlusion (as seen here) and ischaemic damage affects the largest myelinated fibres before the small.

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Case 7
Leg Swelling and Painful Feet in a Business Man

Michael S. Zandi, Zane Jaunmuktane, Sebastian Brandner, and Hadi Manji

History

A 60 year old company director developed gradual onset of pain in the lateral aspect of his right leg into the lateral part of the foot. This was followed by numbness and paraesthesiae, and then weakness in dorsiflexing the foot. A few months later he developed the same symptoms in the left foot. Subsequently, he developed numbness on the tip of the left index finger, and difficulty unscrewing lids and doing up his buttons. He noticed swelling around the ankles. There was mild erectile dysfunction, but no other autonomic symptoms. At presentation, roughly a year after onset of symptoms, he could walk only small distances independently and used two crutches on occasion. He was taking gabapentin for pain.

Examination

On examination he appeared pale. Systemic examination revealed mild pitting oedema at the ankles. There was no lymphadenopathy or rash.

He could stand on his toes but not his heels. Cranial nerves were normal.

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On inspection, there was loss of hair in the distribution of the common peroneal nerves bilaterally. Reflexes were present throughout but depressed at the ankles. Power was normal in the upper limbs apart from left abductor pollicis brevis (APB) which was graded MRC 4/5. In the lower limbs, dorsiflexion was graded 4+/5 bilaterally, EHL 0/5 on the right, 4+/5 on the left, toe flexion 4–/5 bilaterally, ankle inversion 5/5 bilaterally, ankle eversion 4/5 on the right, 5/5 on the left. Sensation to pin was reduced in the radial aspect of the forearm bilaterally and symmetrically from the knees distally. Vibration sense was reduced to the ankle on the right, and joint position sense reduced to the ankles.

Investigations

Blood tests revealed a raised ESR of 41 mm/h (1-20), CRP of 26 mg/L (0-5), and elevated rheumatoid factor (1:1280) and ANA (1:80 with a speckled pattern). He was mildly anaemic with Hb of 12.5 g/dL. A faint IgG lambda band was found on immunofixation. Vitamin B12, ANCA, ENA, CCP, anti-myelin and paraneoplastic antibodies were normal or negative.

A ***urine dip test*** was normal.

Neurophysiology (Tables 7.1 and 7.2)

Table 7.1 Sensory and mixed nerve conduction studies

	Amplitude (μV)	Onset latency (ms)	Conduction velocity (m/s)
Right sural	NR	NR	
Right superficial peroneal	NR	NR	
Left sural	NR	NR	
Left superficial peroneal	NR	NR	
Right median	6	2.8	49
Right ulnar	8	2.2	54
Right radial	34	1.6	62

Table 7.2 Motor nerve conduction studies

	Amplitude (μV)	Latency (ms)
Right median (SE on APB)		
CV (wrist-elbow)	53 m/s	
CMAP (wrist)	6.1 mV	4.0 ms
CMAP (elbow)	6.1 mV	7.9 ms
Minimal F-wave latency (wrist)	28.5 ms	
Left posterior tibial (SE on AH)		
CMAP (ankle)	1.8 mV	6.2 ms
Minimal F-wave latency (wrist)	52.7 ms	
Right common peroneal (SE on EDB)		
CMAP (ankle)	NR	NR
CMAP (fib. neck)	NR	NR
Left common peroneal (SE on EDB)		
CV (ankle – fib. neck)	44 m/s	
CMAP (ankle)	3.9 mV	4.3 ms
CMAP (fib. neck)	3.7 mV	11.3 ms
Minimal F-wave latency	49.1 ms	
Right posterior tibial (SE on AH)		
CMAP (ankle)	3.1 mV	4.1 ms
CMAP (pop. fossa)	6.4 mV	5.0 mV
Minimal F-wave latency	51.0 ms	

Concentric needle EMG – severe and acute denervation of right extensor hallucis. Denervation is also seen in right EDB and left AH.

Conclusion

There is an asymmetric lower limb peripheral neuropathy with absence of lower limb sensory potentials bilaterally and denervation of right EHL, EDB and left AH.

Sural nerve biopsy – see Fig. 7.1.

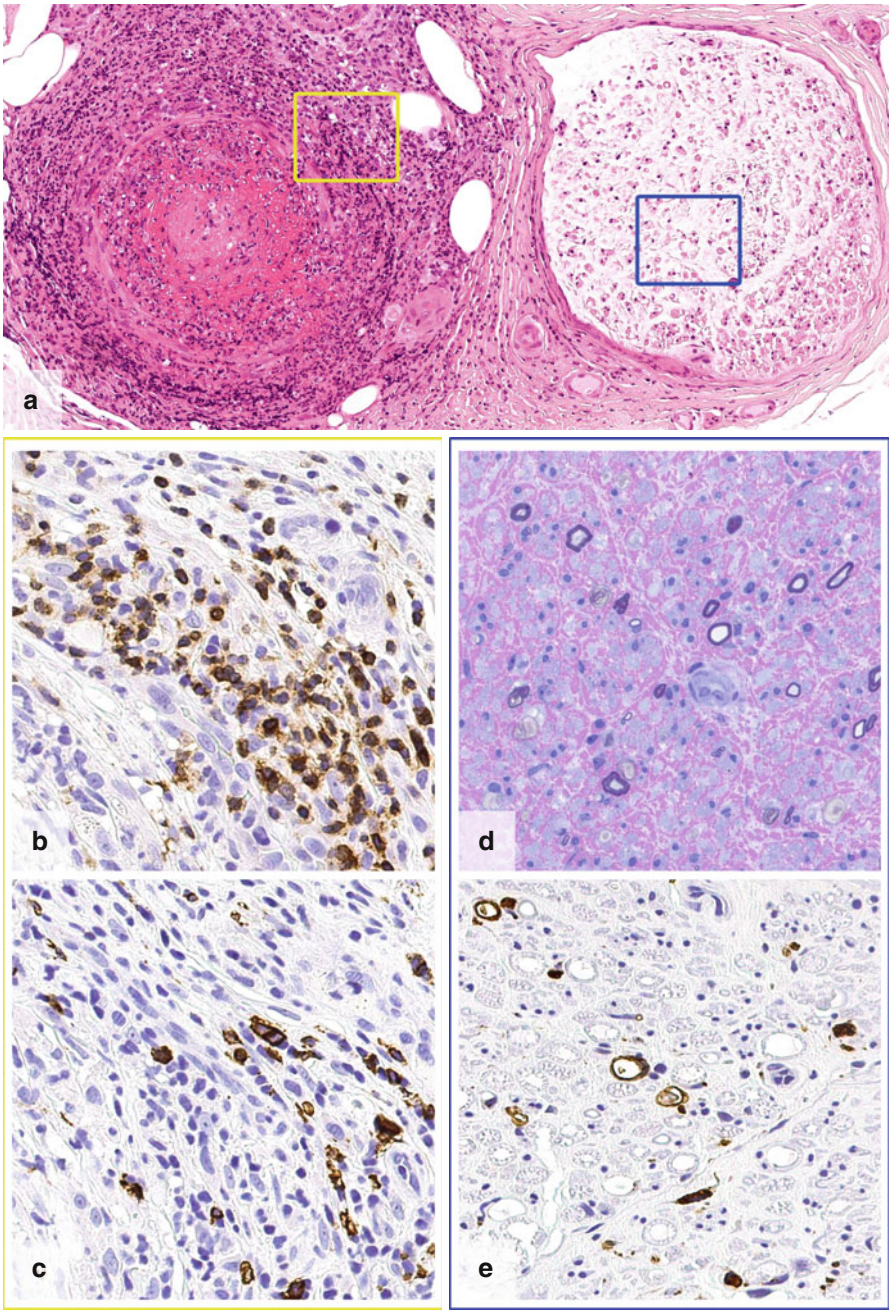

Fig. 7.1 Morphological appearances of vasculitic neuropathy (sural nerve). Haematoxylin-Eosin stained section (**a**) shows thrombosis and inflammation with leukocytoclastic reaction and fibrinoid necrosis in the wall of an epineural artery (**a**). Immunostaining for CD3 (**b**) and CD20 (**c**) confirms a mixed infiltrate of T lymphocytes and B lymphocytes in the vessel wall. In the adjacent nerve fascicle there is widespread loss of large myelinated fibres and active axonal degeneration (**d**). Immunostaining for CD68 highlights numerous macrophages surrounding degenerating axons (**e**). Scale bar: 100 μm in **a** and 50 μm in **b**–**e**

Diagnosis

Vasculitis (nerve specific).

Discussion

The initial symptoms may reflect either a central, radicular or peripheral nerve disorder, but the pattern of weakness, diminished reflexes and hair loss suggests a mononeuritis multiplex. The focal distribution of symptoms suggested an acquired and inflammatory aetiology. The peripheral oedema raises the possibility of vasculiltis (with or without the nephrotic syndrome) or POEMS, in particular with the IgG lambda band, though this was small in this case. An infiltrative lymphoma is also in the differential.

A diagnosis of nerve-specific vasculitis was made. There were no clinical or laboratory features to suggest a systemic vasculitis. He was treated with pulsed methylprednisolone, 1 g daily for three days, followed by cyclophosphamide. He has been maintained on azathioprine and prednisolone 10 mg daily. At 28 months after symptom onset he had only weakness of EHL bilaterally. However, he still has significant neuropathic pain managed with gabapentin and nortryptiline.

Vasculitis of the peripheral nerves is rare, and may be primary, e.g. due to polyarteritis nodosa or the Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis), or secondary to systemic conditions such as sarcoidosis, HIV and hepatitis C. Lymphomatous infiltration of nerves is an important mimic. The pathology of peripheral nerve vasculitis is of involvement of the vasa nervorum by vasculitis leading to ischaemia and infarction of nerves. Lymphocytic infiltration without necrosis is often seen in biopsy samples. Vasculitis rarely affects peripheral nerves in isolation, and the peripheral nerves may be the first organ involved in systemic vasculitis or other organ involvement may be sub-clinical, but sustained isolated peripheral nerve vasculitis is reported and carries a better prognosis than systemic vasculitis. In isolated peripheral nerve vasculitis presentation is usually with an asymmetric patchy neuropathy, but a symmetric apparently length dependent neuropathy may also occur. The CSF is often normal and peripheral nerve biopsy alone is usually sufficient to make the diagnosis. There is no high quality independent evidence for the treatment of isolated vasculitic neuropathy, and so regimens are based on those for primary vasculitis, e.g. high dose corticosteroids and cyclophosphamide for induction followed by a steroid sparing agent such as azathioprine.

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Case 8
A Man with Back Pain and Weight Loss

Matthew R.B. Evans and Hadi Manji

History

A 70 year old right handed retired bricklayer with hypertension presented with a 4 month history of moderately severe, nagging lower back and buttock pain radiating to the anterior thighs bilaterally, though worse on the right than the left. He had numbness to the level of the ankles bilaterally, and over the preceding 2 months had developed progressive weakness and wasting of the right thigh. The upper limbs, cranial nerves and sphincter function were not involved.

He did not smoke cigarettes, drank ~28 units of alcohol/week and ate a normal diet.

Examination

On examination he was thin. General examination was normal. Cranial nerve examination was normal. Upper limb examination was normal apart from wasting of the first dorsal interosseous (FDI) muscles bilaterally with weakness of FDI and abductor digiti minimi, consistent with bilateral ulnar neuropathies. In the lower limbs, there was significant wasting of right quadriceps with fasciculations. There were occasional fasciculations in the right calf. The was weakness in the right leg – hip flexion MRC 2/5 with normal hip extension; hip abduction was normal with weakness of hip adduction (4/5); Knee flexion 4+/5 with 1/5 knee extension. There was no weakness distally. The left leg was normal in strength. The right knee jerk and both ankle jerks were absent. Sensation to pin was reduced medially in the right lower leg.

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Investigations

Blood tests including vasculitic and autoimmune screen were normal. Random glucose was elevated at 16.1 mmol/L. PSA was raised at 70ug/L (0–4.10).

CSF was acellular with normal glucose. Protein 0.99 g/L (0.25–0.4). Viral PCR negative. Oligoclonal bands were negative in both CSF and serum. Cytology negative

MRI of the lumbosacral spine/plexi and pelvis with contrast was normal.

Neurophysiology (Tables 8.1 and 8.2)

Table 8.1 Sensory and mixed nerve conduction studies

	Right		Left	
	μV	m/s	μV	m/s
Radial (forearm-wrist)	NR		NR	
Median (F2-wrist)	NR		NR	
Median (F3-wrist)	NR		NR	
Median (palm-wrist)	NR		NR	
Ulnar (F5-wrist)	NR		NR	
Sural (calf-ankle)	NR		NR	
Superficial peroneal (calf-ankle)	NR		NR	

Table 8.2 Motor nerve conduction studies

	Right	Left
Median (SE on APB)		
DML	4.2 ms	–
CV (wrist-elbow)	44 m/s	–
CMAP (wrist)	3.1 mV	–
CMAP (elbow)	2.9 mV	–
Minimal F-wave latency (wrist)	31.6 ms	–
Ulnar (SE on ADM)		
DML	3.1 ms	3.8 ms
CV (wrist-below elbow)	51 m/s	51 m/s
CV (around elbow)	32 m/s	26 m/s
CV (above elbow-axilla)	56 m/s	53 m/s
CMAP (wrist)	5.4 mV	2.1 mV
CMAP (below elbow)	5.1 mV	2.1 mV
CMAP(above elbow)	4.4 mV	1.9 mV
CMAP (axilla)	4.3 mV	1.8 mV
Minimal F-wave latency (wrist)	34.4 ms	36.8 ms

Table 8.2 (continued)

	Right	Left
Common peroneal (SE on EDB)		
DML	4.5 ms	4.3 ms
CV (fib. neck-ankle)	32 m/s	35 m/s
CV (pop. fossa-fib. neck)	52 m/s	37 m/s
CMAP (ankle)	0.3 mV	1.2 mV
CMAP (fib. neck)	0.3 mV	1.0 mV
CMAP (pop. fossa)	0.2 mV	1.0 mV
Minimal F-wave latency (wrist)	–	57.4 ms
Posterior tibial (SE on AH)		
DML	4.1 ms	4.0 ms
CV (pop. fossa-ankle)	38 m/s	37 m/s
CMAP (ankle)	2.9 mV	4.0 mV
CMAP (pop. fossa)	1.5 mV	3.5 mV
Minimal F-wave latency	57.9 ms	57.9 ms

Conclusion

There is a severe sensory and mild axonal polyneuropathy with absent sensory nerve action potentials in both upper and lower limbs. The lower limb motor responses from intrinsic foot muscles are slightly reduced for age and the conduction velocities are slightly slow. F waves (where obtainable) are slightly prolonged. There are active and chronic neurogenic changes in the right quadricep muscle. In addition, there is electrophysiological evidence of bilateral mild to moderate ulnar neuropathies at the elbow level.

Diagnosis

Diabetic lumbosacral plexus radiculoneuropathy (Bruns-Garland syndrome).

Discussion

The clinical findings are that of a right lumbosacral plexopathy, predominantly affecting the femoral nerve. The sensory loss is confined to the distribution of the right saphenous nerve, a branch of the femoral nerve. Clinically, there is also mild involvement of the right obturator nerve. Electrophysiology is supportive, and in addition reveals the presence of a severe polyneuropathy (likely due to the new diagnosis of diabetes mellitus) and bilateral ulnar neuropathies.

Diabetic lumbosacral radiculoplexus neuropathy, also known as Bruns-Garland syndrome, typically develops in older patients (median age 65 years) with relatively recently diagnosed or well-controlled Type II diabetes mellitus. In one series, it was recorded as the presenting feature of diabetes in 7 out of 33 patients. In our case, absent ankle jerks and distal sensory loss reflect the diabetic sensorimotor polyneuropathy which is often present at diagnosis, and proven electrophysiologically in this case to be mild-moderate in severity, suggesting that diabetes has been present for at least several years. Biopsy of the intermediate cutaneous nerve of the thigh may reveal microvasculitis.

As in this case, the onset is most often heralded by pain, often severe, deep and burning or aching in quality, affecting any or a combination of the lower back, thigh and buttocks. Weakness follows days to several weeks later in this same distribution and can be severe. Although distal onset can occur; 12 out of 33 patients in one series, weakness is typically proximal and unilateral at onset. The contralateral leg becomes affected in almost all cases, however the weakness tends to remains asymmetric throughout the course of the illness. Occasionally, the patient may develop so called 'diabetic paraplegia'. Weight loss occurs in most patients and can be dramatic. Sensory loss and new or worsened autonomic involvement can also occur.

Treatment is symptomatic, there being no proven treatment which is effective in halting progress or expediting recovery. A recent systematic review found no randomised controlled trials evaluating immunotherapy in diabetic amyotrophy. The degree of recovery is variable and most patients are left with some neuropathic pain and/or mild to moderate motor deficits. At 2 years, ~10 % will still be wheelchair dependent.

Idiopathic lumbosacral plexopathy, also referred to in the literature as non-diabetic lumbosacral radiculoplexus neuropathy is rare though probably under recognised. It is clinically very similar to diabetic lumbosacral plexus radiculoneuropathy, presenting as a subacute, painful asymmetric lower limb neuropathy. Distal cutaneous nerve biopsy shows features of nerve ischaemia due to microvasculitis. It is usually monophasic though recovery is often incomplete.

Neoplastic infiltration of the lumbosacral plexus can occur in multiple forms of cancer and is the presenting feature of pelvic, retroperitoneal or abdominal malignancy in ~15 %. In this case, the raised PSA suggests a diagnosis of prostate adenocarcinoma however this was subsequently discounted after prostatic biopsy.

Compressive etiologies, including psoas or iliacus muscle abscess/haematoma are considered but excluded by history and imaging. Similarly, lumbosacral plexus ischaemia due to underlying atherosclerotic disease or aortic dissection each have a distinct clinical history.

Although rare, both systemic and non systemic vasculitides have been reported to cause lumbosacral plexopathy. Indeed, lumbosacral plexopathy has been reported as the presenting feature of sarcoidosis.

Finally, lumbosacral plexopathy has been described due to infection with herpes varicella zoster, epstein barr virus, cytomegalovirus, HIV and Borrelia burgdorferi, and may mimic the Bruns-Garland syndrome.

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Case 9
A Man with Progressive Weakness and Muscle Twitching

Michael P. Lunn

History

A 63 year old TV technician presented with a 4 month history of progressive limb weakness.

He first noticed his walking becoming slow and laboured with a feeling of his leg muscles becoming increasingly weak. He noticed a tendency to falling and progressive difficulty rising from a chair. After 2 months he felt as if his arms were also becoming weak. He thought that the symptoms had stabilised for a couple of months but on clinical review 4 weeks later he had developed foot-drop gait and his arms were weaker. He was limited to walking 150 m and had new difficulties in turning a key and opening a jar, as well as retrieving objects from a high shelf.

On direct questioning there was minimal sensory involvement with subjective tingling at the finger tips.

There was no fatiguability and no cramps, but he was occasionally aware of fasciculation. There were no difficulties with swallowing, breathing, sleep, or autonomic function. He was cognitively and emotionally normal.

There was no family history. He was a non-smoker who drinks no alcohol.

Examination

He had difficulty rising from a chair, his gait was unsteady and he was unable to stand on his toes or heels. Romberg's test was negative.

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Cranial nerve examination was normal. There was no facial weakness, neck flexion and extension were normal as was the tongue.

In the limbs, fasciculations were noted in all four limbs, but tone was normal. There was proximal and distal weakness in the upper limbs and distal weakness on the lower limbs. 10 m walk 9.3 s with aid.

All reflexes were present but depressed.

There was no sensory deficit identifiable at the bedside on testing large or small fibre modalities.

Investigations

Blood and urine tests – FBC, ESR, vitamin B12, folate, TFT, LFT all normal. CK 388 IU/L (38–204). Serum protein electrophoresis, immunofixation, urinary Bence -Jones protein all negative. ANA weakly positive – speckled. ENA, RF, ANCA negative. Antiganglioside antibodies negative.

CSF – protein 1.20 g/L (0.25–0.40), no white cells. CSF and serum glucose normal.

Neurophysiology (Tables 9.1, 9.2 and 9.3)

Table 9.1 Sensory and mixed nerve conduction studies

	Right		Left	
	μV	m/s	μV	m/s
Radial (forearm-wrist)	22	53		
Median (F2-wrist)	5	48 (post warming)	6	41 (not warmed)
Median (F3-wrist)	9	48	5	43
Median (palm-wrist)	14	50	30	42
Ulnar (F5-wrist)	6	51	4	42
Sural (calf-ankle)	16	48	20	43
Radial (forearm-wrist)	22	53		
Median (F2-wrist)	5	48 (post warming)	6	41 (not warmed)

Table 9.2 Motor nerve conduction studies

	Right	Left
Median (SE on APB)		
DML	4.6 ms	5.5 ms
CV (wrist-elbow)	34 m/s	29 m/s
CMAP (wrist)	6.4 mV	4.4 mV
CMAP (elbow)	2.3 mV	2.1 mV
Minimal F-wave latency (wrist)	Absent	Absent
Ulnar (SE on ADM)		
DML	4.3 ms	3.9 ms
CV (wrist-below elbow)	24 m/s	28 m/s
CV (around elbow)	53 m/s	41 m/s
CMAP (wrist)	9.6 mV	11.7 mV

Table 9.2 (continued)

	Right	Left
CMAP (below elbow)	3.5 mV	5.5 mV
CMAP (above elbow)	3.5 mV	4.5 mV
Minimal F-wave latency (wrist)	Absent	Absent
Common peroneal (SE on EDB)		
DML	6.5 ms	5.3 ms
CV (fib. neck-ankle)	44 m/s	
CV (pop. fossa-fib. neck)	41 m/s	
CMAP (ankle)	2.9 mV	1.8 mV
CMAP (fib. neck)	2.3 mV	
CMAP (pop. fossa)	2.2 mV	
Posterior tibial (SE on AH)		
DML	4.8 ms	4.8 ms
CV (pop. fossa-ankle)	40 m/s	36 m/s
CMAP (ankle)	11.0 mV	8.1 mV
CMAP (pop. fossa)	6.4 mV	5.0 mV
Minimal F-wave latency	71.8 ms	74.9 ms
F-wave CV	33.0 m/s	31.5 m/s

Table 9.3 Concentric needle EMG

	Spont. activity		MUAP configuration			Recruitment	Interference pattern
	Fibs/PSW	Other	Duration	Amplitude	Polyphasia		
Right tongue	0	0	N	N	N	N	N
Right FDIO	0	Fasc.	↑	↑	↑	Reduced, large units recruiting early	↓
Right vastus medialis	0	0	↑	↑	↑	Reduced, large units recruiting early	↓
Right tibialis anterior	1+	0	↑	↑	↑↑	Reduced, large units recruiting early	↓
Right gastrocnemius (medial head)	0	0	N	N	↑	Reduced, large units recruiting early	↓
Right rectus abdominus	0	0	N	N	N	N	N

Conclusion

1. Normal sensory studies in the lower limbs.
2. No focal slowing demonstrated in the lower limb motor studies however prolonged F wave latencies noted.

3. Distal conduction blocks (below elbow) associated with focal slowing noted in both ulnar and median nerves. The sensory SNAPs are borderline bilaterally.
4. Mild chronic denervation changes in the upper and lower limb muscles and SCM but normal findings on sampling of the rectus abdominis and tongue. Spontaneous activity only noted in the TA.

There are multiple points of conduction block associated with focal slowing in the forearms, minor sensory abnormalities in the upper limbs, absent/prolonged F wave latencies. These features are suggestive of a form of CIDP which is predominantly motor with conduction blocks.

Diagnosis

Chronic inflammatory demyelinating polyneuropathy (CIDP) – motor predominant.

Clinical Course

He was treated with IVIG 2 g/kg over 5 days and 3 weeks he improved significantly and was functionally almost normal. One week later he had a flu vaccination and 3 weeks after this an upper respiratory tract infection. A week after the URTI his condition worsened and his 10 m walk deteriorated from 6.5 to 7.9 s. He was treated with further courses of IVIG at 8 week intervals, eventually settling on a dose of 1.2 g/kg every 8 weeks, dipping in functional activity 2 days prior to admission.

Discussion

The diagnosis of CIDP is clinical with supportive evidence where necessary. The EFNS/PNS guidelines provide a good framework for diagnosis. Progressive proximal and distal weakness with hypo or areflexia over eight or more weeks, with or without sensory and cranial nerve involvement is the key to diagnosis. This patient worsened in a stepwise manner and then relapsed after successful treatment fulfilling the time criteria.

Neurophysiological testing with electromyography is mandatory and the finding of a patchy demyelinating motor and sensory neuropathy with dispersion and conduction blocks narrows the differential diagnosis significantly. Supportive diagnostic information can be obtained from the LP with albuminocytological dissociation, but raised protein is found in <90 % of patients. A biopsy is unnecessary unless patients fail to respond to two first line therapies. Thickening and enhancement of nerve roots on MRI is helpful if present but is patchy and difficult to quantify on most current MRI scanners.

Motor CIDP is not uncommon. Although the clinical picture appears to be completely motor, the sensory nerve conduction abnormalities support the diagnosis of CIDP and support the exclusion of a lower motor neurone MND. Motor CIDP may worsen with steroid treatment and so this is best avoided, at least as first line treatment. IVIG is preferred.

Reference

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Case 10
A Woman with Burning Hands

Mohamed Mahdi-Rogers, Matilde Laurá, and Mary M. Reilly

History

A 59 year old woman presented with a 3 year history of impaired sensation and episodes of burning pain in her fingers. She had similar but milder symptoms in her feet. These sensory symptoms were more prominent in the cold. She had no limb weakness or autonomic symptoms. She did not report any skin rash. There was no other relevant medical history in particular there was no history suggestive of cerebrovascular or cardiac disease. She did not smoke and drank four units of alcohol per week.

She was the third of six siblings (two older sisters, two younger brothers and a younger sister). Her siblings and their children had no history of neurological disease.

Her father was reported to have Fabry disease and died at the age of 69 from heart failure. Her mother died aged 89 but had no relevant medical history. Further extensive family history on both sides of the family was unremarkable except for sudden death of a maternal uncle at the age of 40.

Examination

Blood pressure was 107/67 and a regular pulse of 87 beats per minute. Heart sounds were normal. Chest was clear to auscultation. There was no rash.

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Cranial nerve examination including fundi, visual fields and hearing were normal.

There was no wasting in the limbs. Tone, power, reflexes and co-ordination were normal.

The skin of both palms was red, shiny and appeared thickened.

There was reduced pinprick sensation in the fingertips and forefeet with preserved temperature perception. Vibration and joint position sense were normal.

Investigations

Blood tests – including random glucose, HBA1C, vitamin B12, TFT and ANA were normal. Oral glucose tolerance test was normal. A paraprotein was not detected. Renal function was normal.

Neurophysiology

The sensory and motor nerve conduction findings in the upper and lower limbs were within normal limits for age. The thermal thresholds for detection of hot and cold sensation were within normal limits in the hands and feet.

Cardiac assessment

Echocardiogram showed normal left ventricular internal dimensions and normal wall thickness with good function and no valvular abnormalities. ECG was unremarkable showing no conduction defect.

MRI brain

There were a few non-specific high T2 and FLAIR hyperintensities scattered in the deep white matter of the frontal and parietal lobes in both hemispheres. There was no significant cerebral volume loss. The remaining intracranial appearances were normal.

Genetic test

Exons 1–7 of the alpha-galactosidase (GLA) gene were sequenced. She was found to be heterozygous for the Arg112His mutation in Exon 2.

Diagnosis

Fabry disease.

Discussion

This patient's presentation was that of small fibre neuropathy with trophic changes in her hands despite the normal thermal thresholds. Epidermal nerve fibre density is a more sensitive test for small fibre neuropathy though that was not done in this

case. Diabetes and impaired glucose tolerance which are the most common causes of small fibre neuropathy were excluded by relevant blood tests.

Given the family history, the possibility that her symptoms could be due to her being a heterozygote carrier of Fabry disease was raised. Subsequent genetic testing confirmed this suspicion.

Fabry disease is an X-linked lysosomal storage disorder caused by defects in the GLA gene. The abnormal gene results in a deficiency in alpha-galactosidase A which leads to accumulation of glycosphingolipids particularly globotriaosylceramide in various tissues. It is suggested that the mechanism of organ damage in Fabry's is in part due to hypoperfusion caused by the excess glycosphingolipids in the vascular endothelium particularly those in the kidneys, heart, nervous system and skin.

The classic phenotype of Fabry disease is seen in males with less than 1 % α-Gal A enzyme activity. The onset of the disease in these affected males is usually in childhood or adolescence with acroparesthaesia (episodes of severe extremity pain), development of vascular skin lesions called angiokeratomas, hypohidrosis (reduced sweating), characteristic corneal opacities where lines radiate from a point in the centre of the cornea, and kidney disease which can present as haematuria, proteinuria or isosthenuria (inability to concentrate the urine). Renal function deteriorates slowly over time and these patients typically reach end-stage renal failure by their third to fifth decade.

A major cause of morbidity and mortality in middle age men is cardiac and cerebrovascular disease manifesting as left ventricular impairment, ischaemic heart disease, cardiac arrhythmias, transient ischaemic attacks and stroke.

Chronic gastrointestinal symptoms such as abdominal pain, nausea and diarrhoea and impaired hearing are other common symptoms seen in patients with Fabry disease

The presentation in heterozygous females is variable and ranges from living a normal life span without any symptoms of Fabry disease to having a clinical picture similar to males with the classic phenotype. In general, heterozygous females such as this patient have milder symptoms and the disease starts at a later age compared with males. In a study of 303 female patients with Fabry disease, 77 % had neurological involvement, 59 % developed cardiac disease and 40 % had renal impairment. The onset of symptoms in these patients was later than that seen in affected males but most had developed symptoms by their third and fourth decades of life. The differing clinical presentation in female heterozygotes is thought to be due to variation in X chromosome inactivation during embryonic development.

Measurement of alpha-galactosidase A enzyme activity in plasma or peripheral blood leucocytes is a reliable method of diagnosing Fabry disease in males but sequencing the GLA gene to identify the disease causing mutation is the only dependable way to confirm the diagnosis in females. Although detecting a low level alpha-galactosidase A enzyme activity is diagnostic in heterozygote females, it is not a sensitive test given that these individuals can have a normal alpha-galactosidase A enzyme activity. Given that there was a positive family history in this case, we proceeded directly to genetic testing.

Enzyme replacement therapy is indicated when affected males reach adolescence. Symptomatic children and severely affected females with high risk of developing significant cardiac, cerebrovascular, renal and neurologic complications should also received enzyme replacement therapy. This patient did not receive enzyme replacement therapy because she had no evidence of major organ involvement.

Patients should be offered genetic counselling. A female heterozygote has a 50 % chance of transmitting the defective GLA mutation to each child. There are also implications for her wider family. She has two brothers, but given that Fabry disease is X-linked, there is no male to male transmission, so her two brothers and their children will not be affected given her inheritance was paternal. Her two older sisters will be carriers as an affected male transmits his mutation to all of his daughters. Consequently, any of her nephews and nieces from her two older sisters will have a 50 % chance of inheriting the defective gene.

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Case 11
Unsteadiness – Neither Cerebellar Nor Vestibular

Ross Nortley, Zane Jaunmuktane, Sebastian Brandner, and Hadi Manji

History

A 61 year old man presented with a 5-year history of slowly progressive balance difficulties and numbness in the lower limbs. He had noticed that his balance seemed to deteriorate further when he closed his eyes whilst showering.

He denied pain, paraesthesiae or weakness and had not experienced upper limb symptoms.

Three years previously he had undergone anterior cervical decompression when cervical MRI had shown moderate to severe cervical spondylosis. His symptoms however, had continued to progress.

He had stopped smoking 10 years ago. There was no notable family history.

Examination

Cranial nerve examination was unremarkable

Tone and power were normal in the upper limbs. There was no pseudoathetosis.

Reflexes were depressed or absent in the upper limbs.

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Upper limb sensation to light-touch, pinprick and vibration was normal, as was proprioception.

In the lower limbs, tone and power were normal. There was bilateral heel-shin ataxia, which was not worse when performed with his eyes closed.

Knee and ankle reflexes were absent and the plantar response was flexor on the left and extensor on the right.

On sensory testing, there was loss of fine touch and pinprick to knee level bilaterally. Vibration sense was impaired to the level of the costal margin bilaterally and proprioception to the hip joint level bilaterally. Romberg's test was positive and his gait was markedly ataxic.

The history and examination were consistent with a slowly progressive sensory ataxia.

Investigations

Blood and urine investigations found to be normal or negative included the following: Vitamin B12 and folate, homocysteine and methylmalonic acid, Vitamin E, Immunoglobulins, Protein Electrophoresis including by immunofixation, ACE, ANA, ENA, ANCA, anti-neuronal antibodies, HIV I&II serology and urinary Bence-Jones protein.

Antiganglioside antibodies

Anti-GM1 IgG Antibody	Negative	Titre 1 in 1000
Anti-GD1b IgM Antibody	Positive	Titre 1 in 20,000

Cerebrospinal Fluid

<1 WBC/mm^3
Total Protein 0.66 g/L (0.13–0.4)
Glucose 4.0 mmol/L (2.2–4.2) (matched blood glucose 4.8)
CSF and Serum Oligoclonal Bands – negative

Neurophysiology (Tables 11.1 and 11.2)

Table 11.1 Sensory and mixed nerve conduction studies

	Amplitude (μV)	Onset latency (m/s)	Peak latency (ms)	Conduction velocity (m/s)
Right median (F3-wrist)	4	2.9	3.7	52.5
Right ulnar (F5-wrist)	3	2.3	3.0	60.5
Radial (forearm-wrist)	18	1.8	2.4	61
Right sural (calf-ankle)	9	2.8	3.5	48
Right superficial peroneal	2	2.9	3.7	45
Left sural (calf-ankle)	8	2.4	3.3	55.5
Left superfical peroneal	3	2.2	3.0	49

Table 11.2 Motor nerve conduction studies

	Right	Left
Right median (SE on APB)		
Distal motor latency	4.1 ms	–
Conduction velocity (wrist – elbow)	53 m/s	–
MAP (wrist)	8.5 mV	–
MAP (elbow)	8.0 mV	–
F Latency	30.6 ms	–
Right ulnar (SE on ADM)		
Distal motor latency	4.1 ms	–
Conduction velocity	54 m/s	–
MAP (wrist)	10.5 mV	–
MAP (above elbow)	9.1 mV	–
F Latency	30.4 ms	–
Common peroneal (SE on EDB)		
Distal motor latency	7.7 ms	5.2 ms
Conduction velocity (fibular neck – ankle)	34 m/s	48 m/s
MAP (ankle)	0.4 mV	0.3 mV
MAP (fibular neck)	0.4 mV	0.5 mV
F Latency	Unobtainable	Unobtainable
Right posterior tibial (SE on AH)		
Distal motor latency	5.1 ms	–
MAP (ankle)	2.0 mV	–
F latency	60.9 ms	–

Summary findings

1. All sensory potentials are small or at the lower limit of normal for amplitude. Conduction velocities were within normal limits.
2. Upper limb motor conduction is normal. Lower limb motor responses are small. Motor conduction velocities are within normal limits for the size of the action potentials recorded.
3. F-latencies where recordable were within normal limits for height
4. Needle EMG showed neurogenic changes in the left Tibialis Anterior. Other muscles sampled were normal.

Conclusion

A relatively mild large fibre axonal motor and sensory neuropathy with no demyelinating features.

Somatosensory evoked potentials (Table 11.3)

Table 11.3 Upper and lower limb SSEP

	Right		Left	
	μV	m/s	μV	m/s
Median nerve				
N20 (scalp)	1.8	22.2	2.8	22.3
N14 (Cv2)				
N13 (Cv2)	1.4	15.8	1.5	16.3
N11 (Cv7)				
N9 (Erb's)	2.9	12.0	4.0	11.3
Tibial nerve				
P40 (scalp)	Undetectable		Undetectable	
N20 (T12/L1)	Undetectable		Undetectable	
P8 (Popliteal fossa)	10.6	0.32	10.9	0.22

Summary findings

In the upper limbs peripheral, cervical and cortical somatosensory evoked potentials to stimulation of either arm were of normal amplitude, latency and morphology. In the lower limbs, popliteal responses were clearly seen bilaterally with symmetrical latencies which were within normal limits. However, lumbar and cortical evoked potentials were absent despite good co-operation from the patient.

Conclusion

The lower limb SSEPs were undetectable suggesting dysfunction along somatosensory pathway from both legs. Whilst this finding did not anatomically localise the level of the dysfunction along the pathway, the relatively normal peripheral responses on the nerve conduction studies lent favour to a site of dysfunction either in the nerve roots proximal to the dorsal root ganglion or the posterior columns. There was no demonstrable dysfunction in the somatosensory pathways from the upper limbs.

Left Sural Nerve Biopsy (see Fig. 11.1.)

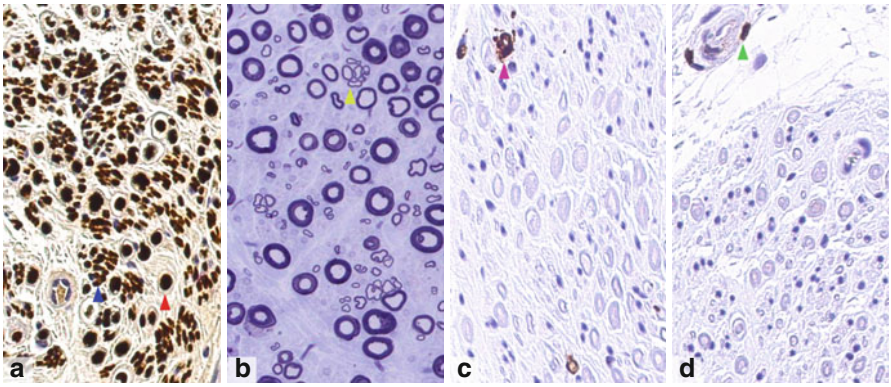

Fig. 11.1 Morphological appearances of sural nerve biopsy. Immunostaining for neurofilaments (**a**) shows mildly reduced density of larges fibres (*red arrow*), while the small fibres are well preserved (*blue arrow*). Semithin resin section (**b**) stained with toluidine blue accentuates mild large myelinated fibre loss and shows several regeneration clusters (*yellow arrow*). Immunostaining for CD68 (**c**) reveals only occasional macrophages in the endoneurium (*pink arrow*) and that for CD3 (**d**) shows rare T lymphocytes in the vicinity of an endoneural blood vessel (*green arrow*). The appearances are those of mild axonal neuropathy. The cause of the neuropathy is not ascertained on the nerve biopsy. Scale bar: 20 μm

Conclusion

Mild axonal neuropathy with evidence of regeneration. There is no definite evidence of nerve inflammation or demyelination.

MRI Whole Spine

The spinal cord returned normal signal. The anterior cervical decompression at C5/6 was adequate. The cauda equina appeared normal.

Pre and Post Gadolinium MRI of the Brachial Plexus

The study demonstrated bilateral thickening of the lower brachial plexus particularly involving the C6-C8 nerves, inferior trunks and divisions of the plexus. There was perhaps equivocal subtle enhancement of the affected nerves.

Diagnosis

Proximal sensory immune polyradiculopathy.

Discussion

Sensory Ataxia may be caused by a lesion anywhere along the sensory pathway comprising the dorsal columns, the dorsal root entry zone, the dorsal roots, the dorsal root ganglia and the sensory nerves. Disorders which can cause a predominant sensory ataxia include: Diabetes, vitamin B12 and vitamin E deficiency, copper deficiency, vitamin B6 excess; infectious diseases – syphilis, HIV and Hepatitis C; neoplastic and paraneoplastic disorders (anti-Hu antibody associated); lymphoma and CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins and antidisialosyl antibodies): inherited disorders- hereditary sensory neuropathies, Fredreich's ataxia, spinocerebellar ataxia Type-4, abetalipoproteinaemia and mitochondrial disorders (eg: SANDO – sensory ataxic neuropathy, dysarthria and ophthalmoparesis); inflammatory/autoimmune disorders- Sarcoid, Sjögren's disease, acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and Miller Fisher syndrome, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), chronic immune sensory polyradiculopathy (CISP) and anti-myelin-associated glycoprotein (MAG) neuropathy.

In this patient, somatosensory evoked potential testing (SSEPs) proved to be the key investigation in localising the site of the sensory pathway dysfunction. The relatively normal nerve conduction studies and the absence of an identifiable lesion on repeat MR imaging of the spinal cord suggested localisation of the pathological proximal to the dorsal root ganglion. MRI imaging of the brachial plexus also proved helpful, showing proximal nerve root thickening and post-contrast enhancement, to provide further evidence that a pathological process was affecting the proximal nerve roots. The modestly, but persistently elevated CSF protein level was also supportive of inflammation of the proximal roots, as was the presence of a raised IgM GD1b antibody which is known to be associated with acquired inflammatory polyradiculopathies.

The treatment options include intravenous immunoglobulin, plasma exchange and corticosteroids.

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Case 12
A Young Man with Blurred Vision and Foot Drop

Michael P. Lunn

History

A 37 year old mechanic presented with a 6 month history of stabbing chest and arm pains. He subsequently developed persistent calf aching. Within the next 6 months he developed difficulties walking, increasing lower limb sensory disturbance and bilateral foot drop. He reported that his hands and feet had become red and a little swollen. He also reported blurred vision which became disabling. Subsequently, his weakness progressed and he was confined to a wheelchair for longer journeys. He had erectile dysfunction and increased sweating.

Examination

On examination he had tanned skin, leukonychia, clubbing and hirsutism. Distal upper and lower limb swelling with erythema was noted.

He had papilloedema (Fig. 12.1) but the remainder of the cranial nerves were normal.

Examination of the limbs revealed distal weakness and wasting in the upper and lower limbs. He was areflexic. Joint position, vibration, pinprick sensation were reduced to the mid forearms and groin.

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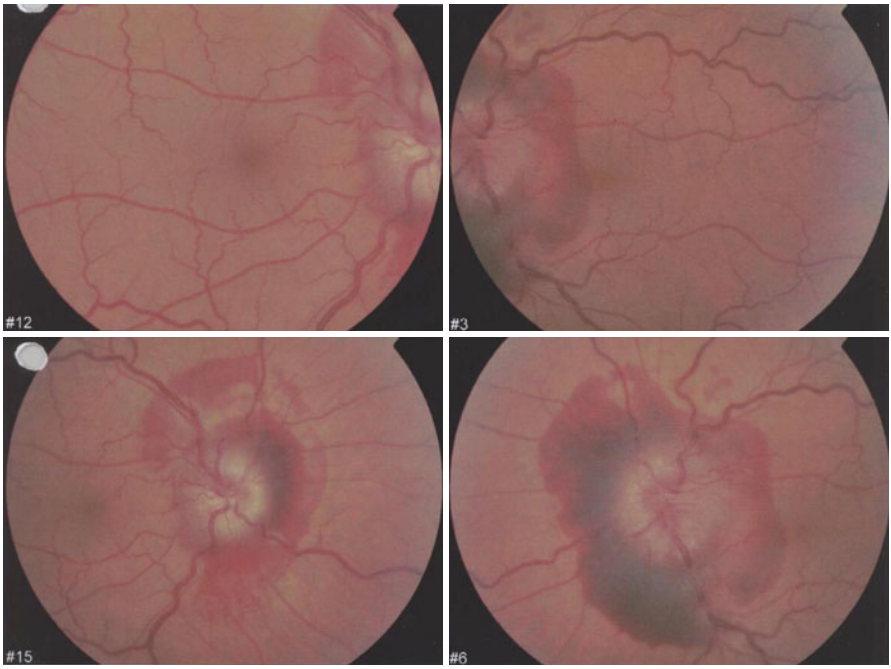

Fig. 12.1 Fundal photographs showing haemorrhagic papilloedema typical of POEMS syndrome (cheese and tomato appearance)

Investigations

Blood and urine tests – Hb 185 g/l (130-170), platelets 652×10^9/L (150-400), primary hypogonadism, hypothyroidism and mild cortisol deficiency. IgG lambda paraprotein. Kappa/Lambda light chain ratio 0.23 (0.26-1.65). No urinary Bence-Jones protein. Serum VEGF 10728 pg/ml (<771)

CSF – <1 WBC/mm^3, protein 2.72 g/L (0.25-0.4) with normal glucose, negative cytology and negative oligoclonal bands.

MRI lumbosacral spine – L3 osteolytic lesion.

CT body – multiple osteosclerotic and osteolytic lesions throughout the axial spine and ribs. Hepatomegaly.

Bone marrow biopsy and trephine – <5 % lambda restricted CD20+ CD138 weak + cells and no evidence of plasma cell dyscrasia on trephine.

Neurophysiology (Tables 12.1, 12.2 and 12.3)
Summary findings

1. Lower limb sensory and motor responses are absent.
2. Upper limb sensory and motor responses are small with slowing of conduction velocity. The only asymmetry noted is of the median CMAP amplitudes (R > L).

Table 12.1 Sensory and mixed nerve conduction studies

	Right		Left	
	μV	*m/s*	*μV*	*m/s*
Radial (forearm-wrist)	8	38		
Median (F2-wrist)	2	30	2	34
Median (F3-wrist)	No response		2	34
Median (palm-wrist)	3	26	4	30
Ulnar (F5-wrist)	2	36	1	35
Ulnar (palm-wrist)	3	35	1	34
Sural (calf-ankle)	No response		No response	

Table 12.2 Motor nerve conduction studies

	Right	Left
Median (SE on APB)		
DML	8.4 ms	7.4 ms
TLI	0.41	0.36
CV (wrist-elbow)	23 m/s	30 m/s
CMAP (wrist)	1.7 mV	0.4 mV
CMAP (elbow)	1.2 mV	0.1 (dispersed)
Minimal F-wave latency (wrist)	Absent	Absent
Ulnar (SE on ADM)		
DML	5.0 ms	5.2 ms
TLI	0.61	0.59
CV (wrist-below elbow)	23 m/s	23 m/s
CV (around elbow)	22 m/s	27 m/s
CV (above elbow-axilla)	32 m/s	28 m/s
CMAP (wrist)	1.3 mV	1.3 mV
CMAP (below elbow)	0.8 mV	0.7 (dispersed)
CMAP (above elbow)	0.8 mV	0.6 mV
CMAP (axilla)	0.7 mV	0.6 mV
Minimal F-wave latency (wrist)	77.0 ms	74.1 ms
F-wave CV	20.6 m/s	21.5 m/s

No motor responses from common peroneal nerve (EDB or TA) or posterior tibial nerve (AH)

Table 12.3 Concentric needle EMG

	Spontaneous activity		MUAP configuration				Interference pattern
	Fibs/PSW	Other	Duration	Amplitude	Polyphasia	Recruitment	
Right deltoid	0	0	N	N	N	N	N
Right FDIO	1+	Fasc. CRD	↑↑	N	↑↑	Reduced	↓↓↓ (single units)
Right rectus femoris	0	0	↑	N	↑↑↑	Reduced	↓↓↓ (single units)
Right vastus medialis	0	0	↑	↓↓	↑↑↑	Reduced	↓↓↓ (single units)

3. There is evidence of temporal dispersion of left median and ulnar motor responses across the forearm.
4. Distal motor latencies and F-wave latencies are prolonged but consistent with segmental velocities.

Conclusion – There is a severe demyelinating sensory and motor peripheral neuropathy with temporal dispersion. EMG findings are consistent with a predominantly demyelinating pattern with only relatively mild secondary axonal loss.

Sural nerve biopsy
Demyelinating and axonal neuropathy without clear macrophage associated demyelination. Loosened myelin was seen on electron microscopy.

Diagnosis

POEMS (Polyneuropathy, organomegaly, endocrinopathy, M-band protein, skin changes).

Treatment

He underwent a Melphalan 200 peripheral blood stem cell autograft transplant with minimal toxicity and was discharged. Eight months following discharge he was walking with a single walking pole and strength had started to improve distally. Papilloedema, hepatomegaly and most of the skin changes had resolved.

Discussion

The diagnosis of POEMS syndrome should be considered within the differential diagnosis of patients presenting with demyelinating neuropathies. Patients may present appearing to have CIDP, but a history of pain or aching calf muscles, a history of distal swelling in the upper or lower limbs especially that appears vasogenic, and reports of changes in the skin and nails are highly significant clues to the diagnosis of POEMS. Even without these, rapid progression, pronounced distal weakness and the early appearance of axonal changes in otherwise demyelinating neurophysiology should increase the clinician's level of suspicion. A lack of significant response to standard CIDP treatment with corticosteroids and IV immunoglobulin should also raise a red flag.

The diagnosis (Table 12.4) requires the cardinal features of a polyneuropathy and a paraprotein; the presence of the latter in a patient under 40 years of age is in itself significant. Supportive major criteria of one of Castleman disease (also known

Table 12.4 Criteria for the diagnosis of POEMS syndrome*

Mandatory major criteria	1. Polyneuropathy (typically demyelinating) 2. Monoclonal plasma cell-proliferative disorder (almost always λ)
Other major criteria (one required)	3. Castleman disease[a] 4. Sclerotic bone lesions 5. Vascular endothelial growth factor elevation
Minor criteria	6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) 7. Extravascular volume overload (edema, pleural effusion, or ascites) 8. Endocrinopathy (adrenal, thyroid[b], pituitary, gonadal, parathyroid, pancreatic[b]) 9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails) 10. Papilledema 11. Thrombocytosis/polycythaemia[c]
Other symptoms and signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhoea, low vitamin B_{12} values

The diagnosis of POEMS syndrome is confirmed when both of the mandatory major criteria, one of the three other major criteria, and one of the six minor criteria are present

[a]There is a Castleman disease variant of POEMS syndrome that occurs without evidence of a clonal plasma cell disorder that is not accounted for in this table. This entity should be considered separately

[b]Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion

[c]Approximately 50 % of patients will have bone marrow changes that distinguish it from a typical MGUS or myeloma bone marrow. Anaemia and/or thrombocytopaenia are distinctively unusual in this syndrome unless Castleman disease is present

as giant or angiofollicular lymph node hyperplasia), sclerotic bone lesions and now an increased VEGF and one of the several minor criteria make the diagnosis. The ability to assay VEGF has made a great difference to the ease of diagnosis.

Treatment options are increasing. For a solitary lesion, radiotherapy with or without surgery may be sufficient. Melphalan and steroids or other chemotherapy regimens have a poor therapeutic response. However a recent paper by Li et al. suggested that this may be better than previously thought. In young patients with a good pre-morbid condition, autologous stem cell transplantation is the treatment of choice and has extremely good medium term results. Mortality rates are quoted as between 2 and 4 %, perhaps slightly higher than autografts for other haematological conditions. Early promise with the anti-VEGF monoclonal antibody Bevacizumab, has been disappointing but lenalidomide (anti-IL6) has had some positive reports in case reports and small series where it is used in conjunction with other chemotherapy.

Biochemical relapse is not uncommon, occurring in about a quarter of patients at 5 years. However a rising VEGF level or return of paraprotein is not always accompanied by return of neurological disability.

Recovery is always slow with patients failing to make any forward progress for months and sometimes 2 years pass before initial significant recovery becomes evident.

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Case 13
Progressive Motor Weakness in a Somalian Man

Mohamed Mahdi-Rogers, Matilde Laurá, and Mary M. Reilly

History

A 43 year old man from Somalia, who moved to the United Kingdom at the age of 26, presented with a 20 year history of progressive leg weakness. He was normal at birth and his motor milestones were not delayed. He played football and had normal motor function in the first two decades of life. He developed a limp in his early 20s and began to experience pain in his feet for several days after playing football such that he had to stop playing. His legs became weak and this gradually deteriorated over the ensuing 20 years. He started using splints at age 26 years and a crutch at 40. His hands became weak at age 41 with wasting of the intrinsic hand muscles. He had no sensory symptoms.

His parents were in their 70s and both well. He had five brothers and three sisters with no history suggestive of neurological disease. He had five healthy children ranging in age from 4 to 17 years. There was no family history of consanguinity.

Examination

He walked with a waddling gait and had bilateral foot drop.

Cranial nerves were normal as too was neck strength.

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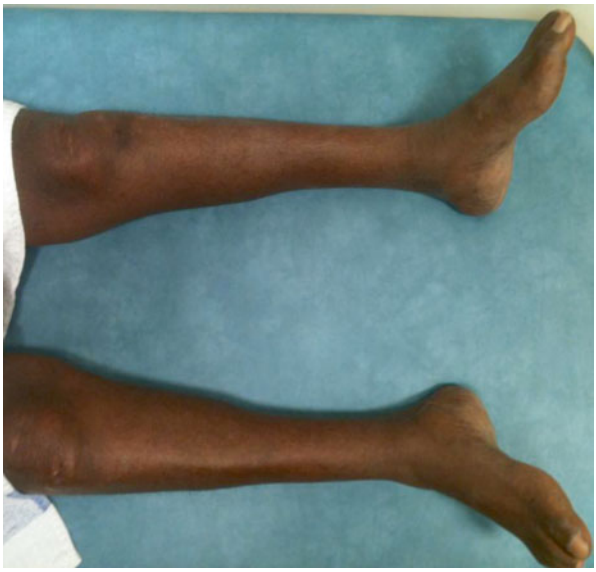

Fig. 13.1 Patient's lower limbs showing severe distal wasting involving both the anterior and posterior aspects of the legs

There was no scapula winging. Distal upper limbs including flexors of the forearms and intrinsic hand muscles were wasted with the first DIO more affected than the APB muscles. There was weakness of the first DIO to MRC grade 1/5 and the APB to grade 4/5 bilaterally. In the lower limbs, there was wasting from mid-thigh distally symmetrically (Fig. 13.1). There was weakness of knee flexion and extension to MRC grade 4/5 bilaterally and no movement below the ankles. Upper limb reflexes were just present however lower limb reflexes and plantar reflexes were absent. All sensory modalities were normal.

Investigations

Laboratory tests including serum lead and white cell enzymes were normal.

Neurophysiology (Tables 13.1 and 13.2)

Table 13.1 Sensory and mixed nerve conduction studies

	Right		Left	
	μV	*m/s*	*μV*	*m/s*
Median (F3-wrist)	33	62	33	60
Ulnar (F5-wrist)	19	60	19	58
Sural (calf-ankle)	18	35	21	35
Superficial peroneal (calf-ankle)	10	42	15	34

Table 13.2 Motor nerve conduction studies

	Right	Left
Median (SE on APB)		
DML	3.9 ms	4.0 ms
CV (wrist-elbow)	54 m/s	54 m/s
CV (elbow-axilla)	–	50 m/s
CMAP (wrist)	5.8 mV	5.5 mV
CMAP (elbow)	5.7 mV	5.0 mV
CMAP (axilla)	–	4.8 mV
Minimal F-wave latency (wrist)	31.4 ms	30.9 ms
Ulnar (SE on ADM)		
DML	3.4 ms	4.9 ms
CV (wrist-below elbow)	48 m/s	41 m/s
CV (around elbow)	56 m/s	67 m/s
CV (above elbow-axilla)	43 m/s	–
CMAP (wrist)	0.5 mV	0.2 mV
CMAP (below elbow)	0.5 mV	0.2 mV
CMAP (above elbow)	0.5 mV	0.1 mV
CMAP (axilla)	0.5 mV	0.2 mV
CMAP (Erb's)	0.2 mV	–
Ulnar (SE on FDIO)		
DML	4.5 ms	3.5 ms
CV (wrist-below elbow)	56 m/s	59 m/s
CV (around elbow)	42 m/s	63 m/s
CV (above elbow-axilla)	56 m/s	52 m/s
CMAP (wrist)	0.7 mV	1.3 mV
CMAP (below elbow)	0.5 mV	1.1 mV
CMAP (above elbow)	0.3 mV	1.2 mV
CMAP (axilla)	0.3 mV	1.0 mV
CMAP (Erb's)	–	0.7 mV

Conclusion

Sensory responses are within normal limits. In the hands, the ulnar CMAP amplitudes are attenuated from both ADM and FDIO, but the median responses are normal. Distal motor latencies and motor conduction velocities are commensurate with the degree of motor axonal loss. Motor responses are absent in the lower limbs.

Concentric needle EMG

Needle EMG shows severe denervation in a distal to proximal gradient in the legs. Denervation is confined to the ulnar innervated muscles in the upper limbs.

Genetic test

A heterozygous mutation (Ser135Hys) in the Heat Shock Protein B1 (HSPB1) gene was identified.

Diagnosis

Distal hereditary motor neuropathy type 2B (HMN2B).

Discussion

This man presented with weakness progressing slowly in a length-dependent manner without accompanying sensory loss. The neurophysiology also showed a symmetrical length-dependent motor neuropathy with preserved sural nerve action potentials. His waddling gait raised the possibility of a proximal myopathy but there were no features on needle EMG to support this. The clinical picture and accompanying neurophysiology were consistent with a distal hereditary motor neuropathy (distal HMN). As there was no family history, it was important to exclude causes of a pure motor neuropathy such as multifocal motor neuropathy with conduction block or motor chronic inflammatory demyelinating polyradiculoneuropathy (the clinical picture is atypical and there is no block or demyelination on NCS), lead toxicity and hexosaminidase deficiency.

The clinical presentation of distal HMN can be similar to the axonal form of Charcot-Marie-Tooth disease (CMT2) and differentiating the two clinically can sometimes be challenging. Neurophysiology helps distinguish the two disorders because the sensory nerve action potentials should always be reduced or absent in CMT, but always normal in distal HMN. The two disorders can be allelic with a number of genes including GARS, HSPB1 and HSPB8 causing both, although always with a motor predominant phenotype.

HMN2 is the classic form of autosomal dominant (AD) distal HMN and is due to mutations in the HSPB8 (HMN2A), HSPB1 (HMN2B) and HSPB3 (HMN2C) genes. HSPB8 and HSPB1 also cause CMT2L and CMT2F respectively when there is sensory loss. There are many other forms of HMN but the genes are only known for about 20 % of cases of which the main ones are described below.

Mutations in BSCL2, GARS and REEP1 cause AD HMN5, which is upper limb predominant. Mutations in SLC5A7 and DCTN1 cause AD HMN7A and HMN7B respectively both of which are characterised by additional vocal cord paralysis. Autosomal dominant missense mutations in senataxin (SETX) can cause a form of distal HMN with pyramidal features but nonsense mutations in the same gene cause autosomal recessive ataxia with oculomotor apraxia type 2. Recently, a form of congenital spinal muscular atrophy which is lower extremity predominant (SMALED) has been shown to be due to both mutations in DYNC1H1 and BICD2. HMN6, an unusually severe autosomal recessive form of distal HMN due to mutations in IGHMBP2. It presents in infancy with respiratory symptoms and distal limb involvement (called spinal muscle atrophy with respiratory distress type 1). There is one X linked form of distal HMN due to mutations in the ATP7A gene (SMAX3).

This case illustrates that genetic neuropathies should be considered in the differential diagnosis even in the absence of a positive family history. Extensive family histories are not always available; relatives may not have lived long enough to develop the disease, and if mild, the disease may not have been noticed by relatives. Non-paternity can also complicate the interpretation of a family history. With dominant diseases, de-novo mutations can occur and with recessive diseases and small families it is not unusual to have a negative family history.

As with most genetic neuropathies, the management of distal HMN is focused on symptom management including the use of physiotherapy, orthotics, orthopaedic interventions, pain therapy and providing genetic counselling for diagnostic, predictive, prenatal and more recently pre-implantation testing.

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Case 14
A Man with a Pacemaker Develops Difficulty Walking

Mohamed Mahdi-Rogers, Matilde Laurá, and Mary M. Reilly

History

A 66 year old man presented with a 2 year history of gradually progressive leg weakness and difficulty getting up from a chair. He also complained of numbness associated with sharp shooting pain up to his knees. In the past, he had experienced pins and needles in the thumb, index and middle finger in his right hand and similar but milder symptoms in his left hand, which led to the diagnosis of bilateral carpal tunnel syndrome. He subsequently underwent decompression of the right carpal tunnel without any improvement in his symptoms. Four months after the onset of the upper limb symptoms, he developed progressive right foot drop and paraesthaesia in the lateral aspect of his right foot, followed within 6 months by a similar problem in the left foot.

He had a permanent pacemaker inserted for ventricular standstill 4 years prior to his first presentation to neurology. He had lost half a stone in weight but otherwise had no systemic symptoms. He subsequently started experiencing nocturnal diarrhoea, nocturia and erectile dysfunction.

His father died at 76 years of age, 8 years after a progressive illness affecting his arms and legs without bulbar involvement that was diagnosed as motor neurone disease.

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Examination

Cranial nerves were unremarkable.

There was distal wasting of upper and lower limbs, right more than left. There was distal weakness in the upper limbs: first DIO was graded MRC 4/5 on the right and 3/5 on the left; APB was graded 2/5 on the right and 3/5 on the left; ADM and FPL were graded 4/5 bilaterally.

In the lower limbs there was proximal and distal weakness with hip flexion, knee flexion and knee extension all graded 4/5 bilaterally; ankle dorsiflexion was graded 3/5 on the right and 4/5 on the left. Ankle plantarflexion was graded 2/5 on the right and 4/5 on the left.

The reflexes were present but reduced in the upper limbs and absent in the lower limbs; plantars were downgoing.

There was patchy sensory loss in the distribution of the right median, ulnar and radial nerves and in the left globally up to the elbow. In the lower limbs, pinprick was reduced to the knees in a patchy manner. Vibration was reduced to the wrist on the right and to the metacarpo-phalangeal joint on the left and was present at the ankles. Joint position sense was normal.

His supine blood pressure was 132/71, with a heart rate of 81 beats per minute (bpm) and after 3 min standing his blood pressure was 117/69 with a heart rate of 86 bpm.

Investigations

Blood tests including glucose, CK, vitamin B12, folate, homocysteine, TFT and ANA were normal. No paraprotein was detected on serum protein electrophoresis or by immunofixation. ANCA, ENA and Rheumatoid factor were negative. Hepatitis B and C serology were negative. Urinary Bence-Jones protein was not detected. He had no cryoglobulins.

Neurophysiology

Sensory responses were absent throughout. Distal motor latency to APB was prolonged bilaterally, left more than right. Motor responses from APB were small on both sides, left more so than right. There was variable forearm motor slowing. Lower limb motor responses were either small or absent. EMG showed chronic neurogenic changes in a length-dependent pattern but there was no active denervation.

Serum amyloid P component (SAP) scintigraphy

No major visceral amyloid deposition was demonstrated (the heart was not viewed)

Echocardiogram

The interventricular wall thickness was 12 mm with some infero-basal left interventricular wall hypokinesis and mildly impaired systolic function. The diastolic function was difficult to assess due to paced beats but appeared abnormal.

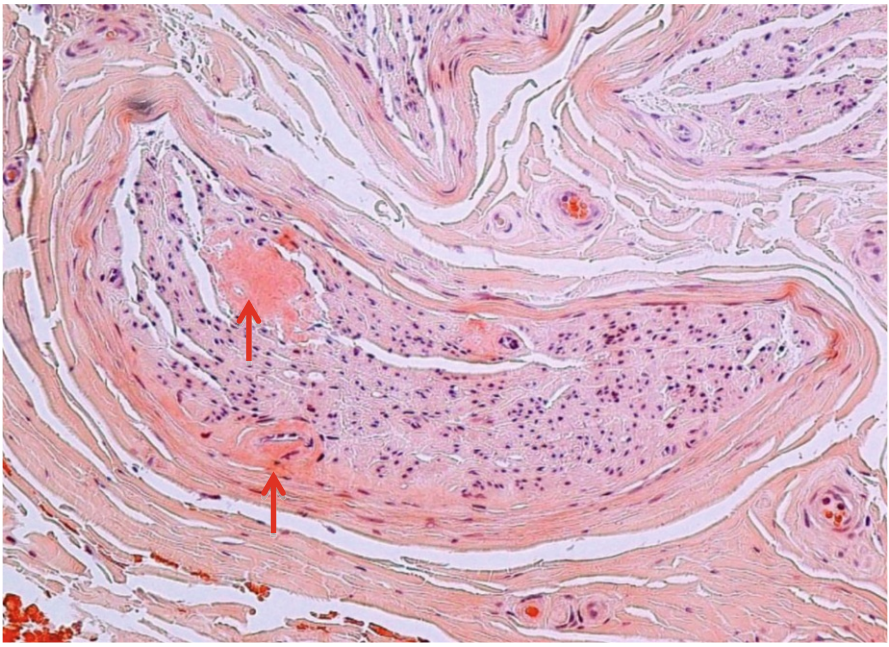

Fig. 14.1 Eosinophilic hyalinised material (*arrows*) shows positive reaction with Congo red stain consistent with amyloid deposits

Nerve biopsy
Amyloid deposits were detected in the sural nerve (Fig. 14.1).

Genetic test
Sequencing of the transthyretin (TTR) gene identified a Val30Met mutation.

Diagnosis

Familial Amyloid Polyneuropathy (FAP) due to TTR Met 30 mutation.

Discussion

The initial clinical presentation of multiple mononeuropathies (bilateral carpal tunnel syndrome and bilateral foot drop) was suggestive of a vasculitic neuropathy. However, the history of ventricular standstill requiring a pacemaker and the subsequent development of autonomic symptoms raised the possibility of amyloid polyneuropathy. It is common for patients with amyloidosis to develop carpal tunnel syndrome many years before complaining of other symptoms, as was the case in this patient.

Nerve conduction studies showed a predominantly length-dependent sensory-motor axonal neuropathy but there was also evidence of patchy slowing of motor conduction and prolongation of distal motor latency. This pattern sometimes results in patients with amyloid polyneuropathy being misdiagnosed with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Prominent neuropathic pain indicating small fibre involvement is common in amyloid polyneuropathy and can help differentiate it from CIDP.

The development of autonomic dysfunction including orthostatic hypotension, alternating diarrhoea and constipation, urinary incontinence and impotence also helps to distinguish amyloid polyneuropathy from CIDP although these symptoms may not be apparent when the patient first presents. The superimposed bilateral median neuropathy (carpal tunnel syndrome) found on nerve conduction studies is also in keeping with a diagnosis of amyloid polyneuropathy.

If neuropathic pain in the extremities is the predominant initial complaint, then differential diagnoses include causes of small fibre neuropathy such as diabetes, impaired glucose tolerance, HIV and nutritional deficiency. Autonomic and cardiac symptoms or the rapid progression of the neuropathy to involve large fibres helps differentiate amyloid polyneuropathy from the others.

Individuals suspected of having amyloid polyneuropathy need a tissue diagnosis, and if neuropathy is the presenting feature, a nerve biopsy is often done looking for amyloid deposition in the endoneurium, epineurium and surrounding vessels and to exclude other diagnoses such as vasculitis or CIDP. Amyloid is often patchy so a negative biopsy does not exclude the diagnosis. If the index of suspicion is high this biopsy should be repeated and or another affected tissue such as the rectum or abdominal fat biopsied. Amyloid stains positive with Congo red (Fig. 13.1) and gives an apple-green birefringence when viewed under polarised light.

Progressive neuropathy is a common feature in both familial amyloid polyneuropathy and monoclonal immunoglobulin light-chain (AL) amyloidosis and the biopsy findings are similar.

To confirm the diagnosis of familial amyloid polyneuropathy, direct DNA sequencing of the TTR gene should be performed. This patient had a Val30Met mutation. The Val30Met is the most common TTR mutation caused by a valine to methionine substitution at position 30 of the TTR gene. This mutation is endemic in certain parts of Portugal, Japan and Sweden. In areas outside the endemic areas like the UK, the age of onset is often older as in this case.

TTR related Familial Amyloid Polyneuropathy has an autosomal dominant pattern of inheritance. Each child of an individual who is heterozygous for any TTR mutation has a 50 % chance of inheriting the mutation. There was no obvious family history in this patient although there was speculation about whether his father's neurological condition was actually familial amyloid polyneuropathy rather than motor neuron disease given its duration.

Appropriate management of autonomic dysfunction and optimal treatment of neuropathic pain are important in improving patient's quality of life. Patients with significant sensory loss should be advised about foot care in order to prevent painless ulcers. Implantation of a cardiac pacemaker is indicated if there is evidence of

sick sinus syndrome or second-degree or third-degree AV block. Decompressive surgery can be performed for symptomatic carpal tunnel syndrome and vitrectomy in those with vitreous deposits.

The only specific treatment for TTR-related familial amyloid polyneuropathy is orthotopic liver transplantation to remove the source of abnormal TTR production. Orthotopic liver transplantation is not recommended for individuals with severe peripheral neuropathy, marked autonomic dysfunction or significant cardiac involvement. Many patients (especially the elderly) may also be too unwell to tolerate liver transplantation. Patients with the Val30Met mutation benefit more from liver transplantation compared to those with non-Val30Met mutations. Although this patient has Val30Met mutation, his age, history of conduction abnormalities necessitating pacemaker and echocardiogram findings of a cardiomyopathy meant he was not considered suitable for liver transplantation.

Genetic counselling should be offered to all patients with TTR related familial amyloid polyneuropathy.

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Case 15
Cramps, Weakness and Fasciculations

Richard W. Orrell

History

A 50 year old right handed man presented with slowly progressive weakness in the right hand for 6 months. He had noticed loss of muscle bulk over the dorsum of the right hand. There was no pain, and sensation was normal. The left arm was normal. He had noticed twitching of the muscles in both arms for 1 year, and more recently in the left leg. In the past 2 months he had developed cramps in the left upper arm with prolonged use, aching behind his knees with exercise, and severe nocturnal cramps in his calves. He had difficulty opening jars, holding a knife, cutting food, and had to hold a razor with his fist rather than fingers.

Examination

Cranial nerve examination was normal.

There was mild wasting of all muscles in the right hand (Fig. 15.1). Fasciculations were present in the right forearm extensor muscles. There was weakness of the APB, FDIO and ADM muscles as well as wrist extension and less so of wrist flex-

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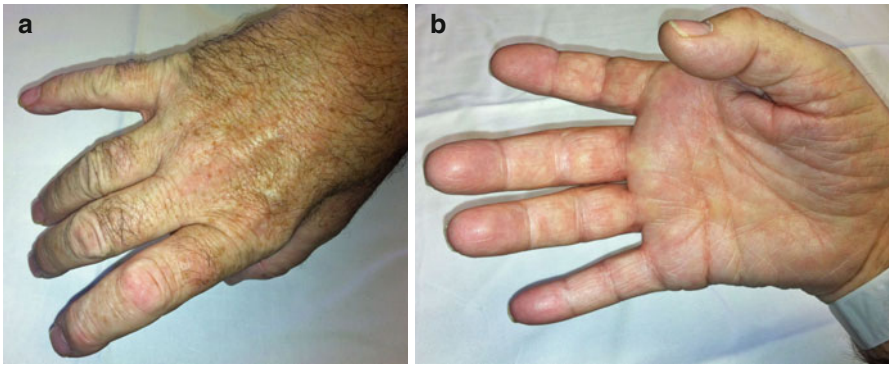

Fig. 15.1 (**a**, **b**) Appearance of the right hand 10 years following onset of weakness. There is relative preservation of muscle bulk.

ion. Sensation was normal. Reflexes were present and symmetrical, requiring reinforcement in the upper limbs. Neurological examination of the legs was normal. Plantar responses were flexor.

Investigations

Blood tests were normal, including creatine kinase. IgG and IgM antiganglioside GM1 antibodies were negative.

CSF examination was acellular. Protein was normal (0.48 g/L), glucose 4 mmol/L. Oligoclonal bands were present in the CSF but not in the serum.

MRI of the brain and spine was normal.

Nerve conduction studies (Fig. 15.2) showed normal sensory conduction. There was evidence of conduction block in the left ulnar nerve, with absent F waves in the right and left ulnar nerves. There was mild prolongation of F waves in the right median nerve (33.9 ms), and absent F waves with slowing of conduction (23 m/s) in the left median nerve. There was evidence of conduction block in the right peroneal nerve and left posterior tibial nerve, and absent F waves in these nerves bilaterally.

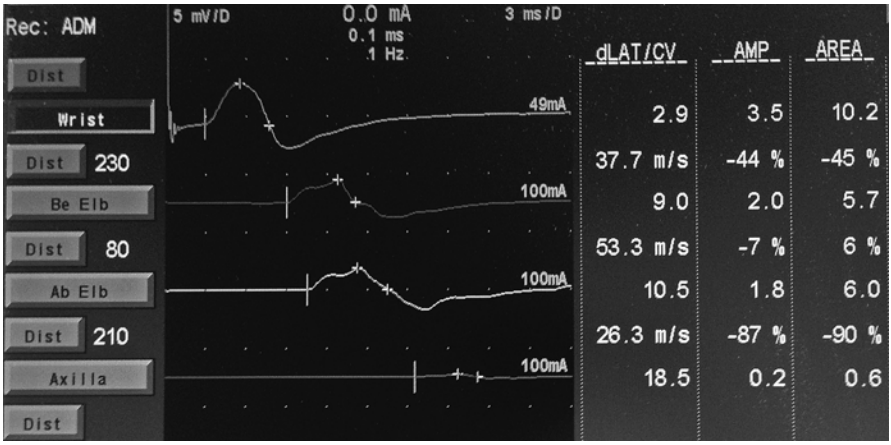

Fig. 15.2 Nerve conduction study of the left ulnar nerve. There is slowing of motor conduction in the left forearm (38 m/s) and upper arm (26 m/s), with conduction block in the forearm, and normal conduction at the elbow (53 m/s)

Concentric needle EMG
revealed mild increased insertional activity, patchy fibrillations, and occasional fasciculations, with moderate polyphasic large units in left biceps. There were polyphasic units in right deltoid, biceps, left first dorsal interosseous, and right and left tibialis anterior. In right first dorsal interosseous there were occasional spontaneous complex repetitive discharges, with single units firing rapidly.

Diagnosis

Multifocal motor neuropathy with conduction block.

Treatment

Following an initial intravenous infusion of immunoglobulin, 2 mg/kg over 5 days, he noticed reduced cramps and improved power, from around day 4 following the infusion. There was at least 50 % improvement. There was mild residual weakness

in the small muscles of the right hand. Fasciculations were present in the right triceps only. He had a recurrence of weakness in the right hand, responding to further immunoglobulin infusions. At 10 years following the initial infusion, he has required a mild increase in frequency of infusions from every 8 weeks to every 5 weeks in order to maintain right hand function.

Discussion

The initial presentation with asymmetrical progressive weakness in the hands, and more generalised fasciculations, raised the possibility of motor neuron disease or amyotrophic lateral sclerosis. The nerve conduction studies and EMG confirmed this was a motor neuropathy, but with features of multifocal conduction block and conduction slowing. The presentation in a young man, affecting hand muscles, is typical of multifocal motor neuropathy with conduction block. Although a rare condition, the distinction from amyotrophic lateral sclerosis is important as this is a treatable condition. Distinction from chronic inflammatory demyelinating polyradiculopathy (including the multifocal, asymmetric, sensorimotor Lewis-Sumner syndrome) is also important as treatment with steroids and plasmapheresis may be detrimental in multifocal motor neuropathy.

The cause of multifocal motor neuropathy with conduction block is presumed to be inflammatory. It is recognised that nerve dysfunction is more widespread than the sites of conduction block. High titres of antibodies to the ganglioside GM1 occur in 50–60 %, but are also found in other neuropathies (especially motor) and are not specific or diagnostic.

Treatment efficacy with immunoglobulin has been demonstrated in randomised controlled trials. Repeated infusions are usually needed. Despite repeated infusions there is usually a slow progression of the underlying weakness, presumably related to secondary axonal degeneration. Prednisolone and plasmapheresis are usually ineffective, and may cause a deterioration. Other immunosuppressants, including cyclophosphamide have been used anecdotally.

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Case 16
A Lady with Weakness Since Childhood

Robin Howard

History

This 52 year old lady was first noted to have developed deterioration in motor skills at the age of 2½ years with progressive difficulty rising from the floor unaided. All her motor milestones were delayed. She remained mobile for some years with bilateral calipers and a spinal jacket but became wheelchair bound in her early teens. Following the growth spurt, she developed increasingly severe lumbar scoliosis with impaired sitting, posture and head control. She was unable to sit straight without a back brace.

In her mid 20s there were considerable concerns about poor nutritional intake. Percutaneous endoscopic gastrostomy was undertaken. She developed symptoms of nocturnal hypoventilation with progressive breathlessness, orthopnoea and disturbed sleep at the age of 36. She was then commenced on nocturnal ventilation via a NIPPY ventilator and a face mask. Over the next 10 years she had multiple admissions to hospital because of severe bronchopneumonia but was able to cope with appropriate bracing and seating.

She continues to require ventilatory support with a NIPPY used for about 12 h at night but still experiences recurrent chest infections. She continues to receive nutritional support via her gastrostomy but is also taking a normal oral diet.

She continues to cope well with her disability and is able to maintain a responsible job as a senior public servant with the support of carers.

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Examination

On examination, there was profound physical impairment. She was wheelchair bound and used a powered chair. There was marked facial and bulbar weakness. There was severe limb wasting with contractures and only flickers of movement in both hands. There was a severe kyphoscoliosis with fixed flexion contractures at the hips.

Investigations

Neurophysiological studies in childhood showed extensive anterior horn cell disease. Needle muscle biopsy confirmed a neurogenic picture with grouping of fibres by type and size.

Diagnosis

Deletion of exon 7 of the SMN gene - Type III spinal muscular atrophy.

Discussion

Spinal muscular atrophy (SMA) represents a group of predominantly autosomal recessive disorders characterised by degeneration of anterior horn cells and bulbar nuclei without corticospinal or sensory neuron involvement. SMA is the second most common autosomal recessive disease of childhood (1/6000–10,000 live births). There are three clinically distinct types which develop in childhood.

SMA Type I (infantile, Werdnig–Hoffmann) develops in infancy with failure to achieve a sitting posture and death by 2 years. There may be loss of fetal movements *in utero* and the baby is born floppy with a weak cry and failure to suck, swallow and achieve head control or sitting posture. Contractures develop after immobilisation and death usually occurs by 2 years as a result of respiratory failure.

SMA Type II (intermediate) – muscle weakness develops after 6 months and manifests as motor development delay. Independent sitting is achieved but not walking. Kyphoscoliosis, severe contractures, skeletal deformity and respiratory muscle weakness may lead to death in early adulthood but prolonged survival is possible if respiratory involvement is limited or with appropriate ventilatory support.

SMA Type III (juvenile, Kugelberg–Welander) becomes symptomatic in early childhood (<18 months) and patients achieve mobility. Fasciculations, cramps and a fine tremor are common and there is proximal limb weakness and wasting more prominent in the lower limbs. SMA III is highly variable and often stabilizes. Prognosis can often be predicted by the age of onset and severity. SMA III may be compatible with normal life expectancy.

Genetics and aetiology – The most common types of SMA are associated with defects in ribonucleic acid (RNA) processing. Spinal muscular atrophy types I–III and some of type IV (95 % of the total SMA cases) are associated with reductions in the product of the survival of motor neurone 1 (SMN1) gene (chromosome 5q11.2–5q13.3). The SMN1 gene encodes a protein involved in RNA metabolism and the severity of the phenotype correlates with the level of SMN1 protein. In the majority of patients it is functionally absent and survival depends on the expression of the SMN2 gene.

Management – There is no specific treatment available for SMA. The management largely involves the treatment of musculoskeletal complications which vary with age of onset and severity. Ventilatory support may be necessary in SMA II and III. Invasive respiratory support leads to improved survival in some patients. Non-invasive ventilation may be necessary if nocturnal hypoventilation develops. Scoliosis develops if there has been paraspinal weakness prior to the growth spurt and spinal correction may be necessary to preserve mobility and ventilatory function. The provision of walking aids including braces and calipers may allow younger patients to remain ambulant for many years.

Treatment and management for SMA has improved to such an extent that many patients are surviving into adulthood. Clinics often need to be multidisciplinary with input from neurology, respiratory, gastrointestinal, orthotic and nursing services. Independent mobility may be lost in teenage years and appropriate wheelchair and even driving provision must be considered. Planning for further education, work, pregnancy, independent living and genetic counselling is often necessary.

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Case 17
A Man with an Insidious, Painful Mononeuropathy

Michael P. Lunn

History

A 68 year old man was referred with a 3 year history of a painful right leg. The pain was initially intermittent on the lateral aspect of the right calf and had gradually become more persistent and spread to the sole of the foot, the back of the leg, and the buttock. Within 6 months the painful area had become numb, and within 1 year there was progressive leg weakness. The pain was severe, worse when lying down, and he could achieve only partial pain relief with opiates. He had longstanding constipation, but no recent change in bladder or sexual function.

Four years earlier he had undergone a radical prostatectomy for a Gleason grade 3 + 3 prostatic carcinoma followed by radiotherapy to the prostatic bed. He was started on goserelin injections. His prostate specific antigen level had reduced to 3.14 μg/L (0-4.10). He had well controlled non-insulin dependent diabetes and hypertension.

Examination

On examination there was wasting of the right gluteus maximus and hamstrings, without fasciculation. Tone was normal. Hip flexion and knee extension power was MRC grade 5/5. However, there was weakness of hip extension to 4/5, knee flexion to 3/5, and ankle dorsiflexion and plantarflexion to 0/5. Reflexes were present with reinforcement at the knee but absent at the ankle. There was sensory loss to pinprick in the distribution of L5 to S3 dermatomes on the right, whereas perianal sensation was spared (S4 and S5). There was impaired proprioception and vibration sense to the right knee. Examination of the arms and the left leg was normal.

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Investigations

CSF – This patient had three lumbar punctures looking for carcinoma cells within the cerebrospinal fluid. These were normal.

Neurophysiology (Tables 17.1, 17.2 and 17.3)

Table 17.1 Sensory and mixed nerve conduction studies

	Right		Left	
	μV	*m/s*	*μV*	*m/s*
Sural (calf-ankle)	No response		No response	
Superf. peroneal (calf-ankle)	No response		No response	

Table 17.2 Motor nerve conduction studies

	Right	Left
Common Peroneal (SE on EDB)		
CMAP (ankle)	No response	No response
Posterior Tibial (SE on AH)		
DML		8.8 ms
CV (popliteal fossa – ankle)		34 m/s
CMAP (ankle)	No response	0.6 mV
CMAP (popliteal fossa)		0.5 mV
Minimal F-wave latency		Absent
Common Peroneal (SE on EDB)		
CMAP (ankle)	No response	No response

Table 17.3 Concentric needle EMG

	Spontaneous activity		MUAP configuration				
	Fibs/ PSW	Other	Dur.	Ampl.	Poly.	Recruitment	Interference
Right vastus medialis	0	0	N	N	N	N	Inconsistent.
Right semimembranosus	2+	0				No MUAPs under voluntary control	
Right gluteus maximus	2+	0				No MUAPs under voluntary control	
Right tibialis anterior	2+	0	↑↑	↓↓	↑↑	Reduced, large units recruiting early	↓↓↓ (single units)
Right gastrocnemius (lh)	2+	0				No MUAPs under voluntary control	
Left vastus medialis	0	0	N	N	N	N	N
Left gluteus maximus	0	0	N	N	N	N	N
Left tibialis anterior	0	0	↑	↑	↑	Reduced	↓
Left gastrocnemius (mh)	1+	0	↑	N	↑	Reduced	↓↓

Conclusion

Upper limb sensory and motor studies are normal. There is severe and asymmetric involvement of the lower limbs in both motor and sensory studies, both proximally and distally. This would suggest extensive postganglionic root and proximal plexus involvement.

MRI (Fig. 17.1) – 3 Tesla T1 (with and without gadolinium), T2 and T2 fat saturated magnetic resonance imaging of the pelvis, lumbosacral spine, and plexus was performed. This showed enlargement and thickening of the right L5, S1, and S2 nerves, with S1 being most abnormal. The differential diagnoses for the scan appearances included a peripheral nerve sheath tumour (PNST), lymphoma, metastatic tumour (most commonly colorectal cancer, genitourinary cancer, breast tumours, retroperitoneal or pelvic sarcomas, or lymphoma), and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). No lymphadenopathy was seen.

Biopsy – A sacral laminectomy and S1 nerve root biopsy were performed. Histology showed a malignant epithelial tumour with papillary architecture and focal gland formation (Fig. 17.2). The tumour cells stained positive for prostate specific acid phosphatase and prostate specific membrane antigen, confirming metastatic prostate carcinoma. There was no evidence of bone metastases on bone scanning, or of recurrent local prostatic tumour.

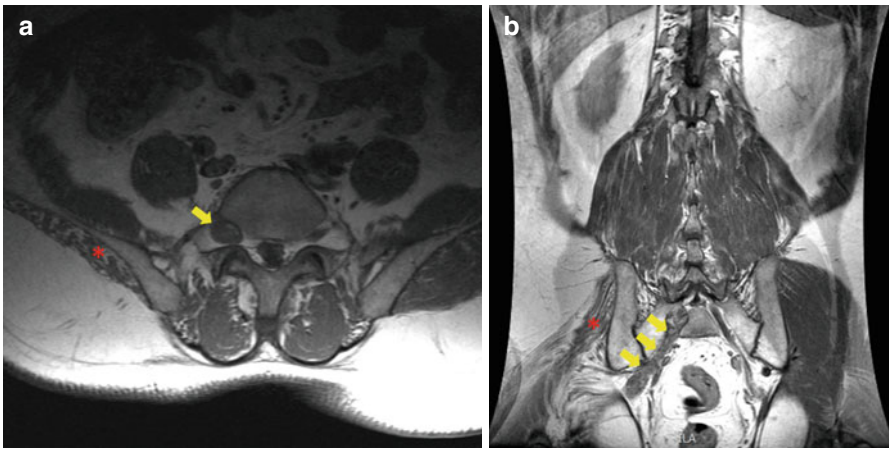

Fig. 17.1 Axial (**a**) and Coronal (**b**) T1 weighted magnetic resonance imaging scan showing abnormal signal within the thickened right S1 nerve (*yellow arrows*) and abnormal signal in the atrophic and denervated gluteal muscles on the right (*red asterisk*). The normal S1 nerve can be seen on the left for comparison

Right S1 nerve root biopsy (Fig. 17.2)

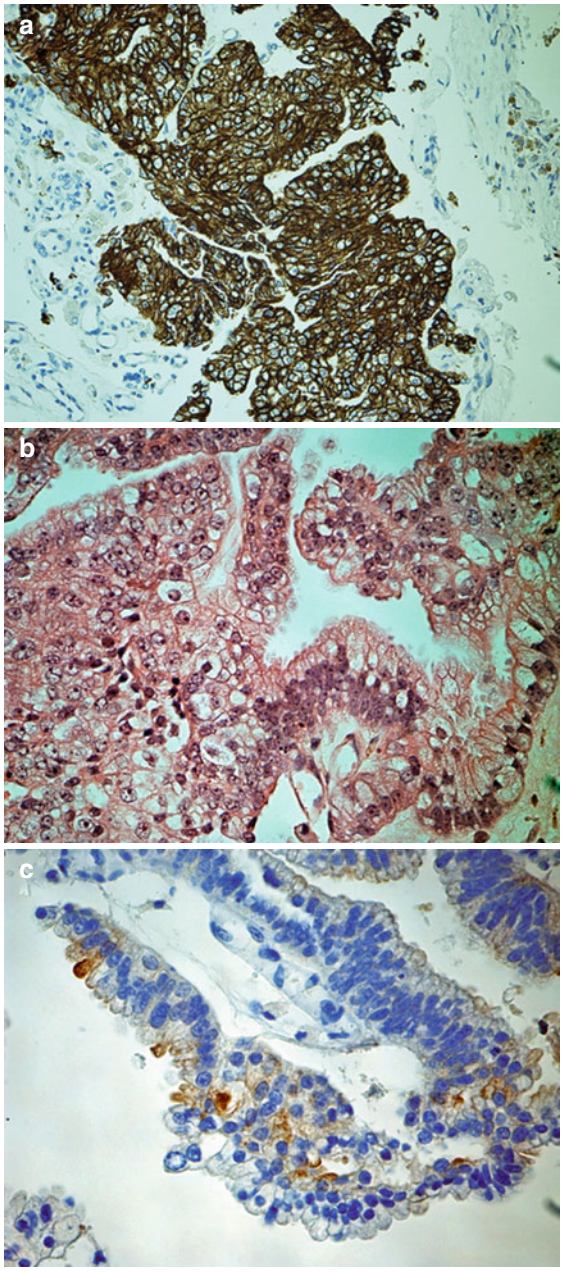

Fig 17.2 (**a**) Tumour cells deposited within the nerve staining strongly for pancytokeratin (Magnification×200). (**b**) H&E section of well differentiated tumour within the peripheral nerve (no peripheral nerve visible) with tall columnar cells with basal vesicular nuclei, prominent nucleoli and atypical cytoplasmic vacuoles (Magnification×200). (**c**) Scattered tumour cells revealing weak positive staining for PSA (Magnification×200)

Diagnosis

Infiltration of spinal nerve roots and plexus by prostate cancer.

The patient was managed with an opiate analgesic regime. He was already on androgen blockade with bicalutamide. No changes were made to his systemic treatment, but 18 fractions of adjuvant local radiotherapy were given. His progressive neurological disorder remained arrested at 12 months follow-up with better control of pain.

Discussion

In this case, involvement of peroneal and tibial territories localises the lesion anatomically to the sciatic nerve or above. Involvement of the gluteus maximus (innervated by the inferior gluteal nerve) puts the lesion very high within the proximal plexus or nerve roots. Careful sensory examination localises this lesion to multiple nerve roots.

MRI neurography is becoming an important tool in extending examination and neurophysiological findings. 3 Tesla magnets have improved resolution to the level of fascicles in large nerves (for example the sciatic nerve). Smaller nerves (e.g. radial and proximal median nerves) with a smaller fascicular structure are more difficult to examine. The identification of nerves as either normal or abnormal and the pattern of that abnormality over the length of the nerve and its enhancement characteristics are almost all that can be reliably reported. Still smaller nerves (sural or pudendal for example) remain too difficult to differentiate reliably from surrounding tissues and are often confused with associated vessels.

In a patient with a progressive neurological disorder with significant pain, and a history of cancer, recurrence or spread is highly likely.

The differential diagnosis includes a range of peripheral nerve sheath tumours (PNSTs). PNSTs may be benign (schwannomas, neurofibromas, and perineuriomas) or malignant (malignant schwannomas and neurofibrosarcomas). Malignant peripheral nerve sheath tumours are mostly painful and may have a predilection for the brachial plexus. Perineural involvement of local prostatic nerves by prostate carcinoma and retrograde spread to the roots is the most likely route of disease in this rare case.

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Case 18
A Lady with Head Drop

Sanjeev Rajakulendran and Dimitri M. Kullmann

History

A 64 year old woman presented with a 4 week history of diplopia and a 'sticking sensation' in her throat. A week later, her speech became slurred, she experienced swallowing difficulties, drooping of both her eyelids and weakness in her arms and legs. Shortly afterwards, she experienced difficulty in holding her head up. In addition, she complained of progressive breathing difficulties which culminated in type II respiratory failure requiring intubation and ventilation. Past medical history was notable for hypertension and diverticular disease.

Examination

There was bilateral partial ptosis and horizontal ophthalmoplegia which was more marked on left lateral gaze. Her speech was slurred and dysphonic. Neck flexion was graded MRC 4/5, shoulder abduction 3/5 and hip flexion 3/5 with relative preservation of distal strength. Reflexes were present and symmetrical and plantar responses were flexor. Sensory examination was normal.

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Investigations

Routine ***blood tests*** were all normal including CK. Acetylcholine receptor antibodies were negative.

Vital capacity - 2.0 L on presentation but dropped to <1.0 L.

Arterial blood gas - PO_2 of 8.9 kPa and PCO_2 of 7.2 kPa.

Nerve conduction studies and concentric needle EMG
Repetitive nerve stimulation (RNS) of her right abductor pollicis brevis and abductor digiti minimi demonstrated a significant decrement (>10 %) in the compound muscle action potential amplitude (CMAP). In addition, single fibre EMG (sfEMG) revealed increased jitter consistent with a neuromuscular junction disorder.

Diagnosis

Anti-MuSK antibodies were positive, confirming the diagnosis of MuSK Myasthenia Gravis.

Discussion

The differential diagnosis here is between myasthenia gravis (MG) and botulism as both may present initially with oculobulbar symptoms, prior to the onset of limb weakness and respiratory distress. However, the time course of her illness and the lack of autonomic impairment, particularly the absence of large unreactive pupils would favour MG. The oculopharyngeal-brachial variant of GBS also enters the differential diagnosis, however the lack of sensory features and intact reflexes would make this less likely. Inflammatory, infective or malignant processes affecting the brainstem may also rarely present in a similar way.

Anti-MuSK antibodies are directed against a post-synaptic muscle specific tyrosine kinase. MuSK interacts with lipoprotein-related protein 4 (LRP4), antibodies which have recently been reported in individuals with MG who are negative for both acetylcholine receptor and MuSK antibodies. The MuSK/LRP4/DOK-7 complex plays an important role in the clustering of post-synaptic acetylcholine receptors.

MuSK MG exhibits a female predominance (80 %) with a generally later age of onset in comparison to females with acetylcholine receptor antibody MG (AChR MG). The clinical spectrum of MuSK MG includes a phenotype indistinguishable from AChR MG as well as an isolated neck extensor weakness with respiratory distress. However the most striking manifestation of MuSK MG is oculo-facio-bulbar muscle weakness with respiratory compromise. Individuals with MuSK MG tend to have more frequent respiratory crises.

Response to cholinesterase inhibitors is often poor and patients generally require treatment with steroids and/or azathioprine. Treatment-resistant MuSK MG has been reported to respond better to plasma exchange than to IVIG, in contrast to AChR MG, where both are equally effective. There are encouraging reports of the efficacy of Rituximab. In contrast to AChR MG, thymectomy is not considered beneficial.

Reference

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Case 19
Preserve Your Health, Not Your Vegetables

Sanjeev Rajakulendran and Dimitri M. Kullmann

History

A 37 year old woman presented with a one day history of dysphagia, slurred speech and difficulty in breathing, followed shortly by weakness of her legs. Two days previously she had awoken with diplopia. Her symptoms progressed. Three days into admission, her vital capacity fell to 450ml. She was intubated and ventilated.

Examination

Examination on admission revealed bilateral ptosis. The pupillary responses to light and accommodation were preserved. She exhibited horizontal diplopia, mild bilateral facial weakness and a slurring dysarthria. In addition, proximal muscle strength was slightly reduced. The reflexes were present and symmetrical. The plantar responses were flexor. Sensory examination was normal to all modalities. Her cough and gag reflexes were both reduced. She was intubated and ventilated. On re-examination 10 days later, there was complete ptosis with slow eye movements and bilaterally sluggish pupillary responses to light.

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Investigations

Blood tests - acetylcholine receptor antibody negative.

Edrophonium test - negative.

MRI Brain - normal study.

Initial EMG - normal study.

Repeat EMG and a ***diagnostic test*** were performed.

Stool sample - PCR positive for Clostridium Botulinim type 1A.

Diagnosis

Food-borne botulism.

Discussion

The pattern of muscle weakness with an oculo-bulbar and respiratory predominance, along with her age and gender raised the possibility of myasthenia gravis (MG) and in particular, MuSK MG.

The patient had a negative edrophonium test shortly following her admission. In addition she had a trial of IVIG and prednisolone without any clinical benefit. These findings would be atypical for acetylcholine receptor positive MG (AChR MG) but not unusual for MuSK MG. Repeat single fibre EMG undertaken 10 days into her admission demonstrated abnormal jitter in the right deltoid suggestive of a neuromuscular junction disorder.

The other important diagnosis to consider is botulism. Supportive features here include the early involvement of ocular and pharyngeal muscles followed by limb weakness, and the temporal profile of her illness. In addition, the reduced pupillary responses to light suggestive of autonomic involvement would also be in favour of botulism. Indeed, the patient had recently returned from a trip where she had eaten home-preserved vegetables. With this in mind her stool sample was tested, revealing positive PCR for Clostridium Botulinum type 1A.

Clostridium Botulinum is a gram positive, rod-shaped, obligate anaerobic, spore-forming bacterium which produces seven subtypes of botulinum neurotoxin (A – G) of which types A, B, E and F are pathogenic in humans. The toxin exerts its effects by cleaving SNARE proteins required for vesicular exocytosis at the presynaptic nerve terminal, thus preventing the release of acetylcholine at the neuromuscular junction and autonomic synapses. The closely related tetanus neurotoxin has a similar action although is transported retrogradely to central inhibitory synapses.

The clinical classification of botulism is based on the mode of exposure. Food-borne botulism may arise from the consumption of inadequately sterilised preserved canned foods. The first symptoms may be gastrointestinal prior to the onset of descending flaccid paralysis. Wound botulism may occur in heroin users following 'skin popping'. Absorption of the toxin following honey ingestion occurs in infant botulism in those under the age of one. A similar syndrome can rarely occur in adults, particularly those with a history of Crohn's disease, abdominal surgery or achlorhydria. Finally, iatrogenic botulism may very rarely occur in those individuals who are treated with botulinum toxin for medical or cosmetic purposes. In the absence of relevant antecedent pointers, food-borne botulism is the most likely mode of exposure in the case reported here.

Management of food-borne botulism is principally supportive although if suspected early after exposure, anti-toxin may be given.

Reference

Sobel J. Botulism. Clin Infect Dis. 2005;41:1167–73.

Case 20
A Man with a Dry Mouth and Weakness

Sanjeev Rajakulendran and Robin Howard

History

A 64 year old man had been aware of a dry mouth and mild limitation of his exercise capacity for 3 months. He was admitted to intensive care with increasing confusion and unsteadiness. His condition had deteriorated because of progressive respiratory insufficiency and he eventually required intubation and ventilation. A tracheostomy was undertaken.

Examination

When sedation was reduced, examination showed mild facial and bulbar weakness, severe fatigable proximal limb and diaphragm weakness. The reflexes were reduced but enhanced after tonic contraction of the muscles.

Investigations

Routine ***blood tests*** were normal. Acetyl-choline receptor antibodies were negative. Voltage gated calcium channel antibodies were positive.

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CT scan showed hilar and mediastinal lymphadenopathy with pulmonary consolidation, most marked at the left base.

Neurophysiology
Sensory studies were normal but the compound muscle action potential amplitudes were small. Repetitive stimulation at 3 Hz elicited a further reduction in amplitude. However maximal exercise elicited an increase in CMAP amplitude of over 100 %.

Sputum cytology showed severe dysplasia but no definite malignancy.

CT guided biopsy confirmed small cell lung cancer (SCLC).

Diagnosis

Lambert Eaton myasthenic syndrome associated with small cell lung cancer.

Treatment

He was treated with a course of plasma exchange. There was marked improvement in limb strength and he was eventually weaned from ventilatory support. He received prednisolone in doses up to 60 mg/day and subsequently a course of intravenous immunoglobulin.

He was also treated with six cycles of chemotherapy for his SCLC, which continues to remain in remission. Neurological function improved and he became fully mobile with walking aids. There is mild residual proximal weakness.

Discussion

Lambert-Eaton myasthenic syndrome (LEMS) is an uncommon autoimmune disorder of neuromuscular junction transmission characterised by proximal muscle weakness and autonomic disturbance. LEMS is associated with antibodies directed against the voltage-gated calcium channel (VGCC) which is a large transmembrane protein with multiple subunits. These antibodies interfere with the normal calcium flux required for the release of acetylcholine (ACh). This leads to reduced ACh release from the presynaptic nerve terminals, despite normal ACh vesicle number, normal ACh presynaptic concentration, and normal postsynaptic acetylcholine receptors.

Approximately one-half of LEMS cases occur in association with malignancy, mainly small cell lung cancer (SCLC) whilst the remaining cases are generally associated with other autoimmune disorders, such as type 1 diabetes mellitus or thyroid disorders.

LEMS generally presents with progressive proximal weakness, often of the pelvic girdle and legs, which may be fatigable. The reflexes are typically depressed or absent although recovery of lost reflexes and improvement in muscle strength may occur after vigorous, brief muscle activation (post-tetanic or post-exercise potentiation). Autonomic manifestations are common and include dry mouth, blurred vision, constipation and erectile dysfunction. Ocular symptoms, especially ptosis and diplopia, and bulbar weakness (dysarthria, dysphagia, and difficulty chewing) may occur. Respiratory muscle (particularly diaphragm) weakness is uncommon but respiratory failure may occur late in the course.

The diagnosis of LEMS is usually made on clinical grounds and confirmed by the presence of antibodies directed against VGCCs and by electrodiagnostic studies. There is a characteristic electrophysiologic pattern which supports the diagnosis of a presynaptic neuromuscular junction (NMJ) disorder and is distinctly different from the changes seen in MG. The compound muscle action potential (CMAP) of resting muscle in patients with LEMS usually has a significantly reduced baseline amplitude. Following high frequency (10–50 Hz) repetitive nerve stimulation (RNS) or brief (e.g., 10 s) maximal isometric muscle activation, there is a significant increment with a marked increase in the CMAP amplitude. With low frequency (2–3 Hz) RNS, there is often a modest decrement, similar to that seen in the postsynaptic NMJ disorders.

Investigation for and treatment of any underlying malignancy is fundamental to the management of patients with Lambert-Eaton myasthenic syndrome (LEMS).

Symptomatic therapies for LEMS include medications that increase the amount of acetylcholine available at the postsynaptic membrane. These are guanidine, aminopyridines such as 3,4-Diaminopyridine (3,4-DAP), and acetylcholinesterase inhibitors such as pyridostigmine. Immunologic therapies for LEMS include plasma exchange, intravenous immunoglobulin, and oral immunosuppressive agents. These agents are thought to dampen the immune response by reducing the antibodies directed at voltage-gated calcium channels in the presynaptic terminal of the neuromuscular junction.

References

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Case 21
A Man with Difficulty Chewing Gum and an Ominous Family History

Richard W. Orrell and Kin Y. Mok

History

A 50 year old man first noticed difficulty in chewing gum. He then developed slurring of speech, and was unable to speak after 9 months. At 12 months from onset of symptoms he had difficulty swallowing, was choking on liquids, and had to take thickened feed. He was particularly troubled by spasms of his jaw. In addition he had noticed muscle twitching in the arms and legs. There was no weakness or spasm in the arms and legs, and sensation was normal. Vision and hearing, bladder and bowel function, and breathing were normal. He was otherwise well. His mother had died of motor neuron disease age 65 years. This had commenced in her arms and legs, and then involved the bulbar muscles.

Examination

On examination he had great difficulty speaking. There was a spastic appearance to the face, with reduced rate of eye closure and mouth movement. He had a spastic dysarthria with difficulty opening the mouth. There was clonus of the jaw, and a very brisk jaw jerk. There was reduced tongue movement with reduced size, but no fasciculation. Cranial nerve examination was otherwise normal.

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He walked normally. There were fasciculations in both quadriceps muscles, but no clear muscle wasting. There was increased tone most marked in the left leg and left arm, less so in the right leg. There was mild reduction of power in the fingers on the left, and in left big toe extension. Sensation was normal. Reflexes were generally abnormally brisk, with bilateral flexor plantar responses. Neck flexion and extension was normal.

Investigations

Routine ***blood tests*** were normal.

MRI brain and spinal cord was normal.

Nerve conduction studies showed normal motor and sensory conduction. EMG of the limbs showed mild features of active and chronic partial denervation with occasional fasciculations. EMG of the tongue was normal.

Neuropsychological testing (when still able to speak) showed he was functioning in the low average range on the verbal scale of the WAIS-R and in the average range on the performance scale. This indicated mild intellectual under-functioning on tests with a verbal component. Consistent with this, his performance was weak on a verbal recognition memory test and on a verbal fluency test, which is sensitive to frontal lobe dysfunction. Performance was also low on another frontal executive test.

Genetic testing for mutations in *SOD1* was normal.

Diagnosis

Examination of the hexanucleotide repeat length in the chromosome 9 open reading frame 72 (*C9ORF72*) showed this to be abnormally expanded (Fig. 21.1) confirming a diagnosis of familial amyotrophic lateral sclerosis with mild cognitive impairment.

Treatment

He was treated with riluzole 50 mg twice daily to slow progression of motor neuron disease. Treatment with baclofen and tizanidine was not helpful. Fluoxetine was taken to stabilise mood. Botulinum toxin injection of the masseter muscles relieved the jaw spasm. He also had injection of the parotid gland to reduce saliva production. Percutaneous endoscopic gastrostomy (PEG) was performed to facilitate nutrition and hydration.

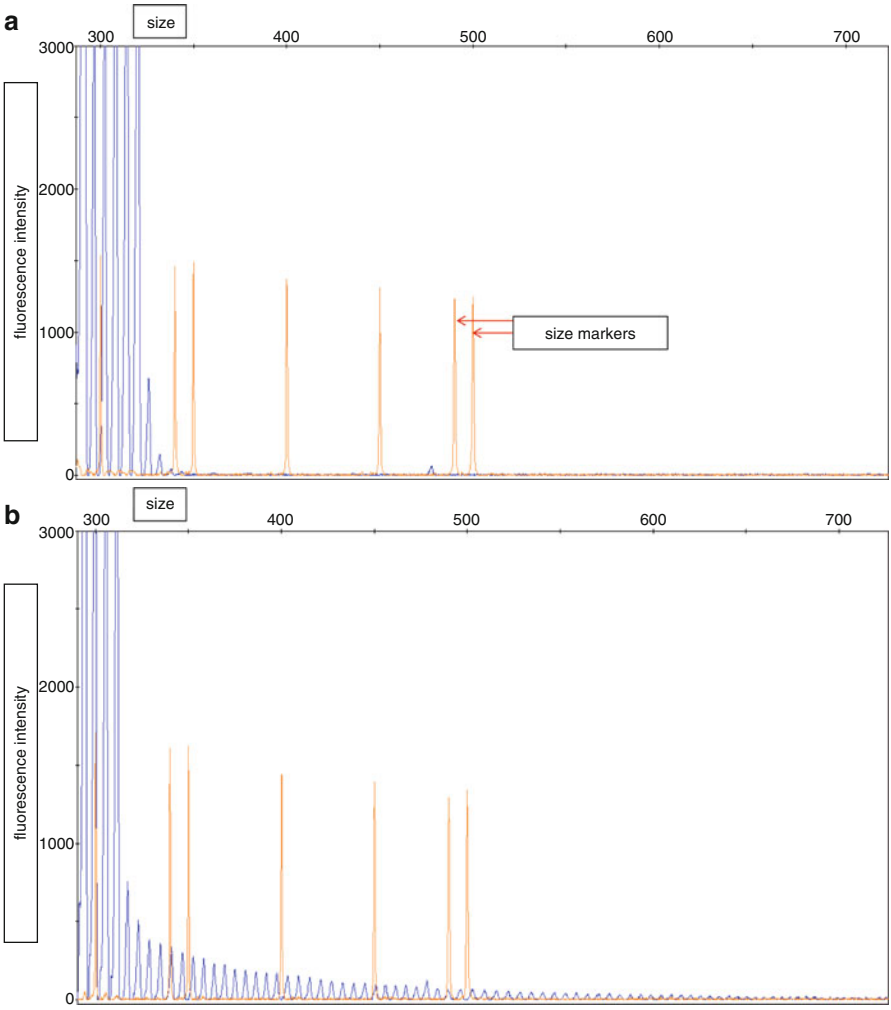

Fig. 21.1 Repeat-primed PCR analysis of hexanucleotide repeat in C9ORF72, in normal and expanded individuals (see Majounie et al. 2012 for details). (**a**) A normal individual with less than 10 repeats. (**b**) An affected individual with an expansion of more than 70 peaks. The full length is determined by Southern Blot. There is a saw tooth tail pattern with peaks in 6 base pair periodicity

Discussion

The presence of upper and lower motor neuron features in limbs and bulbar muscles, with asymmetry and progression, points to a diagnosis of amyotrophic lateral sclerosis or motor neuron disease. Riluzole is licensed to slow the progression of the disease. It is usually well tolerated, but has low efficacy, and average survival from onset to death remains around 3–5 years. Additional management is symptomatic, and in this instance included baclofen and tizanidine for limb spasticity, botulinum

toxin for jaw spasticity (and also to reduce salivation), and fluoxetine for mood stabilisation and relief of depression. PEG is important in maintaining nutrition and hydration, and minimising aspiration.

His mother had previously died of motor neuron disease. Around 5 % of patients with MND/ALS have a family history of the condition. The most common genetic change in these families is a GGGGCC hexanucleotide repeat expansion in *C9ORF72*, accounting for around 30 % of the families. This expansion is also found in patients and families with frontotemporal dementia (FTD), and there appears to be a clinical and molecular overlap between patients with FTD and ALS. It is increasingly recognised that patients with ALS may have a varying degree of cognitive involvement, especially a frontotemporal dementia.

Other genes recognised in ALS, usually with autosomal dominant inheritance include *SOD1* (copper/zinc superoxide dismutase) accounting for around 20 %, TAR DNA-binding protein (*TARDBP*) and Fused in Sarcoma/Translocated in Liposarcoma (*FUS/TLS*). The latter two genes account for around 5 % of cases each. The frequency differs between populations. An increasing number of additional genes are being identified accounting for the remainder of cases. Up to 7 % of apparently sporadic patients may have the C9ORF72 expansion, and around 1 % have *SOD1* or other genes, but it is probable that many of these represent individuals where the family history is not clear, the family small, or there is incomplete penetrance.

Reference

Majounie E, Renton AE, Mok K, et al. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. Lancet Neurol. 2012;11:323–30.

Case 22
A Patient with an Acute Syndrome, Recovers and Represents Years Later

Robin Howard

History

A 32 year old right handed nurse received the oral polio vaccine at the same time as her 4 week old daughter because there was some doubt about her previous vaccination history. Ten days later she noticed a heavy aching feeling in her legs, more marked on the right. This started with a stabbing tender sensation in the right hip. She noticed it was difficult to get up from a crouch on the floor and she had difficulty climbing stairs. Her symptoms worsened over 4 weeks and then stabilised. She continued to experience aching in her legs when going upstairs but was able to return to work.

Examination

On examination 4 weeks after her first symptom, straight leg raising was 80° bilaterally but with a positive sciatic stretch test on the left. She had difficulty walking heel to toe and rising from a squat. Cranial nerves were normal with no facial weakness. In the limbs there was mild wasting of the right vastus lateralis but no fasciculations. Tone was normal. There was mild proximal weakness of the arms and legs and also some truncal weakness. Coordination was intact. Tendon reflexes were reduced. Sensation was normal.

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Investigations

Routine investigations were normal.

CSF was unremarkable with protein 0.5 g/L (0.25-0.4), normal cell count, negative oligoclonal bands and enterovirus PCR.

Concentric needle EMG was normal.

Diagnosis

Subsequently, poliovirus DNA was found in the CSF on PCR suggesting a diagnosis of vaccine associated paralytic poliomyelitis (VAPP). A Poliovirus neutralisation test from when she was first seen in clinic confirmed exposure to all three poliovirus subtypes.

Continuing History

She recovered from the acute illness but presented 15 years later with a 6 year history of slow deterioration in her functional capacity. She was aware of fatigue, persistent muscle ache and pain in her arms and legs. Over the 2 years prior to presentation she had become aware of increasing weakness and difficulty getting up from the floor. She was undertaking vigorous exercise in the gym, weight lifting up to three times a week but became increasingly tired and had been unable to sustain this level of exercise.

Examination

Systemic examination was normal. There was no cranial nerve weakness but there was mild weakness of neck flexion. The truncal muscles were a little weak and she had difficulty sitting up from a lying position but there was no focal limb weakness.

Diagnosis

Post-polio syndrome.

Discussion

Poliomyelitis is caused by an enterovirus of high infectivity transmitted via orofaecal contact. The virus multiplies in the lymphatic tissue of the pharynx and intestine for 1–3 weeks before it is either contained by a local immune response or a

viraemic phase occurs. The virus continues to be excreted in the saliva for 2 or 3 days and in the faeces for 2–3 weeks. The infection rate is extremely high although it is probable that 95 % of all infections are either asymptomatic or characterised by an abortive 'flu-like' illness. Epidemics of polio occurred, most commonly, during the summer months, in the temperate climates of the Northern Hemisphere and the incidence was greatest where children bathed together.

Following the introduction of mass vaccination programmes in the late 1950s and early 1960s the incidence of paralytic poliomyelitis was dramatically reduced, however global vaccination was not possible. Furthermore, oral polio virus (OPV) vaccine derived poliovirus is attenuated but it may mutate and acquire properties similar to the wild type. This can result in vaccine associated paralytic poliomyelitis (VAPP) occurring in recipients, particularly if they have B-cell immunodeficiency. Similarly vaccine derived poliomyelitis (VDP) may occur in contacts, particularly in regions with low immunisation rates. Once again the virus may mutate – it will then affect unimmunised direct contacts (e.g. those who change the nappies of infants who have recently received OPV) especially if they are immunosuppressed. This is the likely mechanism in the present case.

In North America, Europe, Japan, Australia and New Zealand, the ongoing occurrence of VAPP and VDP in the face of the elimination of wild type polio has led to the increased use of Inactivated Polio Vaccine (IPV) culminating in the present recommendations of an all IPV schedule.

Post-polio Functional Deterioration (The 'Post-Polio Syndrome') – Following recovery from the acute illness and a period of rehabilitation, most people maintain stable function for many years. However, it has become increasingly clear that many patients develop new disabilities after a prolonged period of stability. These late functional changes were recognised and defined medically in terms of progressive muscular atrophy, weakness, pain and fatigue.

Most patients are aware of impairment of activities of daily living, mobility, upper limb function and respiratory capacity. They often describe an insidious onset of progressive impairment but sometimes functional deterioration occurs as a consequence of a clear precipitating event such as a fall or intercurrent illness. There may be prolonged fatigue following physical activity, or difficulty in recovering from periods of immobility. They often experience new musculoskeletal symptoms including cramps and fasciculations, increasing weakness of a limb or the trunk, unreliability in a previously stable joint (often in the upper limbs), pain in muscles and joints and changes in the joint (often with a tendency to trip or fall). Other prominent symptoms may include respiratory and swallowing difficulties and sleep disturbance.

The nature of 'post-polio syndrome' remains controversial, with most definitions continuing to suggest that the new symptoms and signs should be unrelated to any orthopaedic, neurological, respiratory or systemic medical illness. However, these criteria are somewhat inconsistent because most patients with post-polio functional deterioration have considerable pre-existing orthopaedic and neurological impairment rendering them vulnerable to the development of new disabilities. Thus, new impairments may often occur as a consequence of prolonged stresses on skeletal deformity and previously weakened muscles, including entrapment neuropathy, radiculopathy and orthopaedic problems.

The effective management of post-polio functional deterioration requires a multi-disciplinary approach involving both specific treatment of increasing impairment and a process of enabling the patient to cope with new disabilities. Physicians must recognize that patients may note changes in function that are not manifest by increasing weakness on neurological examination. What appears, on examination, to be a slight worsening of a severe disability, may have devastating functional consequences to the patient.

Although there are few prospective studies, experience suggests that post-polio functional deterioration is not necessarily an on-going process. Fatigue and reduced mobility often may progress only slowly, or stabilise. The extent of functional deterioration also depends on the severity of the existing disability. The prognosis will also depend on the nature of any underlying cause for the functional deterioration.

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Case 23
A Man with Recurrent Chest Infections

Robin Howard

History

A 62 year old man presented with recurrent respiratory tract infections culminating in the development of type II respiratory failure.

His birth and infancy were normal. Symptom onset was around the age of 6 with ptosis, restricted eye movements and weakness of the face and legs. By the age of 8 years, he was unable to run and was noted to have developed progressive, fatigable limb weakness. A diagnosis of muscular dystrophy was made at the age of 15, although myasthenia was considered as a possibility. Neostigmine was instituted at that time and this led to a significant improvement. It has been continued long-term.

He remained symptomatic throughout adult life but there was only slow progression in limb weakness. He used a walking stick from his 40s and later regularly used a wheelchair. He did not seek further medical advice until the age of 52 when he consulted a neurologist because of concerns about passing the condition on to his child. Congenital myasthenia was suspected at that time.

He presented in type II respiratory failure following an episode of pneumonia. In retrospect, he described preceding symptoms of chronic nocturnal hypoventilation including orthopnoea and disturbed sleep. Tracheal intubation and ventilation was undertaken for 2 weeks and then he was weaned to intermittent ventilation via a face mask. This proved inadequate to support ventilation necessitating a tracheostomy. He has since continued to receive nocturnal ventilation via the tracheostomy.

The myasthenic symptoms have worsened with increasing fatigue.

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Examination

On examination there was mild bilateral ptosis, marked ophthalmoplegia with up gaze and abduction most severely affected. There was generalised weakness of the facial muscles and limbs, particularly shoulder abductors, elbow flexors, forearm extensors and the small muscles of the hands and of dorsiflexion. He walked with a stick and used a wheelchair for longer distances.

Investigations

Neurophysiology demonstrated clear evidence of abnormal neuromuscular junction transmission. On repetitive stimulation there was a 50 % decrement of compound muscle action potential amplitude in abductor digiti minimi. Single fibre EMG showed abnormal jitter with blocking in 75 % of sampled pairs. EMG sampling showed some myopathic features. His weakness showed a dramatic response to intravenous edrophonium.

Genetic studies showed a mutation in the CHRNE gene leading to a diagnosis of Congenital Myasthenia due to a kinetic abnormality of the ACR ('slow channel syndrome').

Diagnosis

Congenital myasthenic syndrome (CHRNE gene mutation).

Management

He was subsequently treated with Fluoxetine titrated to 80 mg per day in addition to neostigmine and pyridostigmine. Oral Salbutamol was commenced at the age of 65 and led to a dramatic improvement in limb strength.

Discussion

Congenital myasthenic syndromes (CMS) are a heterogeneous group of genetic disorders caused by abnormalities of the neuromuscular junction (NMJ) that interfere with normal synaptic transmission. They are generally autosomal recessive and are conventionally classified according to the site of defective neuromuscular

transmission (presynaptic, synaptic and post-synaptic) although diagnosis increasingly depends on the identification of the specific gene defect.

The conditions are rare but important to distinguish from seronegative myasthenia gravis because of the implications for management and genetic advice. Presynaptic deficits are due to reduced numbers of acetylcholine (ACh) molecules per synaptic vesicle, impaired quantal release mechanisms or reduced efficacy of individual quanta. Synaptic impairment is due to endplate acetylcholine esterase deficiency. However, the commonest causes are postsynaptic and due to a mutation in the genes encoding the AChR subunits that can either impair ion channel gating or reduce the number of end plate receptors leading to slow channel, fast channel or AChR deficiency syndromes. Slow channel syndromes are dominantly inherited and are due to prolonged ion channel activation.

The classification of CMS is summarised in Table 23.2. The different syndromes are classified according to the underlying gene defect and molecular mechanism.

CMS may present in infancy with hypotonia, failure to thrive, delayed motor milestones and unexplained apnoeic episodes. In children and adults the conditions are manifest as fatigable or fluctuating, ocular, facial and bulbar weakness although limb and truncal wasting and weakness may also be prominent. The weakness tends to progress during adolescence but then often stabilizes. There may be episodic worsening of the weakness, possibly triggered by intercurrent events such as pyrexia. There may be a positive family history.

In infancy, CMS may mimic muscular dystrophy, congenital and metabolic myopathy, spinal muscular atrophy or structural brainstem anomalies. In children and adults it is necessary to distinguish CMS from seronegative myasthenia gravis, forms of motor neurone disease (MND), limb girdle muscular dystrophy (LGMD) and neuropathies (see Table 23.1).

In slow channel syndromes, the age of onset of symptoms is variable and can occur from the neonatal period, though onset in childhood or adulthood is more common. Frequent presenting complaints are difficulty in running and weakness of neck flexion with weakness usually apparent in upper and lower limbs. However, cervical and distal upper limb muscles particularly the finger extensor muscles may be selectively affected.

Treatments for slow channel syndromes are fluoxetine and quinidine. Both of these block the AChR channel in its open state and thus limit the excess cational flow through the channel and thus the motor end plate. The mainstay of treatment in AChR deficiency is acetylcholine esterase inhibitors and/or 3,4-Diaminopyridine. Both drugs effect an increase in concentration of ACh in the synaptic cleft but they may worsen symptoms in slow channel syndromes.

Table 23.1 Causes of congenital myasthenia

Diagnosis	Defect in NMJ	Gene	Clinical features	Treatment
Pre-synaptic defect				
Choline acetyl transferase (Chat) deficiency	Failure of ACh re-synthesis or packaging	CHAT	Recurrent apnoeic spells Impaired pupillary responses	Refractory to cholinesterase inhibitors
Synaptic				
End plate acetylcholinesterase deficiency	Failure to anchor AChE in synaptic cleft	COLQ	Recurrent apnoeic episodes from infancy Variable myasthenic symptoms between attacks. Axial weakness	Reduced active signal transmission Cholinesterase inhibitors or 3–4 DAP Ephedrine
Post-synaptic defect				
AChR deficiency				
AChR mutation	Reduced number of end plate receptors. Non functioning ε subunit replaced by foetal γ	CHRNE CHRNA CHRNB CHRND	Neonatal onset. Severe ophthalmoplegia, ptosis & feeding difficulties. Mild bulbar or respiratory involvement Generalised weakness	Reduced active signal transmission Cholinesterase inhibitors or 3–4 DAP
AChR kinetic abnormality				
Slow channel	Prolonged ion channel activation in response to ACh	CHRNE CHRNA CHRNB CHRND	Variable age of onset. Autosomal Dominant Cervical weakness with mild bulbar or respiratory involvement. Weakness and wasting in extensor and distal muscles due to endplate myopathy caused by prolonged channel activation (depolarizing block)	Drugs which block AChR ion channel when in an ‘open state’ Fluoxetine, Quinidine

Fast channel	Abnormally brief ion channel activation in response to ACh	CHRNE CHRNA CHRNE	Respiratory insufficiency at birth. Recurrent respiratory crises. Severe ophthalmoplegia	Reduced active signal transmission Cholinesterase inhibitors or 3–4 DAP
AChR clustering pathway				
Rapsyn mutation	Deficiency and instability of AChR at motor endplate	RAPSN	Arthrogrypsis multiplex congenita. Early onset associated with hypotonia, bulbar and respiratory impairment Facial malformations, contracture of hands and ankles Episodes of respiratory failure Tendency to improve with time	Reduced active signal transmission Cholinesterase inhibitors or 3–4 DAP
DOK 7	Binds to MuSK which controls the aggregation of AChR. Incomplete synaptogenesis results	DOK 7	Highly variable Proximal > distal limb girdle weakness Childhood – waddling gait, falls. Ptosis, stridor, bulbar and respiratory impairment Benign forms may develop in adults	Deterioration with pyridostigmine 3–4 DAP Ephedrine, Salbutamol

ACh acetylcholine, *AChR* acetylcholine receptor, *CMS* congenital myasthenia syndrome

Table 23.2 Differential diagnosis of CMS

Neonatal	Spinal muscular atrophy Congenital myopathies – central core, nemaline, myotubular Congenital muscular dystrophy Mitochondrial myopathy Brainstem anomaly Mobius syndrome Infantile Botulism Autoimmune MG
Older patients	Motor neurone disease Peripheral neuropathy Congenital muscular dystrophy – Fascioscapulohumoral, Limb girdle Mitochondrial myopathy Myasthenia Gravis (AChRAb, MuSKAb, SNMG)

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Case 24
A Medical Student with Episodes of Weakness and Sensory Disturbance

Mohamed Mahdi-Rogers, Zane Jaunmuktane, Matilde Laurá, and Mary M. Reilly

History

A 25 year old female medical student presented with tingling and mild weakness in her left little and ring fingers. She had also experienced occasional tingling in the lateral three fingers of the left hand as well as in the right hand especially after prolonged writing. At age 14 years, she developed intermittent clawing of the left hand and difficulty moving the left little finger with associated tingling while doing certain activities such as rowing, playing the clarinet and piano. She had an episode of left foot drop at age 24 years without an obvious cause which improved gradually over 4 weeks. She also developed a transient patchy area of numbness in her right upper arm after carrying a backpack.

There was no known family history.

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Examination

Gait was normal but she struggled to stand on both heels. There was normal muscle bulk except for wasting of the EDB muscle bilaterally. The only weakness was in the left ADM muscle at MRC grade 4/5. Reflexes were all present. Sensory examination showed reduction of pinprick in the left ulnar distribution and in the distal part of the left common peroneal nerve.

Investigations

Neurophysiology (Tables 24.1 and 24.2)

Table 24.1 Sensory nerve conduction studies

	Right		Left	
	μV	*m/s*	*μV*	*m/s*
Radial (forearm-wrist)	–	–	20	50
Median (F3-wrist)	4	37	12	43
Ulnar (F5-wrist)	10	44	5	48
Sural (calf-ankle)	–	–	11	34
Superficial Peroneal (calf-ankle)	–	–	4	37

Table 24.2 Motor nerve conduction studies

	Right	Left
Median (SE on APB)		
DML	4.9 ms	4.4 ms
CV (wrist-elbow)	53 m/s	55 m/s
CMAP (wrist)	8.1 mV	8.4 mV
CMAP (elbow)	7.9 mV	8.6 mV
Ulnar (SE on ADM)		
DML	3.2 ms	3.4 ms
CV (wrist-below elbow)	57 m/s	61 m/s
CV (around elbow)	40 m/s	32 m/s
CMAP (wrist)	10.9 mV	10.4 mV
CMAP (below elbow)	11.1 mV	10.2 mV
CMAP (above elbow)	10.0 mV	8.1 mV
Common Peroneal (SE on EDB)		
DML	–	5.9 ms
CV (fib. neck-ankle)	–	40 m/s
CV (pop. fossa-fib. neck	–	29 m/s
CMAP (ankle)	–	2.2 mV
CMAP (fib neck)	–	1.6 mV
CMA{ (pop. fossa)	–	1.8 mV

Conclusion
The sensory conduction velocities are all mildly slow particularly the median sensory conduction across the right wrist. The median distal motor latencies are prolonged but the median motor conduction velocities are normal. Ulnar motor conduction velocities across the elbows are slowed but normal elsewhere. Peroneal motor conduction velocity across the left fibular head is also slow.

Genetic test
Screening for a 1.4 megabase deletion of chromosome 17 which includes the PMP22 gene was positive.

Diagnosis

Hereditary neuropathy with liability to pressure palsies (HNPP).

Discussion

The long history of recurrent pressure induced transient sensory disturbances and the episode of foot drop suggest the possibility of HNPP. The neurophysiological findings of widespread abnormalities of nerve conduction with slowing particularly across points of compression with an emphasis on the right median nerve at the carpal tunnel, left ulnar nerve at the elbow and left peroneal nerve at the fibular head are also consistent with the diagnosis of HNPP.

Most patients with HNPP present with recurrent episodic pressure palsies but there are atypical presentations such as transient focal sensory symptoms and a scapuloperoneal syndrome. The presentation of pressure palsies in HNPP is similar to those of acquired compressive neuropathies so HNPP should be considered in patients with recurrent pressure palsies even in the absence of a family history. HNPP can affect the brachial plexus and if this is recurrent, hereditary neuralgic amyotrophy caused by a mutation in the SEPT9 gene should be considered. However, the very severe pain that occurs in hereditary neuralgic amyotrophy helps differentiate it from HNPP.

It is generally not difficult to differentiate HNPP from CMT as patients with the former give a clear history of recurrent pressure palsies. The phenotype can be very similar to CMT when HNNP patients have accumulated neurological deficits. The neurophysiological findings which are usually patchier in HNPP than in the common forms of CMT1 should enable distinguishing of the two conditions.

HNPP is an autosomal dominant condition usually caused by a deletion of the same 1.4 megabase portion (the region containing the PMP22 gene) of chromosome 17 that is duplicated in CMT1A. Point mutations in PMP22 rarely cause HNPP. An important diagnostic clue is that although patients may present with only one clinically affected nerve, there is always a more generalised but patchy demyelinating neuropathy on nerve conduction studies.

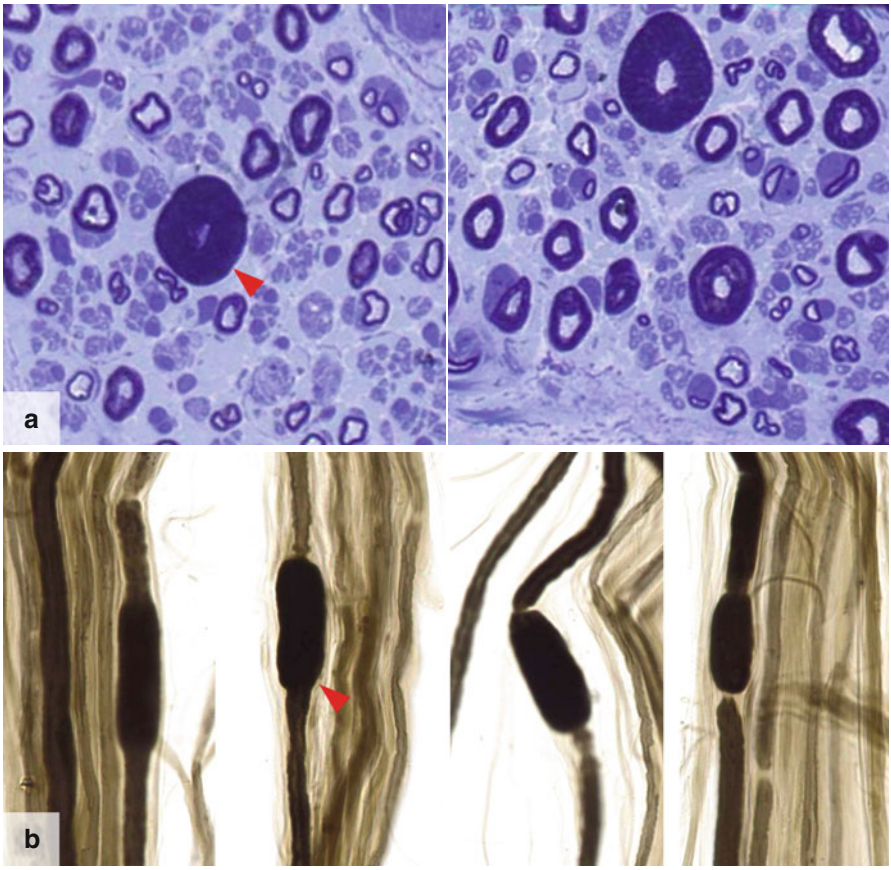

Fig. 24.1 Morphological appearances of sural nerve biopsy from a patient with hereditary neuropathy with liability to pressure palsies. Semithin resin section (**a**) stained with toluidine *blue* shows several large fibres with markedly thickened myelin sheaths (*red arrow* highlights one of the abnormal fibres). Teased nerve fibre preparation (**b**) stained with osmium tetroxide highlights frequent myelin thickenings – *tomacula* along individual myelinated fibres (*red arrow* highlights one *tomaculum*) in keeping with tomaculous neuropathy. Scale bar: 20 μm in (**a**) and 50 μm in (**b**) (Image courtesy of Zane Jaunmuktane and Sebastian Brandner)

Nerve biopsy may show evidence of demyelination and "tomaculous" (focal, sausage-like enlargement of the nerve) changes (see Fig. 24.1). A nerve biopsy is no longer needed in suspected cases of HNPP since genetic testing is widely available.

Patients with HNPP should be advised to avoid activities that will predispose them to pressure palsies such as prolonged sitting with legs crossed, resting on elbows on hard surfaces or tasks that require repetitive movements of the wrist. It is very important that patients inform their doctors about this condition if they are due to have surgery or give birth, during which patients may be in the same position for a prolonged time. Management of nerve palsies is usually conservative, for exam-

ple, an ankle-foot orthoses can improve the gait in a patient with foot drop and just as in acquired cases, a wrist splint can help if a patient with HNPP develops carpal tunnel syndrome.

Once the diagnosis of HNPP is established, genetic counselling should be offered and the patient informed that each child has a 50 % risk of inheriting the mutation. The condition is usually mild with appropriate avoidance of pressure.

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Case 25
Weakness in an Indian Man

Robin Howard

History

A 60 year old right handed Indian man presented with a 2 month history of worsening confusion and weakness. He had been aware of increasing unsteadiness of gait with several falls. For several months he had experienced weight loss, poor appetite, abdominal pain and constipation. He was admitted via A&E as he had become acutely confused and agitated with word finding difficulties and right sided facial droop. There was a past medical history of 'arthritis', hypertension, NIDDM and hypercholesterolaemia. Medications included aspirin, pravastatin, bendroflumethiazide, amlodipine and gaviscon. He was a non-smoker who drank 35 units alcohol/week.

Examination

On examination he was clinically anaemic. Systemic examination was unremarkable.

He was confused and became increasingly drowsy, developing a lobar pneumonia and klebsiella septicaemia for which he was intubated and ventilated. Following recovery 1 week later, he was noted to have marked facial and bulbar weakness. In the limbs, there was extensive wasting but no fasciculations. Tone was flaccid and there was severe distal weakness (grade 1–2/5) in the arms and legs with moderate limb girdle weakness (grade 4/5). He was areflexic. Co-ordination could not be assessed and sensation was normal.

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On systemic examination, bluish lines were seen along the margin of the gums, at the base of the teeth.

Investigations

Full blood picture - Hb 86 g/L (130–170), MCV 78.6 fL (80–99).

Blood Film - Microcytosis, ansocytosis and basophilic stippling. Serum lead level of 16 μg/dL (normal range <0.5).

Nerve conduction studies confirmed the presence of a severe axonal motor neuropathy.

Diagnosis

Lead neuropathy.

Further History

On detailed discussion with the patient and his wife, he described regular visits to a village in Gujarat where he obtained Ayurvedic herbal remedies for joint pains. Subsequent analysis of one of the tablets confirmed an extremely high lead content. The lead content per tablet was 21.4 mg (WHO lead intake/day 250 mcg/day in a 70 kg adult).

Treatment

He was treated with parenteral chelation therapy using calcium disodium EDTA. At 5 months follow up there was no facial or bulbar weakness and he was able to walk with one stick. He has continued to require intermittent chelation therapy.

Discussion

Adult lead poisoning can present with nonspecific symptoms and signs such as abdominal pain, constipation, irritability, difficulty concentrating, and anaemia.

Most cases are due to work place exposure such as smelting or manufacturing and use of batteries, pigments, paint, solder or lead alloys. Lead poisoning is

recognised to occur in those taking Ayurvedic medications and in those cooking or eating from lead-glazed tableware and cookware.

Acute clinical manifestations of lead toxicity are varied but the classical triad is abdominal pain ("lead colic") and constipation, anaemia (with basophilic stippling on blood smear) and neuropathy. Other features include joint/muscle aches, short-term memory problems and difficulty concentrating.

Chronic clinical manifestations include continued decline in neurocognitive function, nephropathy, hypertension, and increased risk of stroke and cardiovascular mortality. There may be a bluish discolouration of the gums just adjacent to the base of the teeth, often associated with periodontal disease.

Peripheral neuropathy frequently manifests with "wrist/ankle drop" due to axonal degeneration that primarily affects motor nerves. This may then worsen to involve the extensor and proximal muscles, usually in the upper limbs. There are usually no sensory signs (in contrast to other metal neuropathies).

In addition to taking an occupational/environmental history, blood lead level remains the mainstay of diagnosing lead toxicity. Bone lead concentration measured by x-ray fluorescence is a rapid, non-invasive measurement of lead in bone that is becoming increasingly standardised, although availability in most areas is limited. Neurophysiology may show evidence of motor axonal loss but in milder cases there may be prolonged distal latencies and occasionally mild slowing of NCV and sensory involvement.

Management of patients with elevated lead levels generally consists of removal of lead exposure and, in cases of high blood lead levels [usually >50 μg/dL (2.42 μmol/L)], consideration of chelation therapy to increase excretion.

Calcium disodium ethylenediaminetetraacetate (EDTA) is an older chelating agent, introduced in the early 1950s, which must be administered intravenously or intramuscularly, usually for a 3–5 day chelation period. It increases the urinary excretion of lead through the formation of non-ionizing salts. Treatment with CaEDTA should be performed in a hospital setting by clinicians experienced with chelation, in patients with normal renal function, and with careful monitoring of renal and other parameters. Penicillamine is also an effective chelating agent which can be given orally. DMSA (2,3-dimercaptosuccinic acid, succimer) is a newer oral chelation agent that is approved for the treatment of lead-poisoning in children, and has also been found to be effective in adults.

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Case 26
A Man with Episodes of Shoulder Pain and a Weak Arm

Mohamed Mahdi-Rogers, Matilde Laurá, and Mary M. Reilly

History

A 69 year old man presented with a history of recurrent neurological symptoms, which started when he was aged 35 years. His first problem was excruciating pain in the left shoulder following a flu-like illness. The pain lasted for about 2 weeks after which he was left with left arm weakness and scapula winging which gradually recovered. He had identical symptoms in the right arm 2 years later, again following a flu-like illness, and this took a year to recover. He then remained completely well until aged 65 when he had a severe flu-like illness and subsequently developed left recurrent laryngeal nerve palsy. This did not recover but he managed to compensate well, maintaining a reasonably good voice. Three years following the laryngeal nerve palsy, following an infected ulcer of the right thumb, he developed severe right sided shoulder pain similar to previous episodes which lasted 4 or 5 days this time without associated weakness.

At the time of presentation, he also reported a 12 month history of sensory disturbance in the median nerve distribution of the left hand and in the ulnar distribution of the right hand which occurred only when he was lying on his back in bed at night.

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He was of British descent with no family history of neurological disease except for one son aged 39 years, who had an episode of brachial neuritis aged 17 years.

Examination

Cranial nerve examination was normal.

The APB muscle was wasted bilaterally: left hand worse than right. There was mild weakness of the first DIO muscle at MRC grade 4/5 bilaterally and of APB which was graded 4/5 on the right and 3/5 on the left. Supraspinatus and infraspinatus were also weak at grade 4/5. Tinel's sign was positive over the left median nerve at the level of the carpal tunnel. Lower limb power was normal. All reflexes were present and symmetrical, and plantars were down-going. Vibration sense was impaired to the knees bilaterally but other sensory modalities were preserved. His gait was normal. Chest examination revealed decreased air entry at the right base.

Investigations

Chest X-ray revealed a raised right hemi-diaphragm.

Neurophysiology (Tables 26.1 and 26.2)

Table 26.1 Sensory and mixed nerve conduction studies

	Amplitude (μV)	Onset latency (ms)	Peak latency (ms)	Conduction velocity m/s
Right Median (F3-wrist)	3.0	3.9	4.4	42.5
Right Ulnar (F5-wrist)	5	2.8	3.3	46.5
Right Radial (forearm-wrist)	15	1.9	2.5	51.5
Left Median (F3-wrist)	Absent			
Left Ulnar (F5-wrist)	4	2.7	3.4	44.5
Right Sural (calf-ankle)	Absent			
Right Superf. peroneal (calf-ankle)	5.0	2.8	3.6	38.5
Left Sural (calf-ankle)	6.0	3.8		37.5

Table 26.2 Motor nerve conduction studies

	Right	Left
Median (SE on APB)		
DML	4.3 ms	13.3 ms
CV (wrist-elbow)	46 m/s	–
CV (elbow-axilla)	48 m/s	–
CMAP (wrist)	5.4 mV	0.1
CMAP (elbow)	4.7 mV	–
CMAP (axilla)	4.8 mV	–
Minimal F-wave latency (wrist)	32.5 ms	–
Ulnar (SE on ADM)		
DML	2.7 ms	2.9 ms
CV (wrist-below elbow)	51 m/s	–
CV (around elbow)	48 m/s	–
CV (wrist-above elbow)	–	49 m/s
CV (above elbow-axilla)	53 m/s	–
CMAP (wrist)	9.9 mV	9.6 mV
CMAP (below elbow)	7.5 mV	–
CMAP (above elbow)	7.6 mV	8.8 mV
CMAP (axilla)	7.4 mV	–
Minimal F-wave latency (wrist)	31.7 ms	–
Common Peroneal (SE on EDB)		
DML	5.0 ms	–
CV (fib neck-ankle)	40 m/s	–
CMAP (ankle)	0.9 mV	–
CMAP (fib neck)	0.8 mV	–
Second lumbrical/interosseous DML		
Right Median	8.3 ms	–
Right Ulnar	2.8 ms	–

Conclusion

The left median SNAP was absent. Other sensory responses in the upper and lower limb were small or at the lower limit of normal. Distal motor latency to left APB was prolonged with a small CMAP. The distal motor latency to APB on the right was normal. Forearm motor conduction velocities were normal. Distal lower limb motor responses were small.

Concentric needle EMG showed only minor changes suggestive of denervation in the distal muscles innervated by the ulnar nerve, with essentially normal findings elsewhere.

Genetic tests

Full sequencing of the septin 9 (SEPT9) gene including assessment for rearrangements and deletions found no mutation. There were no deletions or point mutations in the PMP22 gene.

Diagnosis

Hereditary Neuralgic Amyotrophy and left carpal tunnel syndrome.

Discussion

The patient had a 34 year history of recurrent episodes of brachial neuritis. The multiple episodes of brachial neuritis made hereditary neuralgic amyotrophy (HNA) the most likely diagnosis, the history of a similar event in a son further supporting this impression. As in this patient, the typical age of onset of symptoms in HNA is during the second to third decades of life, but can be earlier or later.

Hereditary neuropathy with liability to pressure palsies (HNPP), which is another cause of recurrent focal neuropathies, was considered as a differential diagnosis but the presence of pain made it unlikely and subsequent genetic testing confirmed that the patient did not have a deletion or point mutation in the PMP22 gene. The preceding infection before most of the episodes is also more common in neuralgic amyotrophy. If this patient was seen after a single episode of brachial neuritis, differential diagnoses would have included cervical radiculopathy, vasculitic mononeuritis multiplex or a shoulder joint pathology such as glenohumeral joint bursitis, but the acute onset of pain, patchy sensory and motor symptoms and the predilection for the brachial plexus in neuralgic amyotrophy would have helped to differentiate it from these other conditions.

Patients start to recover within weeks to months after the onset of symptoms but studies of long term follow-up have shown that more than half of patients have residual weakness, fatigue and pain that affects their quality of life. The long thoracic nerve is most commonly affected leading to winging of the scapula, which this patient had after one of his episodes. Some patients may have involvement of nerves outside the brachial plexus such as the phrenic and recurrent laryngeal nerves. Isolated cranial nerve palsies affecting the facial and hypoglossal nerves have also been reported. The lumbosacral plexus can also be affected. In some families, minor dysmorphic features are associated with HNA, including hypotelorism, epicanthal folds, short stature and cleft palate. Episodes of brachial neuritis or nerve palsies can occur after a recent bacterial or viral infection, vaccination, surgery and parturition.

HNA is an autosomal dominant condition with high penetrance. The only known cause is a defect in the SEPT9 gene (missense mutations or rearrange-

ments). This patient did not have a mutation in SEPT9 despite full sequencing and MLPA but this is not inconsistent with HNA as only about half of the HNA families studied had a defect in the SEPT9 gene, suggesting that mutations in other genes can cause HNA.

There is no diagnostic test for HNA after a single episode of brachial neuritis, and investigations are often carried out to exclude other diagnoses. In cases were there are risk factors, patients should have serological tests for Lyme disease or HIV. Imaging of the brachial plexus often shows T2-weighted hyperintensity within the brachial plexus. MR imaging of the cervical spine may be indicated to exclude multi-level cervical radiculopathy. In patients with lower brachial plexopathy, CT chest is required to exclude a Pancoast tumour. This patient did not have cross-sectional imaging, but a chest x-ray showed a raised hemidiaphragm likely caused by his phrenic nerve palsy.

A recent Cochrane review did not identify any randomised controlled trials in neuralgic amyotrophy (acquired or genetic). There is therefore no evidence based treatment for neuralgic amyotrophy. An open label study reported faster recovery and a reduction in pain in patients given oral prednisolone within the first month of the disease. Optimal pain management is crucial as this is usually very severe and debilitating. Patients often require opiates and agents with proven efficacy in neuropathic pain such as gabapentin, pregabalin and tricyclic antidepressants. Rehabilitation with input from physiotherapy and occupational therapy is sometimes required.

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Case 27
A Man with Painful Feet and Hand Ulcers

Mohamed Mahdi-Rogers, Matilde Laurá, and Mary M. Reilly

History

A 49 year old man presented at age 29 with numbness and episodes of shooting pain in the extremities. Numbness had started in the hands but within 6 months he began to experience symptoms in both feet. He also tripped while walking. He was well at birth and had attained normal developmental milestones. He had no problems at school. He developed bilateral foot drop within 2 years of his initial presentation. There was no history of autonomic dysfunction such as erectile dysfunction, urinary and bowel symptoms or orthostatic dizziness.

There had been very gradual progression of sensory symptoms. There was a history of recurrent hand ulcers since the onset of symptoms.

There was no other significant medical history and he was taking no medication. He drank excessive amounts of alcohol when he first presented but had since become teetotal.

He had two sons with no neurological problems but his daughter developed symptoms similar to his, aged 17 years. His mother had a painful sensory neuropathy.

Examination

Blood pressure was 120/60 with no postural drop. Cranial nerve examination was normal.

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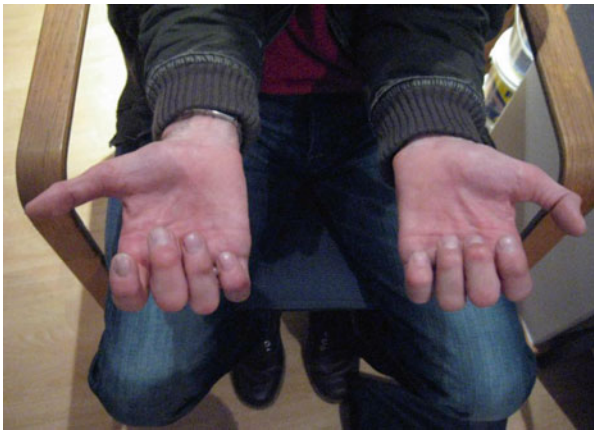

Fig. 27.1 The patient's hands showing wasting of small muscles, contraction of finger flexors and a purplish discolouration

There was severe wasting of the distal upper limbs and from the thighs distally in the lower limbs. There was thinning of the small muscles of the feet but no pes cavus. There were contractions of the finger flexors of both hands (Fig. 27.1) and three finger ulcers. There were two bruises on the toes. Peripheral nerves were not thickened.

There was marked distal weakness in the upper and lower limbs bilaterally. Upper limb reflexes were present, knee and ankle jerks absent and both plantar reflexes down-going. Vibration sense was impaired to both ankles, to the right wrist and was normal in the left upper limb. Proprioception was impaired in the fingers and to the right ankle and left knee. Pinprick was reduced up to the elbows and to the top of the thighs. Romberg's sign was positive, and his gait was ataxic.

Investigations

Blood tests including fasting glucose, HBA1C, vitamin B12, methylmalonic acid, homocysteine, vitamin B6, vitamin B1, folate and ANA were all normal. No paraprotein was detected.

Neurophysiology (Tables 27.1 and 27.2)

Table 27.1 Sensory nerve conduction studies

	μV
Right Median (F3-wrist)	Absent
Right Ulnar (F5-wrist)	Absent
Right Radial (forearm-wrist)	Absent
Left Radial (forearm-wrist)	Absent

Table 27.2 Motor nerve conduction studies

	Right	Left
Median (SE on APB)		
DML	5.8 ms	5.9 ms
CV(wrist-elbow)	31 m/s	24 m/s
CMAP(wrist)	0.7 mV	1.1 mV
CMAP(elbow)	0.5 mV	1.1 mV
Ulnar (SE on ADM)		
DML	4.1 ms	–
CV(wrist-below elbow)	32 m/s	–
CV(around elbow)	27 m/s	–
CMAP(wrist)	1.3 mV	–
CMAP(below elbow)	1.0 mV	–
CMAP(above elbow)	0.8 mV	–
Common Peroneal (SE on TA)	Absent	–

Conclusion
Sensory potentials are absent throughout. Motor conduction velocities are all slightly slow with small CMAPs.

Genetic test
Sequencing of the SPTLC1 gene identified the C133W mutation.

Diagnosis

Hereditary sensory and autonomic neuropathy type 1 (HSAN1).

Discussion

The strong family history of neuropathy suggests the likelihood of a genetic neuropathy. The prominent sensory involvement with pain and recurrent ulcers makes hereditary sensory and autonomic neuropathy (HSAN) more likely than CMT in which motor involvement predominates.

Genetic testing subsequently identified the C133W mutation in the SPTLC1 gene, which is the gene that causes hereditary sensory and autonomic neuropathy type 1 (HSAN1). His mother and other affected members of the family had the same mutation.

The hereditary sensory and autonomic neuropathies are rare, genetically and clinically heterogeneous and have been traditionally classified into five types based on clinical presentation. Patients generally have severe sensory impairment and can present with autonomic disturbances including fever, anhidrosis, blood pressure fluctuations and gastrointenstinal disturbances. Motor involvement may also be

present. Sensory loss may lead to complications such as recurrent ulceration, osteomyelitis and amputations.

The commonest form of hereditary sensory and autonomic neuropathy in the UK is HSAN1 caused by mutations in the SPTLC1 gene. The term hereditary sensory neuropathy (HSN) is more appropriate as there is usually no autonomic involvement. As seen in this case, British patients with the C133W SPTLC1 mutation have severe sensory loss and variable motor involvement which can be moderate or severe. Neurophysiology is usually consistent with an axonal sensory and motor neuropathy although some individuals such as this patient have slowing of motor conduction velocities in the demyelinating range. It can also be challenging to differentiate HSAN1 secondary to SPTLC1 mutations from CMT2B caused by RAB7 mutations but the lancinating neuropathic pain in patients with SPTLC1 mutations can be a pointer to this diagnosis. RAB7 mutations are also much rarer in the British population.

The most important issue in the management of patients with HSAN1 is prevention of complications occurring secondary to severe sensory loss. Educating patients about foot-care is crucial in this regard. Patients may require prompt treatment with antibiotics if they develop infected ulcers. As for all genetic conditions, appropriate counselling is essential.

Other forms of HSAN are rarer. HSANII is autosomal recessive. Its onset is much earlier compared to HSAN1 which typically begins in the second or third decade of life. HSANII is a severe sensory neuropathy with prominent sensory complications caused by mutations in the WNK1 gene. There have been recent reports of mutations in the FAM134B and KIF1A genes causing the HSANII phenotype. The Riley-Day syndrome is a distinctive autosomal recessive neuropathy, which occurs in Ashkenazi Jews. Autonomic dysfunction is the prominent feature of Riley-Day syndrome, but it also affects the peripheral nervous system, especially the sensory nerves. It is caused by mutation in the IKBKAP gene. HSAN IV and V are both autosomal recessive neuropathies characterised by congenital insensitivity to pain. HSAN IV (also called congenital insensitivity to pain with anhidrosis) presents with a severe sensory neuropathy, anhidrosis and mental retardation. The causative gene is NTRK1. HSAN V is similar but patients do not have the mental retardation or marked anhidrosis seen in NTRK1 and also NGFb mutations.

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Case 28
A Psychologist with Wrist Drop

Matthew R.B. Evans, Rahul Phadke, and Hadi Manji

History

A 26 year old right handed man presented with an 18 month history of isolated left hand weakness. Over this period, he had noticed that after using the left hand, the 4th and 5th fingers would become weak causing him to drop objects. There were no sensory symptoms, pain, cramps or muscle spasms. There was no significant past medical or family history.

Examination

Cranial nerve examination was normal.

Left upper limb examination revealed wasting over the dorsal aspect of the hand with weakness of extension in all fingers and the thumb, (MRC grade 4-/5). There was mild weakness of wrist supination. Sensory examination was normal throughout. Reflexes were all present and symmetrical. Lower limb and right upper limb examination was normal. When seen several months later, he had developed mild wrist extension (4/5) weakness though the remainder of the neurological examination remained unchanged.

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The clinical examination localises the lesion to the left posterior interosseous nerve (PIN). Lack of sensory findings is consistent given that the PIN is a pure motor nerve.

Investigations

Blood tests were normal, including full blood picture, renal and liver function, random glucose, CRP, ESR, ANA, ANCA, ENA and Anti-GM1 antibodies.

Neurophysiology confirmed the clinical suspicion, with findings consistent with a severe, incomplete lesion of the left posterior interosseus nerve, the lesion site localised to the level of the supinator muscle. There were reduced CMAP amplitudes of the left radial nerve to extensor indicis proprius without clear focal slowing. Nerve conduction studies were otherwise normal. There was active denervation of all muscles innervated by the posterior interosseous nerve including EDC and EIP. There was no denervation in brachioradialis, triceps and ECR.

Forearm MR imaging with gadolinium revealed a nodular, minimally enhancing lesion arising from the posterior interosseous nerve just distal to the radiocapitellar joint. The neuroradiological findings were thought typical of intraneural perineurioma (Fig. 28.1).

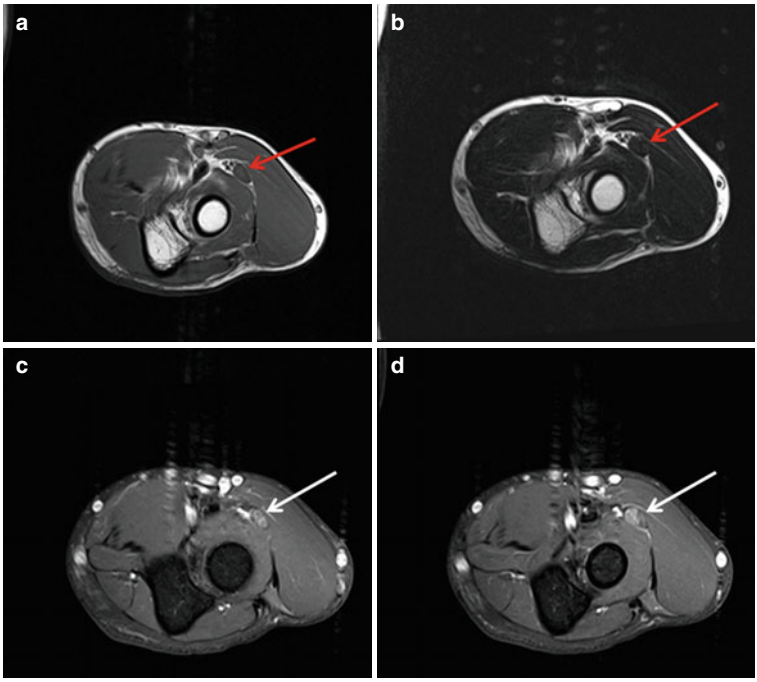

Fig. 28.1 MRI left elbow – T1w (**a**), T2w (**b**) and T1 post-gadolinium (**c**, **d**). A 10 mm, nodular, minimally enhancing mass is seen to arise from the left posterior interosseous nerve (*white arrow*), just distal to the radiocapitellar joint, as it courses between the brachioradialis and the supinator. The mass appears homogenous and hypointense on T1 and T2 weighted images (*red arrow*)

The left PIN was explored and the peripheral nerve surgeon noted the possibility of 'hypertrophic neuropathy' at the level of the supinator.

Posterior interosseous nerve biopsy revealed findings consistent with an intraneural perineurioma (A representative biopsy of a median nerve perineurioma is illustrated in Fig. 28.2).

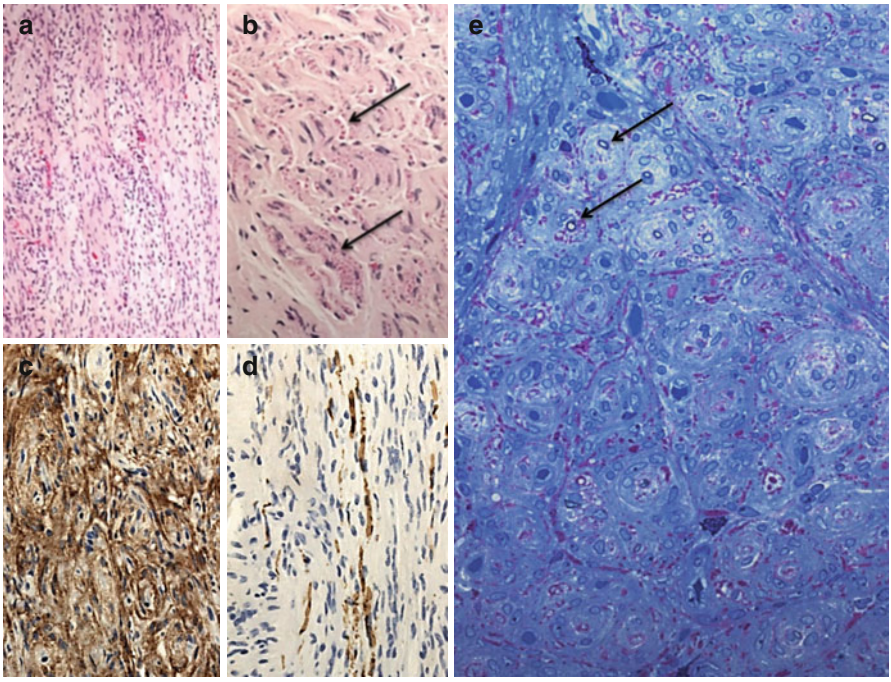

Fig. 28.2 Representative biopsy of a median nerve perineurioma is illustrated. A haematoxylin and eosin stained longitudinal section through the nerve shows an expansile lesion at one end (**a**) comprising cytologically bland spindle cells proliferating and expanding the fascicle, effacing the axons. Myelinated nerve fibres (*arrows*) are seen coursing along the fascicle at the end distant to the lesion (**b**). Epithelial membrane antigen, a marker of perineurial cells strongly labels the spindle cell proliferation (**c**) whereas occasional surviving axons are highlighted by immunolabeling for neurofilaments (**d**). A resin semi-thin transverse section through the lesion stained with MBA-BF reveals tightly packed 'onion bulb' formations of concentric layers of proliferating perineurial cells. Some of these structures contain myelinated fibres at their centre (*arrows*) (**e**).

Diagnosis

Left posterior interosseous intraneural perineurioma.

Discussion

The initial consideration in this case is the differential diagnosis of a subacute, painless, posterior interosseous mononeuropathy.

PIN lesions can be classified into non-compressive and compressive. In terms of the former, inflammatory processes should be considered. These include nerve ischaemia or infarction due to vasculitis though isolated, painless PIN involvement over this extended time period would be unusual. In addition there are no systemic features and blood tests are normal. Brachial neuritis may present with an isolated mononeuropathy however the history here is not in keeping with that diagnosis.

Multifocal motor neuropathy with conduction block (MMNCB) is an autoimmune inflammatory condition with antibodies directed against a component of the peripheral nerve myelin sheath. It can present with a mononeuropathy which may affect the PIN. Although wasting can develop; prior to development of axonal loss, weakness in the presence of normal muscle bulk is one of the hallmarks of this condition. In this case, anti-GM1 antibodies were negative, and conduction block was not detected on nerve conduction studies.

Individual nerves are rarely the site of direct neoplastic infiltration, though painless or painful involvement has been reported with both lymphoma and leukaemia. Motor neuron disease may initially mimic PIN palsy. Finally, it is important to consider mechanical limitations to finger extension in the differential diagnosis. Extensor tendon rupture or subluxation may mimic a PIN palsy clinically.

It is important to note that although MR imaging in this case, suggests a compressive lesion; non-compressive aetiologies should always be considered, given that MRI findings in some inflammatory neuropathies, may be indistinguishable from those seen in mass lesions.

In terms of the latter, PIN compression by an intrinsic or extrinsic mass is well described. One may expect pain with a compressive lesion, although this is not always the case. Weakness of all finger extensors rather than of individual fingers may be a pointer toward a structural lesion rather than an inflammatory one, though this is not a specific finding. Compression may be from adjacent anatomical structures in the forearm, the patient presenting with progressive symptoms, and the lesion clinically localised to the level of the arcade of Frohse. Benign nerve tumours including lipoma, neurofibroma, intraneural perineurioma, schwannoma and angiomyofibromas should be considered. Other causes include ganglion cysts arising from the proximal radioulnar joint, elbow joint septic arthritis and peri-elbow rheumatoid synovitis. Of interest, cases of intermittent symptoms attributable to PIN compression have also been reported in a violinist, dairyman and a swimmer

amongst others; thought to be due to prolonged repetitive forearm movements or to repetitive forearm pronation and supination.

Intraneural perineurioma, also known by several other names including hypertrophic neuritis, is a benign neoplasm of usually, a single peripheral nerve, with unique morphologic, ultrastructural, and immunoreactive features. Given its' relative rarity, maintaining a high index of suspicion is critical to diagnosis. In their large, retrospective series of 32 cases with pathologically proven intraneural perineurioma, Mauermann et al noted a median age at onset of 17y with a median lag time to diagnosis of 3 years. Most presented with weakness or wasting, whilst only 3 had numbness or pain prior to weakness developing. Presentation was most often with a mononeuropathy though 5 presented with a plexopathy. Mauermann et al found the sciatic nerve or its' branches, followed by radial, ulnar and median nerves to be the most frequently affected.

Neurophysiology confirms focal peripheral nerve involvement in most cases, however given the sometimes very proximal location of the lesion, MR imaging has become an invaluable diagnostic tool, revealing a characteristic pattern of T1 isointense, T2 hyperintense, and avidly contrast enhancing most often fusiform nerve enlargement. Definitive diagnosis is made on targeted nerve fascicular biopsy (Fig. 28.2), though this may not be necessary if the clinical picture, neurophysiology and imaging are congruent.

Though benign, intraneural perineurioma does progress slowly, and may cause significant morbidity related to loss of sensorimotor function. Tumours have not been shown to spread to new nerves, and there has been no report of malignant transformation. Surgical treatment options include resection of tumour with interpositional autologous nerve grafting, though this may cause further sensorimotor deficit. Tendon transfer may be considered in certain cases, though often a watchful approach is preferred.

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Part II
Muscle Disorders

Case 29
Longstanding Drooping Eyelids

Robert D.S. Pitceathly, Shamima Rahman, and Michael G. Hanna

History

A 64 year old woman originally presented at the age of 55 years to the neurology clinic with bilateral ptosis, ophthalmoplegia, fatigue, and exercise intolerance. Her ptosis was first noticed in her 30s and had progressively worsened necessitating bilateral anterior levator resection. Her referral was prompted by a more recent history of vertical diplopia whilst watching television which was worse when she was tired towards the end of the day. She had removal of bilateral congenital cataracts and primary amenorrhoea. There was no family history of neuromuscular disease.

Examination

She was unable to stand from a low seated chair with her arms crossed. Her gait was ataxic and Romberg's test was negative. There was head titubation. She had bilateral ptosis and almost complete ophthalmoparesis. There was no evidence of retinopathy. Swallowing and speech were normal and there was mild neck flexor and extensor

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weakness. In the limbs, there was mild proximal upper and lower limb weakness. Reflexes were intact and plantar responses were down-going. There was mild bilateral upper limb ataxia which was predominantly left sided. Sensory examination was normal. Cardiovascular examination was normal.

Investigations

Random blood glucose, thyroid function, plasma lactate and creatine kinase were normal. Nerve conduction studies were normal and electromyography showed mild myopathic changes in the facial and upper limb muscles. Muscle biopsy revealed frequent cytochrome *c* oxidase deficient fibres as well as ragged red fibres consistent with mitochondrial disease (Fig. 29.1). Southern Blot analysis confirmed multiple mtDNA deletions (Fig. 29.1g) and DNA analysis of POLG 1 demonstrated compound heterozygous missense mutations: H227L + D890V.

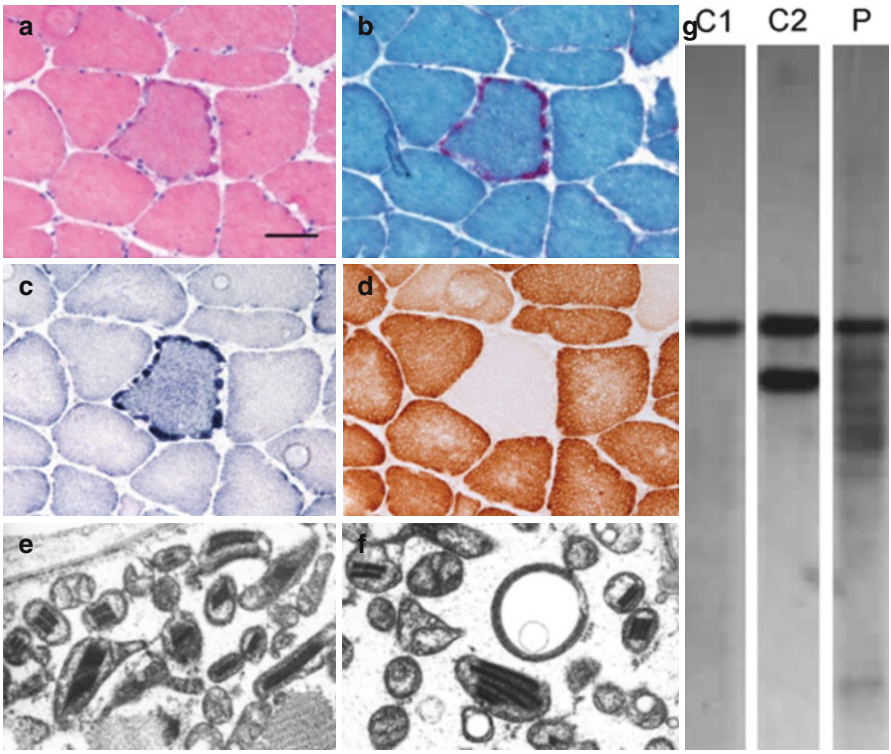

Fig. 29.1 Ragged red fibre visualised in H&E (**a**), Gomori trichrome (**b**) and succinate dehydrogenase (**c**) preparations. Histochemical staining for cytochrome *c* oxidase revealed significant numbers of fibres with deficient enzyme activity (**d**). Ultrastructural examination confirmed structurally abnormal mitochondria with type I paracrystalline inclusions (**e**) and ring forms (**f**). Bar in A represents 50 μm in A—D and 500 nm in E and F. Southern blot analysis of mitochondrial DNA extracted from muscle tissue using PvuII restriction endonuclease showing normal control subject in lane 1 (*C1*); patient with single deletion of mitochondrial DNA in lane 2 (*C2*); and patient with multiple deletions of mitochondrial DNA in lane 3 (*P*) (**g**)

Diagnosis

POLG-related mitochondrial disease

Discussion

POLG is a nuclear gene which encodes the catalytic subunit of the only known animal mitochondrial DNA (mtDNA) polymerase. Mutations in POLG disrupt mtDNA replication and can cause multiple large-scale mtDNA deletions, mtDNA depletion (reduced mtDNA copy number), and point mutations in mtDNA, and are associated with an heterogeneous clinical spectrum. The most common manifestation seen in adults with POLG mutations is chronic progressive external ophthalmoplegia (CPEO) with secondary accumulation of multiple mtDNA deletions. POLG mutations may be inherited in an autosomal dominant or recessive manner or arise as sporadic de novo dominant mutations. The main differential diagnosis of CPEO due to mitochondrial disease is a single mtDNA deletion and the m.3243A > G point mutation in mtDNA. Other causes of CPEO include oculopharyngeal muscular dystrophy, myasthenia gravis, and some cases of congenital myopathy and muscular dystrophies.

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Case 30
Drooping Eyelids Plus

Yehani Wedatilake and Shamima Rahman

History

A 17-year-old female of European descent presented with gradual onset of droopy eyelids which was first noted 5 years prior to presentation. She had a longstanding history of poor weight gain and growth from early childhood. She also described generalised fatigue.

She was born by spontaneous vaginal delivery at 39 weeks of gestation after a normal pregnancy and her birth weight was 3.2 kg. There were no neonatal problems and she achieved her developmental milestones appropriately throughout childhood. Menarche was at 16 years. She was the younger child of healthy unrelated parents and her 19 year old brother did not report clinical problems. There was no family history of neuromuscular disease.

Examination

Neurological examination demonstrated small muscles throughout her body, her weight was 28.5 kg and her BMI 12. Her tandem gait was imbalanced. Romberg's test was negative. In her limbs, muscle tone was normal but mild weakness (MRC grade 4/5) was noted on neck flexion and hip flexion. Tendon reflexes were normal. She had bilateral ptosis and restricted extraocular movements bilaterally. There was severe limitation of up gaze, moderately limited down gaze and relative sparing of lateral gaze (Fig. 30.1). On fundoscopy there was "salt and pepper" pigmentary retinopathy. Her hearing was normal.

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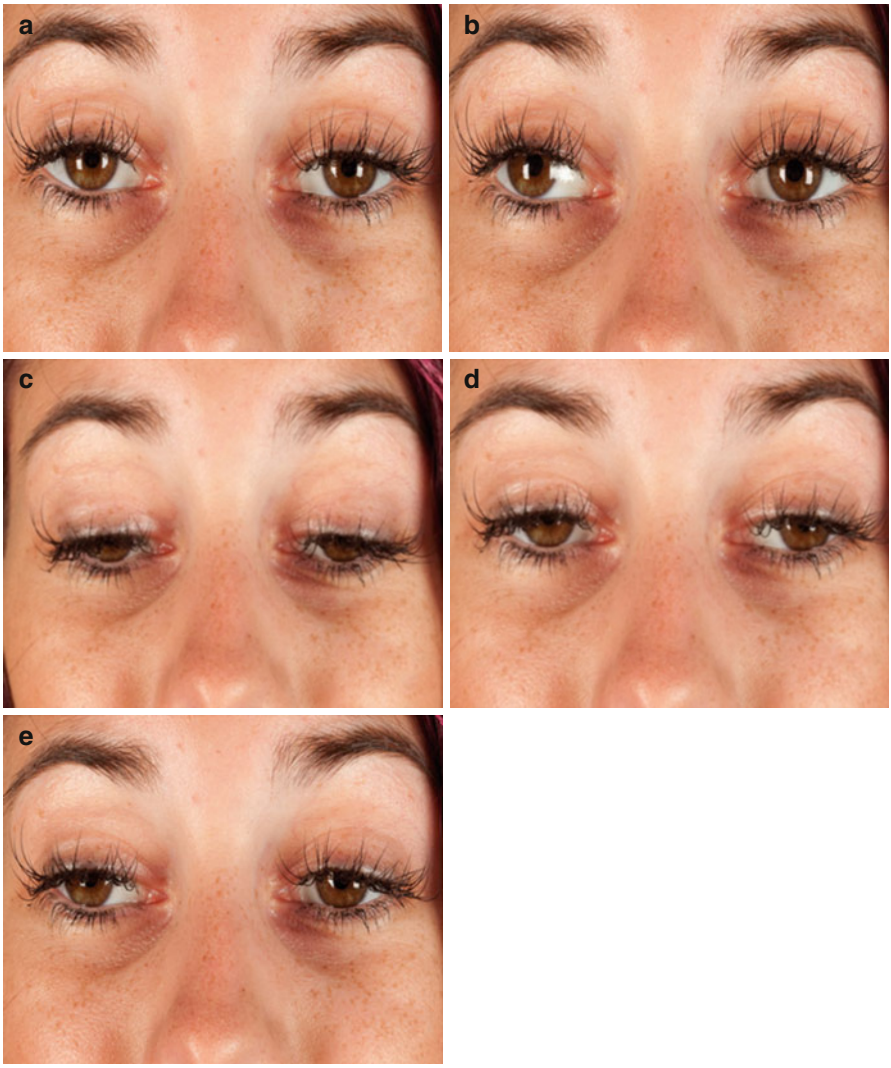

Fig. 30.1 Bilateral ptosis and external ophthalmoplegia in Kearns-Sayre Syndrome: bilateral partial ptosis (**a**) with restriction of ocular movements in all directions of gaze as patient attempts to look up (**b**) down (**c**) left (**d**) and right (**e**)

Investigations

The results of blood, cardiac, neuro-imaging and muscle investigations are summarised in Table 30.1.

Screening for large-scale mitochondrial DNA (mtDNA) rearrangements, mtDNA deletions and the common mtDNA point mutations m.3243A>G, m.8344A>G and m.8993 T>G/C was negative in DNA extracted from blood. Muscle biopsy was

Table 30.1 Investigations in a teenager with ophthalmoplegia and pigmentary retinopathy

Investigation	Value (reference range)
Blood lactate	**4.3–6.9 mmol/L**(<1.65)
Creatine kinase	137 IU/L (26–140)
Plasma glucose	4.9 mmol/l (3.9–5.8)
Plasma alanine	**819 µmol/L** (225–560)
Plasma acylcarnitine profile	Normal profile
TSH	1.16 mIU/L (0.27–4.20)
Free T4	15.1 pmol/L (12.0–22.0)
ECG	Normal sinus rhythm
Echocardiogram	Normal cardiac structure and function
MRI brain	Normal intracranial appearances, with no evidence of brain atrophy or white matter lesions
Muscle histology	Ragged-red and cytochrome *c* oxidase negative fibres
Muscle mitochondrial respiratory chain enzymes (expressed as ratio to citrate synthase)	
Complex I (NADH ubiquinone oxidoreductase)	**0.064** (0.104–0.268)
Complexes II + III (Succinate cytochrome *c* reductase)	0.112 (0.040–0.204)
Complex IV (Cytochrome *c* oxidase)	0.024 (0.014–0.034)

therefore performed at 17 years. This demonstrated ragged-red and cytochrome oxidase (COX)-negative fibres (Fig. 30.2), which were suggestive of a mitochondrial disorder. Long-range PCR of muscle DNA demonstrated a large-scale mtDNA deletion, which was confirmed by Southern blot analysis, and also detected in DNA extracted from urinary epithelial cells.

Diagnosis

Kearns-Sayre syndrome with genetically confirmed large-scale mt DNA deletion in muscle.

Discussion

Kearns-Sayre Syndrome (KSS) is a mitochondrial disorder, which is defined by the triad of onset before 20 years of age, progressive external ophthalmoplegia and pigmentary retinopathy. In addition, at least one of the following is usually present including a cardiac conduction defect, high CSF protein or cerebellar ataxia. There is often multi-system involvement, which may include short stature, diabetes mellitus, hypoparathyroidism, growth hormone deficiency, sensorineural deafness, dementia, renal tubular acidosis, cerebral folate deficiency, myopathy and

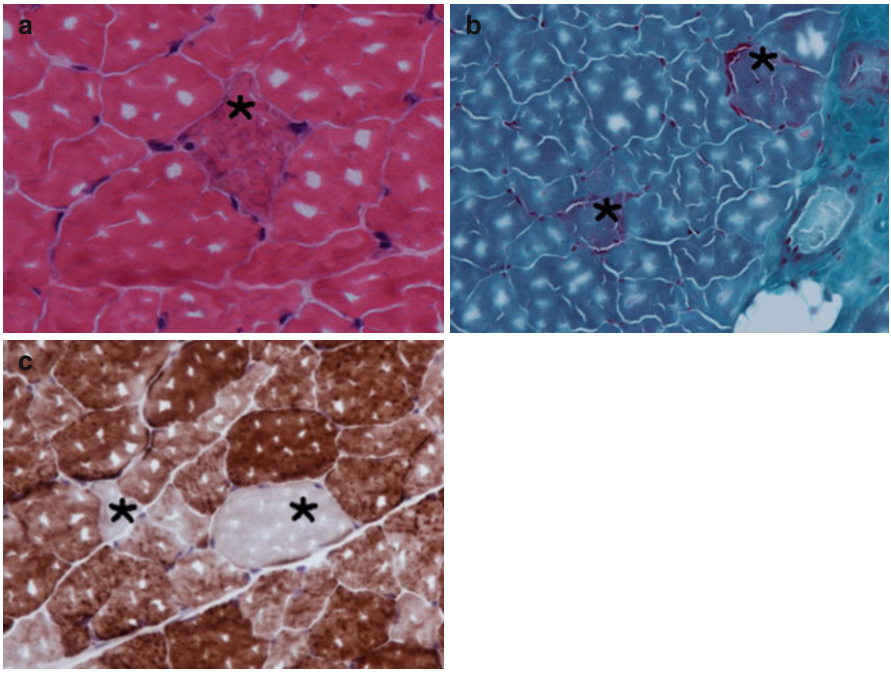

Fig. 30.2 Muscle histology and histochemistry: Characteristic ragged red fibres evident on Hematoxylin–Eosin staining (**a**) and modified Gomoritrichrome staining (**b**). Cytochrome *c* oxidase (COX) staining demonstrated pale COX negative fibres (**c**). Abnormal fibres indicated by *asterisks* (Images courtesy of Dr Thomas Jacques)

oesophageal dysmotility. Patients with KSS often have a very gradual onset of bilateral symmetrical ophthalmoplegia and diplopia. Muscle histology typically shows ragged-red fibres and respiratory chain enzyme analysis may reveal reduced activity of one or more of the enzyme complexes containing mtDNA encoded subunits.

Approximately 90 % of patients with KSS have a single large mtDNA deletion. Varying amounts of normal and "deleted" mtDNA are found in different tissues (known as 'heteroplasmy'), and the deletion may not be detectable in blood cells. It is therefore usually necessary to screen muscle mtDNA for deletions using the techniques of long-range PCR and Southern blot analysis. Interestingly, recent studies have indicated that it may be possible to detect mtDNA deletions in urinary epithelial cells from affected patients, even in cases where they cannot be detected in blood. The mtDNA deletion in KSS is almost always sporadic and occurs *de novo* either in the mother's oocyte or in the embryo. Consequently,the risk of recurrence within a family is extremely low and there is no family history.

Clinical follow up should involve surveillance for endocrine disorders, diabetes mellitus, deafness and heart block. Treatment is supportive with eyelid surgery for ptosis, hearing-aids or cochlear implants for sensorineural deafness and cardiac pacing for heart block. Coenzyme Q_{10} may be prescribed, as some patients have

reported subjective improvement in their symptoms. Individuals with low CSF folate should be supplemented with folinic acid, since folate does not cross the blood–brain barrier.

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Case 31
Neither One nor the Other

Umesh Vivekananda and Rosaline Quinlivan

History

A 21 year old gentleman first presented to paediatric services at the age of two. His birth and early developmental milestones were normal and he walked at 1 year but could not jump at presentation. During childhood his motor function steadily deteriorated and he developed lower limb weakness. He did not develop a scoliosis during his childhood years. He can currently walk 10–20 m without aids but has a wheelchair for outdoor use. He does not have respiratory symptoms and does not use ventilatory support. At the age of 13 years, he was noted to have minimal cardiomyopathy with left ventricular inferoposterior hypokinesia on echocardiogram and an ejection fraction of 31 %, for which he takes an ACE inhibitor. There is no family history of a neuromuscular disorder.

Examination

He had short stature, with thin translucent skin and fungal nail infections. He demonstrated no Cushingoid features or cataracts. Cranial nerve examination was normal apart from mild neck flexion weakness MRC grade 4/5. There was no evidence of scoliosis. He had symmetrical proximal upper limb weakness with shoulder

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abduction MRC grade 4–/5 bilaterally and elbow flexion and extension grade 4/5 bilaterally. In the lower limbs he had fixed flexion deformity of both knees, 20° on the left and 10° on the right. There was more marked symmetrical proximal weakness with hip flexion MRC grade 2/5 bilaterally, hip abduction grade 4/5 bilaterally, hip adduction grade 2/5 bilaterally and hip extension grade 2/5 bilaterally. His FEV1 sitting was 2.03 L and FVC 2.04 L. He was normotensive with a blood pressure of 125/70 mmHg.

Investigations

At 7 years of age his creatine kinase was 29,080 IU/L (normal range 55–170 IU/L) and he had a left quadriceps muscle biopsy which demonstrated dystrophic changes with complete absence of sarcolemmal dystrophin (for all three isoforms) demonstrated with immunostaining, with the exception of a few isolated revertant fibres.

Genetic Studies

Frame-shift duplication of exon 2 in the dystrophin gene (Xp21)

Diagnosis

Dystrophinopathy with an intermediate phenotype, but muscle biopsy consistent with Duchenne muscular Dystrophy.

Treatment

This patient commenced steroid therapy when he was 11 years of age at a dose of 0.75 mg/kg/day, which has gradually been reduced to 0.1 mg/kg/day because of side-effects. He remains ambulant, with better motor function than would be expected from someone with complete absence of dystrophin on muscle biopsy, with neither severe enough for a typical Duchenne nor mild enough for a typical Becker phenotype, otherwise called “intermediate phenotype”. He was diagnosed with steroid induced osteoporosis aged 15, and as a result has sustained a number of fractures including of the femur and vertebrae. This is currently

managed with regular bisphosphonate infusions and calcium and vitamin D supplementation. In addition he developed glycosuria aged 18, which resolved with reduction of steroid dose.

Discussion

Duchenne Muscular dystrophy (DMD) is the most common childhood dystrophy, affecting one in 3600 live male births. It is an X-linked recessive disease and is caused by deletions, duplications and point mutations in the dystrophin gene, resulting in absent expression of dystrophin at the sarcolemma. There is a high rate of spontaneous new mutations in the dystrophin gene and no prior history of the disease in the family is recorded in up to 30 % of cases.

The typical form of DMD presents in the first few years of life with either motor/global developmental delay or proximal muscle weakness. One third of patients have associated cognitive dysfunction particularly affecting verbal abilities and autism with behavioural problems due to ADHD is common. The gait is waddling and the child has difficulty rising from sitting, crouching or lying and demonstrates the Gowers' sign. In patients not treated with corticosteroids, the weakness progresses to loss of ambulation on average at 9.5 years (range 6–13) (Griggs et al. 2013). In the 2nd decade respiratory, cardiac and orthopaedic complications develop. Paraspinal weakness and consistent wheelchair-dependence may promote the development of kyphoscoliosis which often requires spinal surgery in the early to mid-teenage years.

Cardiac involvement in DMD leads to impaired contractility leading to arrhythmias and cardiac failure as a pre-terminal event. Progressive weakness of the intercostal and respiratory muscles results in respiratory failure late in the disease, usually by the end of the 2nd decade or beginning of 3rd decade.

The serum creatine kinase level is markedly raised, usually above 10,000 iu/l Electromyography will demonstrate a myopathic pattern and muscle biopsy demonstrates a dystrophic process with variation in fibre size, central nuclei, muscle fibre necrosis, increased connective tissue and fat deposition. Further immunostaining with dystrophin antibodies may show the absence of all three dystrophin epitopes at the sarcolemma. Figs. 31.1 and 31.2 demonstrate the range of findings observed on muscle biopsy in dystrophinopathy.

Without active management, the mean age of death is 19 years (Brooke et al. 1989). However interventions directed at reducing the burden of these complications have steadily made an impact on survival in DMD. Surveillance and early treatment of cardiomyopathy and spinal surgery for scoliosis has been shown to improve survival (Duboc et al. 2005; Bushby et al. 2010). More importantly the availability of home nocturnal ventilation has resulted in improved management of respiratory

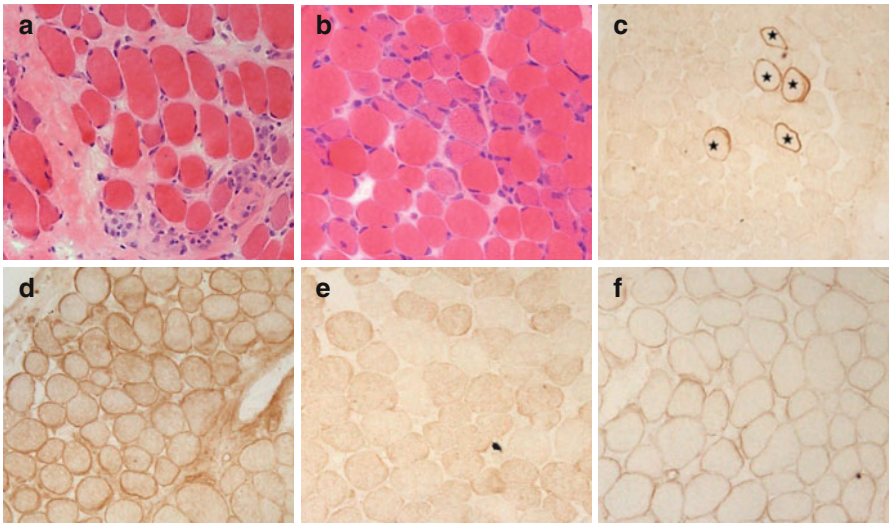

Fig. 31.1 Quadriceps needle biopsy from a 3 year old boy with Duchenne muscular dystrophy carrying a hemizygous nonsense mutation in exon 32 of the dystrophin gene predicted to cause a severe phenotype. Haematoxylin and Eosin stained sections (**a, b**) show moderately severe dystrophic changes including increased fibre size variation and internal nuclei, perimysial and endomysial fibrosis, necrotic fibres and clusters of basophilic regenerating fibres. Immunostaining with the Leica/Novocastra Dys1 antibody (rod domain) shows almost complete absence of dystrophin except strong labeling of a few 'revertant' fibres (**c**); the latter thought to arise by restoration of the reading frame due to exon skipping. In contrast utrophin that is normally restricted to blood vessels and nerves is diffusely over-expressed at the sarcolemma of myofibres (**d**). Other secondary changes in the dystrophin-associated protein complex include virtual absence of sarcolemmal *NNOS* (**e**) and patchy depletion of gamma-sarcoglycan (**f**)

failure. DMD patients often live into their late twenties or thirties with a good quality of life (Eagle et al. 2002).

The use of corticosteroids was first suggested in 1974 and to date are the only pharmacological intervention shown to slow progression of weakness, reduce the development of scoliosis requiring surgery and delay respiratory insufficiency. A recent prospective UK observational study conducted by the North Star Network demonstrated a median loss of ambulation at 12 years with intermittent prednisolone and at 14.5 years with daily prednisolone (Ricotti et al. 2013). The precise mechanism is unknown, but it has been hypothesised that glucocorticoids have anti-inflammatory and immunosuppressive actions, promote myoblast proliferation and reduce muscle necrosis. The most effective therapeutic strategy suggested prednisone 0.75 mg/kg/day or the equivalent deflazacort (0.9 mg/kg/day). To limit side effects an intermittent regimen is opted for in the UK which is usually 10 days taking steroids/10 days without steroids. This patient highlights the significant benefit of steroid therapy as he is still ambulant at 21 years with preserved respiratory and cardiac function. However he has significant side-effects and these require active monitoring and management.

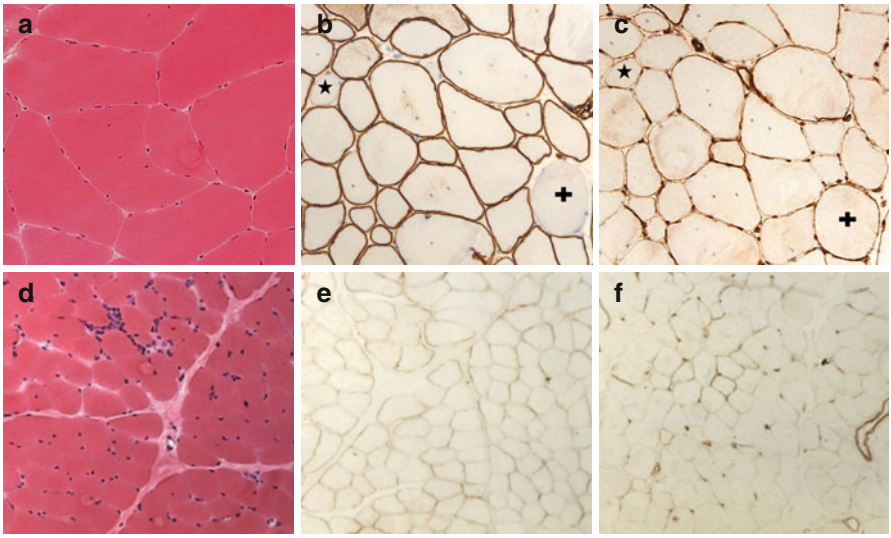

Fig. 31.2 Quadriceps biopsy from a 28 year old female manifesting carrier of Duchenne muscular dystrophy carrying a deletion of exons 45–50 predicted out-of-frame in the dystrophin gene (**a–c**). Haematoxylin and Eosin stained section (**a**) shows mild dystrophic features including abnormal fibre size variation and focal necrosis/regeneration (not shown). Dystrophin immunostaining shows randomly scattered fibres (**b**; *star* and *cross*) lacking sarcolemmal dystrophin resulting in a 'moasic pattern' of dystrophin loss due to random X chromosome inactivation. Utrophin is upregulated on fibres with and without dystrophin (**c**). Quadriceps needle biopsy from a 6 year old boy with Becker muscular dystrophy carrying a mutation in the donor splice site of exon 41 of the dystrophin gene predicted to cause an in-frame deletion and a milder phenotype. Haematoxylin and Eosin stained section shows mild dystrophic changes (**d**). Dystrophin labeling shows an overall reduction at the sarcolemma of most fibres (**e**). Utrophin upregulation is mild-to-moderate, patchy and stronger in some fibres, probably regenerating (**f**)

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Case 32
When Is Myotonia Not Caused By Myotonic Dystrophy?

Dipa L. Raja Rayan and Michael G. Hanna

History

A 51 year old Caucasian male presented with a history of difficulty running from 6 years of age. He also noticed stiffness initially in his lower limbs and trunk which over time progressed to his hands and arms. He found it was worse after a period of rest and when fatigued but improved with repeated movement. His symptoms were not worsened by the cold. He also experienced transient episodes of weakness which would improve with repeated movement. In the last couple of years he developed mild proximal lower limb weakness. He was treated with mexiletine and found this significantly improved his stiffness. One older sister was mildly affected but his other two siblings and parents were unaffected.

Examination

On examination he had generalised muscle hypertrophy which was most pronounced in the calves. He had a stiff gait which improved with repeated movements. He had hand gripmyotonia with warm-up phenomenon and percussion myotonia. There was significant transient weakness (MRC 3⁄5) lasting seconds that improved with repeated activity to baseline. He also had a very mild fixed proximal leg weakness with hip flexion MRC grade 4+⁄5.

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Investigations

EMG demonstrated profuse myotonic discharges in the muscles of all limbs. Short exercise testing showed significant initial decrement of the compound muscle action potential (CMAP) with exercise which improved with subsequent trials (Fig. 32.1). The long exercise (McManis) test was normal. MRI scan demonstrated increased water accumulation in the calf mucles on STIR sequence (Fig. 32.2). Genetic testing confirmed the same two mutations in the patient and his affected sister in the chloride channel gene (*CLCN1 c.*[*180+3A>T* (+) *568G>A*]; *p.*[?(+) *Gly190Arg*]).

Diagnosis

Recessive Myotonia Congenita (Becker's myotonia)

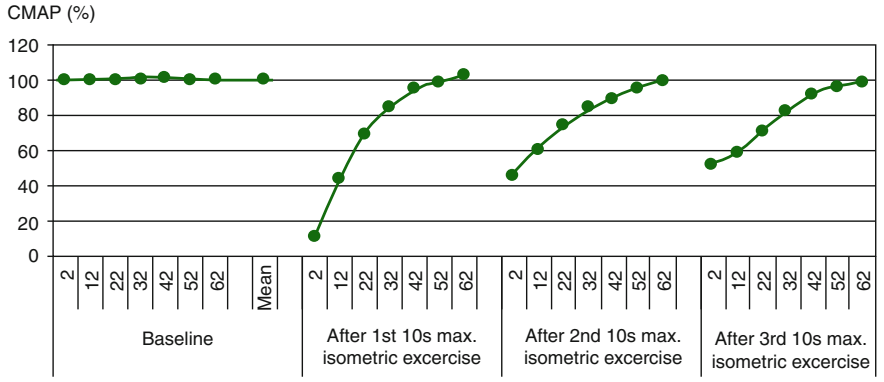
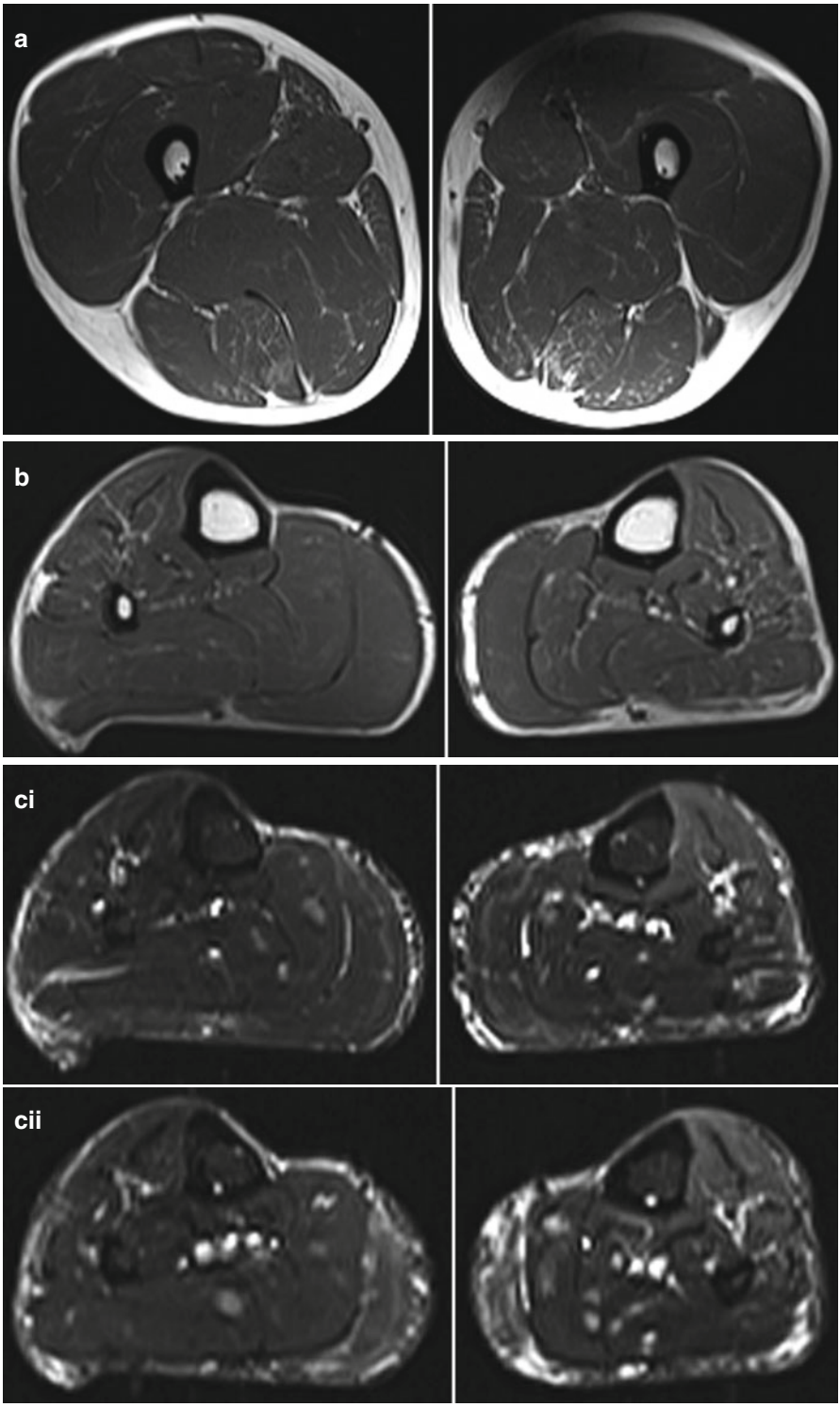


Fig. 32.1 Neurophysiology: short exercise test. The patient is asked to exercise the abductor digitiminimi (*ADM*) for 10 s and the *CMAP* is recorded for 1 min after. This is then repeated 2 further times to see how the drop in *CMAP* changes with exercise. In this case there is a significant initial decrement of *CMAP* with exercise that improves with subsequent trials

Fig. 32.2 MRI of legs: (**a**) T1 image of thighs – this demonstrates the patient's prominent musculature. (**b**) T1 image of calves: normal apart from the enlarged calf muscles. (**c**) *STIR* images of calves: (**i**) central stripe of hyperintensity in the superior portion of medial gastrocnemius (indicated by *red arrows*). (**ii**) Increase in signal in the inferior portion of the medial head of gastrocnemius bilaterally suggesting oedema. There is no evidence of fatty replacement in the thighs or calves


a
b
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cii

Discussion

The clinical presentation and neurophysiology suggested that the patient had a non-dystrophic myotonia. The lack of significant weakness supported a diagnosis of non-dystrophic rather than myotonic dystrophy (DM) type 1 or 2, although DM patients can present with isolated handgrip myotonia without weakness. Transient weakness which improves with warm-up and generalized muscle hypertrophyare characteristic of a myotoniacongenita caused by mutations in the chloride channel, as is the pattern of decrement in the CMAP in the short exercise EMG. Alternative causes of a hereditary myotonia include paramyotoniacongenita and sodium channel myotonia caused by mutations in the sodium channel gene,*SCN4A*. These patients tend to present with cold sensitive myotonia, especially of the face, that worsens with exercise. Hyperkalaemic periodic paralysis may also present with myotonia but patients have more distinct episodes of paralysis.

Myotonia congenita (MC) is the most common muscle channelopathy with an estimated prevalence of 1–10/100,000. MC can be inherited in either a recessive or dominant pattern depending on the type of mutation carried which can make genetic counseling difficult. Patients with recessive MC tend to have more severe generalised myotonia with calf hypertrophy compared to those with dominant MC. Patients often present in childhood with stiffness. Severely affected patients may develop mild proximal weakness in later life but overall patients have a good prognosis. Mexiletine has recently been shown in a randomized controlled trial to significantly improve patient stiffness. If the drug is not tolerated other treatment options include carbamazepine, phenytoin and disopyramide.

Reference

Raja Rayan DL, Hanna MG. Skeletal muscle channelopathies: nondystrophicmyotonias and periodic paralysis. Curr Opin Neurol. 2010;23:466–76.

Case 33
Myotonia and Paralysis-Two Syndromes, One Diagnosis

Dipa L. Raja Rayan and Michael G. Hanna

History

A 63 year old Caucasian man reported being very stiff if he tried to push off from the sprinting blocks from a young age. At age ten, he had an episode of severe weakness and he was unable to get out of bed. He continued to have frequent attacks affecting all four limbs following strenuous exertion lasting from a few days to 2 weeks. He also reported mild focal attacks of weakness. His episodes of weakness and stiffness were exacerbated by exposure to cold and he was unable to open his eyes in a cold wind. In the last 10 years, he began to have fewer attacks of weakness but developed a progressive fixed proximal muscle weakness affecting both arms and legs, worse in the right than the left and he requires a wheelchair to mobilise. He had one daughter who had an episode of weakness following general anesthesia and one unaffected son. Two of four of his siblings were affected although his parents were not known to be affected.

Examination

On examination he had eye closure myotonia which worsened with exertion and lid lag. He also had significant proximal muscle weakness of the legs with hip flexion MRC grade 3/5, and moderate proximal upper limb weakness (shoulder abduction MRC grade 4/5). The rest of his examination was normal.

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Investigations

His CK was raised at 1927IU (<200) and his potassium level was normal. EMG demonstrated profuse myotonic discharges, which were more prominent in the upper limbs. There were mild myopathic features in the proximal upper and lower limb muscles. Short exercise and cooling tests were normal. The long exercise (McManis) test was positive with a maximum amplitude decrement of 55 % (Fig. 33.1). The MRI of his leg muscles (Fig. 33.2) demonstrated fat replacement and water deposition in the thighs consistent with a myopathic process associated with weakness. Subsequent calcium channel (CACNA1S) analysis was normal and sequencing of the sodium channel gene (*SCN4A*) identified the mutation, Met1592Val.

Diagnosis

Hyperkalaemic Periodic Paralysis

Discussion

The patient has a history of episodes of paralysis from a young age with stiffness and a dominant family history. This suggested a primary rather than acquired cause of periodic paralysis. The presence of distinct episodes of paralysis with a cold sensitive myotonia suggested a form of periodic paralysis rather than a non-dystrophic or dystrophic myotonia. The combination of myotonia and paralysis makes the diagnosis of hyperkalaemic periodic paralysis the most likely rather than hypokalaemic periodic paralysis or Andersen-Tawil syndrome in which patients do not have myotonia.

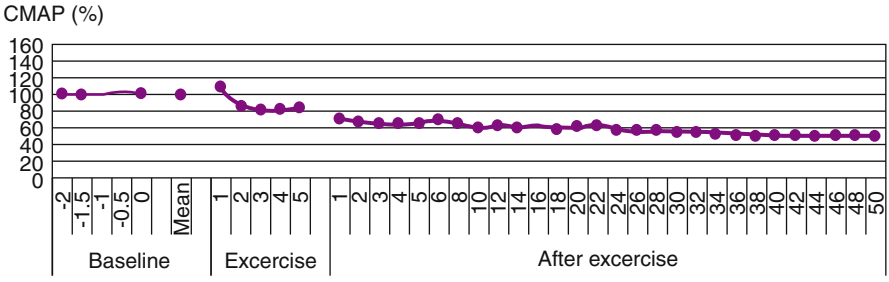

Fig. 33.1 Neurophysiology: long exercise test. This shows the change in compound muscle action potential (*CMAP*) amplitude over 50 min following 5 min of exercise of *ADM*. The maximum decrement is 55 %, consistent with a positive test

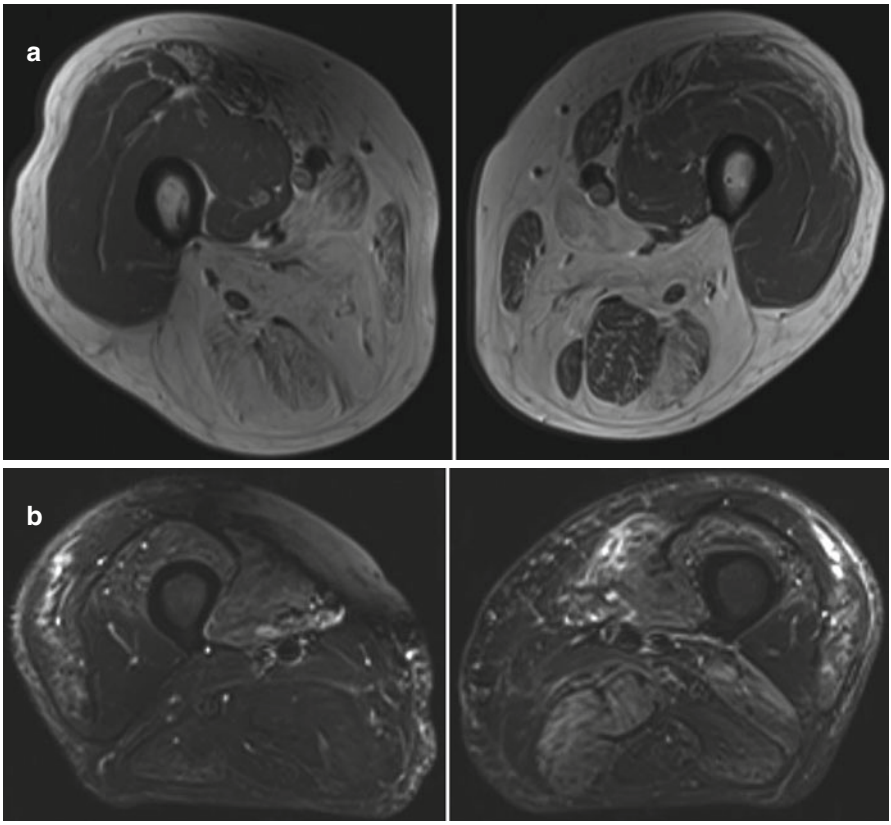

Fig. 33.2 MRI thighs: (**a**) T1 image: this shows almost complete fatty replacement of the muscles of the posterior and medial compartment of thighs on the *right* and to a lesser extent on the *left*. The vastus lateralis muscle bilaterally as well as the inferior portion of the rectus femoris muscle on the *left* are also severely affected. (**b**) STIR image: there is a high signal indicating water deposition in the medial vastus, rectus femoris and vastus lateralis muscles bilaterally as well as the *left* adductor and semimembranosus muscles

Patients with hyperkalemic periodic paralysis typically have both cold sensitive myotonia and episodes of weakness although in some cases, patients may only have attacks of weakness. It is caused by a mutation in the sodium channel gene, *SCN4A* and is dominantly inherited. The episodes of weakness are often associated with a high, or occasionally normal, potassium level. In severe cases, patients may develop fixed proximal weakness in later life, however this tends to be more common in hypokalaemic periodic paralysis. MRI is emerging as a useful tool to assess the severity and potential efficacy of treatment. The degree of fatty change on the scan may provide a measure of the extent of irreversible weakness. The extent of oedema, a represented by high signal on STIR sequences, may be associated with reversible

changes which may respond to treatment. Patients are commonly treated with low potassium meals and either acetazolamide or dichlorphenamide to reduce attack frequency and severity.

Reference

Raja Rayan DL, Hanna MG. Skeletal muscle channelopathies: nondystrophic myotonias and periodic paralysis. Curr Opin Neurol. 2010;23:466–76.

Case 34
Typical Phenotype, MRI and Histology

Jasper M. Morrow, Janice L. Holton, and Matthew J. Parton

History

A 61 year old gentleman first attended clinic at the age of 53 with a 1 year history of difficulty climbing stairs and getting up from low chairs. These symptoms gradually progressed during the subsequent 8 years, requiring aid of one stick when walking and assistance to climb stairs. In addition, he developed progressive swallowing problems over the past 2 years and mild difficulty with fine motor tasks using the hands such as buttoning clothes. There were no sensory symptoms or sphincter disturbance. He had no symptoms suggestive of cardiorespiratory disease.

He had hypertension, gout, type 2 diabetes and hypercholesterolaemia. His current medications were aspirin, metformin, ibersartan, amlodipine, simvastatin, alendronate. At age 54, he was treated with with prednisolone at 60 mg which was tapered to 10 mg over 12 months and continued at a low dose for 6 years. There was no clear clinical benefit with prednisolone.

There was a strong family history of ischaemic heart disease. He was a non-smoker and did not drink alcohol.

Examination

General examination was normal. He needed assistance to stand from a chair. He was able to walk slowly and independently with a hyperlordotic posture and kept his

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Table 34.1 Distribution of muscle weakness

Movement	Right	Left	Movement	Right	Left
Shoulder abduction	4+	4+	Hip flexion	2	4
Elbow extension	4	4–	Hip extension	5	5
Elbow flexion	4	4–	Hip abduction	5	5
Wrist extension	4–	4–	Hip adduction	3	4
Wrist flexion	3	3	Knee flexion	4	3
Finger extension	4	4	Knee extension	2	2
Forefinger abduction	5	5	Ankle dorsiflexion	4+	4
Little finger abduction	4+	4+	Ankle plantarflexion	5	4
Thumb abduction	4+	4+	Ankle eversion	5	5
Long finger flexors	2	1	Ankle inversion	5	4+
Short finger flexors	4	4	Big toe extension	5	5

MRC scale: 5 = normal strength, 0 = no movement

knees locked in extension. In the cranial nerves there was mild weakness of facial muscles and neck flexion, and moderate dysphagia. Other cranial nerves were normal. There was wasting of forearm flexor muscles and anterior thigh muscles bilaterally. Tone was normal. MRC grading of limb strength is detailed in Table 34.1. There was proximal and distal weakness of all four limbs with asymmetry. The weakest muscles were quadriceps and long finger flexors. Reflexes were normal in the upper limb and absent in the lower limbs with flexor plantar responses. Co-ordination and sensation were normal.

Investigations

Creatine kinase was initially 1083 (20–200) which reduced to the normal range after starting prednisolone. Other blood tests including full blood count, renal function, liver function, thyroid function, inflammatory markers and auto-antibodies were normal. Nerve conduction studies were normal and electromyography showed myopathic changes in biceps, rectus femoris, vastus medialis and tibialis anterior. MRI of lower limb muscles demonstrated both fatty atrophy of muscles, most notably quadriceps in the thigh and medial gastrocnemius in the calf, but also hyperintensity on sequences sensitive to muscle oedema (Fig. 34.1). A muscle biopsy was performed (Fig. 34.2).

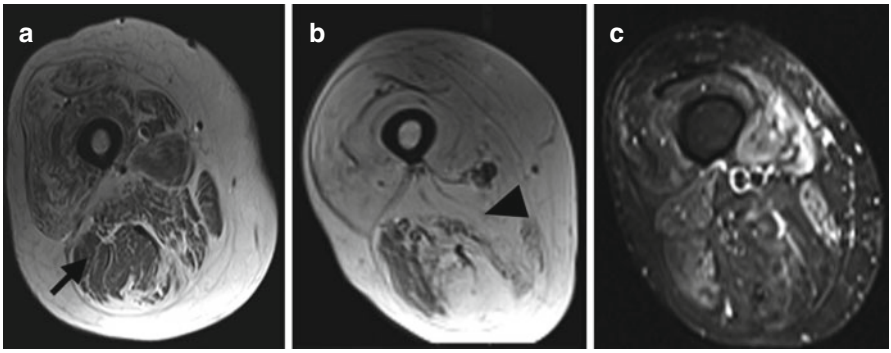

Fig. 34.1 Right thigh *MRI* transverse images. (**a**): T1 weighted sequence age 57, (**b**): T1 weighted sequence age 60, (**c**): *STIR* (short-tau inversion recovery) sequence age 60. In (**a**) there is fatty atrophy greater anterior than posterior, with relative preservation of biceps femoris (*arrow*). In (**b**) taken 3 years later there is clear progression of fatty infiltration, particularly in adductor magnus (*arrowhead*). Hyperintensity within muscles in (**c**) demonstrated abnormal water accumulation within muscles suggesting active disease

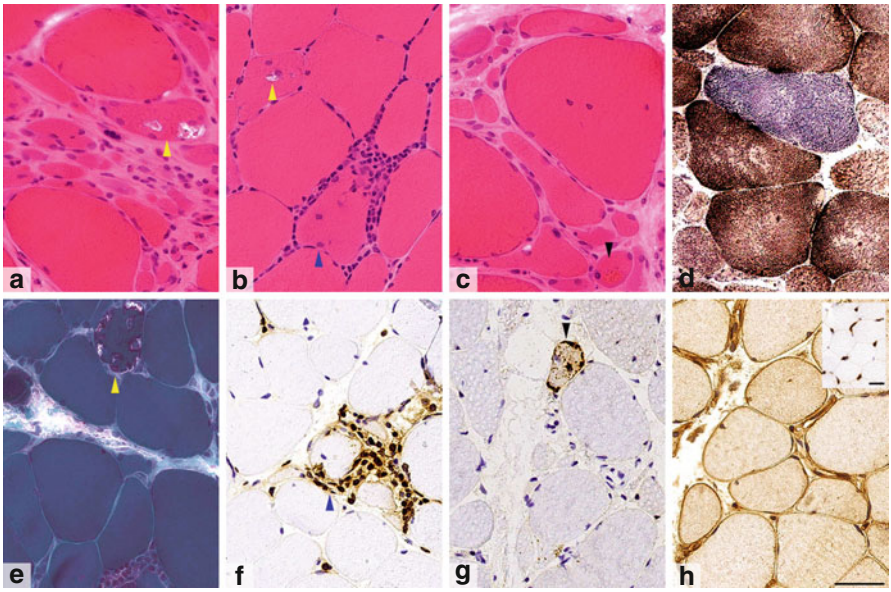

Fig. 34.2 Haematoxylin-Eosin stained sections (**a–c**) show marked variation in fibre size, increase in endomysial connective tissue, rimmed vacuoles (*yellow arrowheads*), inflammatory cells invading intact fibres (*blue arrowhead*) and eosinophilic inclusions (*black arrowhead*) in some of the fibres. Combined cytochrome oxidase/succinate dehydrogenase (*COX/SDH*) histochemical preparation reveals frequent *COX* deficient fibres (**d**). Gomori trichrome preparation (**e**) accentuates the rimmed vacuoles (*yellow arrowhead*). Immunostaining for CD3 (**f**) reveals clusters of T lymphocytes in the endomysium, some of which show invasion into intact muscle fibres (*blue arrowhead*). p62 immunohistochemistry (**g**) highlights sarcoplasmic inclusions in the fibres (*black arrowhead*). Immunostaining for MHC class I shows widespread sarcolemmal upregulation (**h**) when compared with a control from normal muscle (*inset* in **h**). *Scale bar*: 50 μm (Image courtesy of Zane Jaunmuktane and Sebastian Brandner)

Diagnosis

Sporadic Inclusion body myositis (sIBM)

Discussion

The combination of dysphagia, difficulty in climbing stairs and impaired hand function in a man in his 50s was clinically suggestive of sIBM. This was supported by the most severe weakness affecting long finger flexors and quadriceps, the raised creatine kinase level and a myopathic EMG. The diagnosis of sIBM was confirmed by typical changes on muscle biopsy and tubulofilaments on electron microscopy.

Inclusion body myositis is currently classified as an idiopathic inflammatory myopathy, a diagnostic category which includes dermatomyositis (DM) and polymyositis (PM). IBM differs from PM and DM in that it predominantly affects males over the age of 50, the pattern of weakness often affects distal muscles and is poorly responsive to immunosuppressive therapy. The pathogenesis of IBM is complex and poorly understood. Muscle biopsies may show an inflammatory infiltrate with raised sarcolemmal MHC class 1 and degenerative changes such as rimmed vacuoles and proteinaceous inclusions. Whether inflammation or degenerative changes are a primary aetiological event remains uncertain. A number of different diagnostic criteria have been proposed for IBM since there is no definitive test. The recent ENMC criteria are useful as they separate clinical and biopsy criteria (see Table 34.2).

Trials of immunosuppression in inclusion body myositis have had generally negative results. In a randomised control trial of corticosteroids, a reduction in creatine kinase levels was demonstrated but neither improvement nor slowing of clinical progression was demonstrated. Intravenous immunoglobulins have also showed no overall benefit in controlled trials, although improvement in swallowing was seen in a subgroup. IBM was first recognised as a discrete entity from polymyositis when it was noted that patients who failed to respond to immunosuppression had a distinctive clinical phenoptype. For these reasons treatment is not recommended in typical cases of inclusion body myositis, although a trial of steroids and/or IVIg is often given if there is predminant inflammation on the muscle biopsy.

Table 34.2 *ENMC* diagnostic criteria for inclusion body myositis

Classification	Clinical and laboratory features	Pathological features
Pathologically defined IBM	Consistent with IBM	Endomysial exudates and partial invasion of intact fibres and rimmed vacuoles AND Specific features: Congo-red OR Hyperphosphorylated tau (SMI-31) p62/ SQSTM1 or TDP43 OR 15–18 nm filaments
Clinically defined IBM	Duration >6 months, age 30 years, EMG consistent AND Quads weakness >Hip flexor weakness AND Finger flexor weakness >shoulder abduction weakness	Endomysial exudate OR Upregulated MHC Class 1 NO Specific features above
Possible IBM	Duration >6 months, age 30 years, EMG consistent AND Quads weakness >Hip flexor weakness OR Finger flexor weakness >shoulder abduction weakness	Endomysial exudate OR Upregulated MHC Class 1 NO Specific features above

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Case 35
Atypical Phenotype, MRI and Histology

Jasper M. Morrow, Janice L. Holton, and Matthew J. Parton

History

A 60 year old gentleman had a 7 year history of gradually progressive weakness affecting proximal and distal muscles of the lower limbs. He noticed difficulty climbing stairs or hills, a "flat-footed" gait and loss of muscle bulk in his legs. His face, swallowing, and upper limbs were asymptomatic He had no cardio-respiratory, bowel or bladder symptoms.

His birth and developmental milestones were normal and he had continued to play soccer and squash until the age of 50. Past history was notable for a stage IIA testicular teratoma, removed in 1986 followed by chemotherapy with complete and continued remission. A diagnosis of neuralgic amyotrophy was made 2 years prior with associated with a painful right shoulder followed by sub-acute onset of right shoulder girdle weakness following a flu-like illness. He made a spontaneous recovery from this illness. There was no family history of neuromuscular disease. He smoked 15–20 cigarettes per day but drank minimal alcohol.

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Examination

Cardio-respiratory examination was normal. His gait was waddling with bilateral foot drop. Cranial nerve examination was normal including ocular movements, facial power and soft palatal movements. There was reduced muscle bulk in the anterior thigh. There was shoulder abduction weakness to MRC grade 4+/5. In the lower limbs there was MRC grade four weakness of hip flexion and extension, knee extension and ankle dorsiflexion. Reflexes and sensory testing were normal.

Investigations

Creatine kinase was mildly elevated at 308 (20–200). His ANA, ENA, ESR and CRP were negative. EMG showed myopathic changes in quadriceps and tibialis anterior. Nerve conduction studies were normal including repetitive stimulation. Muscle biopsy (Fig. 35.1) showed myopathic changes, a few fibres contained rimmed vacuoles and there were several cytochrome *c* oxidase negative fibres. There was normal immunostaining against dystrophin, sarcoglycans and spectrin.

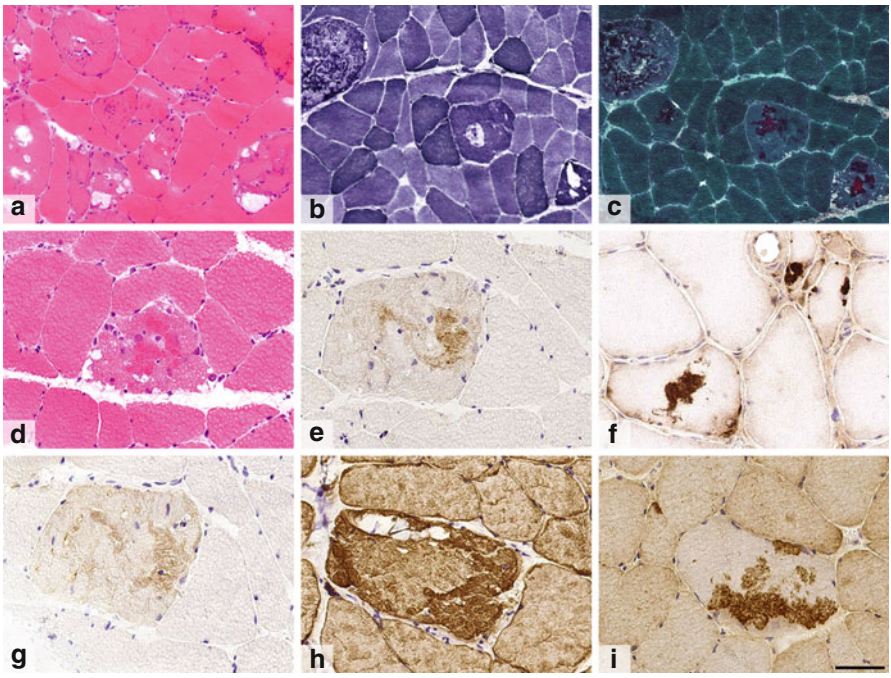

Fig. 35.1 Muscle biopsy. Muscle biopsy of myofibrillar myopathy – myotilinopathy. Haematoxylin-Eosin stained sections (**a, d**) show variation in fibre size, frequent rimmed vacuoles and eosinophilic inclusions in many of the fibres. *NADH* histochemical preparation reveals disrupted myofibre pattern in a proportion of the fibres (**b**). Gomori trichrome accentuates inclusions which are *dark green* or *red* in colour. Rimmed vacuoles are also apparent (**c**). The inclusions show positive labelling for ubiquitin (**e**), p62 (**f**), alpha-B-crystallin (**g**), desmin (**h**) and myotillin (**i**). *Scale bar*: 100 μm (**a–c**); 50 μm (**d–i**) (Image courtesy of Zane Jaunmuktane and Sebastian Brandner)

Diagnosis and Management

A diagnosis of inclusion body myositis was made. The patient received no specific treatment, and continued to be followed. His weakness progressed gradually, particularly of ankle dorsiflexion and he required ankle foot orthoses. He also developed wasting around the shoulder girdle with weakness of infraspinatus and supraspinatus. Weakness of knee extension did not worsen and he did not develop swallowing difficulties or weakness of long finger flexors and therefore his clinical phenotype was not typical of sporadic inclusion body myositis. The muscle biopsy was reviewed, and additional immunostaining was performed which showed very strong cytoplasmic immunoreactivity in several fibres for p62 and myotlin. There was no MHC Class I upregulation on the sarcolemma, the number of COX negative fibres was probably within normallimits for his age and electron microscopy did not show the microfilaments seen in inclusion body myositis. The pathological diagnosis was modified to myofibrillar myopathy. MRI of the lower limb muscles was performed and is shown in Fig. 35.2. Echocardiogram demonstrated regional wall motion abnormalities with a preserved ejection fraction. A subsequent coronary

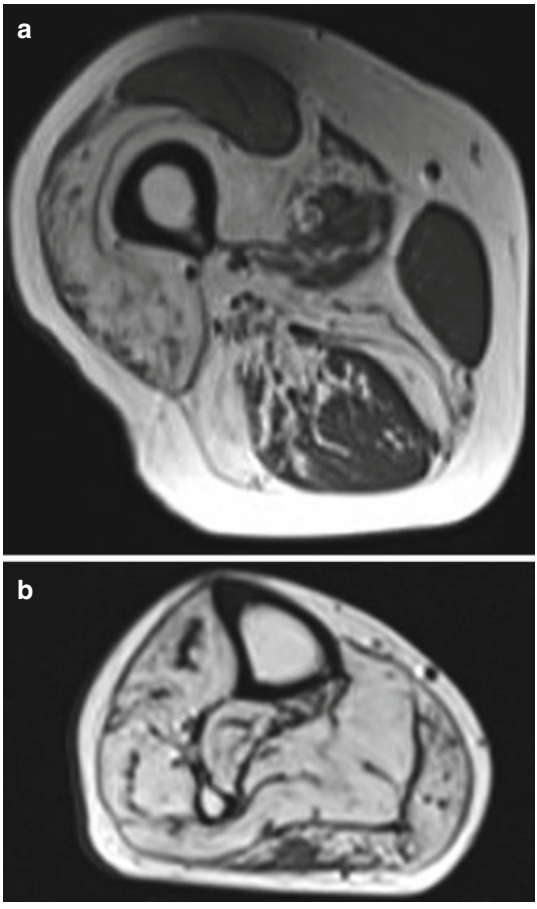

Fig. 35.2 Lower limb MRI. Transverse T1 weighted images through the right thigh (**a**) and calf (**b**). In the thigh marked sparing of rectus femoris, semitendinosus and gracilis is seen with relative sparing of lateral gastrocnemisus in the calf

angiogram did not demonstrate an ischaemic cause for these cardiac changes. The genetic analysis for FSHD1, desmin, alpha-Beta-crystallin were negative. A myotilin heterozygous c.179C>G (p.Ser60Cys) mutation was found which has previously been reported as pathogenic.

Final Diagnosis

Myotilinopathy (heterozygous c.179C>G (p.Ser60Cys) mutation).

Discussion

The clinical presentation of progressive symmetrical weakness without sensory involvement was suggestive of a myopathic process and this was supported by EMG. The mildly increased CK is also supportive of a myopathy, however modest increases in CK (less than 1000) may be seen in denervation. The initial diagnosis of inclusion body myositis was appropriate at presentation. Ankle dorsiflexion weakness is common in IBM, the demographics of the patient was consistent with IBM and the finding of rimmed vacuoles on the biopsy was pathologically supportive. This case demonstrated that there are other myopathies which can demonstrate rimmed vacuoles on biopsy. This case demonstrates the importance of reviewing patients and being alert to developments in phenotype in neuromuscular diseases which are not typical for the presentation diagnosis. The lack of involvement of the long finger flexors, the development of shoulder girdle weakness and the absence of dysphagia with progressive disease were clinically atypical for IBM.

Myofibrillar myopathies (MFM) are characterised by a distinct pathological pattern, consisting of myofibrillar disorganisation, accumulation of myofibrillar degradation products and ectopic accumulation of multiple proteins including desmin, myotilin, dystrophin and sarcoglycans. The clinical presentation is variable in that the pattern of weakness may be proximal, distal or mixed. Cardiac involvement is common and there it is important to make a specific diagnosis to allow appropriate cardiac surveillance and treatment.

There are currently six genes identified in which mutations may cause myofibrillar myopathies: desmin, myotilin, αß-crystallin, Filamin-C, ZASP and Bag3, however the responsible gene remains unknown for 50 % of cases. Once the diagnosis of a myofibrillar myopathy has been raised on muscle biopsy, finding the causative gene may be aided by assessing the pattern on muscle MRI. In myotilinopathy, the typical pattern is for rectus femoris, semi-membranosus and gracilis to be relative spared in the thigh, with relative sparing of lateral gastrocnemius in the calf, which is the pattern seen in this case (Fig. 35.2). This information can be used to guide genetic testing, or confirm pathogenicity of a novel mutation in a known MFM gene.

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Case 36
A Multisystem Muscle Disorder Needs Monitoring

Dipa L. Raja Rayan and Chris Turner

History

A 76 year old caucasian female developed difficulty walking at 56 associated with weakness and stiffness in her handgrip. At 67 she was admitted to hospital with severe dyspnoea and was found to be in decompensated neuromuscular respiratory failure due to chest sepsis. She gradually developed worsening foot drop, hand grip and neck flexion weakness as well as dysphagia. Severe excessive daytime sleepiness became debilitating but she was not able to tolerate non-invasive ventilation or modafinil due to psychiatric side-effects. She required insertion of a pacemaker at 68 and developed chronic atrial fibrillation. She had bilateral cataracts removed at 31. She had two sons, one of who developed symptoms from DM1 age 30. She also had five spontaneous abortions at 3 months gestation.

Examination

On examination she had myopathic facies, bilateral ptosis and weak neck flexion.

Her cough was weak, there was severe weakness of finger flexion and ankle dorsiflexion. Grip and tongue myotonia were present (Fig. 36.1). Her pulse was irregular and she had mild frontal balding.

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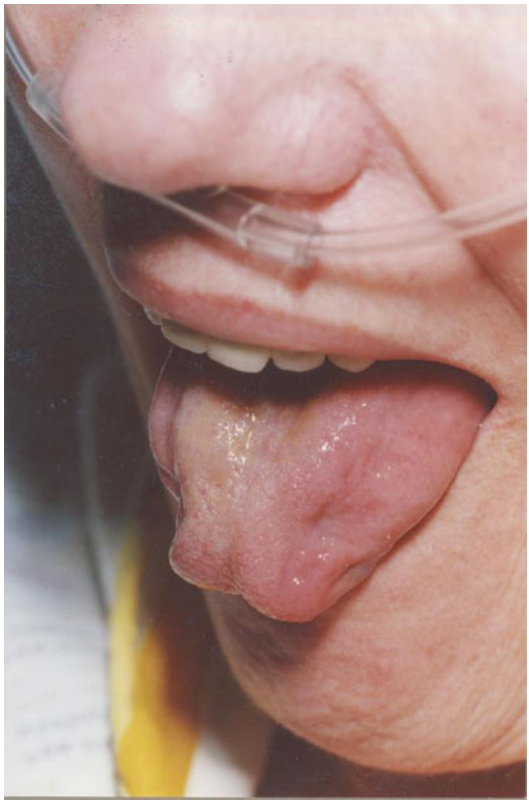

Fig. 36.1 Tongue myotonia following percussion

Investigations

Her CK was normal. EMG demonstrated frequent myotonic potentials with mild myopathic changes. An overnight sleep study showed significant desaturations throughout the night, with the lowest oxygen saturation dropping to 72 % with an average of 85 %. An expansion of the CTG repeat at the 3' end of myotonic dystrophy protein kinase (DMPK) gene was confirmed.

Diagnosis

Myotonic Dystrophy Type 1.

Discussion

The patient developed late-onset myotonia with a typical pattern of weakness, neuromuscular respiratory failure and cardiac dysrhythmias. This suggested a multisystem myotonic disorder suggestive of a myotonic dystrophy. The non-dystrophic

myotonias tend to begin in childhood and do not cause multi-system disease. Myotonic dystrophy type 2 tends to be less severe and less common than type 1.

Myotonic dystrophy type 1 has a prevalence 1 in 7000 in Europe. It is caused by an expansion of the CTG repeat in the 3' untranslated region of the DMPK gene and, as with other trinucleotide repeat disorders, shows anticipation. The repeat size is correlated with an earlier age of onset. A severe congenital form of the disease is almost always due to a maternally inherited mutant allele and is associated with greater than 1000 CTG repeats. Distal weakness of finger flexion and ankle dorsiflexion are typical. Ptosis and facial weakness with frontal balding often gives a characteristic facial appearance. Cardiac brady and tachyrhythmias are common and are a common cause of early mortality. Clinically significant cardiomyoapthy is uncommon. Respiratory problems are the commonest cause of early mortality and are caused by neuromuscular respiratory weakness, dysphagia and primary central apnoea. This may be treated with non-invasive ventilation but this is often not tolerated. The myotonia, if severe, can be treated with mexiletine but this is usually not required. Myotonic dystrophy type 1 may also affect bowel and bladder function as well as causing a specific poorly-defined cognitive phenotype.

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Case 37
The Less Aggressive and Less Common Cousin

Dipa L. Raja Rayan and Chris Turner

History

A 41 year old female presented with progressive severe muscle pain and stiffness. She had difficulty releasing her grip for the last 3 years. The pain was not exacerbated by cold. There was no warm-up phenomenon or episodes of weakness. She was otherwise well and had no cardiorespiratory symptoms, cataracts or sphincter disturbance. Her father had cataracts in his fifties and diabetes. One of her brothers had stiff hands. She had two young children who were both unaffected.

Examination

On examination there was very mild hand grip myotonia with no warm-up phenomenon. Neurological examination was otherwise normal.

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Investigations

Her CK was normal. An EMG demonstrated short bursts of discharges and these were not typical of myotonia. The short and long exercise tests were normal. Genetic testing for DM1 was normal and Zinc Finger Protein 9 (ZNF9) showed expansion of CCTG repeat in intron 1.

Diagnosis

Myotonic Dystrophy Type 2

Discussion

The patient had a late onset mild myotonia with significant pain. She had no other medical problems but there was a family history of early cataracts. The late onset of symptoms is suggestive of a form of myotonic dystrophy. The absence of weakness, mild myotonia and significant painful component makes a diagnosis of myotonic dystrophy type 2 more likely than type 1. A differential of non-dystrophic myotonias should also be considered given the lack of weakness but it is unusual to have such a late onset of symptoms and a normal short exercise test.

Myotonic dystrophy type 2 typically presents in the 3rd decade with mild proximal weakness and myotonia but many patients are symptomatic later in life. Muscle pain, stiffness and fatigue are common. The multisystem features tend to be milder than in DM1 and DM2 has a better prognosis. DM2 is caused by a quadruplet repeat expansion of the CCTG repeat sequence in intron 1 of the ZNF9 gene but expansion size does not correlate with age of onset of disease or show anticipation. Congenital DM2 has not been reported. Patients may also develop cardiac conduction defects, cataracts and type 2 diabetes mellitus and therefore should be screened for these conditions when diagnosed.

Reference

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Case 38
A Common Cause of Progressive Proximal Weakness…

Jasper M. Morrow, Janice L. Holton, and Chris Turner

History

A 34 year old woman presented with a history of gradually progressive proximal lower limb weakness. She was the product of a normal full term delivery, achieved normal motor milestones and was very good at school sports. Her husband noticed mild difficulty climbing stairs from when she was 17. The patient first noticed symptoms at age 28 of difficulty getting up from the floor. Her symptoms progressed gradually with increasing difficulty walking long distances. She had no symptoms related to the cranial nerves or upper limbs.

There was no family history of neuromuscular disease including two siblings and three children. There was no parental consanguinity. There was no past medical history and she took no regular medications.

Examination

General and cardio-respiratory examination were normal. She walked with a waddling gait. Cranial nerve examination was normal including facial muscle power. There was no scapula winging or scoliosis. There was mild symmetrical

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weakness of shoulder abduction (MRC grade 5−/5) with mild weakness of hip flexion (MRC grade 4/5) and knee flexion (MRC grade 4+/5). Her distal muscle power, muscle bulk, reflexes, co-ordination and sensation were normal.

Investigations

Her creatine kinase (CK) was significantly elevated at 1891 IU/L (26−140). Her nerve conduction studies were normal and electromyography demonstrated myopathic motor units in her proximal muscles. Quadriceps muscle biopsy was performed and showed dystrophic features (Fig. 38.1). A lower limb MRI demonstrated fatty replacement of muscle particularly in the posterior thigh (Fig. 38.2). Echocardiogram showed mildly dilated left ventricle (LVEDD 5.5 cm) but normal systolic function. *FKRP* gene analysis demonstrated homozygous mutations c.826C >A (p.Leu276Ile).

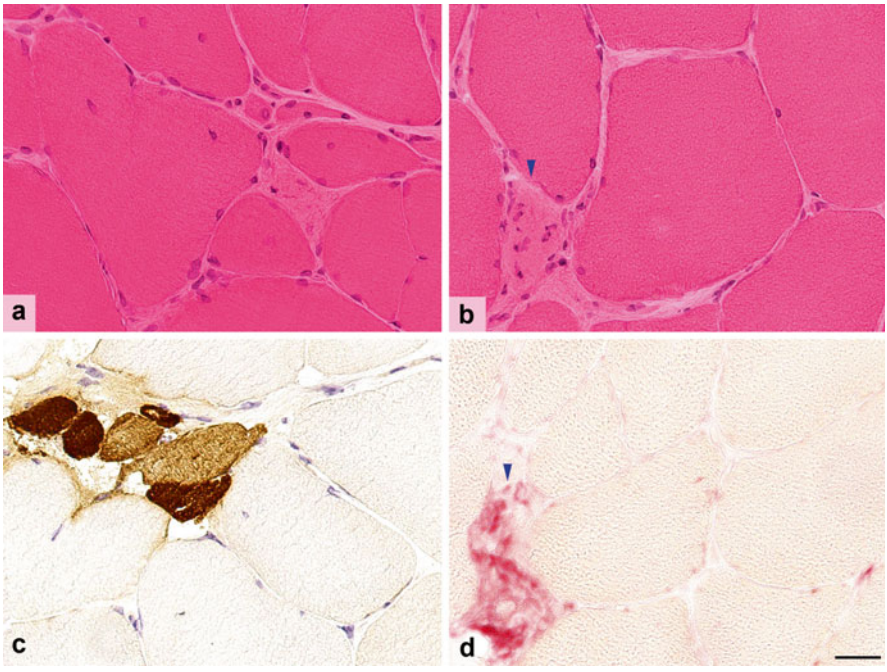

Fig. 38.1 Muscle biopsy of Limb Girdle Muscular Dystrophy type2I. Haematoxylin-Eosin stained sections (**a, b**) show marked variation in fibre size and occasional necrotic fibres (*blue arrowhead* in **b**). Immunostaining for neonatal myosin (**c**) reveals frequent positively labelled fibres. Histochemical staining for acid phosphatase (**d**) accentuates a necrotic fibre overrun by macrophages (*blue arrowhead*). Scale bar: 30 μm (Image courtesy of Zane Jaunmuktane and Sebastian Brandner)

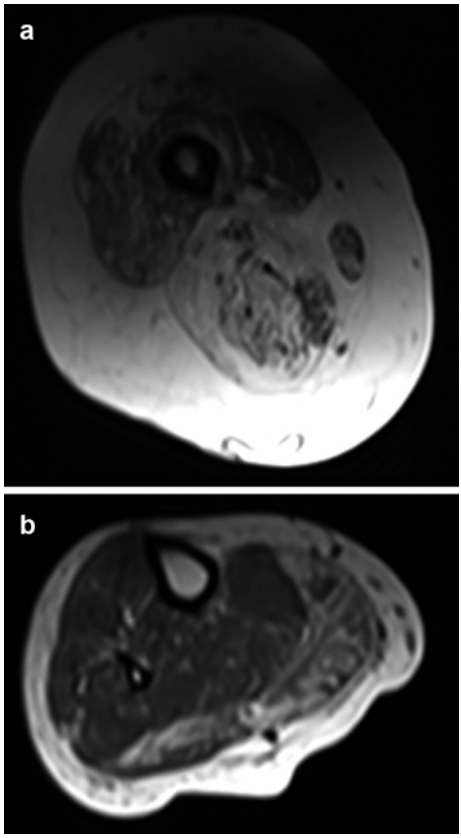

Fig. 38.2 Lower limb MRI: Transverse T1 weighted images through the right thigh (**a**) and calf (**b**). In the thigh fatty infiltration is greater in the posterior than anterior compartment with greatest involvement of biceps femoris. The calf is less affected with mild fatty infiltration of medial and lateral gastrocnemius

Diagnosis

Limb Girdle Muscular Dystrophy Type 2I: FKRP homozygous mutations c.826C >A (p.Leu276Ile).

Discussion

The clinical history is consistent with a myopathic process with proximal weakness, no upper motor neuron signs, normal sensation and intact reflexes. The gradually progressive time-course suggested a degenerative cause which was probably genetic. The clinical diagnosis of a limb girdle muscular dystrophy (LGMD) was supported by a raised CK, a myopathic EMG and a dystrophic muscle biopsy. FKRP is the commonest cause of LGMD in Northern Europe and was an appropriate initial genetic test. Genetic diagnosis is important as it enables genetic counselling for

offspring and other family members, appropriate screening of potential other organ involvement, such as cardiomyopathy, more specific prognostic advice and ultimately, potential future molecular therapy.

LGMDs are classified according to inheritance pattern, with LGMD Type 1 autosomal dominant and LGMD Type 2 autosomal recessive. LGMD are sub-classified according to the responsible gene which currently includes LGMD1A-H for the dominant cases and LGMD2A-S for the recessive cases. There are likely to be further genetic causes for LGMD discovered in the future as many cases remained genetically undefined. The most likely clinical diagnosis can sometimes be narrowed down by clinical features, CK level, muscle biopsy findings, and MRI pattern. A LGMD "genetic panel" using next generation sequencing technology will probably replace the requirement for a muscle biopsy in the near future.

LGMD2I is caused by mutations in the gene encoding Fukutin Related Protein (FKRP) which has a role in glycosylation of alpha-dystroglycan. It is one of a group of disorders associated with abnormal alpha-dystroglycan labelling on muscle biopsy. The other disorders associated with abnormal alpha-dystroglycan usually present with a congenital myopathy and occasionally FKRP-related disease may present at birth. Specific clinical clues to LGMD2I include calf hypertrophy, cardiac and respiratory muscle involvement, and very high CK levels. A specific pattern of muscle involvement may also seen on MRI (Fig. 38.2). LGMD2I is one of the most common forms of LGMD in Northern Europe, with a common mutation (C826A) accounting for more than 90 % of cases. It is therefore reasonable, in a patient with the appropriate genetic background and clinical phenotype, for this specific mutation to be analysed at an early point in the diagnostic workup.

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Case 39
..and the Other Common Cause

Jasper M. Morrow, Janice L. Holton, and Chris Turner

History

A 22 year old woman with Chinese ancestry presented with a 4 year history of gradually progressive proximal limb weakness. She was the product of a normal term delivery. She reported that she "toe-walked" from age six and had bilateral Achilles tendon lengthening surgery age 16. She first noticed symptoms of proximal weakness age 18 with difficulty climbing stairs, raising her arms above her head and currently was unable to perform sit-ups having previously been able to do more than 100 per day. There were no sensory, cranial nerve or cardiorespiratory symptoms and her sphincter function was normal.

There was no past medical history and she took no regular medications. There was no family history including in four siblings and no history of parental consanguinity.

Examination

General examination including cardio-respiratory clinical assessment was normal. She walked with a waddling gait and Gower's sign was positive. Cranial nerve examination was normal. There was winging of both scapulae and an inability to

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abduct her arms above the horizontal. Elbow power was symmetrically weak with elbow flexion MRC grade 3/5 and elbow extension MRC grade 4/5. Distal limb power was normal. Power in the lower limbs was reduced proximally with hip flexion MRC grade 2/5, knee flexion MRC grade 2/5 and knee extension MRC grade 4/5. Ankle power was normal. Reflexes were absent. Sensation and co-ordination were normal.

Investigations

Her creatine kinase (CK) was elevated at 5192 IU/L (26–140). Electromyography showed myopathic units in proximal muscles. The muscle biopsy demonstrated dystrophic changes (Fig. 39.1). Immunohistochemistry showed normal staining for ß-spectrin, caveolin-3, dystrophin, sarcoglycans, dystroglycans, dysferlin, nNOS, but significantly reduced immunolabelling for Calpain-3. An immunoblot

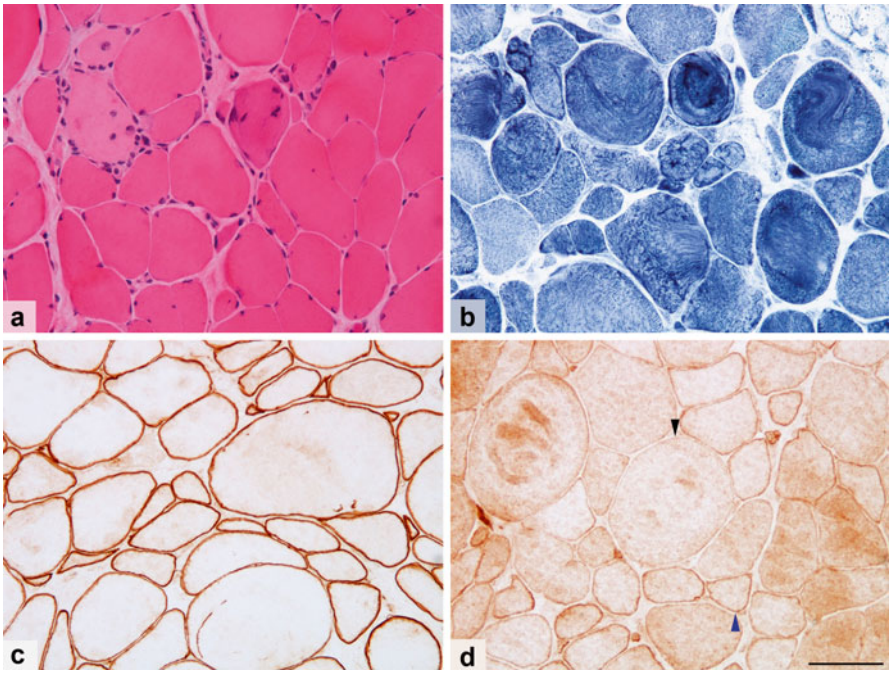

Fig. 39.1 Haematoxylin-Eosin stained section (**a**) shows marked variation in fibre size with disorganized internal cytoarchitecture in a proportion of the large fibres. NADH histochemical preparation (**b**) highlights the whorled and lobulated appearance of many fibres. Immunostaining for spectrin (**c**) shows preserved sarcolemmal labelling in all fibres. Immunostaining for dysferlin (**d**) shows preserved expression in a proportion of the fibres (*blue arrowhead*), while in some fibres there is secondary reduction in the sarcolemmal labelling (*black arrowhead*). Scale bar: 50 μm (Image courtesy of Zane Jaunmuktane and Sebastian Brandner)

demonstrated that the Calpain-3 bands were absent. The genetic testing of the *CAPN3* gene demonstrated the c.1795dupA (p.Thr599AsnfsX33) known pathogenic mutation and c.1518 T>C (p.Ile506Thr) novel sequence variant. Parental testing showed each parent carried one mutation, confirming that the mutations segregated on different alleles.

Diagnosis

Probable Limb Girdle Muscular Dystrophy Type 2A–calpainopathy associated with c.1795dupA (p.Thr599AsnfsX33),a known pathogenic mutation, and c.1518 T>C (p.Ile506Thr), a novel sequence variant, in *CAPN3* gene.

Discussion

The clinical presentation is consistent with an early myopathic process associated with symmetrical proximal weakness. Her very high CK levels and myopathic EMG supported this clinical diagnosis. The gradual progression of symptoms suggested a degenerative condition which was likely to be genetic. The prominent scapula winging and Achilles tendon contractures are often seen in calpainopathy but are not clinically specific. Her muscle biopsy demonstrated a dystrophic process whilst immunostaining and immunoblotting more specifically suggested a calpainopathy. The genetic analysis confirmed a known point mutation and a novel sequence variant. The confirmation of one known mutation and uncertainty over a second mutation is comon in patients often felt to have a calpainopathy. The immunocytochemical and immunoblotting changes as well as the patients phenotype are highly suggestive of a primary calpainopathy and current research is focussing on clarifying other possible mutations that may be missed by conventional PCR testing, such as deletions, in patients suspected to have calpainopathy.

LGMDs are rare and other muscular dystrophies associated with limb girdle weakness, such as dystrophinopathies and myotonic dystrophy type 2, need to be considered. In contrast to FKRP-related LGMD2I, calpainopathy is not associated with prominent cardiomyopathy and respiratory muscle involvement is usually mild.

Reference

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Case 40
A Treatable Systemic Muscle Disease

Michael S. Zandi, Janice L. Holton, and Chris Turner

History

A 52 year old right-handed administrator presented with a 9 month history of limb weakness. She had first noticed difficulty standing from low chairs. Her legs began to give way while walking and she later developed difficulty with chewing and swallowing. She had weight loss of 15 kg.

Examination

On examination her vital capacity was reduced at 1.76 l with otherwise normal respiratory examination. There was no ptosis and eye movements were normal. There was weakness of facial, chewing, neck flexion and tongue movements. In the upper limbs there was symmetrical weakness proximally especially of shoulder abduction at grade 4–/5 MRC scale, and normal power at the elbows, wrists and fingers. In the lower limbs hip flexion was MRC Grade 2/5 bilaterally and normal at the knees, ankles and toes. Reflexes were present and symmetrical and plantar responses flexor. Sensation was normal. There was a swollen purple facial rash on both cheeks.

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Investigations

Creatine kinase was raised at 7588 iU/L (<204). The full blood count showed mild thrombocytopenia (140 $\times 10^6$/L) and ESR was raised at 82 mm/h. ALT was raised at 132 U/L. ANA was positive greater than 1:320 with speckled and diffuse patterns, and anti-Ro and anti-La extractable nuclear antibodies were detected. Serum electrophoresis showed a polyclonal increase in gamma globulins. Normal or negative blood results included TSH, electrolytes and renal function, CRP, ANCA, HTLV antibodies and rheumatoid factor.

The EMG features were suggestive of a active myopathic process. There was florid and widespread spontaneous activity. Motor unit action potential (MUAP) morphology showed highly polyphasic and complex units of small to normal amplitude, in the bulbar, proximal and distal musculature. There was early recruitment at low levels of activation.

Left quadriceps muscle biopsy (Fig. 40.1) demonstrated features consistent with polymyositis with fibre atrophy, variation in fibre size (fibre diameters in the

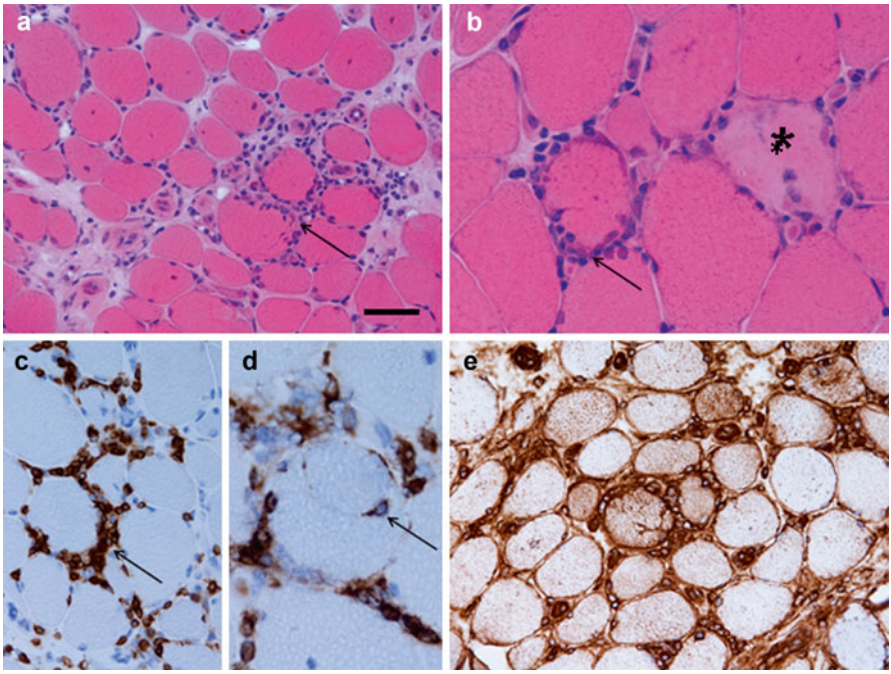

Fig. 40.1 There is an endomysial inflammatory infiltrate with infiltration of non-necrotic fibres by lymphocytes (**a, b**, *arrows*). There is variation in fibre size and fibre necrosis (**b**, *). The lymphocytic infiltrate is composed predominantly of T-cells (**c**) and these can be confirmed to have invaded viable fibres (**d**, *arrow*). MHC class I is expressed on the sarcolemma and often in the sarcoplasm of fibres (**e**). (**a, b**): Haematoxylin and eosin; (**c, d**): CD3 immunohistochemistry; (**e**): MHC class I immunohistochemistry. Bar in (**a**) represents 50 μm in (**a, c, e**) and 25 μm in (**b, d**) (Image courtesy of Zane Jaunmuktane and Sebastian Brandner)

range 10–60 μm), and occasional necrotic fibres. There was increased connective tissue and prominent inflammation. CD3 immunohistochemistry showed frequent endomysial T-lymphocytes, and the majority of these were CD8 positive. There were many endomysial macrophages and occasional B-cells. Elevated MHC Class I was present at the sarcolemma. There was no deposition of complement membrane attack complex (MAC) in capillaries. Staining for neonatal myosin heavy chain demonstrated regenerating fibres. Acid phosphatase was increased in the endomysium compatible with an inflammatory infiltrate. There were no rimmed vacuoles, evidence of vasculitis, ragged red fibres, or cytochrome *c* oxidase deficient fibres. Lipid and glycogen content were normal.

A chest x-ray and whole body FDG-PET were normal.

Diagnosis

Polymyositis.

Discussion

The patient was treated with 3 days of 1 g methylprednisolone followed by oral prednisolone 60 mg o.d. and azathioprine 50 mg od (TPMT normal). Azathioprine caused raised liver function tests, and was replaced with mycophenolate mofetil. Corticosteroids were slowly tapered and she was maintained on mycophenolate mofetil monotherapy at 1 g b.d. She has continued to make gradual functional improvement.

In a woman presenting with a proximal myopathy associated with an elevated CK and positive ANA, Ro and La antibodies the most probable diagnosis was an idiopathic inflammatory myositis, especially polymyositis and dermatomyositis. An inclusion body myositis (IBM) was possible but the typical pattern of isolated long finger flexor and quadriceps weakness was not present, the histological features were not typical of IBM and her CK was too high.

Polymyositis shares many similar pathological features of sporadic inclusion body myositis such as CD8+ T cell cytotoxic infiltrate, raised sarcolemmal MHC class 1 and invasion of otherwise intact fibres by inflammatory cells. Unlike IBM, polymyositis is not associated with prominent p62 positive proteinaceous inclusions and rimmed vacuoles. There is an association of inflammatory myopathies with systemic autoimmunity and autoantibodies, such as ANA, can often be positive. The muscle biopsy is the most sensitive and specific test for polymyositis. There is a paucity of high quality evidence for the treatment of polymyositis, but regimens centred on initial high and then tapering doses of corticosteroid followed by steroid-sparing agents are often successful. Polymyositis is not usually a paraneoplastic disease but lung, bladder and thymoma as well as non-Hodgkin's lymphoma have been described in less than 15 % of cases.

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Case 41
A Blood Vessel Disease Causing Weakness

Michael S. Zandi, Janice L. Holton, and Chris Turner

History

A 21 year old right handed female teacher developed transient hair loss followed 6 months later by a rash on her face, neck and upper chest associated with hyperpigmentation. She developed progressive difficulty climbing stairs and getting out of a chair associated with mild myalgia. She was breathless on exertion and suffered night sweats. Over a 2 week period, her symptoms rapidly worsened, with the development of truncal weakness and she was unable to stand unaided. There was no history of head drop or swallowing difficulties. There was no family history of neuromuscular disease, and she never smoked.

Examination

There was weak neck flexion and extension but otherwise cranial nerve examination was normal. She had severe proximal symmetrical upper and lower limb weakness and mild distal limb weakness. There was no evidence of fatigability. Reflexes were normal and plantars were flexor. Sensation and co-ordination were normal. Her forced vital capacity (FVC) was 50 % predicted value for her height and age. She

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had a heliotropic rash over her forehead, cheeks and upper chest with hyperpigmentation. There were nail fold telangiectasia.

Investigations

Creatine kinase on admission was 16,738 iU/L (<204). ANA was positive with a titre greater than 1:1280 (speckled and diffuse pattern). Her chest x-ray was normal. FBC, U&E, TFT, glucose, B12 and folate, magnesium, iron studies, rheumatoid factor, antiphospholipid antibody screen, anti-double-stranded DNA, ENA (Ro, La, SM, RNP, SCL-70, anti- Jo-1), ANCA were all normal or negative. Transthoracic echocardiogram was normal.

EMG of left deltoid and left rectus femoris supported the clinical suspicion of an active myopathy. There were frequent fibrillations and positive sharp waves with small spiky polyphasic units of low amplitude and short duration. There was rapid recruitment during weak contraction to a borderline interference pattern. Nerve conduction studies were normal in both upper and lower limbs.

A left quadriceps muscle biopsy was performed (see Fig. 41.1), It demonstrated with pathological features consistent with a diagnosis of dermatomyositis. There was variation in muscle fibre size with fibre diameters in the range 10–90 μm. There were frequent round atrophic, necrotic and regenerating fibres and many of these were in a perifascicular distribution. There was a prominent inflammatory infiltrate which was mostly in the perimysium with extension into the endomysium. MHC Class 1 staining was increased at the sarcolemma, and complement membrane attack complex (MAC) deposition was seen in necrotic fibres and at the periphery of several fibres, although it was not seen in the walls of capillaries. There were frequent perimysial and endomysial T-lymphocytes, mostly CD4 positive, with smaller numbers of B-lymphocytes. There were moderate numbers of perimysial and endomysial macrophages. There was no evidence of vasculitis and no ragged red or COX-negative fibres. Lipid and glycogen content were normal. Acid phosphatase activity was increased in areas where there was inflammation. Electron microscopy confirmed the presence of necrotic fibres and an increase in endomysial macrophages and fibroblasts. Several vessels had endothelial tubulo-reticular inclusions.

Serum Jo-1 antibodies were negative. The tumour marker CA 15–3 was noted to be elevated at 45 (0–25), but blood alpha-feto protein, CA 125, CA 19–9, CEA, body FDG-PET scan, CT scan with contrast of chest, abdomen and pelvis, and mammogram were normal or negative. A pelvic USS demonstrated bilateral polycystic ovaries and a left para-ovarian cyst which radiologically was felt to be benign.

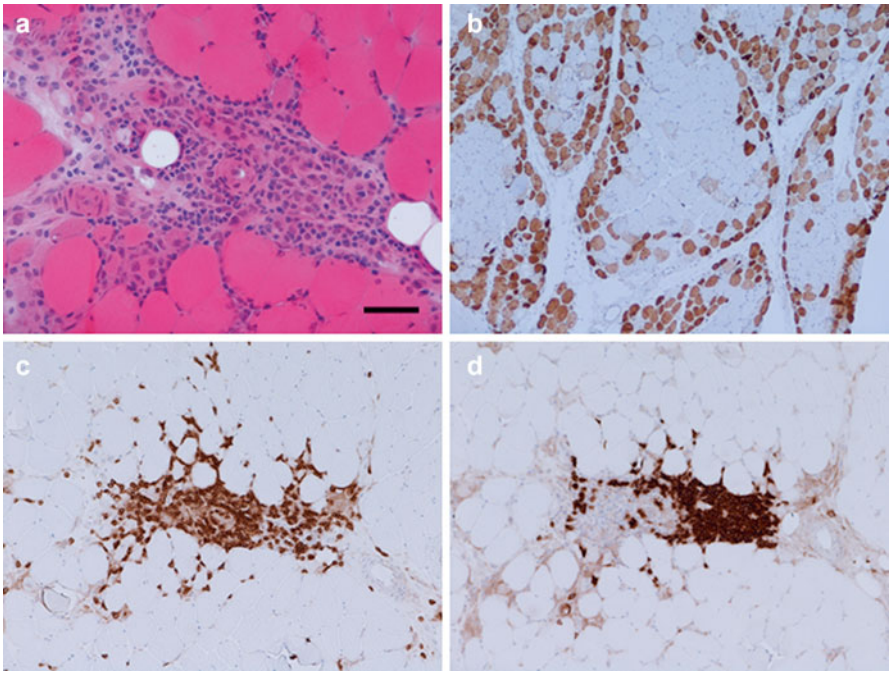

Fig. 41.1 The inflammatory infiltrate is predominantly perimysial in distribution (**a**). Immunohistochemical staining using an antibody recognising neonatal myosin heavy chain emphasises the perifascicular distribution of abnormal fibres which are often atrophic (**b**). The inflammatory infiltrate contains T-lymphocytes (**c**) and also often has a component of B-lymphocytes (**d**). (**a, b**): Haematoxylin and eosin; (**b**): neonatal myosin heavy chain immunohistochemistry; (**c**): CD3 immunohistochemistry; (**d**): CD20 immunohistochemistry. *Bar* in (**a**) represents 50 μm in (**a**), 260 μm in (**b**) and 100 μm in (**c, d**). Image courtesy of Zane Jaunmuktane and Sebastian Brandner

Diagnosis

Dermatomyositis.

Discussion

This young lady developed a proximal myopathy which extended to involve her trunk and distal muscles. This was associated with an elevated CK, a heliotropic rash and a myopathic EMG which made dermatomyositis the most probable diagnosis. This was confirmed with a muscle biopsy. The diagnosis of a typical case of dermatomyositis can often be made clincally. Polymyositis can be associated with a rash, especially when associated with a connective tissue disease. A muscle

biopsy is not performed in some centres to confirm the clinical diagnosis, but we would strongly support this diagnostic procedure as cases may not typical and when patients do not respond to first line immunosuppression then a firm diagnosis can provide confidence in introducing stronger immunosuppression.

This patient was treated with high dose intravenous methylprednisolone for 3 days followed by an oral taper of corticosteroids starting initially at 80 mg per day. She also received a course of intravenous Immunoglobulin at 0.4 g/Kg/day for 5 days because of concerns of type 2 respiratory failure. She made a gradual clinical improvement and was able to mobilise without assistance within 1 month. Azathioprine was introduced as a steroid-sparing agent, but was stopped due to raised LFTs. She was subsequently treated with mycophenolate, which was gradually tapered over 3 years with normalisation of her CK. Mycophenolate was eventually stopped and she established a healthy pregnancy 4 years after disease onset.

Dermatomyositis is an autoimmune disease of muscle which affects children and adults and affects women more frequently than men. The distinct red or heliotrope rash of dermatomyositis often precedes muscle weakness. The vascular endothelium of the endomysial capillaries is the probable antigenic target in dermatomyositis. Perifascicular inflammation and atrophy are a pathological hallmark of the disease. Complement C3 is activated, sometimes causing membrane attack complex (MAC) deposition in capillaries. There is a risk of an associated underlying malignancy particularly in those with onset over 50 years of age. These are commonly ovarian, lung, gastrointestinal tract, lymphoma or breast cancer and it occurs in up to one quarter of all cases, and if not found at disease onset should be sought for at least 5–10 years. There is evidence for the use of intravenous immunoglobulin in the acute setting particularly if patients are globally weak or develop respiratory and/or bulbar failure. Corticosteroids and steroid-sparing agents are the mainstay of therapy and many patients achieve a significant remission with a good outcome.

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Case 42
Antibody-Mediated Muscle Disease?

Alejandro Horga, Zane Jaunmuktane, Janice L. Holton, and Matthew J. Parton

History

A 23-year-old man presented with progressive proximal limb weakness. He used to train as a body builder and, over the previous year, he had noticed a rapid decline in muscle strength and bulk. He first noticed weakness of pectoral and periscapular muscles with winging of the scapulae. This was followed a few months later by proximal leg weakness. He also complained of mild dysphagia but reported no ptosis, diplopia or respiratory difficulty. The onset of symptoms was heralded by a non-pruritic rash on his trunk followed by a flu-like illness. He was not on any regular medication and there was no history of toxic exposure, although he had consumed anabolic steroids. His past medical and family history were otherwise unremarkable.

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Examination

There was no ptosis, ophthalmoparesis or facial weakness. Bulbar function was normal. Neck flexion and extension were weak. Examination of the upper limbs showed bilateral scapular winging, wasting of shoulder-girdle muscles (Fig. 42.1a) with shoulder adduction and abduction weakness (MRC grade 4/5), and elbow flexion weakness (4/5). In the lower limbs, there was weakness of hip flexion (2/5) and knee flexion/extension (4/5). Deep tendon reflexes were preserved. Examination was otherwise normal.

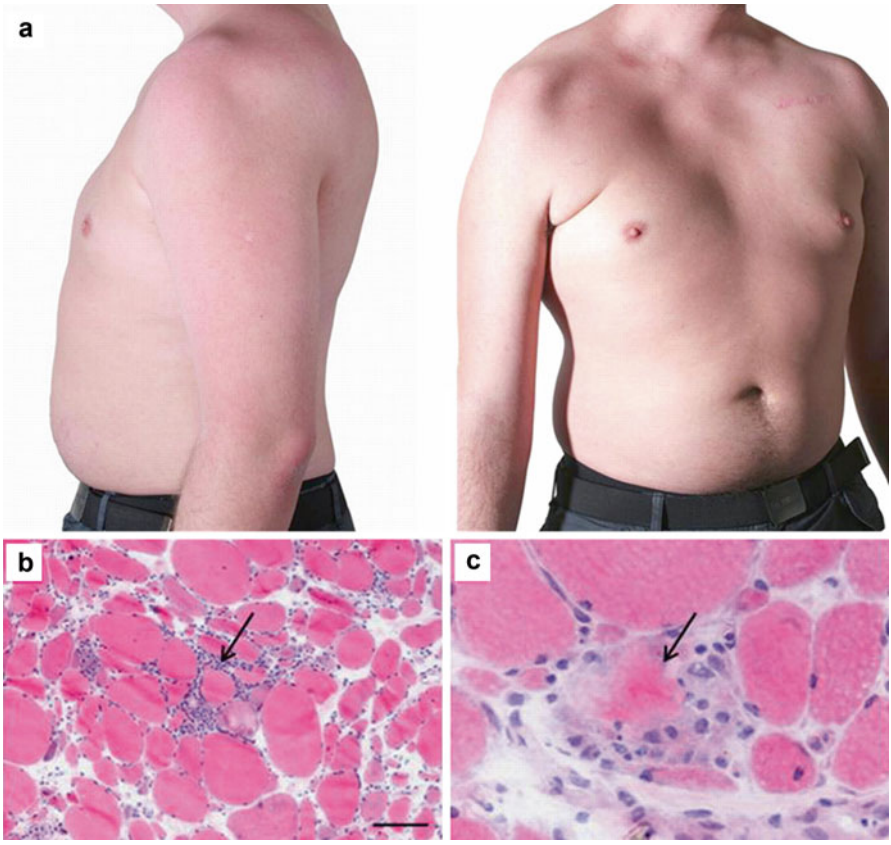

Fig. 42.1 (**a**) Wasting of shoulder girdle and infraclavicular muscles. (**b**, **c**) Muscle histology (H and E) demonstrating occasional endomysial inflammatory changes (*arrow in b*) and scattered necrotic fibres (*arrow in c*). Bar = 100 microns in (**b**) and 50 microns in (**c**) (Courtesy of Zane Jaunmuktane and Sebastian Brandner)

Investigations

Serum CK and ALT levels were raised at 24,000 IU/L (<204 IU/L) and 212 IU/L (<160 IU/L), respectively. EMG showed a myopathic pattern with increased spontaneous activity. Respiratory function tests showed a mild decrease in the FVC to 71 % of predicted. Cardiac assessment revealed a dilated cardiomyopathy and runs of non-sustained ventricular tachycardia that required insertion of an implantable cardioverter defibrillator (ICD). Chest, abdomen and pelvic CT scans were normal.

Muscle biopsy
There was increased variation in fibre size, atrophic and regenerating fibres and increased endomysial connective tissue. Small foci of endomysial inflammation and scattered necrotic fibres were present (Fig. 42.1b, c). Immunohistochemical stains revealed small numbers of CD8+ T-cells in the endomysium and CD68+ macrophages in necrotic fibres. Only very sparse CD4+ T-cells and no CD20+ B-cells were observed. There was no increase in the sarcolemmal expression of MHC-I antigen or deposition of complement attack complex in capillaries.

Genetic testing
Genetic testing for *calpain-3*, *dysferlin*, *FKRP* and *lamin A/C* mutations and for facioscapulohumeral muscular dystrophy was negative.

Serological tests
Screening for ANA, ANCA and rheumatoid factor was negative. Anti-signal recognition particle (SRP) antibodies were present at high titres.

Diagnosis

Necrotizing myopathy associated with anti-SRP antibodies.

Discussion

Four major forms of idiopathic inflammatory myopathy are described: dermatomyositis, polymyositis, immune-mediated necrotizing myopathy (IMNM) and inclusion body myositis. These disorders present with progressive weakness of shoulder and hip girdle muscles except for inclusion body myositis, in which forearm flexor muscles are affected early. A clinically suspected diagnosis is supported by increased levels of CK and myopathic changes on EMG, and confirmed by muscle biopsy. Inflammation is the histologic hallmark, with additional features being specific for each subtype. The differential diagnosis is wide and includes inherited myopathies such as facioscapulohumeral dystrophy and the dysferlinopathies, which may exhibit inflammatory infiltrates on muscle biopsy.

Necrotizing myopathy associated with anti-SRP antibodies is a rare but increasingly recognised form of IMNM with distinctive clinical and pathological features. It typically presents subacutely, although chronic forms are described. Muscle weakness is often severe, symmetrical and predominantly proximal, involving both the upper and lower limbs. Muscle atrophy and dysphagia are common features. Marked elevation of serum CK (3000–25,000 IU/L) is the rule. EMG demonstrates myopathic units, early recruitment and increased spontaneous activity. Muscle biopsy shows scattered necrotic fibres, with or without myophagia, but only rare or absent mononuclear inflammatory cells. Upregulation of sarcolemmal MHC-I expression is absent or weak and focal. Endomysial connective tissue may be increased and capillary density reduced. The capillaries may show increased diameter or deposition of C5b-9 complement. The pathological significance of the autoantibodies against SRP, a cytosolic ribonucleoprotein complex that targets nascent polypeptides into the endoplasmic reticulum, remains to be determined.

The differential diagnosis includes other forms of IMNM such as those associated with neoplasms or with statin use and autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase. Patients may respond to immunotherapy. However, relapses are common during steroid tapering and most patients require long-term maintenance treatment. Residual muscle weakness is frequent.

In the present case, treatment with intravenous methylprednisolone followed by oral prednisolone and methotrexate was initiated. Muscle strength stabilised and CK levels remained between 2000 and 3000 IU/L. However, no clinical improvement was observed and gradual withdrawal of steroids resulted in worsening symptoms. Five years after the disease onset, treatment with a single dose of intravenous cyclophosphamide and two infusions of rituximab led to clinical improvement and slight reduction in CK levels. This allowed the withdrawal of methotrexate and the reduction in prednisolone dosing. Repeat rituximab treatment was given without further improvement but the patient is clinically stable on a low dose of prednisolone as his only immunomodulatory medication. He also takes low dose ACE inhibitor and bisoprolol. The ICD has sensed very brief runs of ventricular tachycardia that have all self-terminated.

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Case 43
When the Wind Comes Back

Robert D.S. Pitceathly, Janice L. Holton, and Rosaline Quinlivan

History

A 24 year old caucasian European man presented following two episodes of rhabdomyolysis. He had suffered exercise-related lower limb pain and exercise intolerance since early childhood and was only able to run short distances during adolescence. Aged 15 years he presented to A + E with weakness of all four limbs and "bloody" urine, after an evening in a night club, and required rehydration. His second admission to hospital aged 24 years occurred after spending 2 h in the gym followed by 3 h dancing. Renal dialysis was never required and there was no family history of neuromuscular disease.

At present he rock climbs and cycles, and although he describes initial fatigue and pain in the fingers and lower limbs these improve with continued activity suggesting a second-wind phenomenon. He manages his symptoms with energy-drinks before, during and after physical exertion and by ensuring a slow warm-up.

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Examination

Gait and cranial nerve examination were normal. There were large muscles throughout the limbs with retained muscle strength and deep tendon reflexes. Plantar responses were flexor. Co-ordination and sensory examination were normal.

Investigations

During attacks of rhabdomyolysis creatine kinase (CK) was > 100,000 IU/L (normal reference range 38–204 IU/L). Baseline CK was 1252 IU/L. All other laboratory investigations including renal function and plasma urate levels were normal.

Genetics

DNA analysis of *PYGM* demonstrated the compound heterozygous mutations R50X + L292P.

Diagnosis

McArdle's disease (myophophorylase deficiency, glycogenosis type V)

Discussion

The clinical history of muscle pain with anaerobic/early exercise, when muscle glycogen stores constitute the main source of energy, associated with a characteristic second-wind phenomenon and myoglobinuria suggested a disorder of glycogen metabolism. The second-wind phenomenon is caused by activation of non-glygenolytic pathways utilising fatty acids and proteins via aerobic metabolism. The excessive glycogen stores and severely reduced/absent myophosphorylase activity in skeletal muscle tissue (Fig. 43.1) also supported a glycogenosis. The most common glycogenosis is McArdle's disease (myophophorylase deficiency, glycogenosis type V) and the patient was found to harbour recessively-inherited mutations in *PYGM*. Alternative diagnoses to consider include Tarui's disease (phosphofructokinase deficiency, glycogenosis type VII), and non-muscle causes such as claudication due to lumbar spinal stenosis or peripheral arterial disease in patients who do not have a characteristic history. A combined aerobic exercise program and high-protein diet may help patients.

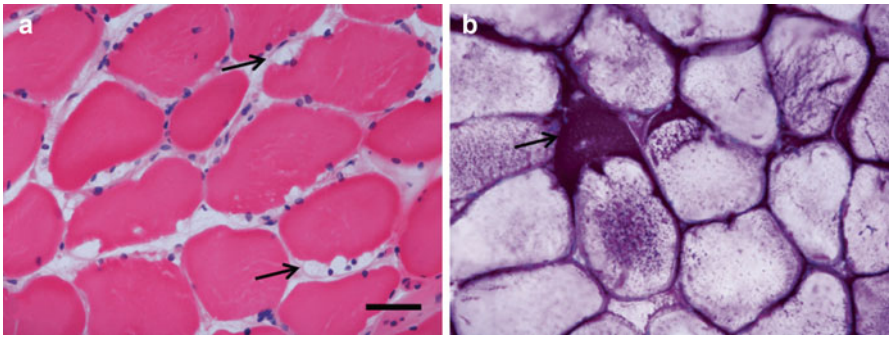

Fig. 43.1 Histological examination of a biopsy from vastus lateralis shows sub-sarcolemmal vacuoles that appear empty on haematoxylin and eosin staining (**a**, *arrows*), but are demonstrated to contain glycogen using Schiff's reagent (**b**, *arrow*). Myophosphorylase was absent but present on vascular smooth muscle. *Bar* in (**a**) represents 50 μm in (**a, b**). Image courtesy of Zane Jaunmuktane and Sebastian Brandner

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Case 44
When the Wind Does Not Come Back

Robert D.S. Pitceathly and Rosaline Quinlivan

History

A 16 year old boy presented following a game of rugby with generalised muscle stiffness and myoglobinuria. This occurred in the context of several episodes of muscle stiffness and pain since the age of 11 years, which would tend to occur after 10 min of walking. There was no associated second-wind phenomenon and no history of hypoglycaemic episodes during infancy. He subsequently developed similar symptoms following a viral infection whilst studying for GCSE examinations which required admission to hospital and treatment with intravenous fluids. Daily muscle cramps, affecting the legs and lower back, and myoglobinuria, similar to those experienced during the viral illness, continued into adulthood. He currently runs two to three times per week and finds a high carbohydrate diet ameliorates his symptoms. His younger brother also has similar muscle-related symptoms with aerobic exercise which are aggravated by viral illness.

Examination

Neurological examination in the patient and his brother was normal.

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Investigations

During an episode of myoglobinuria which required hospitalisation his serum CK was over 150,000 IU/L (normal reference range 38–204 IU/L). Acylcarnitine concentrations from whole blood were determined using tandem mass spectrometry. These were raised at 26 umol/L (normal reference range 4–12 umol/L), with C16 and C18:1 carnitine esters the most prominent finding (see Fig. 44.1). Mitochondrial β-oxidation

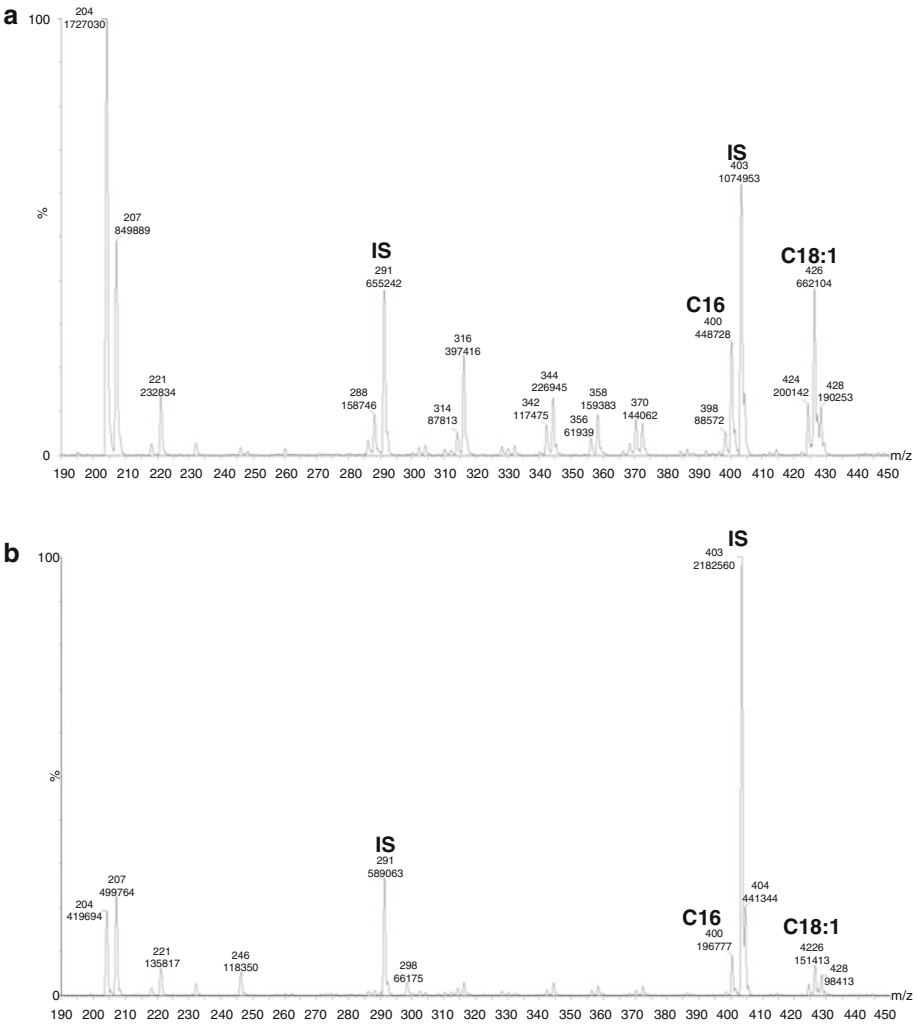

Fig. 44.1 Acylcarnitine profile before and after bezafibrate therapy. Panel (**a**) shows raised *C16* and *C18:1* carnitine esters indicative of CPTII deficiency. On this occasion, C2 and C8–C12 carnitine esters were also raised indicating patient was fasting for some time before the sample was taken. Panel (**b**) shows acylcarnitine profile following Bezafibrate treatment with virtually normal carnitine esters. *IS* internal standard. Key parameters are ratio of C16 and C18:1 to the IS peak between them

flux studies in cultured skin fibroblasts were abnormal and specific enzyme assay of carnitine palmitoyltransferase (CPT) II demonstrated reduced activity. DNA analysis of *CPT2* demonstrated the common homozygous S113L mutation.

Diagnosis

Carnitine palmitoyltransferase II deficiency

Discussion

The clinical presentation of muscle stiffness during or following aerobic/late exercise associated with myoglobinuria and a characteristic acylcarnitine profile is highly suggestive of CPTII deficiency. Adults tend to present with a primary muscle phenotype whilst in infants there is a severe, lethal form, presenting with seizures, liver and cardiac involvement, and a milder phenotype with hypoketotic hypoglycaemia. The latter form may develop into the adult onset myopathic phenotype with increasing age. The diagnosis is confirmed by measuring mitochondrial β-oxidation flux and CPTII enzyme activity in cultured skin fibroblasts, and subsequent genetic analysis of *CPT2*. Muscle biopsy is seldom required and usually normal. Bezafibrate has been shown to enhance CPT2 gene expression in patients with residual CPTII activity. The main differential diagnosis is very long-chain acyl-CoA dehydrogenase deficiency. Measurement of acylcarnitine concentrations and fibroblast studies help distinguish these two disorders of fatty acid oxidation, although acylcarnitine concentrations may be normal in some individuals with CPT2 deficiency.

Reference

Bonnefont JP, Bastin J, Laforêt P, et al. Long-term follow-up of bezafibrate treatment in patients with the myopathic form of carnitine palmitoyltransferase 2 deficiency. Clin Pharmacol Ther. 2010;88(1):101–8.

Case 45
Paralysis Is Only a Part of the Problem

Dipa L. Raja Rayan and Michael G. Hanna

History

A 53 year old Caucasian female had an episode of bilateral leg weakness at age 15 when she was unable to walk or stand. She continued to experience episodes of weakness once every few months in which she would be unable to walk or use her hands. The attacks did not affect her respiratory or bulbar muscles and were precipitated by exercise. The attacks would last approximately 1 week after which she would fully recover. She had minor attacks with pain, cramping and difficulty climbing stairs but only mild weakness. In the last 10 years she had more frequent minor attacks with constant weakness and muscle pain. Her major attacks were controlled by acetazolamide but she developed renal calculi. She also has a history of cardiac arrhythmias from age nine requiring treatment with disopyramide and bisoprolol. Her mother had similar episodes of weakness and died from a cardiac problem at 38. The patient had two affected brothers.

Examination

General examination revealed facial dysmorphism with low set ears, micrognathia, broad based nose, epicanthic folds, high arched palate, clinodactyly and syndactyly (Fig. 45.1). Her neurological examination demonstrated a mild proximal weakness (MRC grade 4+/5) but was otherwise normal.

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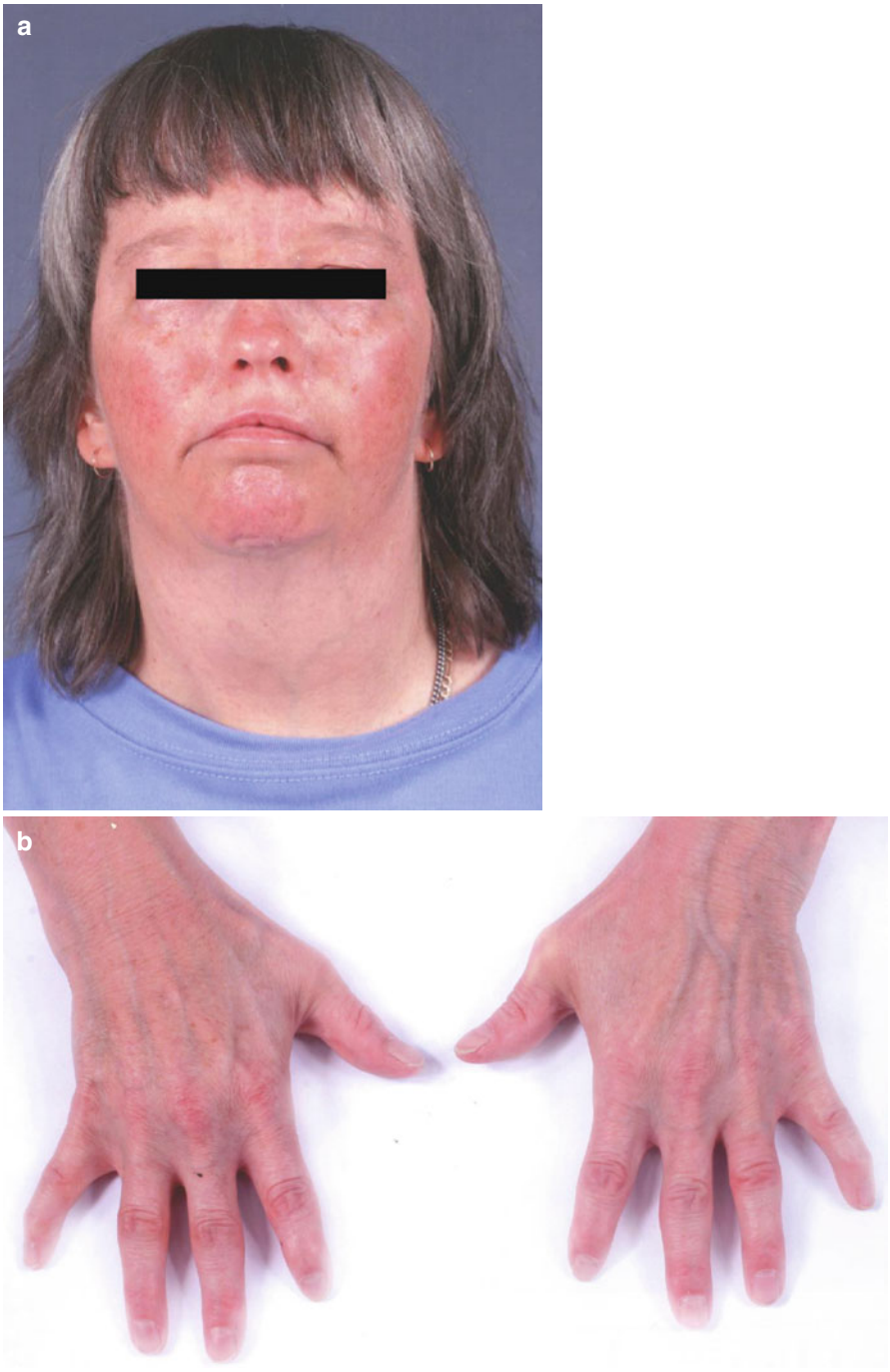

Fig. 45.1 Images of Patient (**a**) Face: demonstrates the small jaw, broad based nose, low set ears and epicanthic folds. (**b**) Hands: clinodactyly of fifth digits (**c**) Feet: syndactyly of second, third and fourth toes

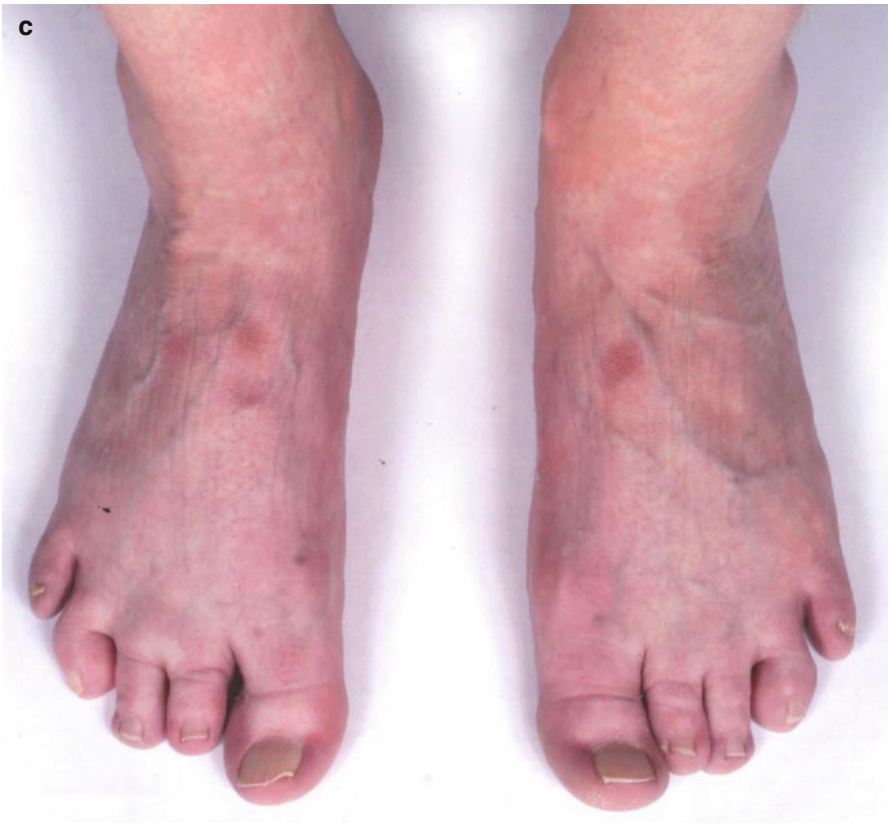

Fig. 45.1 (continued)

Investigations

She had a mildly elevated CK 251 IU (<200). Potassium levels were normal. An ECG showed ventricular bigeminy, long QTc and U waves (Fig. 45.2). EMG was normal. The long exercise test (McManis) was positive and showed a 71 % decrement in CMAP over 50 min (Fig. 45.3). Sodium (*SCN4A*) and Calcium (*CACNA1S*) channel testing were normal. Potassium channel testing (*KCNJ2*) showed the mutation R218W.

Diagnosis

Andersen-Tawil Syndrome

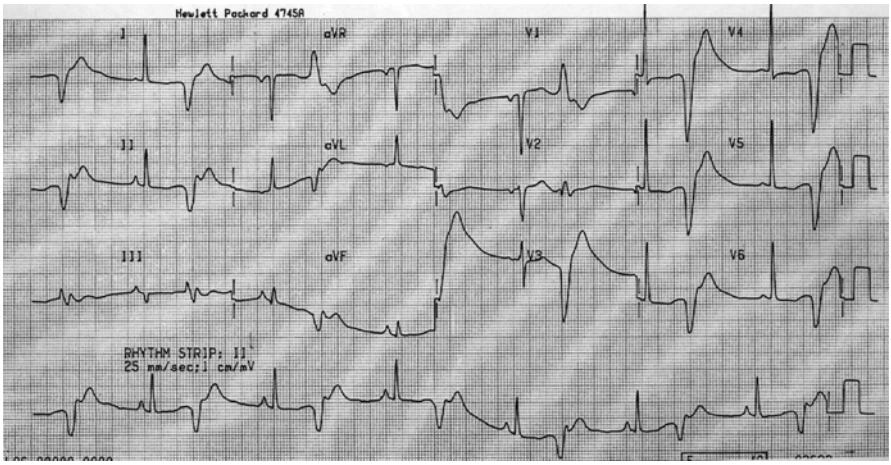

Fig. 45.2 ECG: Shows ventricular bigeminy, long QTc and U waves

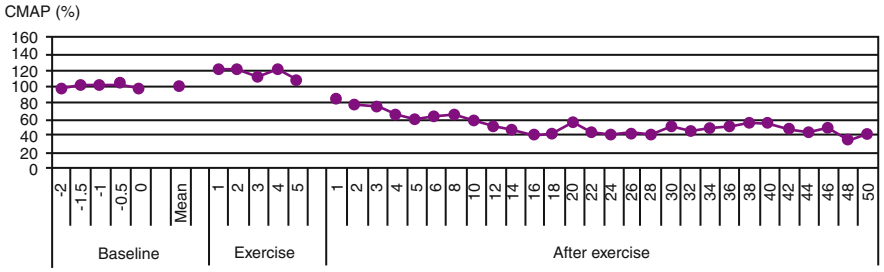

Fig. 45.3 Neurophysiology- Long exercise test: This shows the change in compound muscle action potential amplitude (CMAP) over 50 min following 5 min of exercise of ADM. There is a maximum of 71 % decrement in CMAP

Discussion

The history of inherited episodes of generalised paralysis suggested the diagnosis of periodic paralysis. The triad of episodes of paralysis, cardiac arrhythmias and skeletal abnormalities made a clinical diagnosis of Andersen-Tawil syndrome most probable. Other inherited causes of episodic paralysis are hypokalaemic and hyperkalaemic periodic paralysis but these patients do not have cardiac or skin/bone manifestations. ATS is a very rare dominantly-inherited channelopathy caused by mutations in the inwardly rectifying potassium channel gene *KCNJ2*. It is expressed in muscle, skin, heart, bone and brain. Patients often present with the classic triad of episodes of paralysis, cardiac arrhythmias and skeletal abnormalities, although mild cases may present with only one of these symptoms. Patients should be assessed by cardiology and monitored for arrhythmias as they are at risk of sudden cardiac

death. If frequent arrhythmias are present they should be considered for anti-arrhythmic treatment. The benefit of ICD-pacemaker devices in preventing sudden cardiac death in these patients is unclear and must be assessed on a case by case basis. Episodes of paralysis may occur in both high and low potassium states and therefore patients are commonly treated with acetazolamide or dichlorphenamide. Patients should have regular renal ultrasounds as both these drugs predispose to renal stones.

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Case 46
"Back to the Basics"-Never Forget to Look at the Back

Alejandro Horga and Matthew J. Parton

History

A 46-year-old teacher presented with slowly progressive facial and limb weakness. Her birth and early motor development had been normal. At the age of 27 years she first noticed difficulty raising her right arm to write on the blackboard. Subsequently she developed difficulty whistling, smiling, and closing her eyes. In the limbs, she developed left proximal arm weakness and bilateral foot drop. By her mid-40s she had problems managing stairs and suffered occasional falls. She benefited from bilateral ankle-foot orthoses. She took early retirement on medical grounds because of her physical disabilities. She never had diplopia or dysphagia and there was no suggestion of cardiorespiratory involvement. She had a brother with similar symptoms from the age 16 and their father was also similarly affected.

Examination

She had weakness of eye and mouth closure, a transverse smile and normal eye movements. Neck flexion was mildly weak. Upper limbs examination showed scapular winging and difficulty in raising the arms above the horizontal, which was worse on the right than on the left. In the lower limbs, there was mild weakness of hip flexion and moderate weakness of ankle dorsiflexion. Deep tendon reflexes were preserved. She had no contractures. Sensory testing and general examination were normal.

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Investigations

Serum CK levels were mildly raised at approximately 400–500 IU/L (<204 IU/L). An ECG and EMG at presentation showed no abnormalities.

Genetic testing
Molecular genetic testing of DNA extracted from blood revealed restriction fragments measuring 25 kb with p13E11/EcoRI and 22 kb with p13E11/EcoRI/Bln1, consistent with a contraction of the D4Z4 repeat sequence at 4q35. The same genetic abnormality was identified in the patient's brother.

Diagnosis

Facioscapulohumeral muscular dystrophy (FSHD).

Discussion

FSHD is the third most common muscular dystrophy after the dystrophinopathies and myotonic dystrophy, with an estimated prevalence of around 5/100,000. The disorder is inherited in an autosomal dominant pattern, although 10–30 % of cases result from *de novo* mutations. Clinical onset usually occurs before the third decade but milder cases may remain undiagnosed until later in life or only come to light when a relative is found to have FSHD.

FSHD presents with a distinctive pattern of asymmetric weakness involving the facial, periscapular, humeral, paraspinal, and anterior compartment leg muscles. Symptoms related to facial weakness can occur early in the disease course but difficulty in raising the arms above the head is the most frequent initial complaint. The degree of asymmetry and involvement vary considerably between patients but there is a typical overall pattern of findings on examination. The lower –especially, cheek puff– more than upper facial muscles are weak. Asymmetric scapular winging is very common. In the upper limbs, biceps and triceps muscles are most frequently affected. Pectoral atrophy and lower abdominal weakness are also typical. Lower limb weakness is often distal, characteristically causing foot-drop. Extramuscular manifestations such as high-frequency sensorineural hearing loss and retinal vascular abnormalities are described in 40–60 % of cases but these are usually asymptomatic. Cardiac or respiratory involvement is rare.

There are several muscle conditions which can mimic FSHD, including polymyositis, myofibrillar myopathy, congenital and mitochondrial myopathies, acid maltase deficiency and limb-girdle muscular dystrophies (e.g. LGMD2A). There are, however, some features that favour the diagnosis of FSHD over other myopathies, such as the asymmetry of muscle weakness and wasting, sparing of bulbar muscles and absence of contractures.

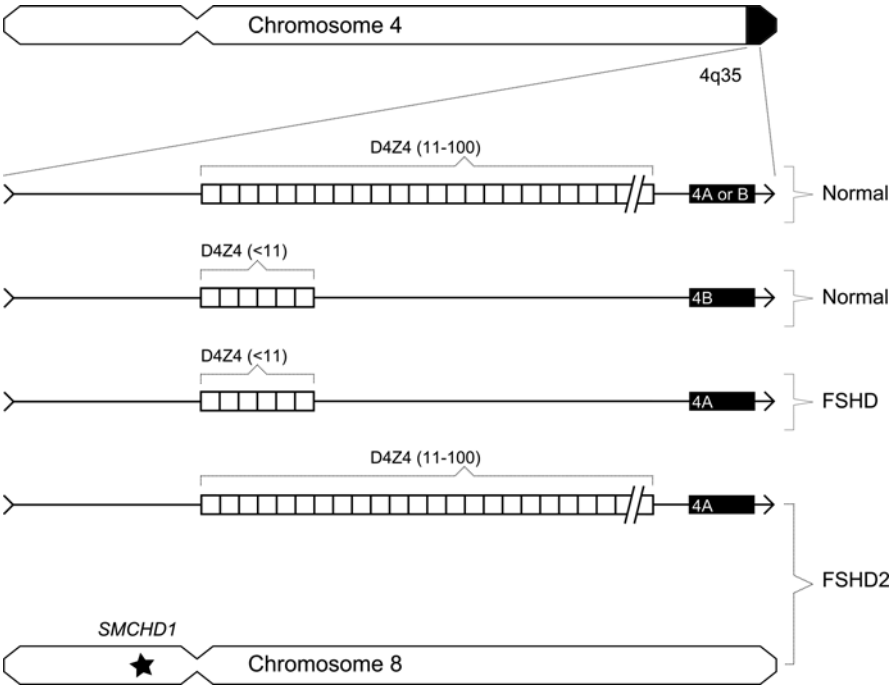

Fig. 46.1 Schematic representation of the genetic mechanisms associated with facioscapulohumeral muscular dystrophy (FSHD). Normal D4Z4 alleles in chromosome 4 have 11 to 100 repeat units. In individuals with FSHD, one of the two D4Z4 alleles has a contraction mutation (1–10 repeat units) on a specific genetic background: a permissive haplotype 4A. However, contraction mutations of the D4Z4 locus on the non-permissive haplotype 4B are non-pathogenic (normal). Individuals lacking the D4Z4 contraction who have both mutations in *SMCHD1* in chromosome 8 and a permissive haplotype in chromosome 4 develop an identical phenotype (FSHD2)

Clinical severity is highly variable but progression of weakness is usually slow. Life expectancy is typically not shortened; however, 20 % of individuals eventually become wheelchair-dependent. Current treatment is symptom-directed. Surgical fixation of the scapula, ankle-foot orthoses and abdominal braces may improve function in selected cases.

The pathogenesis of FSHD is poorly understood and the genetic mechanism is complex. About 95 % of affected individuals have a deletion of a 3.3 kb DNA repeat motif in the D4Z4 locus, which is located in the subtelomeric region of chromosome 4q35. Normal D4Z4 alleles contain 11–100 repeat units. In FSHD, one of the two D4Z4 alleles is contracted to <11 repeat units. This contraction alone, however, is not sufficient to cause the disease. A polymorphic segment telomeric to the D4Z4 locus exists in two allelic forms in the population, 4A and 4B, and FSHD is only associated with 4A alleles (permissive haplotypes; Fig. 46.1).

In FSHD, the contracted D4Z4 allele undergoes changes in its chromatin structure, including DNA hypomethylation and chromatin relaxation. Similar changes are seen in a proportion of patients with an identical phenotype but who lack the D4Z4 contraction (FSHD2). Recent studies indicate that FSHD2 occurs in individuals harbouring both a permissive haplotype on chromosome 4 and heterozygous mutations in the gene *SMCHD1* on chromosome 8 (Fig. 46.1).

Current molecular diagnosis of FSHD relies on the detection of the contraction mutation of D4Z4. This test prevents the need for invasive muscle biopsy and should be considered as the first line investigation for clinically suggestive cases. Molecular diagnosis of FSHD2 is still in a research phase and is not yet available in diagnostic laboratories.

Reference

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Case 47
Is It Time to Take the Heat Out of the Problem?

Alejandro Horga and Rosaline Quinlivan

History

A 35-year-old man suffered three episodes of fever, flu-like symptoms, severe myalgia and myoglobinuria in the previous 2 years. These had followed unaccustomed exertion in hot and humid environments, during trips to India and Brazil. In the days preceding the episodes he had also been drinking alcohol in excess. A rise in serum CK level to 3850 IU/L (<204) was documented during one episode. He was otherwise well and his medical history was unremarkable, although he gave a history of prolonged muscle stiffness following exercise. He had undergone surgery under general anaesthesia in the past with no complications. There was no family history of similar symptoms or anaesthetic reactions.

Examination

Neurological examination was normal except for very mild facial and hip adduction weakness. There was no muscle wasting or rippling.

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Investigations

Blood lactate was mildly raised at 1.96 mmol/L (<1.6 mmol/L). Other laboratory tests, including serum CK, thyroid function tests, plasma carnitine and acyl-carnitine profiles and urine organic acids, were normal. Screening for infections, including dengue, malaria, amoebiasis, toxoplasmosis, brucellosis and intestinal nematodes, was negative. Muscle MRI showed no abnormalities (Fig. 47.1a).

Muscle biopsy

Staining for glycogen, lipid, acid phosphatase, phosphorylase and adenylate deaminase was normal. Cytochrome *c* oxidase (COX) staining showed a preserved two-fibre pattern (Fig. 47.1b). Poorly-defined areas of central pallor were seen in both dark (type I) and light (type II) staining fibres. Electron microscopy showed several fibres with one or more small mini-cores (Fig. 47.1c, arrows) and larger core-like areas (Fig. 47.1d, arrows) of myofibrillar disruption with Z-line streaming.

Mitochondrial respiratory chain enzyme activities in muscle were within normal limits.

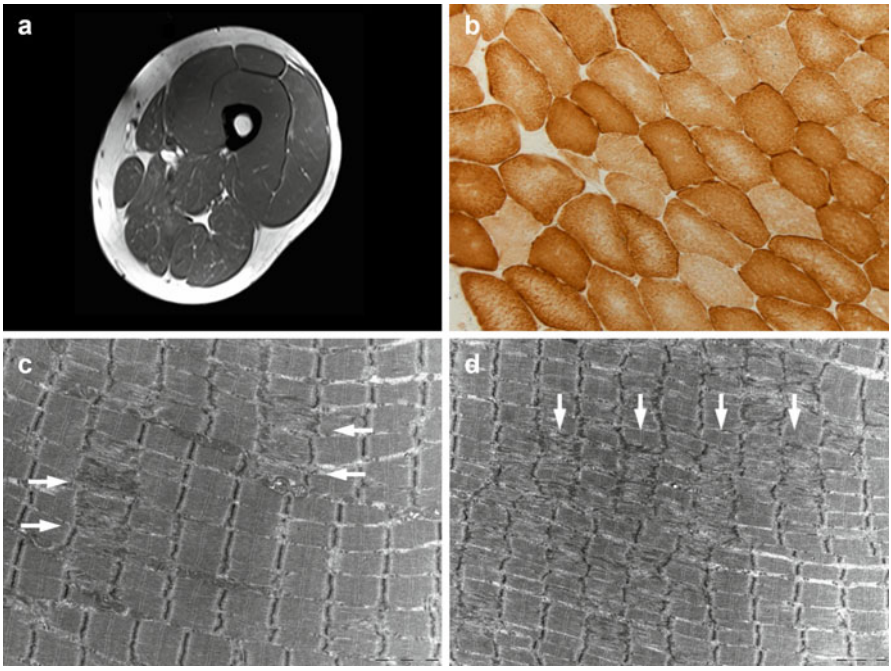

Fig. 47.1 (**a**) Muscle MRI showed no abnormalities. (**b**) Cytochrome *c* oxidase (COX) staining showed a preserved two-fibre pattern. (**c**) Electron microscopy showed several fibres with one or more small mini-cores (*arrows*). (**d**) Larger core-like areas (*arrows*) of myofibrillar disruption with Z-line streaming

Genetic testing

Genetic testing for common mitochondrial DNA point mutations and large scale rearrangements was negative. Sequence analysis of the *RYR1* gene showed a heterozygous missense mutation (p.Lys1393Arg) in exon 28, previously reported as pathogenic in a patient with malignant hyperthermia (MH). A sequence variant of uncertain significance was also detected. His father carried both variants.

Diagnosis

Heat/exercise-induced rhabdomyolysis associated with a MH-causative mutation in *RYR1*.

Discussion

Rhabdomyolysis may result from traumatic, ischemic or toxic injury to the skeletal muscle, infections, and electrolyte or endocrine disorders. Inherited myopathies are also an important cause, especially in recurrent rhabdomyolysis, and include disorders of carbohydrate and lipid metabolism, mitochondrial myopathies, some congenital myopathies and muscular dystrophies and MH. In the present case, the finding of central core-like areas on muscle biopsy suggested an RYR-1 mutation.

MH is a skeletal muscle disorder characterized by susceptibility to volatile anaesthetics or depolarizing muscle relaxants, which trigger calcium release from the sarcoplasmic reticulum via the ryanodine receptor (RyR), leading to muscle contraction and a sustained hypermetabolic state. The disorder manifests with a combination of hyperthermia, hypercapnia, acidosis, tachycardia, muscle rigidity, rhabdomyolysis, hyperkalemia and myoglobinuria, occurring during or shortly after general anaesthesia. Death may result without prompt treatment.

MH is inherited in an autosomal dominant manner. Mutations in *RYR1*, the gene encoding the skeletal muscle RyR, account for 70–80 % of cases. Of note, mutations in this gene are also the most common cause of core myopathies, a group of congenital myopathies, which are allelic with MH. Patients with core myopathies may be susceptible to MH, and those with MH may demonstrate cores on muscle biopsy, as shown in this case.

MH-causing mutations have also been identified in *CACNA1S*, and three additional susceptibility loci have been mapped. The genetic heterogeneity of MH means that a functional diagnostic technique may be used and consists of the *in vitro* assessment of the contracture response of biopsied muscle to caffeine and halothane (IVCT). Patients with negative genetic results should be tested by IVCT.

There is growing evidence suggesting an association between MH, heat stroke (HS) and exercise-induced rhabdomyolysis (ER). Several reports have described cases of MH–like episodes after physical overexertion and environmental heat. In

addition, a proportion of individuals with HS or ER have an abnormal IVCT. Recently, both positive IVCT and *RYR1* mutations have been demonstrated in cases of isolated or recurrent ER, with or without exposure to hot temperatures.

It seems, therefore, that some individuals with HS and ER may be at risk for MH. From the available evidence, it is not possible to establish definite recommendations regarding the need for MH testing in these cases. However, this might be considered in patients with unexplained or recurrent ER or HS, episodes of ER occurring at low levels of activity or persistently elevated CK.

Acknowledgment We thank Dr. Rahul Phadke and Dr. Janice Holton for their assistance with the pathology.

Reference

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Case 48
Praying for an Answer Can Be Helpful

Alejandro Horga and Rosaline Quinlivan

History

A 44-year-old man presented with slowly progressive proximal limb weakness. He had normal early motor milestones and could run and play sports in his childhood. At the age of 10 years he started having frequent falls. At the age of 25 years he could still climb stairs but was not able to run. Sixteen years later he was unable to walk unaided. His family was remarkable for two of his siblings having similar symptoms, with onset in childhood or early adolescence. His mother, maternal grandfather and two other relatives on his mother's side of the family were also affected. None of them had cardiac or respiratory involvement.

Examination

There was hyperkeratosis pilaris over both upper limbs and a keloid scar on the thorax. He was unable to stand without aid and had lumbar hyperlordosis. There was no facial weakness or ophthalmoplegia. Neck flexion and extension were mildly weak. Examination of the upper limbs showed mild left scapular winging, generalised wasting and predominantly proximal weakness. Marked flexion

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contractures of the long finger flexors and left elbow were noted. In the lower limbs, there was severe muscle weakness and wasting proximally. He had calf hypertrophy and normal power distally. The remainder of the examination was unremarkable.

Investigations

Serum CK levels were mildly raised at 422 IU/L (<204). EMG showed small-amplitude, polyphasic MUAPs in proximal lower limb muscles. Cardiac ECHO and ECG was normal.

Muscle MRI

There was fatty replacement of most thigh muscles with relative sparing of the sartorius and gracilis (Fig. 48.1a, arrows) and a central area of abnormal signal within

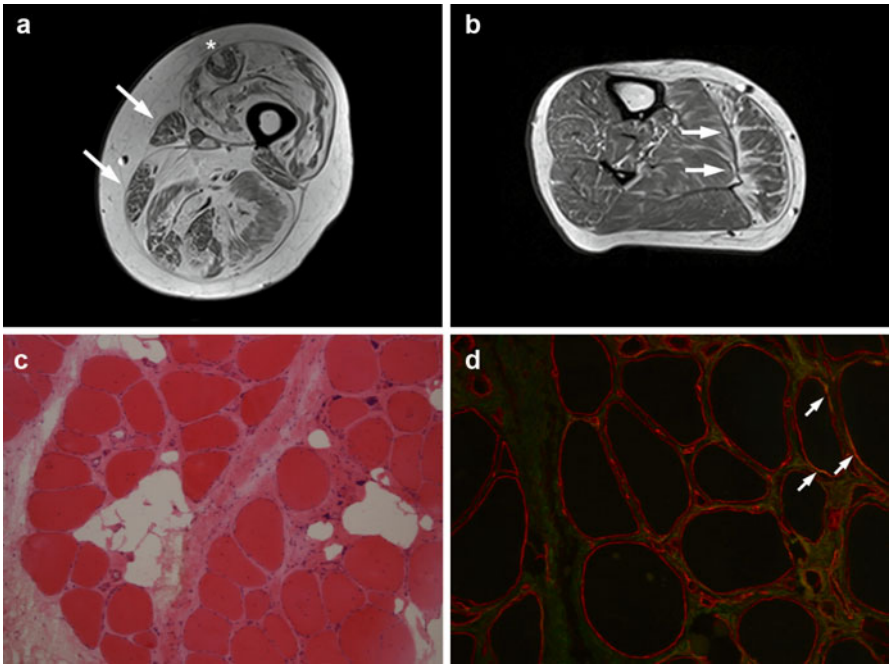

Fig. 48.1 (**a**) Muscle MRI demonstrating fatty replacement of most thigh muscles with relative sparing of the sartorius and gracilis (*arrows*) and a central area of abnormal signal within the rectus femoris (*asterisk*). (**b**) Calf muscles were affected to a lesser degree and a T1-hyperintense rim could be observed between the soleus and medial gastrocnemius (*arrows*). (**c**) H&E stained sections showed marked myopathic changes with fibre hypertrophy and atrophy, increased internal nuclei and diffuse endomysial fibrosis with accompanying focal fat infiltration. (**d**) Immunofluorescence double labeling for collagen VI (*labeled green*) with another basal lamina marker perlecan (*labeled red*) showed marked reduction of collagen VI at the basal lamina of most fibres with excess deposition in the endomysium and perimysium. Traces of collagen VI (composite *yellow*; *arrows*) could be seen on some fibres

the rectus femoris (Fig. 48.1a, asterisk). Calf muscles were affected to a lesser degree and a T1-hyperintense rim could be observed between the soleus and medial gastrocnemius (Fig. 48.1b, arrows).

Muscle biopsy
H&E stained sections showed marked myopathic changes with fibre hypertrophy and atrophy, increased internal nuclei and diffuse endomysial fibrosis with accompanying focal fat infiltration (Fig. 48.1c). Immunofluorescence double labeling for collagen VI (labeled green) with another basal lamina marker perlecan (labeled red) showed marked reduction of collagen VI at the basal lamina of most fibres with excess deposition in the endomysium and perimysium (Fig. 48.1d). Traces of collagen VI (composite yellow; arrows) could be seen on some fibres. Sarcolemmal and nuclear immunostaining revealed no other abnormalities.

Genetic testing
Genetic testing for mutations in *LMNA* and *FHL1* was negative. Sequence analysis of collagen VI genes revealed two previously unreported sequence variants in *COL6A1* and *COL6A2* (c.588 + 19dupC and c.1572 + 3G > A, respectively).

Diagnosis

Bethlem myopathy (BM).

Discussion

Secondary muscle contractures can occur in most myopathies, but early and prominent contractures are a hallmark of Emery-Dreifuss muscular dystrophies (EDMD) and collagen VI-related myopathies. Collagen VI-related disorders present as a phenotypic spectrum from the severe congenital form of Ullrich congenital muscular dystrophy (UCMD) through to milder, later onset forms of BM. In this case, the presence of skin abnormalities, absence of cardiac involvement and the MRI findings supported the diagnosis of BM, which was confirmed by pathological and genetic studies.

Collagen VI is a ubiquitous microfibrillar component of the extracellular matrix. In skeletal muscle, it forms a continuous network connecting the basement membranes with the interstitial collagen fibres. Collagen VI molecules result from the assembly of three peptide chains (α1, α2 and α3) encoded by three different genes (*COL6A1* and *COL6A2* on 21q22.3; and *COL6A3* on 2q37).

UCMD is inherited in an autosomal recessive or *de novo* dominant manner. It presents at birth or early infancy with hypotonia, muscle weakness, motor delay, proximal joint contractures and hyperlaxity of distal joints. Respiratory impairment requiring non-invasive ventilation, scoliosis and loss of independent ambulation often occur within the first two decades of life.

BM is an autosomal dominant condition, characterized by proximal weakness and contractures that frequently affect the long finger flexors, elbows and ankles. Age of onset varies from prenatal to adulthood. The disease is relatively mild and slowly progressive, but more than two-thirds of patients aged 50 years or over require aids for ambulation, and respiratory impairment can occur.

In both UCMD and BM, skin features such as hyperkeratosis pilaris and abnormal scarring may be present. Serum CK levels are normal or mildly elevated. In contrast to EDMD, cardiac involvement is not a feature. Muscle histopathological changes range from myopathic to dystrophic, with collagen VI immunolabeling usually normal in BM and moderately reduced to absent in UCMD.

Muscle MRI can be a useful aid to the differential diagnosis with other myopathies. In BM, MRI typically shows involvement of the peripheral region of the vasti muscles and the central area of the rectus femoris. In UCMD, MRI shows a diffuse involvement of thigh muscles with relative sparing of sartorius, gracilis and adductor longus. There might be overlap between the two entities, as illustrated here. In fact, at calf level, a rim between the soleus and gastrocnemius may be seen in both BM and UCMD.

Acknowledgment We thank Dr. Rahul Phadke for his assistance with the pathology.

Reference

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Case 49
Neuromuscular Junction Dysfunction Is Not Always Myasthenic

Alejandro Horga and Rosaline Quinlivan

History

A 39-year-old man presented with slowly progressive generalized weakness. His past history was remarkable for neonatal hypotonia and delayed motor milestones during infancy. There was a family history of male neonatal death due to hypotonia and muscle weakness on her mother's side of the family. His childhood had been normal and he had played several sports. In his early 30s, he began to notice a slowly progressive decline in his upper and, to a lesser degree, lower limb mobility. He had no swallowing difficulty or respiratory problems. He described no diplopia but developed bilateral cataracts, for which he had surgery in his early 40s.

Examination

He had mild, non-fatigable ptosis, external ophthalmoplegia and facial weakness. There was a high arched palate. Neck flexion and extension were weak. Examination of the upper limbs showed wasting of shoulder-girdle muscles and mild weakness of shoulder abduction. He had normal power distally. In the lower limbs, there was no muscle weakness or wasting. Limb weakness was not fatigable. Bilateral

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contractures of the wrist extensors, finger flexors, quadriceps and hamstrings were noted. There was no rigid spine. Examination was otherwise normal.

Investigations

Serum CK levels were mildly raised at 411 IU/L (<204). Testing for anti-AChR and anti-MuSK antibodies was negative. Other laboratory tests, including thyroid function tests, were normal. Cardiac assessment was unremarkable.

Neurophysiology

Sensory nerve conduction studies showed normal SNAP amplitudes and conduction velocities except for reduced SNAP amplitudes in the lower limbs (sural 2 μV, superficial peroneal 2 μV), possibly as a consequence of a pitting oedema. Motor studies of median, ulnar and tibial nerves showed normal CMAP amplitudes and conduction velocities at the lower limit of normal. Repetitive stimulation (RNS) of the accessory nerve at 3/s with recording from trapezius showed a small CMAP amplitude (baseline to negative peak) of 0.9 mV and a 16 % decrement of this response at rest (Fig. 49.1A), which recovered after short exercise (10 s) to 6 % and reappeared after long exercise (60 s) to 12 %. Routine needle EMG revealed small-amplitude, short-duration polyphasic MUAPs with early recruitment in proximal muscles (Fig. 49.1B, biceps brachii).

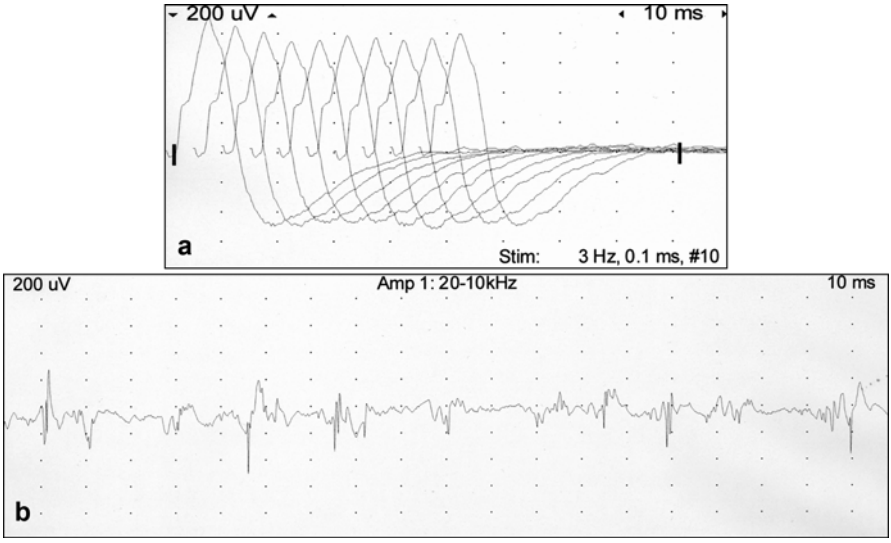

Fig. 49.1 (**a**) Repetitive stimulation (RNS) of the accessory nerve at 3/s with recording from trapezius showed a small CMAP amplitude (baseline to negative peak) of 0.9 mV and a 16 % decrement of this response. (**b**) Routine needle EMG revealed small-amplitude, short-duration polyphasic MUAPs with early recruitment in proximal muscles (biceps brachii in the figure)

Muscle biopsy
A muscle biopsy performed as an infant was reported to show features suggestive of centronuclear myopathy but was not available for review.

Genetic testing
Sequence analysis of the *MTM1* gene identified a previously reported heterozygous missense mutation (p.Leu70Phe) in exon 4.

Diagnosis

X-linked myotubular myopathy.

Discussion

The combination of chronic bilateral ophthalmoplegia and limb weakness is characteristic of neuromuscular junction disorders and some myopathies, namely mitochondrial myopathies, oculopharyngeal muscular dystrophy, oculopharyngodistal myopathy and congenital myopathies (e.g. centronuclear myopathy and multi-minicore disease). In this case, the clinical presentation, laboratory studies and EMG findings were consistent with a chronic myopathy with congenital onset. Given the decremental response with RNS, a congenital myasthenia might have been considered. However, a previous muscle biopsy was suggestive of centronuclear myopathy, which was confirmed genetically. Defects in neuromuscular junction transmission are indeed increasingly recognised in some congenital myopathies and may respond to treatment.

Centronuclear myopathies are a group of pathologically-defined congenital disorders characterized by an increased proportion of small myofibres with centrally located nuclei. Three main forms are described: X-linked recessive, autosomal dominant and autosomal recessive, which are caused by mutations in *MTM1*, *DNM2*, and *BIN1* or *RYR1* genes, respectively.

X-linked centronuclear or myotubular myopathy (XLMTM) typically presents in males with severe generalised hypotonia and weakness at birth, often associated with respiratory insufficiency and suck or swallowing difficulties. Affected infants often have a myopathic face and external ophthalmoparesis, the latter being uncommon in other neonatal onset congenital myopathies. Additional features are large head size, long body length, cryptorchidism and contractures. In most cases the course is fatal within the first months of life. A proportion of infants may survive into their teens or beyond, but ventilatory support is often required for the duration of life. The myopathy appears to be non-progressive, although myopathy-related complications (e.g. scoliosis, malocclusion or myopia) may develop. Milder phenotypes with slowly progressive or late-onset weakness and longer survival have been also described, as in the present case.

More than 200 different mutations in the *MTM1* gene (Xq28) have been reported among patients with XLMTM. These occur throughout the entire coding region and result in loss-of-function or null alleles. The gene product, myotubularin 1, is a ubiquitously expressed phosphoinositide 3-phosphatase that probably plays an important role in the endocytic pathway. Recent studies in *MTM1* knock-out mice indicate that loss of myotubularin 1 results in structural defects of the skeletal muscle triads and in abnormal calcium release from the sarcoplasmic reticulum.

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Case 50
Carrying Shopping Can Be Difficult, Especially for Men

Chris Turner and Umesh Vivekananda

History

A nineteen year old man presented with a long history of progressive limb weakness and deformity at the elbows. He was the product of a normal delivery with normal feeding and breathing. At one year, his parents noticed that he was unable to support his head independently. He otherwise reached normal motor and cognitive milestones. At four, he was especially slow at running with frequent trips and falls. He continued to be poor at sports and discontinued sporting activity aged twelve. He became progressively more fatigued when walking and using his arms. He also found increasing restriction of movement at his elbows. His swallowing and breathing were normal and there was no clinical history to suggest nocturnal hypoventilation. There was no history of kyphoscoliosis and in general his symptoms were stable with minimal progression over the past few years.

There was no evidence of cardiomyopathy on ECHO or conduction defects on ECG.

He had two brothers who were unaffected but his mother was mildly affected with upper limb weakness. His maternal grandfather developed a similar clinical course.

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Examination

Examination of the cranial nerves demonstrated mild symmetrical facial weakness. His upper limbs and distal lower limbs below the knees demonstrated reduced muscle bulk. There was weakness in biceps to MRC grade 4/5. There was a reduced carrying angle to 140° at the elbow bilaterally associated with contractures in the biceps. Otherwise upper limb power was normal. In the lower limbs, he had preserved power, and he was able to walk on his toes and heels. He was able to rise from crouching with arms crossed. Reflexes were present throughout and sensory examination was normal. General examination was otherwise normal. Lung function testing demonstrated FEV1 3.58 L and FVC 3.76 L. His creatine kinase level was 792 (<240)

Genetic testing
Deletion c.705_722del18 in exon 6 of the emerin gene

Diagnosis

X-linked Emery Dreifuss Muscular dystrophy (EDMD).

Discussion

Emery Dreifuss Muscular dystrophy was first described in 1966 with neuromuscular presentation in early childhood. The course of the disease is slower and more benign in comparison with Duchenne muscular dystrophy. Early loss of ambulation is rarely seen. The phenotype is characterised by three cardinal manifestations. Firstly, contractures of the Achilles tendons, elbows, and/or posterior cervical muscles usually occur early, and before there is clinically significant weakness. Secondly, slowly progressive muscle wasting and weakness with a humeroperoneal distribution occurs early in the course of the disease. Later weakness extends to the proximal limb-girdle musculature. Thirdly, dilated cardiomyopathy usually manifests as spectrum of cardiac conduction defects such as sinus bradycardia, prolongation of the PR interval, or complete heart block. This may necessitate cardiac pacemaker implantation. Atrial paralysis with absent P waves on electrocardiography should always prompt exclusion of this form of muscular dystrophy. Evidence of cardiac disease is usually present by age 30 years and becomes more evident as muscle weakness progresses. Serious cardiac manifestations can arise in the absence of muscle weakness and is a possible cause of sudden death in apparently healthy young adults.

Emerin-associated EDMD is inherited as an X-linked recessive trait and is caused by mutations in the STA gene at Xq28, which encodes the nuclear membrane

protein emerin. In almost all cases, there is complete absence of emerin on muscle biopsy analysis. Immuno-histochemistry of skin fibroblasts may show a mosaic pattern of expression of emerin in female carriers, thus providing a valuable test for identification of such individuals.

The autosomal dominant form of EDMD can present with a more severe clinical phenotype compared with X-linked, but with marked inter-generational variability. It is caused by mutations of the LMNA gene at 1q21. This gene encodes lamins A and C, which comprise part of the nuclear lamina which is a fibrous layer on the nucleoplasmic side of the inner nuclear membrane. Diagnosis of autosomal dominant Emery-Dreifuss muscular dystrophy can only be verified by mutation analysis, and not by muscle protein studies. There is a rare, more serious autosomal recessive form of EDMD, which is also caused by mutations of the LMNA gene as well as other forms of EDMD caused by mutations in other genes such as FHL1.

The diagnosis of EDMD should be considered in any patient with a neuromsucular phenotype who presents with prominent early contractures. The prominent cardiac manifestations should raise early concerns regarding counselling of family members for genetic testing and cardiac screening.

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