Emergencies in Neuromuscular Disorders

Maxwell Damian
Marianne de Visser
Editors

Springer

Emergencies in Neuromuscular Disorders

Maxwell Damian • Marianne de Visser
Editors

Emergencies in Neuromuscular Disorders

Springer

Editors
Maxwell Damian
Cambridge University Hospitals
Cambridge, UK

Marianne de Visser
Department of Neurology
Amsterdam University Medical
Centres, location Academic Medical Center
Amsterdam, the Netherlands

ISBN 978-3-030-91931-3 ISBN 978-3-030-91932-0 (eBook)
https://doi.org/10.1007/978-3-030-91932-0

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Foreword

The birth of respiratory intensive care units (ICUs) is tightly connected with the history of a pandemic neuromuscular disorder (NMD): poliomyelitis. As a child I remember the "whispering" of my parents, and later seeing pictures in newspapers, about "iron lung." Reading much later about the Copenhagen polio crisis in the 1950s when young students were recruited to continuously help with manual ventilation using rubber bags reminded me how as a medical student during war-time related electrical stoppage, I had to "replace" for hours the old Bennett respirator with a similar type of air bag. We have all seen the major advance in the respiratory emergency care for all patients in the seven decades since that global polio epidemic. By 2020, the modern respiratory and emergency care system came again under stress with yet another infection—the SARS-CoV-2 pandemic. Patients with various NMDs were at special risk because of their basic muscle weakness (and at time their immunesuppressant therapy). Thus, a book about the unique emergencies in NMDs patients seems very timely.

Emergency situations in NMDs are related to acute dysfunction of one or more of the three organs: muscle, heart, and kidney. Acute generalized weakness of skeletal (voluntary) and respiratory muscles can lead to quadriplegia and generalized hypoxia. Cardiac failure and conduction defects are also known features of some hereditary and acquired myopathies. Rapid rhabdomyolysis is a major risk for renal function. Such situations may complicate various NMDs or even be their presenting feature. Thus, early recognition and prevention combined with urgent treatment, usually in an ICU, is of utmost importance.

Drs Maxwell Damian and Marianne de Visser have edited this very important book which is filling a needed gap in the comprehensive treatment of myopathies, neuromuscular junction disorders, neuropathies, and motor neuron disorders. Dr. Damian is a very active neurological consultant and ICU physician from Cambridge (UK), who specializes in emergency treatments of NMDs. He was the leading force behind an international group of neuromuscular experts (which Prof de Visser and myself were part of) which continuously generated guidelines about the management of NMD patients during the SARS-CoV-2 pandemic. Prof de Visser from Amsterdam (the Netherlands) is a world-known leader in neuromuscular disorders.

Her constant drive to dissipate the knowledge in various fields of NMDs is evident not only by her long publication list, but also by her activity in various international neurological societies in which she played a leading role. I was honored to collaborate with both of them in academic teaching in the NMD field and they are clearly most suitable for the production of this book. They have indeed assembled a group of leading experts to generate this publication (and contributed chapters in their field of interest).

The book covers many aspects of the emergency conditions which are typical for NMDs. Early recognition and evaluation of the emergency situation is of prime importance and two chapters are devoted to it. Respiratory management is discussed not only in the acute critical care but two chapters discuss also weaning patients from respiratory support and also chronic ventilation enabling many patients with NMDs to continue social and even productive life with chronic breathing support. Emergencies in specific conditions are reviewed in seven separate chapters of this book (from motor neuron disorders, through peripheral neuropathies and neuromuscular junction, myopathies and various metabolic myopathies). One should remember that ICU hospitalization may by itself be a risk for neuromuscular complications and chronic sequelae and a full chapter is devoted to this under-recognized topic. We should commend the Editors for not forgetting ethical and social aspects of emergencies in NMDs devoting a chapter to palliative care and another to countries with limited resources to administer the most advanced emergency treatment to their patients.

In summary, this book is an important addition not only to the NMDs experts but also to physicians of various fields of medicine who deal with such patients.

Professor (Emeritus) of Neurology Zohar Argov
Hadassah Medical Center
Jerusalem, Israel

Faculty of Medicine
Hebrew University of Jerusalem
Jerusalem, Israel

Preface

Neuromuscular disorders are a heterogeneous group of conditions with genetic, inflammatory, metabolic and sometimes infectious backgrounds. These conditions rarely present as a neuromuscular emergency, although many chronic neuromuscular disorders carry the potential for acute deterioration or may rarely manifest primarily as acute illness.

Expertise on neuromuscular disorders is often concentrated in highly specialized neuromuscular clinics that focus on diagnostics and long-term management rather than on the management of emergency situations. Therefore, neuromuscular patients presenting with acute illness are initially likely to be managed by physicians who have little or no experience of treating patients with neuromuscular disease. The potential for misinterpretation of clinical symptoms and signs, misdiagnosis, and mismanagement is therefore high. Conversely, and especially if there is comorbidity, misdiagnosis of the acute episode may occur if the patient is initially evaluated by a neuromuscular expert with limited exposure to emergency medicine. Ideally, neuromuscular experts will advise on timely specialist tests in the acute setting in consultation with emergency physicians if a neuromuscular patient is presented as an emergency.

This was the rationale for writing *Emergencies in Neuromuscular Disorders*. This comprehensive book addresses the emergencies in neuromuscular disease from the perspective of timely recognition and assessment, diagnosis and management. The book fills the gap in guidelines by providing an evidence-based guidance for the adult or pediatric neurologist confronted by an acutely ill patient in a potentially life-threatening situation.

Each chapter is strictly organized around case vignettes that emphasize clinical relevance. The electronic supplementary material is provided as an integral tool to facilitate accessibility and understanding of a notoriously difficult field of neurology. The role of patients, who are increasingly involved in many management decisions, is highlighted in a chapter on ethical issues discussing withholding or withdrawing life-sustaining therapy, patient end-of-life values, wishes, and preferences, and on advance directives. Finally, at the end of each chapter, there is a set of

questions which is meant to serve as a learning aid by assessing the knowledge from the preceding chapter.

The publication is aimed equally at the non-specialist neurologist/pediatrician (in training) in frontline clinical practice confronted by a rare disorder needing immediate management decisions, at the clinical specialist referring for guidance in specific management aspects, and at the specialist researcher keen to maintain clinic relevance.

We chose the authors of each chapter based on their expertise in their field, and we are extremely grateful for their contributions. A special thanks also goes to Jan Kuks who was responsible for the self-assessment questions.

We hope that you will enjoy reading this book and develop a greater confidence in caring for your patients with neuromuscular disorders if they present in an emergency situation.

Ipswich, Suffolk, UK — Maxwell Damian
Amsterdam, The Netherlands — Marianne de Visser

Contents

Contributors

Jelle van den Ameele Department of Clinical Neurosciences, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK

MRC Mitochondrial Biology Unit, University of Cambridge, Cambridge, UK

Jean Bergounioux Service de Neurologie Pédiatrique et Réanimation, DMU Santé Enfant Adolescent (SEA) Hôpital Raymond Poincaré, APHP Université Paris-Saclay, Garches, France

UMR U1179 (INSERM/UVSQ) Handicap neuromusculaire: Physiopathologie, Biothérapie et Pharmacologie appliquées (END-ICAP), Versailles, Montigny-le-Bretonneux, France

Maxwell Damian Cambridge University Hospitals, Cambridge, UK

Essex Cardiothoracic Centre, Basildon, UK

Philip Van Damme Department of Neurosciences, Experimental Neurology, and Leuven Brain Institute (LBI), KU Leuven—University of Leuven, Leuven, Belgium

Laboratory of Neurobiology, VIB, Center for Brain and Disease Research, Leuven, Belgium

Department of Neurology, University Hospitals Leuven, Leuven, Belgium

Michael A. Gaytant Department of Pulmonary Diseases and Home Mechanical Ventilation, University Medical Center Utrecht, Utrecht, the Netherlands

Stefanie Glaubitz University Medical Center Göttingen, Göttingen, Germany

Grainne S. Gorman Wellcome Centre for Mitochondrial Research, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK

NHS Highly Specialised Service for Rare Mitochondrial Disorders, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

Janneke Horn Amsterdam University Medical Centres, location Academic Medical Centre, Amsterdam, the Netherlands

Rita Horvath Department of Clinical Neurosciences, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK

John Van Geest Cambridge Centre for Brain Repair, University of Cambridge, Cambridge, UK

Heinz Jungbluth Department of Paediatric Neurology—Neuromuscular Service, Evelina Children's Hospital, Guy's and St Thomas' NHS Foundation Trust and King's College London, London, UK

Anneke J. van der Kooi Amsterdam University Medical Centres, location Academic Medical Centre, Amsterdam, the Netherlands

Nicola Latronico Spedali Civili University Hospital, Brescia, Italy

Hadi Manji National Hospital for Neurology and Neurosurgery, London, UK

Blaise Mbieleu Service de Neurologie Pédiatrique et Réanimation, DMU Santé Enfant Adolescent (SEA) Hôpital Raymond Poincaré, APHP Université Paris-Saclay, Garches, France

Unité Neuromusculaire de l'Enfant, Centre de Référence Maladies Neuromusculaires Nord-Est Ile de France (Filière FILNEMUS), Paris, France

Garches-Necker-Mondor-Hendaye Consortium (GNMH), Reference Center on Neuromuscular Diseases for the European Network (Euro-NMD), Paris, France

Pinki Munot Great Ormond Street Hospital, London, UK

Gaurav Nepal Department of Internal Medicine, Tribhuvan University Teaching Hospital, Kathmandu, Nepal

Yi Shiau Ng Wellcome Centre for Mitochondrial Research, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK

NHS Highly Specialised Service for Rare Mitochondrial Disorders, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

Rajeev Ojha Department of Neurology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal

Helene Prigent UMR U1179 (INSERM/UVSQ) Handicap neuromusculaire: Physiopathologie, Biothérapie et Pharmacologie appliquées (END-ICAP), Versailles, Montigny-le-Bretonneux, France

Garches-Necker-Mondor-Hendaye Consortium (GNMH), Reference Center on Neuromuscular Diseases for the European Network (Euro-NMD), Paris, France

Service de Physiologie et Explorations Fonctionnelles, DMU Handicap et locomoteur, Hôpital Raymond Poincaré, APHP Université Paris-Saclay, Garches, France

Susana Quijano-Roy Service de Neurologie Pédiatrique et Réanimation, DMU Santé Enfant Adolescent (SEA) Hôpital Raymond Poincaré, APHP Université Paris-Saclay, Garches, France

Unité Neuromusculaire de l'Enfant, Centre de Référence Maladies Neuromusculaires Nord-Est Ile de France (Filière FILNEMUS), Paris, France

UMR U1179 (INSERM/UVSQ) Handicap neuromusculaire: Physiopathologie, Biothérapie et Pharmacologie appliquées (END-ICAP), Versailles, Montigny-le-Bretonneux, France

Garches-Necker-Mondor-Hendaye Consortium (GNMH), Reference Center on Neuromuscular Diseases for the European Network (Euro-NMD), Paris, France

Alejandro A. Rabinstein Mayo Clinic, Rochester, MN, USA

Jens Reimann University of Bonn Medical Centre, Bonn, Germany

Annika Saak Universitätsklinikum Carl Gustav Carus Dresden, Dresden, Germany

Jochen Schaefer Universitätsklinikum Carl Gustav Carus Dresden, Dresden, Germany

Jens Schmidt University Medical Center Göttingen, Göttingen, Germany

Benedikt Schoser Department of Neurology, Friedrich-Baur-Institute, Ludwig-Maximilians-University Munich, Munich, Germany

Laurent Servais Department of Paediatrics, MDUK Neuromuscular Centre, University of Oxford, Oxford, UK

Division of Child Neurology, Department of Pediatrics, Neuromuscular Reference Center, University Hospital Liège and University of Liège, Liège, Belgium

Varun Sethi Imperial College Health Trust, London, UK

Gentle Sunder Shrestha Department of Critical Care Medicine, Tribhuvan University Teaching Hospital, Kathmandu, Nepal

Jennifer Spillane The National Hospital for Neurology and Neurosurgery, University College Hospital, London, UK

Marianne de Visser Amsterdam University Medical Centres, location Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

Hannah A. W. Walter Amsterdam University Medical Centres, location Academic Medical Centre, Amsterdam, the Netherlands

Eelco F. M. Wijdicks Neurocritical Care Services, Mayo Clinic Hospitals, Rochester, MN, USA

Lokesh Wijesekera Ipswich Hospital and Cambridge University Hospital, Cambridge, UK

Peter J. Wijkstra Department of Pulmonary Diseases and Home Mechanical Ventilation, University Medical Center Groningen, Groningen, the Netherlands

Derek Willis Severn Hospice, Apley Castle, Telford, UK

Tracey Willis The Muscle Team, Robert Jones and Agnes Hunt Hospital, Oswestry, UK

Chapter 1
Recognition and Assessment of the Neuromuscular Emergency

Maxwell Damian and Marianne de Visser

Introduction

Case Vignette 1

A 60-year-old man was admitted to ICU because of nocturnal breathlessness. He reported fatigue and shortness of breath since 1 year and had recently developed difficulty climbing stairs and muscle cramps. Two years earlier, he had developed distal numbness and had been diagnosed with a polyneuropathy. At that time, an elevated creatine kinase level of 500 U/l was ascribed to "alcohol abuse." Electrophysiological studies had showed evidence for an axonal polyneuropathy with denervation but no additional brief short-duration action potentials indicating a myopathy, His brother had been diagnosed with axonal Charcot–Marie–Tooth (CMT) disease, and therefore, he was also diagnosed as having CMT.

Examination in the ICU revealed prominent diaphragmatic weakness with orthopnea and use of auxiliary respiratory muscles at rest, proximal weakness of upper and lower limbs, mild distal sensory disturbances, areflexia, and a tremor of the hands. CK was 568 U/L, and the EMG was consistent with an axonal neuropathy once again. We did the following test: acid maltase in leukocytes and fibroblasts, which showed <10% activity confirming the clinically suspected diagnosis of Pompe disease. Because of his symptoms and recorded hypoxemia and hypercapnia, he was referred to the Home Ventilation Service and benefitted from noninvasive home ventilation for another 10 years.

M. Damian (✉)
Cambridge University Hospitals, Cambridge, UK
Essex Cardiothoracic Centre, Basildon, UK
e-mail: msdd2@cam.ac.uk
M. de Visser
Amsterdam University Medical Centres, location Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands
e-mail: m.devisser@amsterdamumc.nl

M. Damian, M. de Visser (eds.), *Emergencies in Neuromuscular Disorders*,
https://doi.org/10.1007/978-3-030-91932-0_1

Learning Points
Pompe disease must be considered in any case of diaphragmatic failure; a neuromuscular diagnosis in a different member of the family may be a "red herring."

Neurological emergencies are traditionally dominated by life-threatening disorders of the central nervous system, such as cerebrovascular accidents, traumatic brain injury, and catastrophies of the spinal cord. Outcomes from such life-threatening conditions have improved significantly over recent decades, with the recognition of neurocritical care as a distinct field of neurology increasingly providing evidence-based treatment in specialist neurocritical care units.

Neuromuscular disorders are an extremely diverse group of conditions with genetic, inflammatory, and metabolic backgrounds. In the past, as well as under specific conditions, infectious diseases may be prominent as before widespread polio vaccination was available or today in geographical locations where West Nile Virus or Zika virus are endemic [1, 2]. Overall, the individual conditions that may cause a neuromuscular emergency are rare, often extremely so, and expertise is often concentrated in highly specialized neuromuscular units that focus on diagnostics and long-term management of neuromuscular disease rather than on the management of acute emergencies. They are therefore seldom closely linked to emergency departments and acute units, which can delay communication. For this reason, although many chronic neuromuscular disorders carry the potential for acute deterioration or may rarely manifest primarily as acute illness, they are initially likely to be managed by doctors who have little or no experience of treating patients with a neuromuscular diagnosis. The potential for misinterpretation of clinical signs, misdiagnosis, and mismanagement is therefore high, and often, by the time a neuromuscular specialist becomes involved, critical mistakes have been made. Conversely, and especially if there is comorbidity, misdiagnosis of the acute episode may occur if the patient is evaluated by a neuromuscular expert with limited exposure to acute medicine. Ideally, neuromuscular experts will advise on timely specialist tests in the acute setting (see Case Vignette 1).

While ultimate confirmation of the diagnosis may involve sophisticated laboratory tests, biopsies, and genetic analyses, the main risks to the patient arise not from absence of resources, but from mistakes in clinical judgment. Neuromuscular diagnosis starts with pattern recognition (Table 1.1). The initial important diagnostic decisions are most of all dependent on clinical knowledge, experience, and attention to clinical signs. Therefore, improved clinical skills can be beneficial to neuromuscular patients in all environments.

This chapter seeks to outline the clinical pathway to recognition of a neuromuscular emergency in adults and ensure early management is best suited to achieve a good outcome in any hospital setting.

Table 1.1 Clinical patterns in neuromuscular emergencies

Conditions presenting with rapidly progressive weakness	
Acute poliomyelitis	Asymmetric, proximal and distal weakness, bulbar, respiratory; fever and myalgia
Neoplastic radiculopathy	Asymmetric, cranial, proximal and distal weakness; cognitive changes
Guillain–Barré syndrome	Symmetric, proximal and distal weakness; areflexia, mild sensory; respiratory involvement; autonomic signs. Miller–Fisher syndrome overlaps with ophthalmoplegia; pharyngo-brachio-cervical variants with prominent axial and upper limb weakness
Brachial plexopathy	Asymmetric, proximal and/or distal weakness of the upper limbs, pain; one-third has bilateral plexopathy; rarely diaphragmatic involvement.
Vasculitic neuropathy	Asymmetric, stuttering, systemic features, pain
Acute porphyria	Symmetric, rapidly progressive, with abdominal pain and often psychiatric symptoms
Myasthenia gravis (MG)	Fluctuating, asymmetric, often cranial, bulbar and proximal; MG with MuSK antibodies predisposes to respiratory weakness
Botulism	Descending, ocular and pharyngeal, symmetric with pupillary dilatation and abdominal symptoms
Acute inflammatory myopathy	Symmetric, progressive weakness, dermatomyositis with rash, and in some cases (MDA5 antibody-related) with interstitial lung disease (ILD); antisynthetase syndrome with mechanic's hands and ILD; immune-mediated necrotizing myopathies are often severe and may include involvement of respiratory muscles
Periodic paralysis	Symmetric, sudden, often overnight, no cranial or respiratory involvement, electrolyte abnormalities
Rhabdomyolysis	Symmetric, proximal weakness, history of exercise, toxins or fever, recurrent if lifestyle or genetic predisposition
Acute quadriplegic myopathy	Persistent generalized weakness after ventilation, NMJ blockers, corticosteroids in patient in the ICU for another disease
Conditions presenting with cardiorespiratory or other emergencies, e.g., seizures, rhabdomyolysis	
5q spinal muscular atrophy (SMA)	Symmetric, proximal weakness, and atrophy, calf hypertrophy may occur SMA type 3 or 4
Bulbospinal muscular atrophy (Kennedy disease)	Symmetric, proximal weakness, bulbar weakness, perioral fasciculations, gynecomastia; sometimes prominent laryngospasm
Amyotrophic lateral sclerosis (ALS)/ progressive muscular atrophy	Asymmetric proximal or distal, atrophy of hand muscles, bulbar (ALS), fasciculations; rarely presentation with respiratory failure
Myotonic dystrophy 1 and 2 (DM)	Facial, bulbar and distal weakness, action and percussion myotonia, proximal weakness in DM2; respiratory and cardiac involvement frequently occurs in due course
Pompe disease	Symmetric proximal upper and lower limb weakness, ptosis, scapular winging; may present with respiratory failure

(continued)

Table 1.1 (continued)

Dystrophinopathies (DMD, BMD, carrier)	Large calves, proximal weakness and atrophy, scapular winging; cognitive dysfunction in DMD
Limb girdle muscular dystrophy	Symmetric, proximal weakness, and atrophy
Myofibrillar myopathy	Often distal weakness and atrophy; respiratory and cardiac involvement in due course
Mitochondrial myopathy	Oculomotor and cranial weakness, small stature, deafness, diabetes; cardiac involvement
Congenital myopathies, e.g., SEPN1	Proximal muscle weakness, scoliosis, long-standing constitutional features, and very slow progression even with sudden decompensation
Hereditary myopathy with early respiratory failure (HMERF)	Proximal and/or distal weakness of legs>arms; contractures and muscle atrophy may suggest unrecognized chronic myopathy; early respiratory involvement

Presentation in the Emergency Department

Weakness is most often the leading clinical feature of a neuromuscular emergency and may be generalized or focal. If there is a clear history of ascending weakness with a history of respiratory infection in the preceding weeks, the admitting doctors may consider a diagnosis of Guillain–Barré syndrome as it is by far the most common new-onset neuromuscular condition seen in the emergency department [3]. However, often the history first taken is sketchy, and time-sensitive diagnostic protocols, most often related to stroke management, are activated. In rapid onset of tetraplegia, brain imaging is performed to exclude a brain stem vascular event, and only when imaging is negative, the pattern of weakness, absence of long tract signs, and preserved consciousness may prompt a more detailed history. Occasionally, unresponsiveness due to tetraplegia mimics coma and GBS has been reported to mimic brain death [4, 5]. This may happen particularly if the patient presented needing emergency resuscitation as hypoxic brain injury is suspected when the patient apparently does not wake up.

Case Vignette 2

One of the authors was called to a patient who failed to respond to painful stimuli and had persistent fixed pupils on sedation hold the day after cardiopulmonary resuscitation; the possibility of brain death had been raised. There was no detailed history of the circumstances leading to the cardiac arrest available. Brain imaging was normal. On examination, an absence of tendon reflexes was noted, but the electroencephalogram was normal, including preserved reactivity to sensory stimuli (in the absence of any clinical reaction). A more detailed history confirmed preceding rapidly progressive weakness, with a suggestion of respiratory failure preceding cardiac arrest, and a diagnosis of GBS was later confirmed.

Learning Points
The clinical diagnosis of brain death should not be considered in the absence of a precise history, and the absence of a motor response can be caused by neuromuscular paralysis.

Acute onset of predominantly lower limb weakness or urine retention as a presenting symptom is typically taken to indicate a spinal disorder in the emergency department, and a spinal series of imaging is the first consideration. Neurological assessment is requested when the orthopedic protocol has been cleared.

Focal involvement of respiratory muscles, oropharyngeal weakness, and aspiration may cause admission (Case Vignette 1) for respiratory failure, and the patients may first come under the respiratory team. Astute respiratory physicians may bear in mind the possibility of neuromuscular illness causing restrictive respiratory failure, but sometimes the focus is then placed on obstructive lung disease, comprehensive investigations for respiratory muscle weakness are not done, and the diagnosis may be delayed if neuromuscular respiratory failure is not considered [6, 7].

Less frequently, cardiomyopathy and heart failure, severe dysrhythmia, and dysautonomia may be the life-threatening or leading symptoms, and signs in the limbs are overlooked. Patients may present as medical emergencies, without primary muscle disease being suspected, or they may be detected through family investigations if a family member has come to emergency care. The most common conditions in which cardiac dysrhythmia can be life-threatening in the absence of other symptoms are myotonic dystrophy and laminopathy (see also Table 1.2) [8–10].

Table 1.2 Genetic myopathies in which cardiac involvement may be leading

Myopathy	Characteristics
Dystrophinopathy	Duchenne/Becker muscular dystrophy, including late-onset Becker; carriers
Myofibrillar myopathy (MFM)	MFM 1 (desmin; arrhythmia, and dilated cardiomyopathy (DCM)), 2 (αB-crystallin, arrhythmia), 4 (ZASP; DCM), 6 (BAG3; hypertrophic cardiomyopathy) most commonly affected
Laminopathy (Lamin A/C)	Limb gidle muscular dystrophy (LGMD 1B) and Emery-Dreifuss Muscular Dystrophy (EDMD) 2 and 3 with tendency to conduction defects and ventricular fibrillation; allelic congenital cardiomyopathy syndromes
LGMDR 3–6 (sarcoglycanopathies)	<20% develop cardiomyopathy
LGMDR9 (Fukutin-related muscular dystrophy, FKRP)	A majority of cases develop cardiomyopathy; can be presenting feature; arrhythmia less common
Myotonic dystrophy (DM)	DM1: Increasing conduction defects with age; rarely sudden cardiac death (SCD) in asymptomatic young patients; DCM late DM2: SCD does occur

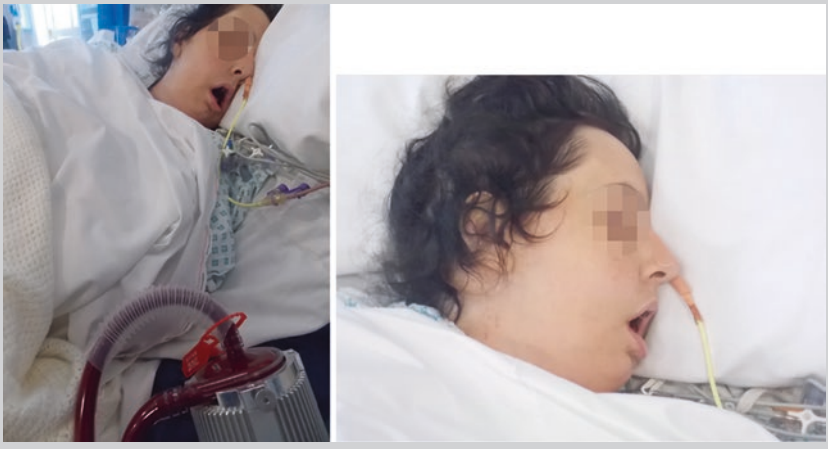
(continued)

Table 1.2 (continued)

Myopathy	Characteristics
Metabolic myopathies	Glycogenoses (GSD 3, 4, PGBM1, TPID, Danon); mitochondrial myopathies
Emery–Dreifuss muscular dystrophy X-linked (EDMD1)	Syncopal attacks (early onset with high CK); bradycardia; risk of embolism and stroke
Amyloidosis	Background of MGUS or TTR mutations; sensory neuropathy and rarely myopathy
Myosin heavy chain gene mutations	MYH7 with combined myopathy and early cardiomyopathy (Gowers–Laing distal myopathy MPD1)

Case Vignette 3

A 35-year-old female underwent extensive cardiac assessments for a progressive cardiomyopathy over the course of a year. She was admitted to the ICU as an emergency for catastrophic heart failure, where a biventricular assist device was implanted for bridging to super-urgent transplant. There, her facial expression with an "appearance of sleepiness" (facial diplegia and bilateral ptosis) led to neurological consultation, which revealed mild weakness of calf muscles. There was no myotonia and EMG could not be done, but there was a history of three miscarriages. Myotonic dystrophy type 1 was confirmed in genetic analysis.

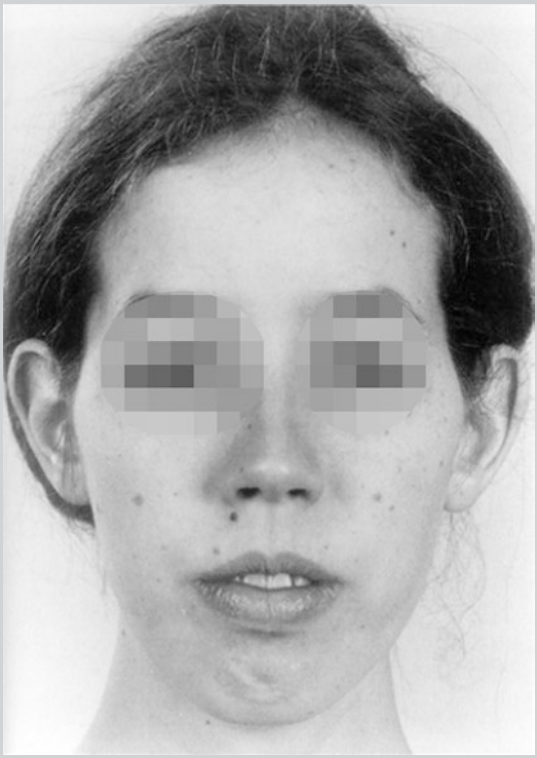


Learning Points

Severe cardiac disease may be the manifesting symptom of myotonic dystrophy, but often a careful history reveals characteristic features that have been missed.

Case Vignette 4

A 24-year-old man suffered a cardiac arrest at age 24 years during a family gathering after engaging in sports. He could not be resuscitated and died. A family investigation was carried out. His sister had never experienced syncopal attacks, palpitations, or dizziness, but her ECG showed a left axis deviation and a slight prolongated PQ interval of 200 ms. A diagnosis of myotonic dystrophy type 1 was genetically confirmed after her facial appearance was noted (below), and a cardioverter defibrillator was implanted as a precautionary measure.



Renal failure may be the leading feature of rhabdomyolysis, and an underlying neuromuscular cause only emerges after repeated events [11, 12].

Finally, fatiguing weakness may be fluctuating and therefore considered spurious or nonorganic, although fortunately the emphasis in the emergency department on *not* missing a life-threatening condition means that more often functional

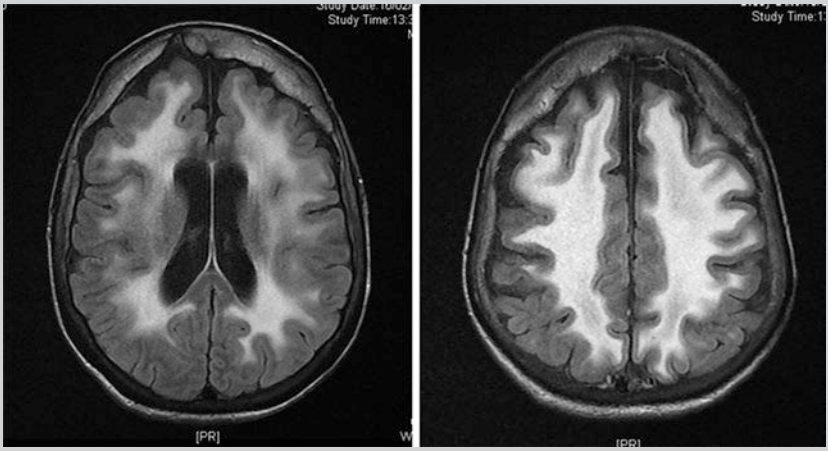
disorders are referred as possible myasthenia [13]. Unilateral ptosis is a common presentation of myasthenia gravis at onset, and this frequently leads to investigations such as CT or MRI angiography to exclude a carotid aneurysm, a situation that arises not infrequently in outpatient assessment. This is of course reasonable, particularly where fatiguing is not obvious—relying on the absence of pupillary dilatation to rule out an aneurysm is no longer normal practice.

For the emergency physician, these situations cannot be fully avoided as time-sensitive protocols often do not allow complex diagnostics or lengthy history-taking. Considering vascular and spinal disorders first is not a clinical error. However, once a condition treatable through interventional radiology or surgery has been excluded, the history should be reconsidered, and signs suggesting an alternative diagnosis such as neuromuscular disease may emerge. Recent developments such as mobile stroke units with telemedicine links from the ambulance to hospital can potentially allow these differential diagnoses to be ruled out before hospital admission.

History-Taking

The main historical indicator of an underlying acute neuromuscular disease is a history of progressive weakness over more than a few hours, often in the absence of sensory symptoms. In patients where there is an underlying chronic, often genetic disorder, the history may reveal a previous physical disability or long-standing mobility problems or nonmuscular features that may point to a specific multisystem disorder [14, 15].

Case Vignette 5
A 43-year-old female had been diagnosed with "muscular dystrophy" in her teens. Since then she had not been under regular neurological follow-up and was cared for at home. She had been homeschooled and was of above-average intelligence. Before the onset of muscle weakness, she had been diagnosed with epilepsy, but this was well controlled by sodium valproate. She was admitted to hospital with a respiratory failure triggered by infection. The intensive care physicians were reluctant to intubate "because of futility and low quality of life," but the patient disagreed. The suspected diagnosis was a laminin α2-deficient congenital myopathy after having an MRI scan of the brain (below), subsequently genetically confirmed.



She required emergency tracheotomy because of an abnormal airway and spent 2 months in the ICU; after further 2 months in a high-dependency unit, she was decannulated and discharged on nocturnal ventilation by mask; she has been back to her normal function for 4 years.

Learning Points
Pattern recognition is essential for a neuromuscular diagnosis and can allow recognition of genetic conditions in time to inform critical decisions (here: recognition of disease with only very slow progression).

The family history may suggest a prevalence of neuromuscular disease or of conditions associated with a genetic disorder (see Case Vignette 4) in which either neuromuscular symptoms or cardiac involvement may be leading (Table 1.1). Finally, a detailed drug and lifestyle history may reveal myotoxic or neurotoxic activities or substances, including medications and nonpharmacological substances as in rare cases of "pica" or geophagia leading to hypokalemic weakness [16].

Neurological Examination

The formal neurological examination must look for features that in most cases exclude a neuromuscular disorder, such as impaired consciousness and special senses; pyramidal signs such as exaggerated tendon reflexes, clonus, and spasticity;

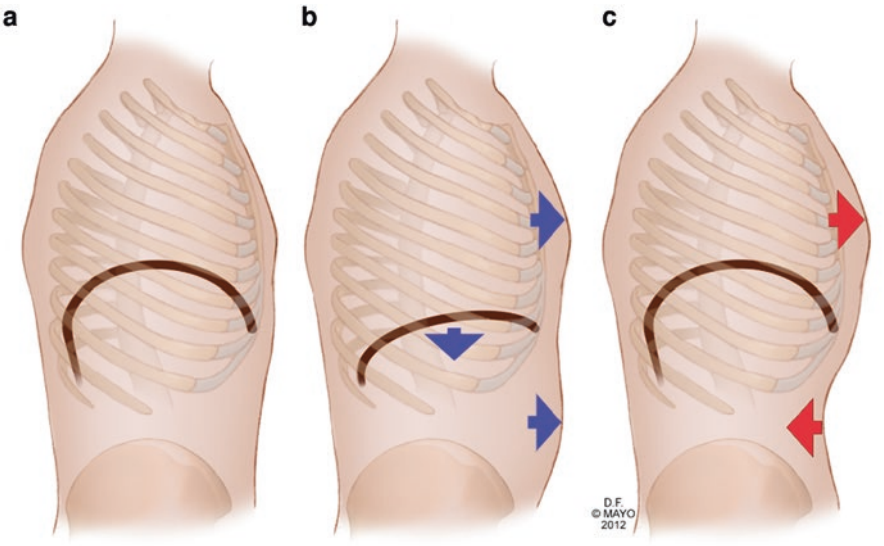


Fig. 1.1 (**a**) Resting diaphragm (expiration); (**b**) inspiration with excursion of chest wall and abdomen; (**c**) "paradoxical breathing" = thoraco-abdominal dyssynergy with chest wall excursion with little increase of intrathoracic volume, and indrawing of the abdomen in diaphragmatic paralysis. (Figure by David Factor, courtesy Dr. EFM Wijdicks)

identifiable patterns of brain stem syndromes; and sensory abnormalities. The examiner must of course be aware of pitfalls and exceptions to this rule—the occasional patient with amyotrophic lateral sclerosis presenting with acute respiratory failure may exhibit upper motor neuron signs; mitochondrial disease may be multisystemic, affecting all areas of the nervous system and other organs as well; myasthenic ophthalmoplegia may mimic internuclear ophthalmoplegia or other brain stem syndromes.

The motor examination must be suitable to pick up particular patterns of weakness rather than scores such as the popular Manual Muscle Test (MMT) score, which is better suited to monitoring the course of weakness. The pattern of weakness (distal vs. proximal; with or without cranial and paravertebral involvement, symmetric or asymmetric, and whether it is with or without sensory abnormalities or pain) can suggest a shortlist of likely causes (Table 1.1). Secondary neuromuscular features narrow down the number of conditions in question and include circumscribed muscle atrophy or hypertrophy. Fasciculations indicate a neurogenic disorder and can be generalized in advanced amyotrophic lateral sclerosis (ALS), or focal in the bulbar palsy variant of ALS, and sometimes the distribution of fasciculation may provide a hint to the diagnosis, for instance, in Kennedy disease with perioral fasciculations. Contractures, scoliosis, rigid spine, camptocormia, and certain constitutional features and characteristics of facial appearance, such as the features of myotonic dystrophy or some congenital myopathies, may be indicative of a

specific disease. These will be discussed in the chapters on the individual disorders, respectively.

Testing for abnormalities of extraocular muscles and oculomotor function is important as characteristic abnormalities can be found in some conditions, whereas other neuromuscular disorders typically spare muscles of the face and eyes. Extraocular muscles are typically weak in neurogenic conditions such as Miller–Fisher syndrome; in neuromuscular junction syndromes such as botulism and myasthenia gravis; and in a range of myopathies that can present acutely, particularly in mitochondrial disease. However, even when a mitochondrial disorder presents acutely with respiratory failure, heart failure, or seizures, the ophthalmoplegia in mitochondrial disease with chronic progressive external ophthalmoplegia (CPEO) does not usually cause diplopia [17]. This helps differentiate it from myasthenia gravis as an alternative diagnosis, where ophthalmoplegia is fluctuating and variable, and causes intermittent diplopia and often also alternating ptosis.

Risk Assessment

The initial clinical assessment needs to include an estimate of the patient's risk of severe morbidity and death in order to judge the need for admission, and determine the correct destination to a ward, to a high-dependency unit (HDU) or the ICU, as well as define a monitoring schedule [19]. The underlying diagnosis, or lack of one, has major implication on outcome, and patients in whom no clear diagnosis can be made, do worst [6]; likewise, the presence of comorbidity will influence outcome, and thereby also management plans for escalation of treatment. Intensive care physicians wish to be confident that there is an acceptable chance of real benefit before embarking on invasive treatment, and the neuromuscular specialist must be able to provide the best possible assessment of the potential outcome. That being said, views on what constitutes "acceptable" quality of life are highly subjective and depend on the cultural environment, and controversy cannot always be avoided.

The history is important to check for the possibility of fluctuation and potential for sudden worsening; if that is not done, the patient's risk level may be underestimated, and this is a reason why patients "crash" in an environment that is not safe. This most commonly happens in the context of an imminent myasthenic crisis. Questioning the patient or family for indicators of chronic hypoxemia or hypercapnia such as interrupted or unrefreshing sleep, increasing daytime somnolence, morning headaches, slurred speech, or slowed thinking is important.

Testing of respiratory and bulbar function is possible even if no equipment is available. Simple testing of respiratory competency includes listening to the patient's voice and ability to complete a full sentence without taking a breath; counting out loud in one breath (whether this is "metronomic" or "as fast as possible" needs to be documented); ability to lie flat or need to elevate the upper body, indicating diaphragmatic weakness; and use of auxiliary respiratory muscles and flaring of

the nostrils in quiet breathing. Paradoxical breathing with thoraco-abdominal dyssynergy occurs when abdominal muscles are unable to produce a "belly band" (Fig. 1.1).

Articulation and swallowing are tested to assess the risk of aspiration; strength of cough can inform whether the patient is able to clear airways, and a weak cough in a patient with respiratory muscle weakness potentiates the risk of chest infection. Impaired attentiveness and arousal can be indicators of elevated CO_2 even when pO_2 is only mildly decreased, and hypercapnia is a cause of secondary impaired consciousness in a patient who passed a blood gas analysis on admission. In most countries, transcutaneous pO_2 saturation can be monitored continuously, but pCO_2 requires invasive blood gas analysis and is only done on "clinical indication," that is, low O_2 saturation, so elevated pCO_2 is often overlooked and unnecessary or even risky transfer for investigations takes place. A further disadvantage of pO_2 monitoring is that values lower than the norm in a patient with underlying chronic neuromuscular disease prompt unthinking application of nasal O_2, which may trigger overt respiratory failure; this happens regularly in the authors' experience, despite all attempts at educating medical and nursing staff. Relying on single blood gas analyses can be misleading in a number of ways: the most dramatic is the situation of impending respiratory failure where the patient recruits auxiliary muscles maximally, briefly normalizing an elevated pCO_2 to avert hypoxia, before acutely failing.

Examination of Cardiac, Autonomic, and Respiratory Function and Skin Inspection

The general medical examination includes checks of cardiac and autonomic function, but the indicators of autonomic function can be discrete, and particularly in GBS occasional catastrophic emergencies on the ward occur when patients with preserved respiration, but with autonomic instability that has been overlooked, develop significant cardiac arrhythmia [18]. The indicators of autonomic dysfunction in GBS that can be tested safely, such as resting tachycardia, loss of heart rate variation, sensitivity to sympathomimetic or beta-blocker medications, or gastrointestinal problems, have a low predictive value for serious dysrhythmia and circulatory compromise, and although ECG monitoring is a minimum, HDU admission is prudent in any patient at risk (see Chap. 7).

There are numerous neuromuscular diseases in which cardiac involvement (hypertrophic or dilated cardiomyopathy and/or conduction abnormalities) is prominent or even leading (Table 1.2). Sudden cardiac death (SCD) as a result of cardiac arrhythmia is the cause of death in 29% of the patients with myotonic dystrophy type 1 [8], and albeit less frequent SCD also occurs in DM2, whereas the muscle weakness is only mild [9].

More formal respiratory function testing is possible at the bedside, but requires expertise from the examiner to be reliable; patient cooperation is also essential. The

authors advocate combining measurements of forced vital capacity (FVC) and peak cough flow (PECF) with mouth pressures (maximum inspiratory and expiratory pressures). Mouth pressures in particular may be difficult to obtain in patients with facial weakness, and "sniff pressures" may be used, when that is the case. In acutely developing respiratory weakness such as GBS, there are well-established guidelines on what values necessitate HDU monitoring and when intubation should not be delayed. In chronic disorders, however, much worse respiratory function may have been tolerated for some time, and the individual situation must be taken into account before embarking on invasive ventilation.

Skin changes can indicate dermatomyositis in rare patients with rapidly progressive weakness or interstitial lung disease (ILD) presenting as emergencies and may also be seen in acute vasculitic neuropathies.

The neuromuscular assessment is complete when there is agreement between the neuromuscular specialist and the admitting team on the following issues:

- Risk assessment (Should the patient be admitted? If so, is a ward admission safe or should the patient be monitored in the HDU/ICU?) [19].
- Monitoring targets (respiratory monitoring and triggers for ICU admission and intubation, and whether cardiac monitoring is needed).
- Escalation procedures (noninvasive ventilation; intubation and mechanical ventilation). The patient's resuscitation status should be known on admission.
- Other interventions if there is a risk of aspiration pneumonia, dehydration or malnutrition, or *retentio urinae.*
- Plan for further investigation and its time frame.
- Appropriate immediate treatments (i.e., whether to start IVIG or plasma exchanges in suspected GBS and MG crisis before electrophysiological confirmation; start steroid treatment for inflammatory myopathy before biopsy).

Failure to make these points clear and document them in the patient's medical chart will lead to misunderstandings of risks, delay in diagnosis, and, regrettably, avoidable complications.

Conclusion

In this introductory chapter, the authors provided an overview on the presentation and assessment of neuromuscular emergencies. Neuromuscular disorders have multifold presentations, which may initially give rise to confusion in acute situations when a neuromuscular expert is not yet present. Muscle weakness of the limbs is the most frequent manifestation, but ocular, facial, bulbar, and diaphragmatic weakness may prevail and hamper a swift diagnosis. Numerous neuromuscular diseases are associated with cardiac conditions, which may also be the presenting symptom and distract from the correct diagnosis. A diagnosis can usually be established by careful history-taking, including that of the family, neuromuscular examination, bedside respiratory testing and consultation of a cardiologist if needed.

In the subsequent chapters, the diseases that can present as an emergency will be addressed in more detail, including the ancillary diagnostic tests and management issues.

This knowledge should lead to improvement of the acute care and outcome of neuromuscular patients; it can help avoid, on the one hand, futile invasive measures and, on the other hand, reduce a long-standing bias against treating people with a disability. Fortunately, patients are increasingly able to drive decisions on their treatment through advanced directives.

Self Assessment Questions

1. Which of the following signs is most characteristic of paradoxical breathing?

   (a) Excursion of chest wall
   (b) Excursion of abdomen
   (c) Indrawing of chest wall
   (d) Indrawing of abdomen (*)

A 42-year-old male presented to the emergency department with progressive diplopia over the past 3 days. He experienced difficulty with swallowing and suffered from constipation. Neurological examination showed diplopia, dilatation of both pupils, bilateral ptosis, dysphonia, and bilateral facial palsy. Deep tendon reflexes were reduced, but there was no limb weakness.

2. Which of the following diagnoses is most likely in this case?

   (a) Botulism (*)
   (b) Inclusion body myositis
   (c) Mitochondrial myopathy
   (d) Myasthenia gravis

A patient with progressive bulbar weakness since a couple of months is brought to the emergency department because of impaired attentiveness and arousal since 2 days. On inquiry, there is no overt limb weakness apart from a right foot drop since about 6 weeks. At examination, there is a drowsy patient with pseudobulbar dysarthria, brisk reflexes including the masseter reflex, and bilateral extensor plantar responses.

3. Which of the following measures is now first mandatory?

   (a) Forced vital capacity
   (b) Full blood gas analysis (*)
   (c) Peak flow measurement
   (d) Transcutaneous O_2 saturation measurement

4. Which of the following neuromuscular diagnoses should be considered first in a 35-year-old tetraplegic patient with a Glasgow coma score of 1–1-tube with normal pupillary reactions?

   (a) Immune-mediated myopathy
   (b) Guillain–Barré syndrome (*)
   (c) Laminin α2-deficient muscular dystrophy
   (d) Myotonic dystrophy type 2

A 65-year-old patient is referred to the emergency room because of respiratory failure that developed within the previous 12 h. There is no history of muscle weakness, and as far as can be diagnosed, muscle force and muscle stretch reflexes are normal.

5. In this situation, a neuromuscular disorder causing respiratory failure may be considered out of the question.

   (a) True
   (b) False (*)

6. Life-threatening cardiomyopathy in a patient with laminopathy is unusual in the absence of prominent skeletal muscle weakness.

   (a) True
   (b) False (*)

7. If there is preserved respiration in GBS, autonomic instability causing cardiac arrhythmia is unlikely.

   (a) True
   (b) False (*)

8. Urine retention may occur in the context of a peripheral neuropathy.

   (a) True (*)
   (b) False

A 29-year-old female was seen by several doctors for attacks of abdominal pain and constipation. In spite of an extensive gastrointestinal work-up, no cause was found. Six months after the start of her abdominal problems, she developed an ascending paresis, leading to ventilatory insufficiency. Nerve conduction studies and CSF analysis within the first days in the ICU revealed no abnormalities. The diagnosis of Guillain–Barré syndrome was surmised, and she was treated with IVIG. On the second day of admission, she had an epileptic seizure. A cerebral CT scan was normal, and no electrolyte abnormalities were found. Glucose metabolism was normal, and there were no signs of an infection. On the fifth day, her urine appeared reddish-brown and darkened in daylight.

9. Which of the following diagnoses should be considered first in this situation?

   (a) Acute porphyria (*)
   (b) Laminin α2-deficient
   (c) Rhabdomyolysis in the context of GBS
   (d) Zika virus neuropathy with kidney injury

A 64-year-old female was artificially ventilated in the ICU because of respiratory insufficiency that developed within 1 week. In the previous months, she had intermittent problems with swallowing, chewing, and double vision. She lost 10 kg of body weight within 3 months. At (limited) clinical examination in the ICU, eye movements were normal, there was a slight asymmetric ptosis of the eyelids, and limb muscle strength appeared normal. CK was within the normal range, AchR antibodies were not detected, and an edrophonium-challenge caused muscarine side effects but no change in her ptosis. Needle EMG showed increased insertion activity but no overt neurogenic abnormalities.

10. Which of the following diagnoses should now be considered in the first place?

    (a) Pompe disease
    (b) Amyloid myopathy
    (c) Mitochondrial myopathy
    (d) Neuromuscular junction disorder (*)

A 17-year-old boy is seen by a cardiologist because of heart failure. His CK was found to be 10,000 U/l. He did not complain of muscle weakness; on inquiry, he mentioned incidental cramps in his lower legs and proximal upper limb musculature. At clinical examination, his muscle strength was normal. There was a striking hypertrophy of his calf muscles.

11. Which of the following diagnoses is most likely?

    (a) Dystrophinopathy (*)
    (b) Laminopathy
    (c) Mitochondrial myopathy
    (d) Myotonic dystrophy type 2

12. Which of the following neuromuscular diseases is associated with sudden cardiac death?

    (a) Axonal CMT (type 2)
    (b) Facioscapulohumeral dystrophy
    (c) Lambert–Eaton myasthenic syndrome
    (d) Myotonic dystrophy type 2 (DM2) (*)

References

1. Leis AA, Stokic DS. Neuromuscular manifestations of west nile virus infection. Front Neurol. 2012;3:37.
2. da Silva IRF, Frontera JA, Bispo de Filippis AM, Nascimento OJMD, RIO-GBS-ZIKV Research Group. Neurologic complications associated with the Zika virus in Brazilian adults. JAMA Neurol. 2017;74(10):1190–8.
3. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. Lancet. 2016;388(10045):717–27.
4. Rigamonti A, Basso F, Stanzani L, Agostoni E, Lauria G. Guillain-Barré syndrome mimicking brain death. J Peripher Nerv Syst. 2009;14(4):316–9.
5. Ravikumar S, Poysophon P, Poblete R, Kim-Tenser M. A case of acute motor axonal neuropathy mimicking brain death and review of the literature. Front Neurol. 2016;7:63.
6. Cabrera Serrano M, Rabinstein AA. Causes and outcomes of acute neuromuscular respiratory failure. Arch Neurol. 2010;67(9):1089–94.
7. Confalonieri M, Vitacca M, Scala R, Polverino M, Sabato E, Crescimanno G, Ceriana P, Antonaglia C, Siciliano G, Ring N, Zacchigna S, Salton F, Vianello A, AIPO Pneumoloped Group. Is early detection of late-onset Pompe disease a pneumologist's affair? A lesson from an Italian screening study. Orphanet J Rare Dis. 2019;14(1):62.
8. McNally EM, Mann DL, Pinto Y, Bhakta D, Tomaselli G, Nazarian S, Groh WJ, Tamura T, Duboc D, Itoh H, Hellerstein L, Mammen PPA. Clinical care recommendations for cardiologists treating adults with myotonic dystrophy. J Am Heart Assoc. 2020;9(4):e014006.
9. Schoser BG, Ricker K, Schneider-Gold C, et al. Sudden cardiac death in myotonic dystrophy type 2. Neurology. 2004;63(12):2402–4.
10. Finsterer J, Stöllberger C, Maeztu C. Sudden cardiac death in neuromuscular disorders. Int J Cardiol. 2016;203:508–15.
11. Scalco RS, Gardiner AR, Pitceathly RD, Zanoteli E, Becker J, Holton JL, Houlden H, Jungbluth H, Quinlivan R. Rhabdomyolysis: a genetic perspective. Orphanet J Rare Dis. 2015;10:51.
12. Zutt R, van der Kooi AJ, Linthorst GE, Wanders RJ, de Visser M. Rhabdomyolysis: review of the literature. Neuromuscul Disord. 2014;24(8):651–9.
13. Frame F, Thompson SA, Mahotra Man T, Edwards MJ, Rosenzweig I. Psychogenic myasthenia gravis. J Neuropsychiatry Clin Neurosci. 2011;23(4):E1.
14. Barohn RJ, Amato AA. Pattern-recognition approach to neuropathy and neuronopathy. Neurol Clin. 2013;31(2):343–61.
15. Barohn RJ, Dimachkie MM, Jackson CE. A pattern recognition approach to patients with a suspected myopathy. Neurol Clin. 2014;32(3):569–93.
16. Trivedi TH, Daga GL, Yeolekar ME. Geophagia leading to hypokalemic quadriparesis in a postpartum patient. J Assoc Physicians India. 2005;53:205–7.
17. Berardo A, Musumeci O, Toscano A. Cardiological manifestations of mitochondrial respiratory chain disorders. Acta Myol. 2011;30(1):9–15.
18. Chakraborty T, Kramer CL, Wijdicks EFM, Rabinstein AA. Dysautonomia in Guillain-Barré syndrome: prevalence, clinical spectrum, and outcomes. Neurocrit Care. 2020;32(1):113–20.
19. Damian MS, Wijdicks EFM. The clinical management of neuromuscular disorders in intensive care. Neuromuscul Disord. 2019;29(2):85–96.

Chapter 2
Diagnostic Tests in the Acute Setting: Strengths and Limitations

Jens Reimann and Lokesh Wijesekera

Introduction: Known and Unknown Unknowns

The patient presenting with the neuromuscular emergency may already have the diagnosis of a neuromuscular disorder and now experiences an acute worsening, or, alternatively, the presenting emergency may be the first clinical presentation of a so far unknown neuromuscular problem.

In the former case, the attending clinician's first job will be to determine whether the acute situation is really related to the known neuromuscular disorder (NMD), and if so, identify the cause of the worsening. Is it increased disease activity of the NMD or is there something else leading to decompensation of the previously more stable situation? It is important to keep in mind that patients suffering from NMD, usually rare conditions, are just as likely to develop the same frequent health problems as everybody else. Thus, a common infection may drive the decompensation of a rare NMD. But the patient might also misattribute signs of an altogether different problem to the NMD, and the neurologist should avoid falling into the same trap. We have seen a patient confuse rhabdomyolysis with acute pancreatitis (see Case Vignette 1), two sporadic inclusion body myopathy (sIBM) cases complaining about acute progression with increased myalgia turned out to have developed additional polymyalgia rheumatica (PMR) and one myotonic dystrophy type I patient became immobile not due to a *Campylobacter jejunii* infection, but due to the resulting Guillain–Barré syndrome (GBS) several days later. Comparing the possible course of a given NMD to the presented symptoms and complaints of the acutely

J. Reimann (✉)
University of Bonn Medical Centre, Bonn, Germany
e-mail: jens.reimann@ukbonn.de

L. Wijesekera
Ipswich Hospital and Cambridge University Hospital, Cambridge, UK
e-mail: Lokesh.Wijesekera@esneft.nhs.uk

M. Damian, M. de Visser (eds.), *Emergencies in Neuromuscular Disorders*,
https://doi.org/10.1007/978-3-030-91932-0_2

ill patient can have pitfalls, even for the digital natives with every database available at the swipe of a thumb.

Still, most of us would prefer this scenario in the emergency situation to the latter option, where a rare and complex neuromuscular disorder must first be diagnosed in order to effectively address the medical emergency. This can make highly specialized technical investigations necessary, which may take time, and for which emergency staff may lack expertise to identify the underlying cause. The more unknowns there are, the higher the chance of missing essential clues.

Of course, the first step into neurological diagnosis will be the patient's history and neurological exam, as detailed in Chap. 1, "Recognition and Assessment of the Neuromuscular Emergency". This will obviously determine the order of differential diagnoses: lively tendon reflexes will push GBS right down the list. However, as the clinician in this situation will have to consider alternative or additional, frequently non-neurological, diagnoses in the setting of the emergency department (ED), it is advisable not only to have a broad understanding of other acute medical emergencies generally (see other textbooks of emergency medicine), but also to use the data that the ED colleagues are going to generate anyway or that they could easily provide within their standard operating procedures (SOPs). This will occasionally also help to bring a neuromuscular emergency gone astray back to neurology when an alternative explanation for the patient's finding has led the case into the care of some other discipline.

A fairly similar situation arises when the patient is in another department's care for a very good reason and the neurologist is now called upon to decide whether a neuromuscular problem is either the cause of or an additional problem in that situation. In this situation, other extensive medical care applications and procedures in the intensive care unit will frequently get in the way of basic approaches to neurological diagnostics.

In this chapter, we look at the usefulness and problems of laboratory parameters, imaging, neurophysiology, and histology in the emergency department (ED) and intensive care unit (ICU) situations. We will also address some standard situations as well as common or critical pitfalls.

Laboratory Values

No assessment will be complete if the patient's electrolyte, serum creatine kinase (CK) activity, and thyroid status are unknown. Further values concerning kidney and liver function as well as inflammatory activity, are usually included in the ED standard and can be extremely helpful, pCO_2 is a major point in assessing the imminent danger of a situation. Others such as lactate can help the neuromuscular clinician but are usually tested with different intentions and can be misleading if considered on their own. For a high lactate, for example, the intensivist might look for sepsis and the surgeon for intestinal ischaemia while the neurologist will consider mitochondrial cytopathy—note that these differential diagnoses may coexist in a NMD emergency.

Some tests take too long to be of any help in the ED situation but should be considered within the first days if not hours because of their importance for further treatment. These include a number of antibodies, particularly for myasthenia gravis (MG) and inflammatory myopathy/immune-mediated necrotizing myopathy (IMNM) but also metabolic measurements (dry blood test for Pompe disease or acylcarnitines or porphyria screening), particularly as the crisis in the adult age is frequently the only situation to secure clearly abnormal results in some metabolic disorders, for instance, acute intermittent porphyria.

Electrolytes (Sodium, Potassium, Calcium, Magnesium)

No neuromuscular membrane will work in its normal way, and neurophysiological testing will be hard to interpret if electrolyte concentrations are abnormal. In particular when the neuromuscular problem arises during complex medical treatments, magnesium should be included as it seems to be the most frequently overlooked iatrogenic electrolyte disorder. Minor electrolyte changes will frequently not lead to a perceivable change, but severe disturbances will manifest with neuromuscular signs and will make the diagnosis of other problems of the neuromuscular system very complicated or even impossible. Note that pathological electrolyte changes can be severe complications of rhabdomyolysis with renal failure or GBS with neuroendocrine abnormalities causing hyponatraemia through SIADH or natriuresis.

Strengths: fast, available, and cheap; *weaknesses:* not specific for underlying disease.

Serum Creatine Kinase Activity

Unfortunately, many factors must be taken into account when evaluating serum creatine kinase (CK) activity, the most readily available and most used test for muscle damage. Table 2.1 gives an overview of some basic values and isoenzyme distributions.

Table 2.1 An overview of CK isoenzymes, associated enzymes, and dynamics (derived from [1–4])

Cytosolic CK isoenzymes		
Designation	Half-life [4]	% of total tissue CK [3]
CK-MM	≥18 h	Skeletal muscle 98%, cardiac muscle 70%, brain 0%
CK-MB	12 h	Skeletal muscle 2%, cardiac muscle 25%, brain 0%
CK-BB	3 h	Skeletal muscle <1%, cardiac muscle 5%; brain 100%

Table 2.1 (continued)

Macro-CK			
Designation	Molecular cause	Disease association	
Type 1	Complex of CK-BB and IgG	Not associated with disease	[4]
Type 2	Polymer of Mt-CK	Liver cirrhosis and neoplastic diseases	[4]

Dynamics after heavy exercise/muscle damage			
Test	Expected peak	Expected return to baseline	
CK	2–4 days	7–10 days	[3]
Myoglobin	1–3 days	2–4 days	[3]
LDH	2–4 days	6–10 days	[3]

A single CK measurement is a fairly straightforward pointer to muscle damage in an otherwise healthy, resting Caucasian patient with normal muscle bulk. However, any deviation from this, more or less a given in a neuromuscular emergency, will make things complicated. Moreover, a patient with high CK might proceed straight into the work-up for myocardial ischemia in some EDs, although troponin test may correct this (see section "Troponins").

Normal CK values differ between persons of different muscle mass and hormones (i.e. classical gender differences), and genetic and ethnic background. The literature on the latter is problematic as it covers only a few ethnicities. A rule of thumb suggesting that the darker the skin, the higher the upper limit of normal (ULN) of CK could be drawn from some published comparisons based on the US population [5], as well as on the population of the Netherlands [1]. However, this pattern is not repeated in every study [2], and literally judging from the colour of skin is problematic from the point of view of ethnic bias, and profoundly flawed as UV exposure or lightening skin treatments typically have no influence on CK. Values of up to 4× the ULN in the White population have been described repeatedly in Black populations, but the published data, for example [1, 2, 5, 6], should be used with caution when judging the CK of an individual non-White case, particularly when dealing with a single measurement. Muscular activity clearly does have an influence on the CK values. Someone performing physical labour or regular intense physical exercise will have a higher baseline CK than a sedentary individual. Overall CK activity of the random person from the street will frequently be above the ULN of the hospital laboratory, which may or may not point to an underlying disease, and detailed patient history is the main insurance for an accurate ad hoc classification.

When CK rises after exercise, several differences between mild to moderate exercise and heavy exercise can be found. In the former, CK will rise within a few hours, peak on post-exercise day 1, and will mostly not exceed twice the ULN. In the latter case, the peak will be on days 2–4 post-exercise and values in excess of 200-fold ULN are seen [3]. This phenomenon, most likely related to the presence and extent of muscle fibre damage, has led some authors to list different CK-MM half-life times with and without muscle soreness [4]. The best answer to many 'CK riddles', however, lies in observing the dynamics of the values. Each of the three true CK isoenzymes found in blood has a different half-life (see Table 2.1), effectively excluding relevant CK elevations by CK-BB in most clinical situations. While

the relation of CK-MB to CK-MM may shift in chronic muscle damage, troponin measurements (see section "Troponins") will clarify if cardiac work-up will be needed. Another confounder, macro-CK (see Table 2.1), does not show dynamic values in contrast to the sequence following real muscle damage. However, as an emergency situation in a patient with known NMD will require observing a dynamic situation (the emergency) overlapping with a theoretically less dynamic situation (the underlying NMD), electrophoresis to exclude macro-CK should be considered early when this question arises.

While most discussions focus on explanations for elevated CK, the fall of CK values is frequently misattributed as therapeutic success when patients are given steroids and/or admitted to ICU. The biochemical effect of steroids on the muscle membrane (and possibly on secondary inflammation), as well as the thorough immobilization in the ICU, will often lower CK values regardless of the disease activity of the NMD and can muddy the waters in deciding on the duration of a course of steroids. This is particularly difficult when a muscle biopsy has been performed too early after an episode of rhabdomyolysis (see below).

Taken together, unless previous measurements are available, the first CK value in the ED will (a) provide a general guide to the differential diagnosis, (b) check for rhabdomyolysis (consider in newly symptomatic patients with total CK > 1000 IU/L/ or > 5 × ULN [7], see Chap. 10), and (c) build the foundation of the analysis of CK dynamics. If severely elevated CK does not begin to fall after day 5, consider ongoing muscle damage.

Strengths: fast, available, dynamic, and extensive published data; *weaknesses:* clear thresholds for normal and abnormal hard to define, and potential confounders (macro-CK and ethnicity).

Troponins

The observation that tests for cardiac troponin, particularly cardiac troponin T (cTnT), will occasionally give elevated values in patients with NMD without a cardiac explanation has been known for decades. The discussion of whether a methodical problem (i.e. limitations of the test) or real expression of cTnT outside the myocardium (i.e. the skeletal muscle) is to blame has not been resolved [8, 9]. The phenomenon is found much less frequently for cardiac troponin I (cTnI) tests. Regardless of whether a patient has a known NMD or not, an acute myocardial infarction can be detected by the combination of clinical signs and/or electrocardiogram (ECG) changes and a *dynamic*, elevated troponin value. However, if a constant pathological troponin is found, a latest generation cTnI test should be used to detect myocardial pathology in an NMD patient—which does not have to be acute ischaemia but could be cardiac involvement as part of the muscle disease or another form of non-ischaemic cardiac disease. Thus, if cTnI is pathologically elevated or if doubts remain, modern myocardial imaging and electrophysiology will be necessary. In contrast, detection of a NMD based on laboratory values in a patient with recent myocardial damage will only work by comparing the levels and dynamics of

the CK in relation to the other markers (see Table 2.1). Extra caution is necessary for patients with chronic renal failure as this is considered the most frequent condition leading to non-cardiac troponin findings.

Strengths: available and defining the threshold for necessity of cardiac diagnostics; *weaknesses:* discussion about specificity ongoing and may distract from the NMD.

Case Vignette 1

A man in his 40s was first seen after treatment for rhabdomyolysis with transient renal failure at another institution, where alcohol abuse and low plasma potassium were assumed to be the cause. Neurological examination was normal. CK was elevated to > 600 U/l (ULN: 190 U/l), but he reported 'chopping some trees' the previous day. Follow-up CK and EMG were normal. Two months later, he came to the clinic with pain in the upper right abdomen, claiming he had 'suffered another episode'. Neurological examination again was normal, CK was 61 U/l, but lipase and amylase values were clearly elevated, and he was admitted with acute pancreatitis, likely due to alcohol abuse. Five years later, now with liver cirrhosis, endocrine and exocrine pancreatic insufficiency but no longer drinking alcohol, he had another EMG due to distal cramps with a CK of > 200 U/l, and now we found spontaneous activity and myopathic MUP. After a further episode of rhabdomyolysis 2 years later, he finally had a muscle biopsy, which showed fibre type II atrophy, scattered necrotic and regenerating fibres, five COX-negative fibres, and two rimmed vacuoles and weak but widespread reactivity with anti-MHC-I. There was no inflammatory infiltrate, just myophagocytosis. CK was > 6,000 U/l at the time. A month later, he was admitted to internal medicine ICU with a CK > 37,000 U/l on suspicion of myocardial infarction with a troponin I value of 2.7 ng/ml (ULN: 0.05 ng/ml). Repeated coronary angiographies failed to show any cause for cardiac ischaemia. We recommended tests for myositis-associated autoantibodies and acylcarnitines. As we had discussed a possible autoimmune cause, the colleagues reasoned that this pointed to myositis and myocarditis as the cause and were encouraged when CK fell under steroid therapy (see course of values in Fig. 2.1*). After 2 months in hospital, the patient self-discharged, but was admitted a few days later with steroid-induced psychosis causing self-harming behaviour. He phoned our clinic from the psychiatric ward asking for a review of his case. Results of previous tests showed slightly elevated acylcarnitines in plasma, and treatment with riboflavin and coenzyme Q10 gradually replaced the steroid, leading to a vast improvement in his physical and psychiatric status. He continues to take at least 100 mg riboflavin per day as his—mildly elevated—CK will rise with lower doses and he will develop muscle pain within a few days. We have classified this case as 'suspected multiple acyl CoA dehydrogenase deficiency' (MADD) as so far no underlying genetic defect has been found, despite whole-exome sequencing.*

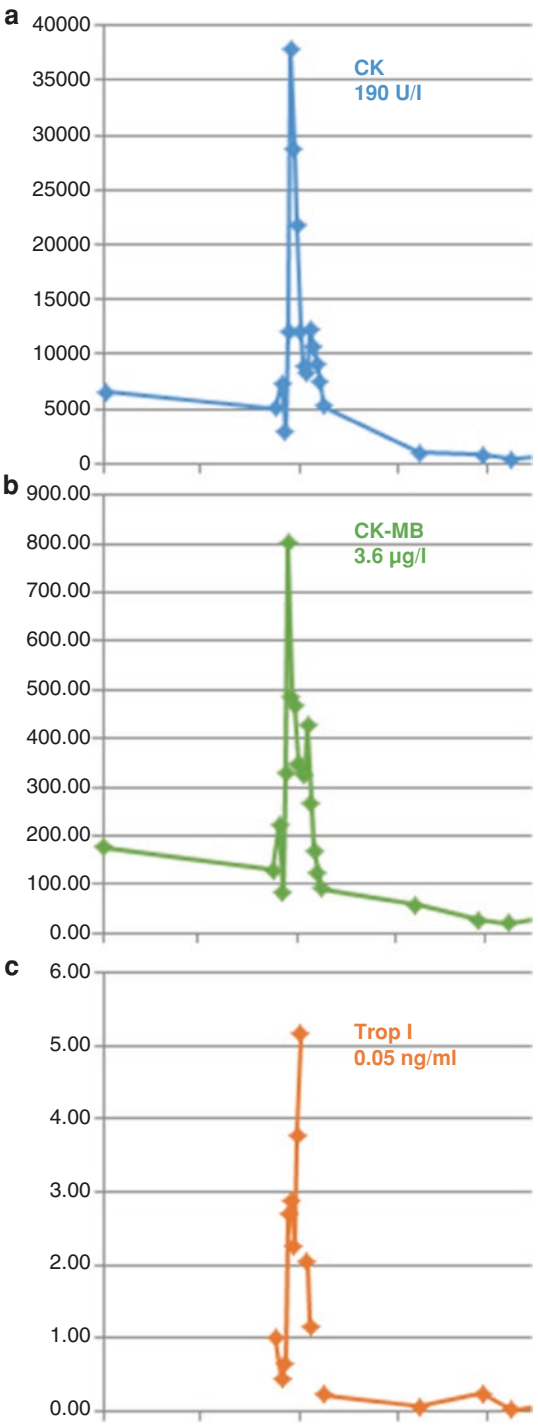


Fig. 2.1 Course of CK, CK-MB, and troponin I measurements in Case Vignette 1. Plotting the courses of CK (**a**), CK-MB (**b**), and Troponin I (**c**) measurements over the time from before muscle biopsy to establishing the riboflavin treatment (X-axis shows months). Indicated are the ULN for the three values

Learning Points

1. **If rhabdomyolysis due to metabolic crisis is a possibility, a treatment attempt with riboflavin for possible MADD is strongly recommended if no other diagnosis is proven.**
2. **Troponin tests can be misleading and are insignificant once a cardiac cause has been excluded.**
3. **Just lowering CK by steroids is not a successful treatment, and side effects may be severe.**

Thyroid-Stimulating Hormone (TSH)

Thyroid function is a master switch of metabolism, and hyper- as well as hypothyroidism can cause impressive changes in skeletal muscle. Interestingly, hyperthyroidism leads to low CK values while hypothyroidism will lead to high CK, but both cause predominantly proximal weakness. TSH therefore will change concordant to CK in these conditions. Thyroid function must be known to assess any neuromuscular case, and thyroid dysfunction will lead to often dramatic worsening of a NMD.

Strengths: fast and available measurement for important influences that are otherwise hard to detect; *weaknesses:* frequently abnormal in the ED and normal in retesting (possibly stress-associated).

C-Reactive Protein (CRP)

Elevated CRP might indicate the systemic inflammatory reaction leading to worsening of a NMD. It is also considered a prime indicator of polymyalgia rheumatica/giant cell arteritis (PMR/GCA) activity, offering this diagnosis as the cause of new muscle pain. However, it is not a good indicator of autoimmune muscle inflammation.

Strengths: fast, available, and dynamic; *weaknesses:* not a good myositis activity marker in muscle.

"Liver Function Tests': Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), and γ-Glutamyl Transferase (γGT)

The serum aminotransferases ALT and AST are generally considered 'liver parameters'. However, these enzymes are also present in skeletal muscle and their plasma levels will rise if considerable leakiness or even destruction of muscle fibres occurs. This phenomenon is usually seen together with CK values well in excess of 5×

ULN. If that is the case, usually these values do not indicate an independent liver pathology and extensive diagnostic work-up (liver biopsy) is not needed. However, if CK is normal or only elevated mildly, one would assume that muscle damage is not sufficient to cause this. Comparing the dynamics of the parameters in question is helpful. ALT values exceeding 15× ULN or a CK/ALT ratio of below 15 should prompt further investigations for additional liver pathology [10]. For reasons of their tissue distributions, bilirubin and γGT will not be elevated due to muscle damage. Yet, γGT is frequently elevated in myotonic dystrophies and a metabolic crisis may affect both liver and muscle, for example, in multiple acyl CoA dehydrogenase deficiency due to *ETFDH* mutations.

Elevation of ALT and AST with normal γGT can also be a hint at acute viral infection, while the elevation of γGT > ALT > AST can be a clue to drug toxicity (e.g. with azathioprine).

Strengths: fast, available, and cheap; *weaknesses:* not tissue specific.

Creatinine

In particular, it is important with regard to kidney damage in rhabdomyolysis and dehydration.

Strengths: fast, available, and cheap; *weaknesses:* not specific for one condition and often abnormal, which makes estimation difficult without previous values.

Erythrocyte Sedimentation Rate (ESR)

Many rheumatologists today find that CRP is a better parameter even in PMR/GCA. Still, it is fast, cheap, and easy to repeat with low inter-rater variability. A patient with an ESR > 50 mm in the first hour without further signs of PMR will have to be looked at for other systemic conditions.

Strengths: fast, available, and cheap; *weaknesses:* unspecific and not a good myositis activity marker.

Blood Count

As a measure of systemic inflammation and hint to acute infection with different patterns for viral, bacterial, and parasitic causes, the humble (but complete!) blood count is not to be underestimated. Detection of anaemia will solve some cases of worsening clinical conditions in NMD. It will also be a clue to the state of some immunosuppressive regimens, at least of the more old-fashioned types (e.g. azathioprine). Note the need to know lymphocyte values for this in the presence of steroid-induced leucocytosis.

Strengths: fast, available, and cheap; *weaknesses:* often unspecific.

Blood Gas Analysis

While O_2 saturation is the most available parameter, pCO_2 is generally the most important in the restrictive disorders resulting from neuromuscular weakness. O_2 saturation in most NMD emergencies will fall only once the hypercapnic patient is deeply unconscious, so O_2 monitoring can lead to a rather false sense of security. Both can be measured transcutaneously, but this will take time and special equipment in the case of pCO_2. Remember that pCO_2 in an awake patient sitting up may be considerably lower than in the same patient asleep and supine. One of the advantages of a full blood gas analysis with pH and base excess is that these parameters may point towards yet compensated problems or alternative causes.

Strengths: essential and dynamic parameters for important function; *weaknesses:* correct sampling and timely testing can be a challenge.

Lactate

While elevated plasma lactate is typical for some disorders [e.g. mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS)] and may indicate metabolic crisis, most frequently this will point to systemic infection. Note that the sample should be drawn without a tourniquet and processed rapidly.

Strengths: dynamic metabolic parameter with clinical consequences; *weaknesses:* easy to produce false elevated values.

CSF

Increased CSF protein without (adequate) increase in CSF leucocytes will point to GBS, spinal stenosis, or ischaemia, but some metabolic conditions will increase CSF protein as well. Pleocytosis in a NMD emergency will mostly indicate a viral infection [e.g. HIV, CMV, West Nile virus, enteroviruses (see section "Virology"), or spirochetosis (borreliosis or syphilis)]. One should include blood *and* CSF glucose and lactate measurements to avoid being confused by granulomatosis, listeria, or meningeal neoplasm, and in the emergency situation also keep an open mind to rare manifestations of subarachnoid haemorrhage by testing CSF ferritin, comparing blood content of consecutive sample vials, and using a centrifuge.

Strengths: fast way to essential parameters and broad spectrum of additional testing available; *Weaknesses:* invasive, potentially dangerous with anticoagulation, increased intracranial pressure, and agitated patients.

Myoglobin

Serum (or plasma) myoglobin not only is a very specific marker of muscle damage, it is also one with a very fast dynamic, exceeding the ULN usually within an hour, peaking a good day earlier than CK or LDH and reaching baseline values usually within 2–4 days [3]. The response to moderate exercise is even faster. This fast clearance can be a problem for the diagnostic use, depending on the time lag between damage and assessment.

However, when the amount of myoglobin released from muscle tissue exceeds the plasma binding capacity and metabolic rate, it will appear in urine. This 'renal threshold' has been referred to be between 0.5 and 1.5 mg/dl and is thereby considerably lower than the values that will produce the brown, foamy urine clinically defining myoglobinuria (given as >100 mg/dl) [11]. Thus, laboratory detection of myoglobinuria by assessing myoglobin in urine or quantitative measuring of myoglobin in serum will be a method to detect the danger of acute kidney failure resulting from this as an alternative or additive measure to applying the more CK-based definition of rhabdomyolysis [7] and treating the patient accordingly.

Strengths: close to the pathophysiology; *weaknesses:* narrow time frame and less published data than for CK.

Immunofixation

Paraprotein-associated NMD can develop rapidly and be clinically severe. While it will usually take a few days to have the result, it is well worth including this in early testing. However, beyond the age of 60, the proportion of the population with a monoclonal gammopathy of unknown significance (MGUS) increases, and thereby the probability that such a finding is associated with the NMD decreases. In this situation, a muscle biopsy to look for nemaline rods or amyloid deposition should be considered.

Strengths: good screening tool for some hard to detect diseases; *weaknesses:* positive results without associated disease, particularly in older patients.

Virology

Viral infections can be responsible for a range of acute neuromuscular problems ranging from, for example, painful neuropathy or myositis in HIV via viral anterior horn cells disease as in poliomyelitis variants (West Nile virus, various enteroviruses, etc.) to GBS following CMV. In most of these cases, PCR diagnostics from CSF and/or blood will be the standard in the acute situation, later confirmed by shifting antibody titre if needed. Unless further data on the patient and the local or

endemic situation gives a clear preference, one will have to cast the net wide in some of these cases in the face of the gamut of candidate viruses.

Hepatitis B and C in contrast will mostly affect the neuromuscular system later in their disease course and indirectly, typically via vasculitic neuropathy.

A multitude of viruses affect skeletal muscle and will lead to viral myositis that usually will be considered by both patient and physician as part of 'flu-like symptoms'. Occasionally, myalgia can be severe and go along with CK values >5× ULN. In our opinion, these are cases to consider for later neuromuscular follow-up checks as some seem to be a bit prone to rhabdomyolysis by other causes, once liver and blood count parameter suggest this is acute viral infection. However, immediate biopsy is more misleading than it can be helpful. If the symptoms are prolonged (i.e. several months), viral antibody titres might be helpful, but this is not an issue in ED treatment.

Strengths: specific, with therapeutic consequences, mostly fast; *weaknesses:* too many viruses to test.

Porphyria Screening

Acute intermittent porphyria is a well-known but frequently overlooked mimic of GBS, particularly the axonal variant [12]. Clinical variability and psychiatric manifestations of the disease will further muddy the waters. In the acute phase, reddish urine, ranging from pink to brown, particularly after it has been exposed to air and light for a short time, is a tell-tale sign. However, detection of urine porphobilinogen is both more sensitive and more specific. Either method can provide a fast first assessment while more complicated biochemical and possibility genetic analysis takes time for confirmation. In rare cases, rhabdomyolysis associated with acute porphyria has been described [13] with hyponatraemia as a frequently suggested link.

Strengths: relatively easy and fast test for a complex differential diagnosis; *weaknesses:* false positive and negative results known.

Toxicology Screening

Unlike chronic conditions, the importance of recreational drugs for neuromuscular emergencies is not as great as general concepts of the toxicity of some substances suggest. Far more frequently than a direct myo- or neurotoxic effect, the situations arising from the drug consumption are important, for instance, immobility on cold, hard surfaces when sedated, hyperactivity under stimulants, nutritional deficits, or defective immune response. Still, it is important for the overall

treatment to know which type of drug has been abused and most urine and blood-based systems will give an answer within hours. It should be noted that most illegal drugs also contain adulterants unknown to users and undetected by the standard drug screening.

Rarer substances and poisonings with effect on the neuromuscular system, however, are often far more complicated to detect and will often require to first identify a laboratory competent to address the individual question. If one considers the necessity of such testing, early sampling and asseveration of plasma and urine are recommended.

Strengths: no good alternatives; *weaknesses:* forensic consequences to think of and storage can be a problem.

Autoantibodies

There are many autoantibodies to be tested, and they all take their time. However, at least in suspected autoimmune myasthenic syndromes, immunemediated necrotizing myopathy (IMNM) and other subtypes of myositis and vasculitic neuropathy, further treatment will often be guided by these antibodies, and one may find it necessary to change the patient's circulating antibodies by IVIG treatment or plasmapheresis in the early days of treatment. Currently, these would be anti-AChR, -MuSK, -LRP4, -titin for myasthenia gravis, anti-VGCC for Lambert–Eaton syndrome, the myositis-specific autoantibodies (anti-TIF1-γ, -MDA5, -SAE1, -Mi2, -NXP2), anti-tRNA synthetase antibodies (anti-Jo1, -PL7, -PL12, -OJ, -KS, -ZO, -EJ), and non-specific myositis-associated antibodies [anti-PM-Scl, -RNP, -Ku, -SSA (Ro52/Ro60), -anti-SSB (La)], as well as anti-SRP and anti-HMGCR for IMNM. Note that anti-titin antibodies will be less specific in patients older than 50 years and that general ANA testing, along with at least the non-specific myositis-associated antibodies, will help interpret these results in the opinion of most rheumatologists. Some myositis-specific antibodies can give very important and reliable clues to neoplastic diseases (for instance, anti-TIF1-γ) or to the risk of severe lung disease (anti-MDA-5). If vasculitis neuropathy is the question, ANA, ENA, ANCA, and anti-CCP should be on the list and at least anti-Hu, anti-CV2, and anti-amphiphysin antineuronal antibodies. As illustrated in Case Vignette 3, tests for recently discovered autoantibodies against the nodes of Ranvier and associated structures may have a significant influence on the treatment of autoimmune neuropathies now, particularly if they are IgG4 [14]. Finding a lab reliably testing 'hot off the press' antibodies can be a challenge. While not in the first line of diagnosis in the ED, there is also no point to wait for these tests.

Strengths: some antibodies can define the diagnosis, treatment, and prognosis with a bit of serum; *weaknesses:* unspecific findings with some antibodies and varying results in retesting.

Case Vignette 2

A woman in her mid-20s showed progressive weakness of proximal leg muscles and foot dorsiflexion for 6 years. She had been in treatment for suspected myocarditis. CK was > 1,000 U/l, and she had a reduced vital capacity of 1.6 l both sitting and supine, previously attributed to her short and slim figure. A muscle biopsy showed fibre type II atrophy, some necrotic fibres and myophagocytosis but no inflammatory infiltrate, no complement deposition beyond the necrotic fibres, and little, focal anti-MHC-I reactivity. A treatment attempt with oral steroids (1 mg/kg daily) did not lead to any improvement, and we began genetic testing. A few months later, she was admitted to cardiology due to worsening dyspnoea, but her—abnormal—ECG had not changed and echocardiography was considered non-conclusive. She was discovered unconscious with a pCO_2 in excess of 120 mm Hg on the ward and had to be intubated. Her CK fell immediately, but respiratory function, attributed to respiratory muscle weakness and insufficient mucus clearance, did not improve (see course of CK in Fig. 2.2*). EMG showed much spontaneous activity and some myopathic MUP in a difficult exam as she fatigued rapidly. Extensive work-up with extensive retesting, including a second muscle biopsy (not much different from the first), turned up anti-SSA (Ro52) antibodies, Sicca syndrome, and Raynaud's disease. The consultant rheumatologist suggested the diagnosis of Sharp syndrome/mixed connective tissue disease, and treatment with cyclophosphamide was started, whereupon she promptly recovered. She reached a critical cumulative dose without being able to discontinue immunosuppression and later developed early ovarian failure. All attempts to reduce immunosuppression led to new cardiac or skeletal muscle symptoms; methotrexate had to be stopped due to liver toxicity, and she developed new cardiac disease activity under mycophenolate mofetil. More than a decade later, her disease activity is under control with rituximab.*

Learning Points

1. **Monitor pCO_2 in a neuromuscular patient with low vital capacity or dyspnoea.**
2. **Immobilization of a NMD patient, particularly under ICU measures, will lower CK. This does not signify treatment success or decreased disease activity.**
3. **Anti-SSA/Ro 52 may not be a particular specific autoantibody, but in connective tissue disease, it should be taken as a warning sign regarding the risk of cardiac involvement [15].**

Comment 1: Treating young women with cyclophosphamide should no longer be practised as it leads to early ovarian failure and a different immunosuppressant will be needed within a few years anyway.

Comment 2: According to Sharp et al. [16], 18 out of 25 patients had muscle symptoms and elevated CK. Also, 8 of these 18 had a muscle biopsy that showed inflammatory infiltrates in 7.

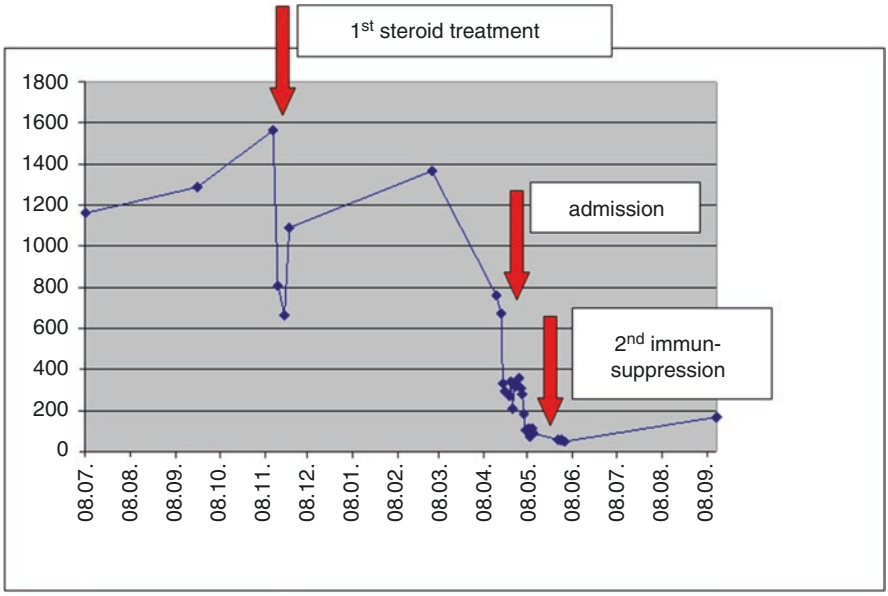


Fig. 2.2 Course of CK in Case Vignette 2. Plot of the CK values against time in months for Case 2. Note how admission to ICU lowered the CK further than steroid treatment though neither did improve the muscle disease

Soluble Interleukin-2 Receptor

Invoking sarcoidosis in the differential diagnosis of a complex unresolved case is almost never wrong. Unfortunately, sIL2R is so frequently elevated in myositis without association to sarcoidosis that it can be used as a myositis activity marker, but not as a differential tool [17].

Strengths: monitoring in sarcoidosis, possibly reducing the need for bronchoalveolar lavage; *weaknesses:* not specific in inflammatory muscle diseases.

Ferritin

Of the described biomarkers for interstitial lung disease (ILD) in inflammatory myopathies, particularly MDA-5-associated dermatomyositis and anti-synthetase syndrome, ferritin is the one that will be available by fast, in-house measurement. Measurements greater than 1500 ng/ml have been reported as a sign of increased ILD activity and worse prognosis [18]. However, the majority of data refer specifically to anti-MDA5 dermatomyositis. Obviously, there are a number of other conditions that will elevate this value (e.g. iron overload, parenchymal liver damage, or some forms of anaemia without iron deficiency).

Strengths: available; *weaknesses:* not specific.

Molecular Genetics

The emergency situation appears to be most unsuitable for the initiation of genetic testing. The patient's informed consent for this while everybody involved has an acute problem on their minds and hands is possible, but not optimal. Moreover, in most settings, this type of diagnostics will take time, usually longer than you wish for an emergency treatment to take. There are issues about availability and costs differing drastically from one country to the other. However, there are offers of 'emergency genetics', most often aiming at the situations where a pregnancy or neonate is thought to be severely affected by a NMD. Moreover, sometimes the specific situation of the patient, family history, or a particular differential diagnosis will best be resolved by genetic testing. Last but not least, some disorders, particularly the DNA repeat-associated muscle disorders (myotonic dystrophy types 1 and 2, as well as facioscapulohumeral muscular dystrophy), can only be confirmed properly by genetic testing. Thus, if these diagnoses have relevance for the acute treatment, there is no point in delaying the analysis.

Strengths: diagnostic in many situations; *weaknesses:* delay, counselling necessary, still relative expensive, and the problem of variants of unknown significance (VUS).

Electrodiagnostic Studies

Introduction

Electrodiagnostic studies (also known as electrophysiological or clinical neurophysiological studies) play a key role in the evaluation of patients with neuromuscular disease and delineate a variety of pathophysiological changes that may otherwise escape detection. The standard electrodiagnostic tests such as nerve conduction studies (NCS) and conventional concentric needle electromyographic studies (EMG) are widely performed both in a routine outpatient setting and in the critical care setting to help investigate a range of neuromuscular disorders involving the anterior horn cells, peripheral nerves, neuromuscular junction, and muscles. Other electrophysiological tests such as repetitive nerve stimulation testing (RNS) and single-fibre electromyography (SFEMG) can demonstrate abnormalities in neuromuscular transmission and augment the sensitivity of the clinical examination. These studies remain an important asset that can help clinicians localize lesions, characterize pathophysiology, understand injury severity, and assess chronicity of a disease process.

Over the decades since these studies have come into use in routine clinical practice, they have also been utilized in the critical care unit setting to investigate a range of neuromuscular disorders such as Guillain–Barré syndrome and

myasthenic crisis (to name but a few). Since the recognition of the entity now known as intensive care unit-acquired weakness (ICUAW), the use of electrodiagnostic tests to further evaluate these patients has become commonplace in the intensive care unit. A distinct benefit of EMG and NCS is that they can be performed at the bedside and are widely available in most tertiary and secondary care settings. A reasonably comprehensive assessment can be made in an examination lasting 30–45 min by an experienced electromyographer, although this may take much longer in a critical care setting depending on the complexity of the case and technical challenges. A preliminary result can often be made available immediately after the test unless advanced quantitative techniques (such as single-fibre EMG or quantitative motor unit analysis) are required as often this would require additional analysis time. Therefore, these studies have a distinct benefit over serological and histopathological studies when the results are time-critical as they would be in an intensive care unit, where urgent treatment decisions need to be made without delay.

Indications

The most common use of electrodiagnostic testing in routine clinical practice is to confirm a suspected clinical diagnosis. When the presentation is classical, often a test such as electrodiagnosis may not be required for diagnostic purposes. However, there may be uncertainty about the diagnosis due to atypical (or less than classical) findings that do not all fit with the suspected disorder, a relatively mild stage of the disease with a minimum of symptoms and signs, or unexpected findings that are not entirely consistent with the primary diagnosis. There may also be other situations where the clinical presentation would fit with more than one neuromuscular disorder and these other diseases will need to be excluded to confirm the primary suspicion. In these situations, electrodiagnostic testing provides confirmatory evidence, which eliminates the need for exhaustive exclusionary further testing or very invasive investigations.

However, the most fundamental use of electrodiagnostic studies is to aid localization of the disorder in the peripheral nervous system and help characterize/classify the disease pathophysiology. Correct localization of neuromuscular disorders within the peripheral nervous system helps narrow the differential diagnosis and therefore avoid unnecessary further investigation. Electrodiagnostic studies have the capability of providing a precision not possible with physical examination alone and are even more valuable in patients who are difficult to examine for one reason or the other.

Given that electrophysiological studies evaluate and quantify nervous system physiology, it is easy to understand how they may play a role in the characterization of disease pathophysiology. The findings of these studies are not strictly specific for any particular aetiology but instead reveal patterns of abnormality that help broadly

classify the disorder as a neuropathic process (peripheral nerve, plexus, nerve root, or anterior horn cell), myopathic disorder, or a disturbance of neuromuscular junction transmission. Such localizing information is particularly valuable in situations when the clinical presentation is atypical, clinical history is difficult to obtain, or when clinical examination is limited (as in when the patient is comatose). For example, a patient in the critical care unit with profound muscle weakness can have a broad differential diagnosis, and it can be difficult to determine from history and clinical examination alone.

In the case of neuropathic lesions, electrodiagnostic (EDX) studies often yield further key information, including the fibre types involved (sensory, motor, or mixed), the underlying pathophysiology (axonal loss or demyelination), and the temporal course of the disorder. The possibility of identification of a demyelinating neuropathy in NCS often makes the requirement for a nerve biopsy less likely. Likewise, the ability of motor nerve conduction studies to demonstrate the phenomenon of motor conduction block (as seen in some autoimmune inflammatory neuropathies) is a rather unique feature which cannot be easily demonstrated by other investigations that assess nerve structure as it is a physiological (rather than structural) concept.

A major benefit of electrophysiological studies is their ability to identify subclinical disease which is below threshold for identification using physical examination alone or based on symptomatology. A typical example of this would be the use of needle EMG to identify subclinical denervation in a patient with amyotrophic lateral sclerosis (ALS) who does not complain of widespread weakness and has only clinical abnormalities on examination limited to one spinal segment. In this situation, identification of denervation changes in apparently unaffected segments further clarifies the clinical diagnosis.

Quantifying the severity of a peripheral neurogenic lesion is possible based on NCS and EMG findings. This in turn helps determine the prognosis for recovery. Neurogenic lesions associated with loss of axons (axonal degeneration) usually have a poorer prognosis and more protracted recovery time when compared to neurogenic lesion that consists of pure myelin dysfunction. Detailed quantification of the severity of pathophysiology of a disease process offers many advantages over purely grading the abnormality clinically according to degree of loss of function. This is mostly important in conditions such as nerve injuries where it is important to define the extent of axonal loss as these lesions would have a poorer long-term prognosis than purely demyelination lesion. The degree of loss of function may be similar in the initial stages of axonal injuries and neurapraxia, and hence, these studies are invaluable to peripheral nerve surgeons to help definite prognosis and need for interventions.

Electrophysiological studies can also be utilized to monitor the evolution of a disease and monitor how it progresses over time. As these studies provide us with the capability to quantitatively measure nervous system physiology, frequently they are used to follow the patient (e.g. with a peripheral neuropathy) to objectively

assess the progression of the condition over time and in some instances the response to treatment. Both NCS and EMG are sensitive enough to detect minor changes over time that are hard to appreciate clinically and are reasonably reproducible on repeated testing. NCS parameters tend to be more commonly used for this purpose than needle EMG, although when quantitative EMG measurements are employed, this too can act as a suitable longitudinal marker. These attributes have made electrophysiological studies a useful tool in research and clinical trials as they tend to be less invasive, less time-consuming, and often more economical than other forms of diagnostic testing that can be used as longitudinal markers.

In certain disease processes, electrophysiological studies can aid how to direct further investigation. A typical example would be determining the site of a suitable nerve to biopsy in a patient with a vasculitic neuropathy in order to maximize the yield of the histopathology. The yield of a nerve biopsy in detecting a suspected inflammatory process would tend to be much higher in an electrophysiological abnormal nerve that does not show marked axonal degeneration. Furthermore, in patients with suspected hereditary neuropathies, the pattern of abnormality in the nerve conduction studies can be helpful in directing the order of genetic testing for various relevant mutations, even if the abnormalities may not be entirely specific for any particular syndrome.

Caveats

There are many caveats to the use of electrophysiological testing in clinical practice. It is crucial to bear in mind that electrodiagnostic tests are not a substitute for a neurological opinion. Electrodiagnosis is an extension of the neurological evaluation and employs the same anatomic principles of localization as the clinical physical examination, searching for evidence of motor and sensory compromise. These studies supplement the history and physical examination, adding precision, detail, and objectivity. Another very important point to remember is that the abnormal findings in the studies are not specific for any specific aetiology; instead, patterns of abnormal findings help classify or categorize the PNS disorder which, when combined with the history, clinical examination, and other investigation findings, allows to eliminate differential diagnoses and strongly favour a remaining differential. For example, abnormal RNS and SFEMG findings are not specific for myasthenia gravis but merely indicate a disturbance in neuromuscular junction transmission and can also occur in reinnervation.

EDX studies are generally well tolerated in the vast majority of patients and are rarely associated with any significant side effects. Both nerve conduction studies and needle electromyography are associated with transient unpleasant sensations in the awake patient, but it is rare for a patient to not be able to tolerate the study to its completion. Needle EMG examination can be difficult in patients who have a needle

phobia, but this can be often circumvented by various measures. A more frequent occurrence is when patients have difficulty relaxing when recording nerve action potentials during nerve conduction studies as muscle artefact often obscures the nerve action potential and can contaminate the readings when the signal is averaged, resulting in suboptimal measurements. A cooperative patient is perhaps the single most important factor in obtaining a meaningful study. Hence, in neonates, the very young paediatric population, and patients with cognitive impairment or psychiatric illness, the examination is difficult and less well tolerated. In these situations, at best, only a very limited study can be obtained.

In patients with pacemakers, cardioverter defibrillators, and other similar cardiac devices, electrical stimulation in NCS can pose risks, and hence, these devices may require temporary deactivation. Needle EMG is a relatively invasive test and, rarely, may be associated with iatrogenic complications, such as pneumothorax, bleeding (particularly intramuscular haematoma formation), and local injury such as swelling. Bleeding risks are much higher in patients on anticoagulation, and ideally these medications should be withheld for a time period prior to the electrodiagnostic study in order for coagulation to normalize. If it is not possible to do this, the needle EMG sampling should be limited to a few superficial muscles and sampling of deep muscles should be avoided in order to prevent the risk of compartment syndrome in a limb from a large haematoma.

Brief Summary of Electrodiagnostic Techniques

Regarding the in-depth discussion of the standard electrodiagnostic techniques, we would like to refer to the literature (Figs. 2.3, 2.4, and 2.5).

Table 2.2 gives an overview of standard electrodiagnostic techniques.

Additional Studies Used in a Critical Care Setting

Phrenic Motor Study

One possible reason intubated patients fail to wean is dysfunction of one or both phrenic nerves. The phrenic nerves are most often affected as a post-infectious process or as a complication of thoracic surgery. However, the phrenic nerves can also be affected by a severe diffuse polyneuropathy, including GBS and critical illness polyneuropathy (CIP). The phrenic motor study can be performed by recording the compound motor action potential (CMAP) from the diaphragm with the active electrode placed two fingerbreadths above the xiphoid process and the reference electrode over the anterior costal margin. The nerve can be stimulated in the lateral neck either posterior to the sternocleidomastoid muscle approximately 3 cm above the clavicle or between the sternal and clavicular heads of the sternocleidomastoid just above the clavicle. A normal phrenic nerve conduction study evokes a CMAP of

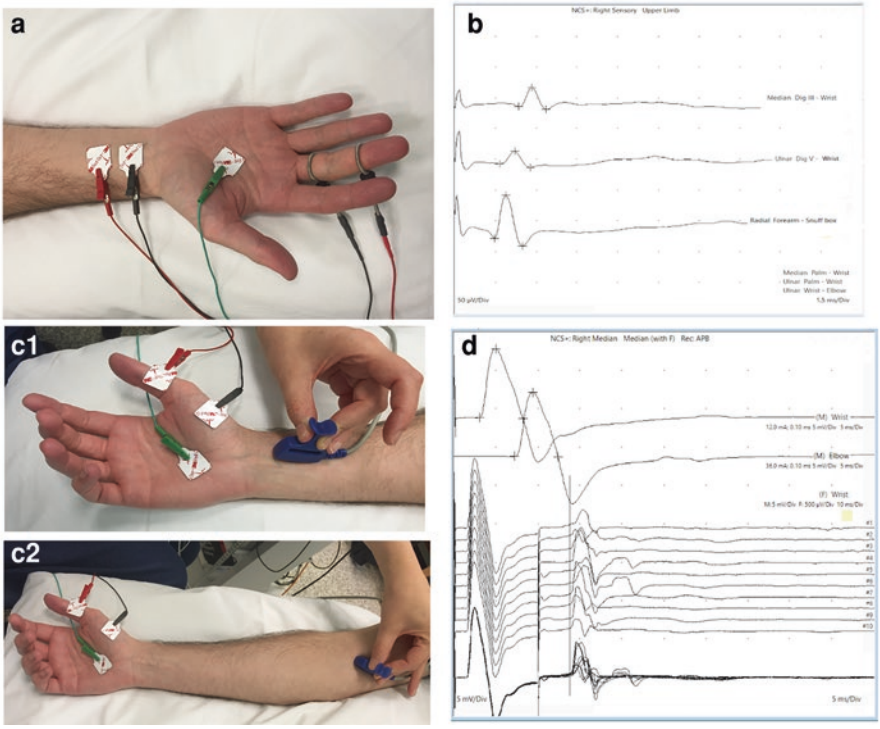


Fig. 2.3 Normal sensory and motor nerve conduction studies. (**a**) – Median nerve sensory nerve conduction study. (**b**) – Sensory nerve action potentials recorded from the median, ulnar, and superficial radial nerves. (**c1**) – Median nerve motor study (distal stimulation at the wrist). (**c2**) - Median nerve motor study (proximal stimulation at the cubital fossa). (**d**) – Above two traces show the compound muscle action potentials from distal median nerve stimulation (above) and proximal stimulation (below). The traces below this show the median nerve F wave studies

only a few hundred microvolts. Thus, the presence of electrical noise, which is not uncommon in the ICU, can easily obscure the response. This study is most helpful if responses on both sides are present and normal or if there is a clear unilateral abnormality on the side where a hemi-diaphragmatic weakness is suspected. If both responses are absent or low in amplitude, it is difficult to draw a firm conclusion; possibly either responses are genuinely absent/small or both responses are abnormal due to technical reasons.

An intact phrenic motor response confirms the integrity of the phrenic nerve. However, several technical problems with this study must be taken into account, especially in the ICU. First, it often is difficult to perform phrenic conduction studies on obese individuals or those with an overly muscular neck. Second, the study cannot be performed safely if the patient has an external cardiac pacemaker in place. Finally, if a central line is present, the study is contraindicated on the side with the catheter.

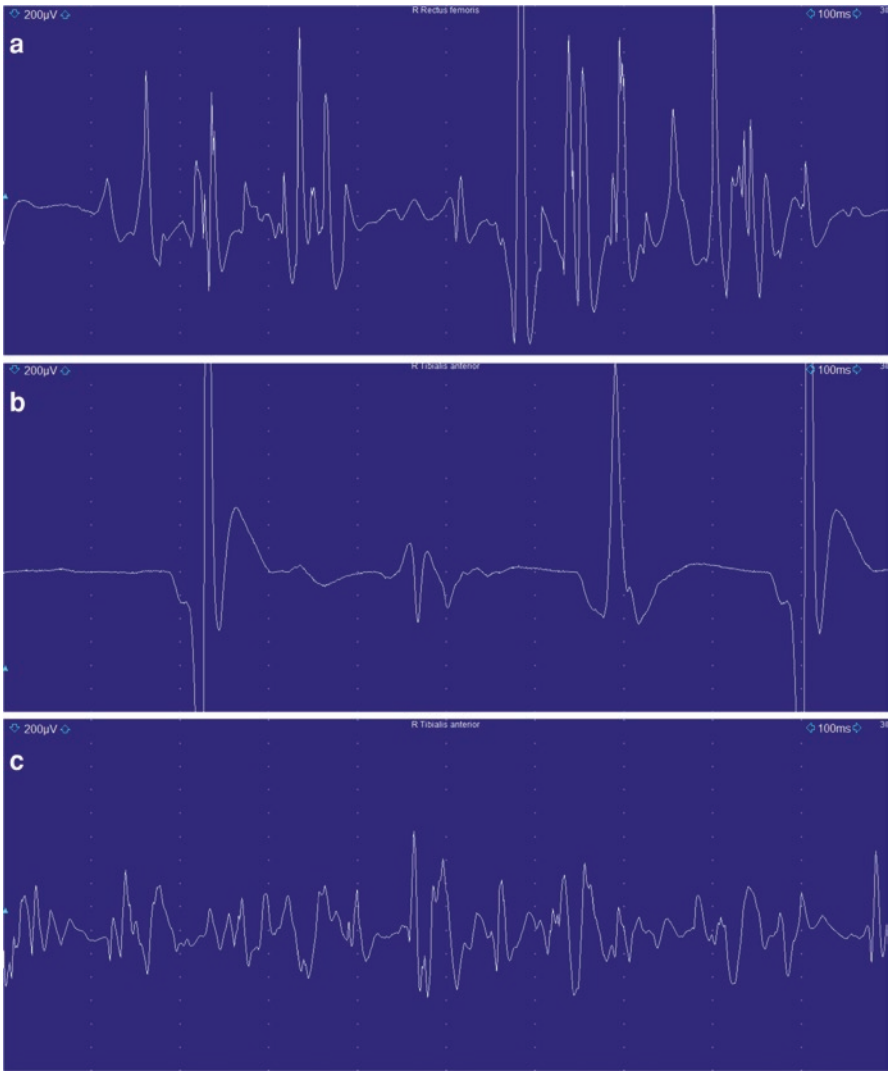


Fig. 2.4 Needle EMG findings in normal and diseased muscle. Needle EMG findings in (**a**) - normal muscle, (**b**) – chronic neurogenic conditions, and (**c**) – chronic myopathic disorders

Diaphragmatic EMG

Needle EMG of the diaphragm is sometimes used in the critical care setting to help determine whether respiratory insufficiency has a neuromuscular basis. More importantly, it can also be used in patients who have a known phrenic nerve palsy to look for signs of reinnervation in order to aid prognosis.

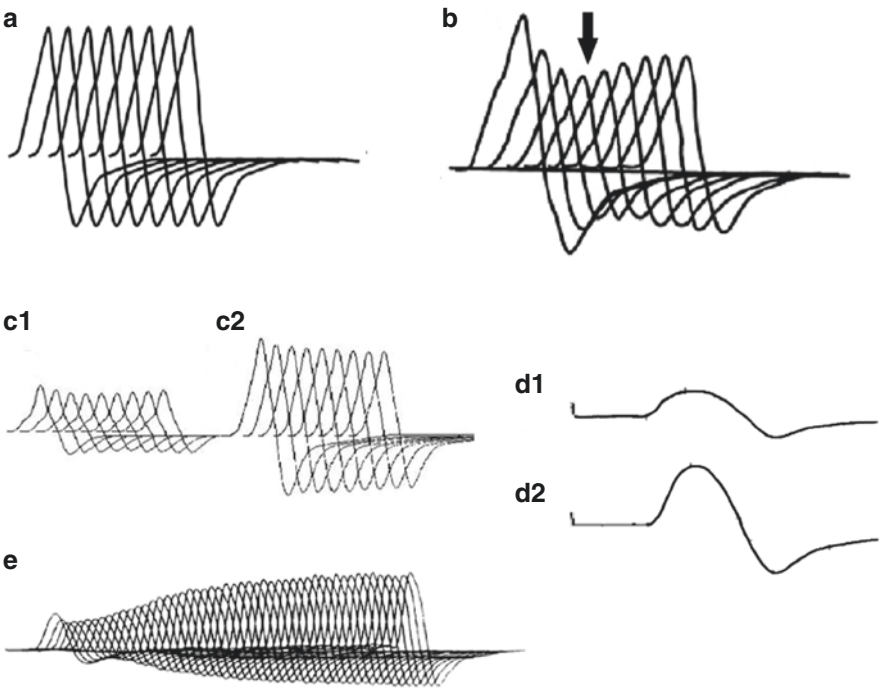


Figure - Repetitive nerve stimulation findings in postsynaptic and presynaptic disorders. a) Normal findings at 3Hz stimulation. b) Decrement at 3Hz stimulation in patient with myasthenia gravis, with black arrow showing maximum decrement with 4th stimulus. c1) 3Hz RNS in patient with LEMS at rest showing a mild decrement. c2) 3Hz RNS in patient with LEMS after 10secs exercise showing post-exercise facilitation in amplitude with mild decrement. d1) Low amplitude baseline CMAP in patient with LEMS at rest. d2) Post-exercise facilitation of the CMAP after 10secs in same patient. e) Rapid rate stimulation at 30Hz in a patient with LEMS showing incremental response.

Abbreviations: RNS - Repetitive nerve stimulation, LEMS – Lambert Eaton myasthenic syndrome, CMAP – Compound muscle action potential

Fig. 2.5 Patterns of repetitive nerve stimulation abnormalities in pre-synaptic and post-synaptic disorders of neuromuscular junction transmission

However, examination of muscles in proximity to the lungs and pleura produces a risk of puncturing the pleura and inducing pneumothorax. The decision to sample the diaphragm hence depends on the experience of the electromyographer and the potential benefit to the patient versus the risk of pneumothorax in that particular patient, especially as patients in intensive care may already have a low respiratory reserve. Although several different techniques are reported in the literature on performing the needle EMG sampling blindly, it would be generally advisable to perform the needle sampling under ultrasound guidance unless the electromyographer is very experienced at sampling this particular muscle.

Table 2.2 Overview of electrodiagnostic tests routinely used in neuromuscular diagnostics

Test	Basic principle of test	Principle metric	Typical findings/ pathology	Caveats and limitations
Nerve conduction studies				
Motor NCS	Supramaximal stimulation of nerve; recording over muscle	Compound muscle action potential (CMAP) morphology and timing; distal motor latency (DML)	↓ Amplitudes with axonal loss ↓ Conduction velocity over whole segment in diffuse demyelination (e.g. CIDP) Conduction block and temporal dispersion (focal/ segmental demyelination: MMN) Normal SNAP despite sensory loss: pre-ganglionic lesion (inflammatory plexus lesions; demyelination; radiculopathy and motor neurone disease)	CMAPs may remain normal for 7–10 days after an acute neural injury
Sensory NCS	Distal nerve stimulation and proximal recording over nerve (=orthodromic technique); proximal nerve stimulation and distal recording over nerve (=antidromic technique)	Sensory nerve action potential (SNAP) amplitude and latency		SNAPs may remain normal for 7–10 days after an acute neural injury. Lower limb SNAP amplitudes (and to a lesser extent conduction velocities) reduce with age and SNAPs are often unrecordable by the eighth and ninth decades
Late responses	F-wave: distal supramaximal stimulation, antidromic propagation to anterior horn cell and return to recording muscle H-reflex: tibial or median nerve submaximal stimulation of increasing intensity, orthodromic propagation via Ia afferents to spinal cord activation motor efferents, and back to recording muscle	F-wave: varying latency of <20 stimuli, F-wave persistence, and chronodispersion H-reflex: latency (typically constant)	↑ F-wave latency: demyelination ↑ Chronodispersion: with normal distal NCS = proximal lesion ↓ Persistence: axonal injury or proximal conduction block ↑ H-reflex latency: demyelination	Persistence varies depending on the nerve tested F-wave may travel by multiple nerve roots, which reduces sensitivity H-reflex may be absent physiologically. Lesion location relatively uncertain

Table 2.2 (continued)

Test	Basic principle of test	Principle metric	Typical findings/ pathology	Caveats and limitations
Repetitive nerve stimulation	Repeated (5–10×) supramaximal stimulation of motor nerve obtaining a series of CMAPs	Amplitude of CMAP; decrement (= >10% decrease) between first and fourth CMAP	↓ Amplitude of initial CMAP in pre-synaptic disorders, but marked incremental increase to rapid (20 Hz) stimulation and post-exercise facilitation in LEMS 'U-shaped' decremental pattern with slow (3 Hz) stimulation in post-synaptic disorders (MG)	Can be technically challenging in non-cooperative patients More specific for detecting a neuromuscular junction disturbance but less sensitive than SFEMG
Electromyography				
Concentric needle EMG	Recording of bioelectric activity with intramuscular needle electrode	Spontaneous activity in muscle; motor unit morphology (qualitative or quantitative); recruitment pattern with minimal innervation; interference pattern at maximal muscle contraction	Fibrillations, positive sharp waves (PSWs), fasciculation potentials, and repetitive discharges are abnormalities of spontaneous activity; abnormal motor unit morphology and abnormal recruitment and interference patterns differentiate between neurogenic and myopathic conditions	Requires patient corporation to assess voluntary activity (hence not possible in comatose or paralysed patients)
Single-fibre EMG (or concentric needle jitter studies)	Special electrodes inserted between muscle fibres of one motor unit to assess timing variability of activation in fibres of one motor unit	Jitter = variability of inter-potential interval (= mean consecutive difference MCD) with voluntary or stimulated activation	↑ Jitter in myasthenic disorders with 'blocking' (=intermittent failure of motor action potential transmission)	Increased jitter and impulse blocking is not specific to primary neuromuscular junction disorders

Direct Muscle Stimulation (DMS)

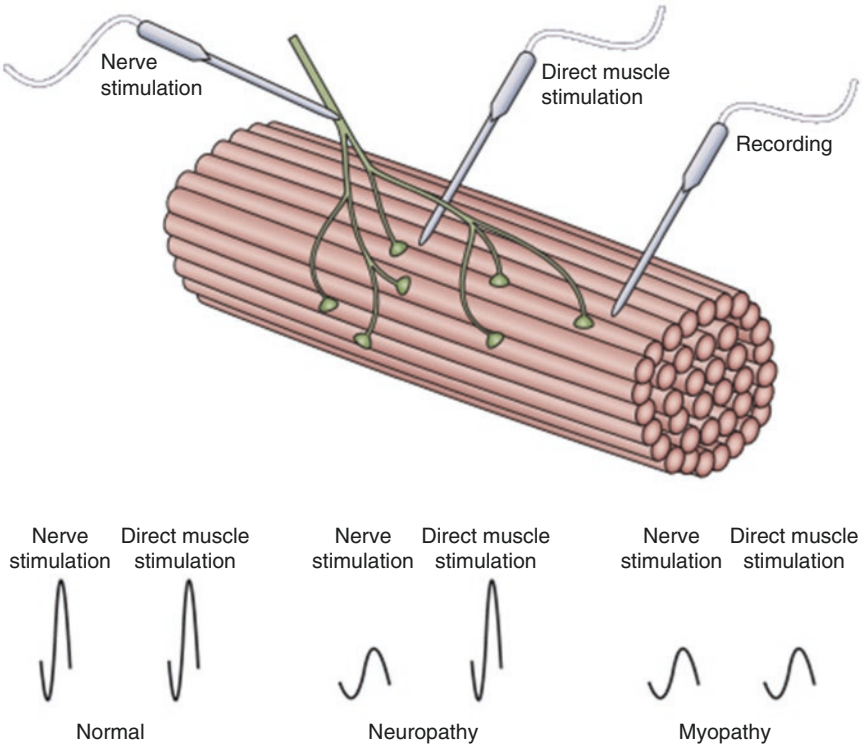
DMS is essentially an extension of nerve conduction studies (except that they are often performed with needle EMG electrodes instead of surface electrodes) and can help differentiate critical illness myopathy (CIM) from CIP. Both CIM and CIP show reduced CMAP amplitudes in the motor nerve conduction studies, and the distinction between them relies upon the findings of the sensory studies or needle EMG studies. However, it can be difficult to obtain sensory potentials in some patients in the critical care unit and needle EMG examination can be inconclusive in patients who are unable to cooperate with assessment of voluntary motor unit activity (making it difficult to assess the motor units), which has led to the use of direct muscle stimulation in some departments. The method can also be extended further in order to study muscle fibre conduction velocity and the excitability of muscle fibres.

This technique involves stimulating the distal segment of a muscle (away from the endplate region) using either surface, sub-dermal, or intramuscular (monopolar) needle electrodes and recording again using either surface, sub-dermal, or intramuscular (concentric) needle electrodes proximally in the muscle in order to record the maximum direct muscle-stimulated CMAP (dmCMAP). The amplitude of the dmCMAP is then compared to the nerve-evoked CMAP (neCMAP), which is obtained by stimulating the distal nerve terminal using surface/sub-dermal or monopolar needle electrode. In CIM, the ratio of neCMAP:dmCMAP amplitude is closer to 1 (even in the situations where both responses are absent), whereas in CIP, the ratio is <0.5 (Fig. 2.6). Abnormal findings from this technique are not specific for critical illness, and axonal nerve injuries may mimic CIP on DMS while some muscle channelopathies such as periodic paralysis may show findings similar to CIM.

Patterns of Abnormalities Encountered in Neuromuscular Disorders in the Critical Care Unit

A variety of neuromuscular neurological conditions can be encountered in the intensive care setting. The following discussion outlines some of the pertinent findings in these groups of conditions.

Mononeuropathies are probably the most common problem encountered in an outpatient setting, and they rarely require urgent testing in the critical care setting. The electrodiagnostic abnormalities are localized to one peripheral nerve and the abnormalities may be localizing or non-localizing, depending on the presence or absence of focal conduction slowing across lesion site. Nerve conductions and needle EMG are normal everywhere, except in the distribution of one nerve. Depending on whether the involved nerve is a sensory, motor, or combination nerve, sensory and motor nerve conductions may be abnormal. Abnormalities in sensory studies identify the lesion as one of peripheral nerve, at or distal to the dorsal root ganglion. Motor studies may show conduction slowing or focal conduction block, typically at a common entrapment site such as the wrist or elbow or at common compressive sites (such



Direct muscle stimulation. Stimulating and recording electrodes are both placed in the muscle so that compound muscle action potentials can be obtained even if the nerve is damaged, as in the neuropathy example shown here. In the case of myopathy, compound muscle action potentials are reduced or absent after both conventional stimulation through the nerve and direct muscle stimulation.

Fig. 2.6 Direct muscle stimulation in intensive care unit-acquired weakness from [71]

as the fibular head and spiral groove). In a non-localizing lesion, however, findings on nerve conductions are limited to signs of axonal loss (decreased amplitudes with normal or slightly slowed latencies and CVs). On EMG, neuropathic abnormalities are limited to the distribution of the involved nerve. Proximal mononeuropathies are difficult to detect in NCS, showing only denervation in the relevant muscle innervated by the nerve. Cranial mononeuropathies are also difficult to study directly using nerve conduction studies (with the exception of the facial nerve where motor nerve fibres can be stimulated and a CMAP obtained), although cranial nerve reflex studies such as the blink reflex or jaw jerk can help in exploring trigeminal nerve lesions.

Generalized peripheral neuropathies are commonly encountered in both the outpatient and critical care settings. Polyneuropathies are recognized by generalized abnormalities in nerve conduction studies and neuropathic findings on needle EMG. Abnormalities in nerve conduction may indicate either demyelination

(conduction slowing, conduction block or dispersion of responses), axonal loss [reduced sensory nerve action potentials (SNAPs) and CMAPs], or a combination of both, depending on the type of the polyneuropathy.

One of the most common patterns is the stocking-glove polyneuropathy, where abnormalities are dependent on the length of the nerve. Thus, in both NCSs and EMG, abnormalities are more prominent distally, worse in the legs than in the arms, and more prominent in distal than proximal segments.

The presence of any significant asymmetry in an axonal polyneuropathy may have important diagnostic significance. An asymmetric pattern may suggest underlying multiple mononeuropathies. Multiple mononeuropathies (often referred to as mononeuritis multiplex) produce a unique pattern in which individual peripheral nerves are affected in a stepwise manner. Most often, this pattern results from an underlying vasculitic neuropathy. If the pattern is not recognized initially, as further nerves become affected, a confluent pattern of nerve involvement will develop that is difficult to differentiate from a typical distal symmetric polyneuropathy.

Case Vignette 3

A 43-year-old man who is normally fit and well developed a chest infection with symptoms lasting 3 weeks (possibly also bowel symptoms with that). Then approximately 6 weeks later, he noted tingling in feet, which then ascended the legs to the genitalia and then the hands. Within a few days, he developed weakness in his legs and began to stumble and then was admitted to the local hospital with ascending paralysis, including the face. Spinal MRI found S1 root impingement but nothing causative of this clinical picture. Initial LP did not have raised protein. He had a course of IV immunoglobulin (IVIG) but proceeded to worsen through it, requiring ICU admission and ventilation. When seen in the intensive care unit, the patient was sedated, occasionally opening eyes to stimulus. There were no movements of limbs (partly sedation-related) but he was areflexic throughout with downgoing plantar responses. His first electrophysiological study showed evidence of a diffuse, non-length-dependent (patchy) sensorimotor peripheral neuropathy with possible partial motor conduction block seen in the left ulnar nerve (forearm). However, there were few other demyelinating features at this stage. The patient was treated with a further course of IVIG but failed to show any clinical response, and therefore, the electrodiagnostic studies were repeated 2 weeks later. At this stage, there were no recordable sensory or motor potentials in the limbs and the needle EMG studies showed widespread fibrillation potentials and positive sharp waves (which were not present in the previous study) and hence the features were felt to favour an axonal form of GBS. The patient continued to show no response to further IVIG treatment and hence was subsequently tested and found to be positive for neurofascin antibodies (NF155 IgG4 antibodies). He was then treated with rituximab, which led to a gradual improvement in muscle strength over several months, and was able to regain mobility after 6 months.

Learning Points

1. **Patients with neurofascin antibody-related autoimmune neuropathies may present acutely, resembling GBS. These patients are refractory to IVIG but responsive to rituximab.**
2. **Electrodiagnostic studies are useful in classifying the type of GBS, monitoring progression/response to treatment, and can be helpful in identifying atypical features that may raise suspicion of an alternative diagnosis.**
3. **Electrodiagnostic studies can be misleading when done too early in autoimmune neuropathies. If there is diagnostic doubt, it is helpful to repeat the test as the condition evolves.**

Guillain–Barré syndrome (GBS) is perhaps the most important polyneuropathy encountered in the acute setting. Although nerve conduction studies are an important diagnostic test in GBS and are crucial in classifying the type of GBS (axonal vs. predominantly demyelinating), these abnormalities may take 2 weeks or more to fully develop and hence the electrodiagnostic findings may be subtle or even normal in the hyperacute stage. Therefore, GBS remains primarily a clinical diagnosis which is supported by laboratory investigations, including electrodiagnostic studies, but only when the results are abnormal.

The pattern of electrodiagnostic abnormality encountered depends heavily on the subtype of GBS. In demyelinating forms such as acute inflammatory demyelinating polyradiculoneuropathy (AIDP), NCS may reveal evidence of patchy focal demyelination, including prolonged or absent F waves (often the earliest abnormality), conduction velocity slowing, conduction block, and temporal dispersion of CMAPs. However, in early AIDP the demyelinating features may only affect the very proximal and very distal segments of the nerves, sparing the intermediate segments, and this makes it difficult to detect the typical focal demyelinating features. Even in the early stages of AIDP, when NCS appears to be unremarkable, needle EMG can show reduced recruitment of voluntary motor units in weak muscles, but this can be very hard to appreciate when assessed qualitatively. In axonal forms of GBS, such as acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN), the features are of a length-dependent or multifocal polyneuropathy with a reduction in the CMAPs and SNAPs without significant demyelinating features.

Thus, abnormalities in NCS and EMG are helpful in classifying the type of GBS and distinguishing predominantly demyelinating forms (such as AIDP) from predominantly axonal forms. However, this cannot be reliably done if the study has been performed too soon to detect axonal degeneration features on needle EMG, which may take 3–4 weeks from onset to fully develop. Therefore, it is often necessary to perform a second study if the initial study has been performed early for diagnostic purposes. It is also important to note that NCS and EMG can be normal throughout in patients with some regional forms of GBS (such as Miller–Fisher syndrome), and when detected may be limited to an isolated reduction in SNAP

amplitudes without any typical demyelinating features such as conduction slowing, unless there is an 'overlap' syndrome with typical GBS. Metabolic disorders such as acute intermittent porphyria can cause peripheral neuropathy, mostly motor in nature and resembling GBS.

Radiculopathies and plexopathies are another common indication for testing in outpatients but only rarely require testing in the critical care setting. In radiculopathies, because the lesion is proximal to the dorsal root ganglia, sensory conduction studies are always normal. Motor conductions also are normal unless muscles used for recording are innervated by the involved nerve roots and the radiculopathy is fairly severe, in which case low CMAP amplitudes may be seen. Radiculopathies are recognized on needle EMG by a pattern of neuropathic abnormalities that share the same nerve root innervation (i.e. myotomal pattern). Although abnormal EMG findings in paraspinal muscles are often described as a helpful feature in most textbooks, these are very seldom seen in routine clinical practice due to overlapping innervation of paraspinal muscles and technical difficulties in precisely sampling paraspinal muscles.

Plexopathies by contrast are typically post-ganglionic lesions and therefore show reduction in SNAPs in addition to reduction in CMAPs, and needle EMG neuropathic abnormalities are present in more than one nerve but are limited to the distribution of one plexus. An important caveat is that when a plexopathy is caused by an inflammatory lesion that results in focal demyelination without axonal loss, as in the case of cervical radiculoplexus neuropathy (brachial neuritis) or lumbosacral radiculoplexus neuropathy. In this situation, the distal studies are normal with preserved SNAPs and CMAP, but with needle EMG showing subacute denervation features in a regional or myotomal distribution, mimicking a pre-ganglionic lesion. Distinguishing these lesions from a radiculopathy using electrodiagnostic features alone can be very difficult and is hence based on history, radiological features, and pattern of further progression.

Chronic motor neuron disorders, such as amyotrophic lateral sclerosis (ALS), occasionally present to the ICU when the neurological condition has not been previously recognized or diagnosed and the patient comes to medical attention because of a concurrent acute medical problem, usually an aspiration pneumonia. The electrophysiological abnormalities are of pre-ganglionic pathology and hence are similar to polyradiculopathies with the exception that the distribution of needle EMG abnormalities is more widespread in advanced disease and frequently involve the bulbar region. The sensory nerve conduction findings are usually normal, and there may be a reduction in CMAPs (focal or widespread) reflecting selective motor axon degeneration, but without any abnormality in motor conduction. EMG shows chronic partial denervation and ongoing reinnervation changes together with active denervation features and fasciculation potentials. In early stages of the condition, fasciculation potentials may be the only readily detectable abnormality in spinal segments that are not clinically affected. Denervation abnormalities in paraspinal muscles (particularly in the thoracic spinal segment) are a diagnostically very helpful finding, much more so than in the case of single-level radiculopathies.

Acute motor neuron disorders such as acute poliomyelitis and polio-like illness are more difficult to recognize initially and can be difficult to distinguish from the GBS variants such as acute axonal motor neuropathies. These present as an acute flaccid paralysis and tend to be seen more commonly in paediatric populations. The most common neuromuscular manifestation of West Nile virus (WNV) infection is a poliomyelitis syndrome with asymmetric paralysis variably involving one (monoparesis) to four limbs (quadriparesis), with or without brain stem involvement and respiratory failure. EMG shows evidence of profound denervation in muscles of the most affected limbs with few or no voluntarily recruited motor unit potentials (MUPs) and absent or markedly reduced CMAPs with normal SNAP amplitudes in nerve conduction studies. These profound denervation changes may persist in follow-up studies in some of the more severely affected cases, reflecting the degree of anterior horn cell loss. Hence, the prognosis for recovery of function is greatly dependent on the degree of motor neuron loss; limbs with absent motor responses and no voluntary EMG activity have a poorer long-term prognosis while those with relatively preserved motor responses and some voluntary activity have a more favourable outcome [19].

Neuromuscular junction disorders are broadly classified neurophysiologically as post-synaptic or pre-synaptic disorders according to the findings on repetitive nerve stimulation. Both pre-synaptic and post-synaptic NMJ disorders show decremental CMAP responses on 3 Hz RNS and display similar findings in single-fibre EMG/jitter studies. Hence, their distinction comes from the findings at higher frequency stimulation, response to exercise, and the amplitude of the resting CMAPs in the motor studies.

In post-synaptic NMJ disorders (e.g. myasthenia gravis), routine motor and sensory nerve conduction studies are normal. Slow RNS (3 Hz) characteristically results in decrements of CMAP amplitude of more than 10%. On needle EMG, MUAPs often are normal in milder cases. With worsening disease, MUAPs become unstable, varying in configuration from potential to potential. In pre-synaptic disorders such as LEMS and botulism, the CMAP amplitudes usually are low at baseline compared with post-synaptic disorders, in which they are normal at rest. Also, marked CMAP increments occur after brief voluntary maximal contraction or 50 Hz RNS (often >100% above baseline) in pre-synaptic NMJ disorders. Needle EMG findings are normal in autoimmune pre-synaptic disorders such as LEMS, but widespread fibrillation potentials and positive sharp waves can be seen in patients with botulism.

Repetitive compound muscle action potentials (R-CMAPs) occur when a single nerve stimulus excites muscle fibres repeatedly, resulting in multiple small after-potentials that occur after the initial main CMAP response. They follow the main CMAP by 3–6 ms and may recur several times at similar intervals. They are more easily detected in small hand and foot muscles [20]. R-CMAPs are sometimes mistaken for artefacts caused by limb movement or activity picked up by the reference electrode in normal motor NCS recordings. These normal variations of CMAP configuration are unchanged in size or appearance by brief isometric exercise or repetitive stimulation. In contrast, R-CMAPs are abolished by a few seconds of exercise

or by 2–3 stimuli of low-frequency repetitive stimulation (i.e. 0.5–2.0 Hz). Although these R-CMAPs can be encountered in other neuromuscular disorders, the 'synaptic' type of repetitive-CMAPs is typically observed in patients exposed to exogenous AChE inhibitors, in congenital AChE deficiency and SCCMS [20].

In myopathic conditions, the sensory nerve conduction findings are invariably normal. The motor conduction features are also normal, and in proximal myopathies the amplitude of the CMAPs is often preserved and is only reduced when the myopathic process also involves distal musculature or is a predominantly distal myopathic process (such as myotonic dystrophy type 1). Needle EMG often shows abnormal spontaneous muscle fibre discharges such as fibrillation potentials and positive sharp waves in affected muscles in addition to increased insertional activity. The findings of these discharges are rather non-specific as they do not help distinguish underlying myopathic process and are also seen in neurogenic conditions. Chronic myopathic disorders may also show other types of abnormal muscle fibre spontaneous discharges such as complex repetitive discharges (CRDs), but these too can be encountered in chronic neurogenic processes. Perhaps the only relatively specific abnormal spontaneous activity seen is the myotonic discharges encountered in muscle channelopathies such as myotonic dystrophy and non-dystrophic myotonias. Other high-frequency discharges occurring spontaneously or with needle electrode movement which are morphologically similar to myotonic discharges can be seen in some myopathic conditions such as acid maltase deficiency myopathy ('pseudo'-myotonic discharges).

Skeletal muscle channelopathies such as periodic paralysis (PP) are a rare but important cause of acute tetraparesis in the intensive care unit. These are rare neuromuscular disorders caused by mutations in skeletal muscle sodium, calcium, and potassium channel genes, and the clinical syndromes resulting in these mutations include hypokalaemic paralysis, hyperkalaemic paralysis, and Andersen–Tawil syndrome. The diagnosis is based on the characteristic clinic presentation and can be confirmed by genetic testing. In the acute work-up of a newly presenting patient in intensive care or in the absence of an identified genetic mutation, the diagnosis largely relies on documentation of low or high potassium levels during attacks. However, this can be supplemented by the finding of myotonia in the needle EMG testing. Furthermore, the pattern abnormalities in long exercise testing (McManis long exercise test) are helpful in classifying the type of PP. The patient is instructed to perform repeated isometric contractions of the abductor digiti minimi muscle over 5 min, and then CMAPs are recorded after supramaximal stimulation of the ulnar nerve, initially every minute and then at 5–10 min intervals for 40–60 min post-exercise. A reduction in post-exercise CMAP amplitude of 40% or more from the baseline (pre-exercise) is considered abnormal.

Critical care unit-acquired weakness (ICUAW) increases intensive care unit morbidity via the inability or difficulty in weaning these patients off mechanical ventilation, and many patients continue to suffer from decreased exercise capacity and compromised quality of life for months to years after the acute event. It is a clinical diagnosis, quite often a diagnosis of exclusion that will only need further investigation if either there is diagnostic uncertainty, no improvement after 1–2 weeks, or the weakness is very severe [21]. Critical illness polyneuropathy (CIP) is a distal axonal

sensorimotor polyneuropathy affecting peripheral nerves innervating limb and respiratory muscles, and critical illness myopathy (CIM) is a primary myopathy unrelated to muscle denervation [22]. The term critical illness polyneuropathy myopathy (CIPNM) is reserved for patients who have electrophysiological and/or histological findings of coexisting CIP and CIM. Some authors suggest that it may be helpful to distinguish CIP from CIM as CIM has better short- and long-term prognosis than CIP [21].

Electrodiagnostic studies, along with nerve and muscle biopsies, are helpful in confirming the diagnosis and distinguishing between the subcategories of ICUAW. However, patients are usually not subjected to biopsies if the clinical and EMG/NCS are diagnostic of one of these subtypes (Table 2.3).

Electrophysiologically, both critical illness myopathy (CIM) and critical illness polyneuropathy (CIP) tend to be symmetrical processes. In CIP, there is a length-dependent reduction in SNAP and CMAP amplitudes on the sensory and motor nerve conduction studies, respectively, with needle EMG showing fibrillation potentials and positive sharp waves together with neurogenic changes (such as reduced motor unit recruitment) in distal limb muscles. By contrast in CIM, the SNAP amplitudes are usually normal (unless there is coexisting CIP). The CMAPs are reduced in amplitude, and needle EMG shows fibrillation potentials and positive sharp waves together with myopathic features (such as low-amplitude and short-duration MUPs or polyphasic MUPs, with rapid/early recruitment and a low-amplitude interference pattern). Moss et al. demonstrated that peroneal and sural nerve amplitudes had the best diagnostic accuracy for diagnosis of CIM/CIP, and the combined accuracy for the amplitudes of both nerves was significantly better than that for each nerve individually [23]. Some multicentre prospective cohort studies have evaluated the use of a unilateral peroneal motor nerve conduction study to accurately screen for CIP/CIM in critically ill patients, and perhaps reduce the need for those who require concentric needle EMG to confirm the diagnosis [23–25]. Unilateral studies are prone to be affected by the presence of unilateral or asymmetrical chronic radiculopathy, and hence these studies show a limited specificity despite good sensitivity. CMAP measured in response to direct muscle stimulation (dmCMAP) might provide additional information to NCS in the early prediction of ICUAW. In one study, the dmCMAP in the first week following admission to the intensive care unit predicted ICUAW upon emergence from sedation with a sensitivity of 83.3%, specificity of 88.8%, and had a reported positive predictive value (PPV) of 0.91 [25]. However, such strategies require further validation and are not routinely undertaken in most departments.

One very helpful finding, which is relatively specific for CIM and help distinguish it from CIP, is prolonged CMAP durations (without abnormal temporal dispersion as seen in some neurogenic conditions) in the routine motor nerve conduction studies. In addition to the prolonged duration, the CMAPs in patients with CIM have an abnormal morphology that consists of the absence of the normal small positive (downgoing) after-phase that is normally present after the initial main negative (upgoing) phase of the CMAP. Instead, these patients with CIM frequently show a monophasic negative potential for the CMAP that has a long tail of the negative phase (see Fig. 2.7). Allen et al. [26] demonstrated significant slowing of muscle

Table 2.3 Electrophysiological studies for the investigation of neuromuscular weakness in the ICU (adapted from [22])

	Technique	Measured variables	Findings in CIP	Findings in CIM
Nerve conduction studies	Motor, sensory, or mixed NCS can be recorded Active recording electrode placed on the centre of a muscle belly over the motor endplate and reference electrode distally over the tendon Stimulation electrode placed over the nerve that supplies the muscle	*CMAP:* Biphasic potential with initial negativity Amplitude: measured from baseline to the negative peak Latency: the time from stimulus to initial CMAP deflection from baseline *Motor conduction velocity:* calculated after stimulation of one distal and one proximal site *SNAP:* Compound potential representing a summation of all sensory fibre action potentials Amplitude, duration, latency and conduction velocity recorded for CMAP	Reduced CMAP and SNAP amplitude Normal or mildly reduced nerve conduction velocity	Abnormal reduction in CMAP amplitude (80% or less of lower limit of normal) Prolonged CMAP duration (2–3 times longer than healthy controls) Relatively preserved SNAP amplitude (80% or greater of lower limit of normal)
Electromyography	Evaluates electrophysiological activity from multiple motor units Concentric needle electrode shaft serves as reference electrode and the active electrode is a very small wire running through the centre of the needle	First part of examination assesses insertional and spontaneous activity at rest MUAPs then recorded during minimal activation or muscle contraction and assessed for duration, amplitude, and number of phases Finally, fullness of the interference pattern of MUAPs at maximal contraction	Long-duration, high-amplitude, and often polyphasic or unstable MUAPs with reduced recruitment and incomplete interference pattern Fibrillation potentials and positive sharp waves can be present or absent	Short-duration, low-amplitude MUAPs with early or normal recruitment and full interference pattern, in conscious and collaborative patients Absent decremental response to repetitive nerve stimulation Fibrillation potentials and positive sharp waves can be present or absent
Direct muscle stimulation (DMS)	Evaluates muscle response to direct muscle stimulation at various depths of the muscle with gradually increasing current till a palpable twitch is elicited	DMSamp (amplitude of muscle response) MNSamp/DMSamp:ratio of motor nerve stimulation amplitude/amplitude of muscle response on DMS DMSlat (latency of muscle response)	MNSamp/DMSamp ratio < 0.5	MNSamp/DMSamp ratio ≈ 1.0 Prolonged DMSlat

CMAP compound muscle action potentials, *MUAP* motor unit action potentials, *SNAP* sensory nerve action potentials

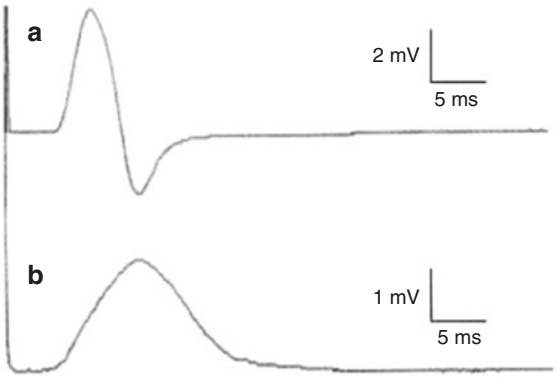


Fig. 2.7 Prolonged CMAP duration in CIM from [26]

Synchronous dispersion causing a prolonged CMAP in a patient with severe CIM **(b)** compared with a CMAP from a control subject **(a)**. Note the absence of the positive phase and the long "tail" of the negative phase in the CMAP from the patient.

fibre conduction velocity (MFCV) and muscle fibre conduction block during the acute phase of CIM, which correlates with prolonged compound muscle action potential (CMAP) duration, clinical severity, and course. These findings support the theory of altered muscle fibre excitability in CIM patients. They used a direct intramuscular stimulation technique using needle electrodes to measure muscle fibre conduction velocities and also employed a paired stimulus protocol (with varying interstimulus intervals) to measure muscle fibre excitability. While these techniques have offered a valuable insight into the possible mechanisms giving rise to CIM, they are yet to gain widespread use in clinical practice for diagnostic purposes.

For peripheral nerve injuries, electrodiagnostic studies are helpful in clarifying the extent of traumatic peripheral nerve injuries and provide some additional information that is difficult to obtain from the clinical examination alone. They are helpful to localize the lesion to either an injury to the peripheral nerve, a plexus injury, or a nerve root avulsion. In the former two conditions, the lesion is post-ganglionic (with the reduction in the SNAP amplitudes) while in nerve root avulsions there is a pre-ganglionic pattern of abnormality (with preserved SNAPs in the clinically affected nerves). These studies are also helpful in clarifying which peripheral nerves are affected and to what extent as this can be difficult to evaluate purely from physical examination. Providing the study has been timed adequately to detect features of axonal loss, electrodiagnostic studies can help grade the severity of nerve injury and help distinguish between neurapraxia and lesions involving axonal loss, which is tremendously helpful in terms of prognosis and timing of recovery. Needle EMG is also invaluable in demonstrating axonal continuity to a muscle that appears clinically largely paretic, which may have implications in the acute surgical management of the nerve injury. However, timing of the study is a vital consideration in evaluating nerve injuries as nerve conduction studies require at least 7–10 days to be able to detect features of axonal loss on sensory and motor nerve conduction studies as Wallerian degeneration takes time to complete. Also, needle EMG will

not be able to detect features of axonal degeneration such as fibrillation potentials and positive sharp waves that can take 3–4 weeks to develop after the insult. In the intervening time period, needle EMG shows either severely reduced recruitment or no voluntary motor unit activity, but this does not distinguish between an axonal lesion and neurapraxia.

Patients with central nervous system disease do not show abnormalities in nerve conduction studies or needle EMG. Chronically debilitated patients may eventually develop muscle atrophy secondary to disuse and subsequently show some reduction in the distal compound muscle action potential amplitudes, but normal needle EMG findings in these muscles help distinguish this from a peripheral neurogenic or myopathic process. Patients with CNS dysfunction often show difficulty in activating muscle contraction fully when examining the interference pattern of voluntary motor unit activity on needle EMG, but with a normal pattern of recruitment of motor units, indicating an intact peripheral nervous system. However, this pattern of reduced activation with normal recruitment is a highly non-specific finding and can also result from pain, poor cooperation, or malingering.

Although there are the neurophysiological techniques such as transcranial magnetic stimulation that assesses the corticomuscular conduction along the corticospinal tracts and peripheral nervous system, they have limited diagnostic value and are generally not utilized in a critical care setting.

Somatosensory-evoked potentials are performed by stimulation of a peripheral nerve and recording evoked responses proximally using surface electrodes from the nerve plexus, lumbar/cervical spine, and contralateral somatosensory cortex. These studies may be helpful in patients who have sensory symptoms where it is difficult to determine if the lesion is central or peripheral, but again are rarely required diagnostically in a critical care setting.

Practical Aspects of Performing Electrodiagnostic Studies in the Intensive Care Setting

The majority of electrodiagnostic (EDX) studies are performed on outpatients. However, in the past several years an increasing number of EDX studies are done on patients in the intensive care unit where the patients typically are profoundly ill, often with several serious overlapping medical problems. Most are intubated and receiving mechanical ventilation, which prevents them from traveling to the EMG laboratory, necessitating a portable study.

There are a number of challenging technical issues unique to performing EDX studies in the ICU. Although the techniques are standardized and straightforward in experienced hands, potential technical problems that are encountered during the studies may interfere with accurate and reliable acquisition of information and interpretation of the data. The most significant environmental factor that causes technical difficulties is ambient electrical noise. Not all observed electrical activity in electrodiagnostic studies originates from the nerve or muscle intended to study.

Although most of the discharges that arise from non-neural tissue or from outside the body have distinct discharge patterns, some others mimic those arising from neural tissue and even an experienced examiner may have difficulty determining its origin. This type of potential interference may be of enormous clinical significance in bedside testing, especially in an intensive care unit, where the activity of numerous monitoring and therapeutic devices generates significant interference, and in some cases no satisfactory recording can be obtained. These artefacts may originate from several sources, such as electrical noise from ventilators, fluid pumps, monitors, and other electrical devices. Similarly, interference from radio broadcasts and mobile phones can be recorded and lessened by relocating the EMG device in the examining room and refraining from using mobile phones. However, given the increasing prevalence of remote communications, these sources of interference may not be completely abolished. Dialysis machines impose a particularly severe artefact on electrodiagnostic studies to the point that the study often has to be delayed until the dialysis episode is completed.

If the nerve is not maximally stimulated (i.e. supramaximally), the number of conducting fibres is underestimated and the recorded amplitude may be falsely low, mimicking disease. Several physiological factors such as limb oedema, skin fibrosis, or obesity may contribute to understimulation. Peripheral oedema is a common problem affecting patients in intensive care, and there are no easy measures to overcome this. While it may be tempting to use subcutaneous needle electrodes to stimulate or record nerve action potentials in patients with severe oedema, this can be associated with the high risk of inducing cellulitis and hence is probably best avoided unless absolutely necessary. Similarly, needle EMG electrode insertion in oedematous limb should be minimized in order to avoid the same complication. Needle EMG sampling is relatively contraindicated in patients who have limb lymphoedema following lymph node excision following cancer surgery, again due to the risk of cellulitis development.

Adequate skin preparation is also vital in order to record good quality nerve action potentials from surface electrodes during nerve conduction studies. Patients who have had oily skin creams or emollients applied will have poor contact with the surface electrodes and issues with increased impedance, affecting the nerve conduction recordings. While it is easy to instruct patients to avoid applying such skin preparations before the test in the outpatient setting, this is not possible to do in the emergency setting of a critical care.

Good patient cooperation is vital for recording quality nerve conduction waveforms and EMG data. Patients who are encephalopathic or comatose will obviously have difficulty in performing the required voluntary activation of muscle contraction to assess the motor unit activity on needle EMG testing. Patient cooperation is also important during nerve conduction studies and when sampling back muscles in a prone patient, and often it may be required that several staff are on hand to help the patient positioned correctly to perform these tests. Patients who are agitated and are unable to keep still during NCS and EMG are undoubtedly the most difficult candidates to study, and often the results obtained from such technically difficult studies are suboptimal, hence, the results must be interpreted very cautiously.

Patients in intensive care units are usually on several medications such as sedatives and muscle relaxant. Thankfully, nerve conduction and EMG findings are not significantly affected by increasing sedative levels as would be seen in electroencephalographic (EEG) or evoked potential studies. Nonetheless, EMG studies are generally avoided in patients who are on muscle relaxant as this would affect repetitive nerve stimulation and EMG findings artificially.

Another very significant but important consideration is the presence of coexisting medical disorders in the critical care unit setting. Critical care unit-acquired weakness is common in patients with prolonged intensive care unit stay, and this may frequently confuse the findings of follow-up studies performed on patients in the critical care unit who were initially admitted with a separate neuromuscular problem such as GBS or myasthenia gravis.

Limitations and Statistical Considerations

There are a number of inherent limitations to the various electrodiagnostic studies. In nerve conduction studies, only a limited repertoire of nerves are examined routinely in the vast majority of situations, and these tend to be distal nerve segments located in the peripheries of the upper and lower limbs. This is primarily related to accessibility of the nerve to stimulate supramaximally more distally as nerves become deeper and inaccessible proximally. In addition, sensory nerve conduction studies can only be performed in distal nerves segments over short recording distances as SNAPs become increasingly dispersed as one attempts to record from the sensory nerves proximally, and this makes it very difficult to discriminate this from a pathological situation.

Although it may be possible to electrically stimulate the motor nerves at the plexus level or even the level nerve roots (using special high-intensity stimulators), this brings about a number of technical issues. Firstly, stimulation of the nerve proximally at a higher intensity frequently leads to co-stimulation of adjacent nerves which can lead to falsely higher amplitudes (which may mask a conduction block) or lead to an abnormal morphology in the distal response (which can be mistaken for a proximal lesion). Secondly, distance measurements become increasingly difficult and inaccurate as the nerves become more proximal as the correct path of the nerve is impossible to determine from superficial landmarks, and this leads to inaccuracies in conduction velocity estimation. Thirdly, proximal stimulation often leads to much more severe movement artefacts coinciding with the electrical impulse as larger muscles in the arm become activated, and this often leads to inaccuracies in measurement of the distal CMAP potential. Finally, and perhaps most importantly, high-intensity proximal stimulation is often poorly tolerated by patients and most sensible electromyographers will not subject a patient to this unless there was a clear likelihood of a meaningful and clinically relevant result being obtained.

Another important point with regard to nerve conduction studies is that not all nerve fibres contained within a peripheral nerve can be studied with the electrical stimulation. Electrical stimulation at humanely tolerable intensities only excites

large myelinated nerve fibres, and hence, it is not possible to examine small unmyelinated nerve fibres (A-delta and C fibres). Therefore, patients with isolated small fibre dysfunction will not be detected in routine nerve conduction studies. Furthermore, conduction velocity measurements are biased towards the fastest conducting fibres, and therefore, a reduction in conduction velocity may not occur until most of these fastest conducting fibres are affected. Therefore, it is possible that some focal demyelinating lesions may go undetected if a few of the fastest conducting fibres remain unaffected.

Needle EMG too has some inherent limitations. The pickup area of a needle electrode is minute, and therefore, one must be cautious in extrapolating the findings to the whole muscle. Although electromyographers will move the sampling needle electrode within the muscle and record from several areas, this may still miss a process that is patchy and does not affect the muscle fairly uniformly. When a particular muscle is sampled, the electromyographer knows they are sampling the correct muscle from a combination of surface anatomy, experience, and, most importantly, activation of the muscle when performing the relevant activation procedure invoking 'crisp' sounding motor unit activity on the EMG monitor (but not when adjacent muscles are activated). However, this can be difficult in the distal upper and lower limbs, particularly when studying small hand muscles or forearm muscles as these muscles are closely situated and have a similar function. Therefore, it is theoretically possible that an incorrect muscle is sampled, particularly if the target muscle is severely atrophic. Deeper lying muscles such as the diaphragm and periscapular muscles can be very difficult to sample, and at times, they require ultrasound guidance to ensure correct muscle is being sampled.

When two processes affect neural physiology in a similar manner, it is not possible to determine which is the more relevant responsible for the patient's current condition. Both diabetes and critical illness polyneuropathy result in axonal-type sensory and motor large fibre polyneuropathies which are electrophysiologically difficult to distinguish, particularly in NCS (although on EMG patients with diabetes would show more chronic denervation changes and less active denervation changes than a patient with CIP). Hence, if a patient with long-standing diabetes were to develop a critical illness-related polyneuropathy, it can be very difficult to distinguish which features are related to the pre-existing condition and which are related to the more recent process. Similarly, when a patient has both a neurogenic process and a myopathy occurring together at the same time, it is very difficult to determine electrophysiologically which is contributing more to their weakness (and hence is more clinically relevant).

Spirometry

In some clinics, a work-up of several spirometric parameters is possible in the ED, and vital capacity (VC), maximal inspiratory pressure (MIP), and sniff nasal inspiratory pressure (SNIP) will be determined to test for diaphragmatic weakness. However, in the vast majority only a hand spirometer will be available to give VC

alone. Comparing VC in sitting and supine position is a reliable test, and a VC fall of 25% or more in the supine position will indicate relevant diaphragmatic weakness [27]. VC below 60% of expected/normative value is considered the threshold for respiratory insufficiency at least in sleep. Obviously, adding pCO_2 to this will help a lot (see section "Blood Gas Analysis"), and patient cooperation is critical.

The cough threshold for mucus clearance is neglected frequently but can be determined by a peak flow measurement available in many ED for obstructive lung disease patients. Values below 160 litre/min indicate increased risk of pneumonia. See diaphragm imaging below (section "Imaging") and Chap. 3 for details.

Strengths: easy test for important values; *weaknesses:* patient cooperation required and need for hygiene precautions.

Imaging

Imaging is mostly used for differential diagnosis such as CNS ischaemia, focal inflammatory changes, or injuries of the musculoskeletal system if one discounts the standard chest X-ray that will be done on the way to ICU. In all conditions known to occur as paraneoplastic disorders, early imaging to identify a tumour can be of enormous importance for the treatment plan. The transport and monitoring of a critically ill patient from the ICU to the MRI scanner, through the exam and back, is not a trivial matter. In contrast, their mobility and flexibility are major advantages of sonographic techniques in ICU medicine.

Unfortunately, there appears to be very little data on the emergency assessment of NMD by imaging techniques even as the amount of especially MRI studies of NMD conditions seems to be growing rapidly. The question of whether a muscle signal in MRI or indeed sonographic assessment can provide an estimation of at least the duration, if not the severity, of the damage cannot be answered with confidence yet. Given the speed of assessment of musculoskeletal injuries in other disciplines, this might be a useful tool in the future. Sonographic assessment of muscle tissue echogenicity so far suffers from lack of an easily available, accepted standard as measurements will change between systems and settings. So far, the sonographic examination of peripheral nerves in particular to detect focal changes (e.g. compression, inflammation, traumatic damage, or neoplasia) and the skeletal muscle MRI for a pattern recognition approach to limit the range of differential diagnoses have made the leap to become standard diagnostic tools. As these examinations will not use contrast agents and typically take 30 min or less, they may well be considered in the emergency setting to answer specific questions in some individual cases.

Neuromuscular imaging techniques are still relatively new diagnostic tools, and both neurologists and radiologists are constantly adding to their experience. Neurologists are still learning how to use these techniques in a gainful manner in emergency medicine and outside the trial and academic setting, and radiologists have in recent years learned to describe damage by individual muscles, not muscle groups, and to no longer classify every oedema in muscle as 'myositis'.

Table 2.4 An overview of skeletal muscle B-mode ultrasound and MRI changes in 'myopathic' and 'neurogenic' damage over time (derived from [28–30])

Change in muscle tissue	Sonographic B-mode	MRI signal	Conditions
None	'Starry night' pattern	T1 > T2, STIR	Healthy skeletal muscle
Oedema	No increase of echogenicity, preserved deep bone reflection	T1(↓), T2↑, STIR↑	Acute denervation[a], rhabdomyolysis, inflammation, early myopathy
Variable fibre size, increased fat and connective tissue[b]	Homogeneously increased echogenicity, loss of deep bone reflection	T1↑, T2(↑), STIR(↓)	Severe, chronic myopathy; muscular dystrophy
Grouped atrophy	Patchy/streaky increased echogenicity, preserved deep bone reflection	T1↑, T2↑, STIR↓	Chronic denervation[c]

Changes in bracket are thought to be weaker or less consistent than those without.
[a]Less than 1 month
[b]Note that T1-weighted MRI will detect fatty degeneration better than ultrasound, while ultrasound will be more sensitive to increased connective tissue
[c]More than 6 months

Table 2.4 gives a very rough overview of skeletal muscle B-mode ultrasound and MRI changes in 'myopathic' and 'neurogenic' damage over time. Below, some points concerning NMD emergencies and imaging findings in individual situations are discussed.

Imaging in the Detection of Acute Muscle Damage, That Is, Oedema

Evidence from published observations suggests that MRI will detect muscle oedema in denervation and rhabdomyolysis at about day 4 after the damaging event [31, 32], occasionally earlier. MRI also seems to be able to tell diffuse damage in rhabdomyolysis from cases including focal myonecrosis, the latter indicated by the 'stipple sign' [33]. However, note that in the vast majority of cases, the cause of damage in these studies was physical, not toxic or due to metabolic disease.

Focal, structural damage to muscle, tendons, joints, and ligaments as a differential diagnosis to the focal onset of an NMD can readily be detected with ultrasound. A recent review concluded that data on the sonographic appearance of rhabdomyolysis was not yet sufficient for everyday diagnostic use [34].

With the present techniques, MRI, that is, T2, STIR sequences, are by far the most sensitive method for the detection of muscle oedema.

Strengths: sensitive and good overview technique; *weaknesses:* time-consuming, expensive, and not specific for a pathophysiology.

Imaging for the Detection (and Possibly Classification) of Acute Peripheral Nerve Damage

Sonographic evaluation of peripheral nerve continuity after traumatic damage is reported with a high sensitivity [35]. One study reported significantly increased cross-sectional area of most peripheral nerves within the first three days of GBS symptoms [36]. It should, however, be noted that these patients did already show neurographic abnormalities at that time point. Sonography was judged 'the most appropriate diagnostic imaging aid' to distinguish chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) from segmental spinal muscular atrophy (sSMA), thereby demonstrating its power to distinguish axonal degeneration from inflammatory demyelination by measurement of cross-sectional areas at least in this setting [37]. MRI neurography, despite the advantages of reaching the deeper structures and independence of angling a transducer along the patient's shape to follow a nerve's course, so far appears less ready for everyday use.

Strengths: sensitive and mobile; *weaknesses:* time-consuming, still need for more experienced examiners, and operator dependent.

Imaging of the Diaphragm

Many imaging modalities can demonstrate the diaphragm and its movement that can be related to respiratory function/weakness. However, ultrasound is clearly the least invasive and possibly the least time-consuming technique. In the ICU, this technique is frequently in use to detect problems in weaning patients from the respirator, and indeed it can be used in ventilated patients, those with severe facial weakness or other abnormalities obstructing spirometric analysis, and will also detect a phrenic nerve damage indirectly [38]. MRI techniques can be used for dynamic imaging as well [39].

Strengths: mobile and less patient cooperation required than for spirometry; *weaknesses:* not that much normative data and experienced examiners available, and operator dependent.

Imaging of the CNS

Spinal Imaging

Spinal ischaemia will frequently not present with classic 'stroke', that is, sudden and complete onset of symptoms, but rather with acute onset but gradual progression of symptoms. It can also manifest with pain. Spinal ischaemia with affection of

the nerve roots, typically when radicular arteries at the thoracolumbar junction are affected, can be hard to differentiate from GBS, even following the course of neurographic changes (see Case Vignette 4). Spinal MRI will be the technique detecting these cases; however, in particular, the ischaemic damage of the spinal cord will frequently not be seen in the emergency investigation but in the follow-up scan a few (5–7) days later. Myelitis, tumour, and disk herniation in contrast can be seen early and even radiculitis can frequently be detected. Note that nerve root abnormalities can be seen in CIDP variants and have been described in CMT (1A).

Strengths: most reliable technique for the body region; *weaknesses:* time-consuming, expensive, supine patient, and delay to definitive findings.

Case Vignette 4

*A man in his early 50s was admitted with paraparesis and a sensory deficit caudal of L1 segment ascending and progressing over the course of 7 hours. Prior to the onset of symptoms, he was on sick leave for a few days due to an upper airway infection. He reported no problems with sphincter function, no genital sensory deficit, and no back pain. Neurological exam showed severe paraparesis with loss of lower limb deep tendon reflexes; touch and temperature were the most affected sensory qualities. Upper limbs were normal. Apart from elevated CRP, the entire lab values, including CSF, were normal. Neurography on day 2 showed prolonged F wave latencies for both tibial nerves, slightly decreased CMAP for right peroneal and tibial nerve. Sensory parameters and upper limb neurography were normal. Spinal MRI on day 1 showed suspected contrast enhancement of lumbar roots (*Fig. 2.8a*). We started IVIG treatment for rapid-onset GBS. Follow-up neurography on day 12 showed loss of CMAP of the right peroneal and left tibial nerve. Loss of F waves of right tibial nerve. Loss of right sural SNAP and slowing of right median nerve conduction velocity. Vital capacity dropped from 5 to 3.5 l, heart rate variability was normal on day 2, but slightly abnormal on day 5. He developed some constipation and urinary retention. We discharged him for early rehabilitation with the request for prompt feedback if he should further lack treatment response. The rehabilitation clinic sent him back 10 days later with no change in the neurological status and now evident incontinence. Repeat lumbar puncture showed mildly elevated CSF protein and 6 leucocytes/µl (ULN: 5). Neurography on day 25 was essentially identical to day 12. However, spinal MRI on day 24 showed T2 lesions of the ventral spinal cord at Th12/L1 with slight haemorrhagic changes and contrast enhancement of conus medullaris, particularly leptomeningeal, and of cauda equina (*Fig. 2.8b, c*). In addition, some dorsal oedema in the tenth thoracic vertebra was found, further illustrating the vascular territory of the affected radicular artery. This confirmed spinal ischaemia with cauda involvement as the cause of his neurological symptoms.*

Learning Points

1. **Spinal ischaemia does not always show the sudden 'stroke' development and can include in particular the ventral parts of cauda equina [40].**
2. **Radiculitis without back pain should always arouse suspicion. However, 'belt-like' pain in spinal ischaemia is not unusual either.**
3. **Spinal ischaemia will very frequently not be detectable on early MRI.**

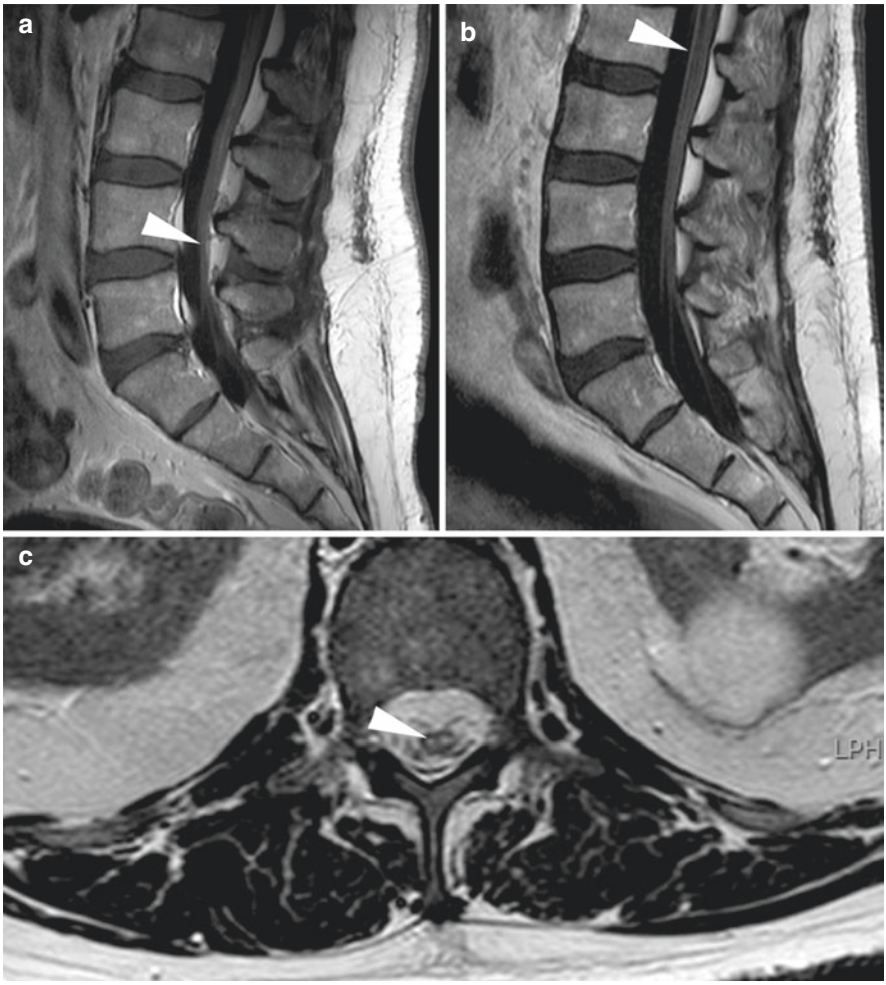


Fig. 2.8 Initial and follow-up spinal MRI of Case Vignette 4. Spinal MRI of Case 4. On day 1, in T1-weighted image with contrast, there appears to be a bit enhancement of cauda parts (arrowhead in **a**). On day 24 in the same technique, this and in particular leptomeningeal enhancement (arrowhead in **b**) is clearly detectable. Moreover, in this scan, T2-weighted images show the 'snake eyes' lesions of spinal ischaemia (arrowhead in **c**)

Brain Imaging

Stroke-Like Episodes

Obviously, a patient with an NMD can suffer a stroke and some manifestations, in particular of episodic NMD, will call for CNS imaging to exclude this. However, in stroke-like episodes, abnormal findings in CNS imaging, usually brain MRI, will be found and have to be attributed correctly to the NMD.

Stroke-like episodes are typical for mitochondrial disorders, particularly for MELAS, associated with the classical *MT-TL1* A3243G point mutation [41]. However, they also occur in patients with other mtDNA point mutations and in disorders caused by *POLG* mutations. In brain MRI, mostly transient cortical or subcortical signal abnormalities can be detected. In contrast to 'real', ischaemic stroke, these are not confined to vascular territories and will often migrate during an episode. Typical stroke-like lesions appear as T2-weighted signal hyperintensities, most frequently in posterior brain regions. Another difference to stroke is that apparent diffusion coefficients (ADC) in a stroke-like episode will often—but not always—show a focal increase in contrast to the decrease found in ischaemia [42]. Note that stroke-like episodes have been reported in other NMDs such as *DMP3*-associated myopathy, likely due to its overlap with the congenital disorders of glycosylation [43], and in patients with *GJB1* mutations causing X-linked Charcot–Marie–Tooth type 1 (CMTX1), for example [44] as a gap-junction dysfunction. These may show different MRI changes. In CMTX1, abnormal signal of corpus callosum appears to be frequent.

Strengths: best and most specific technique for the issue; *weaknesses:* time-consuming, expensive, supine patient, expert reviewer, and additional sequences needed for some questions.

White Matter Abnormalities

White matter changes are far from unusual in neurological emergencies, but in NMD some findings can narrow down the differential diagnosis rapidly. In particular, T2/DWI hyperintensity of centrum semiovale, periventricular, and subcortical white matter is typical for laminin α2-associated disorders caused by mutations in *LAMA2* (congenital muscular dystrophy type 1A, MDC1A, and *LAMA2*-related muscular dystrophies, LAMA2-MD) in patients older than 12 months, including late-onset cases [45, 46]. However, if first observed in emergency imaging after a seizure—another potential manifestation of *LAMA2*-associated CNS pathology—this will sometimes lead the differential diagnosis away from an NMD condition.

In mitochondrial disorders, the spectrum of CNS abnormalities beyond those of stroke-like lesion is unfortunately wide. Changes in white matter, both cerebral and cerebellar, are found, even frank leukodystrophy involving brain stem and spinal cord in leukoencephalopathy with brain stem and spinal cord involvement with

lactate elevation (LBSL) [47]. But cerebral deep grey matter changes, cerebral or cerebellar atrophy, and calcification of deep cerebellar nuclei are also encountered [48]. Note that occipital laminar cortical necrosis may be the result of prolonged seizure activity, episodes that are rather typical for the manifestation of a mitochondrial disorder as an emergency.

In myotonic dystrophies cases, white matter changes will frequently be found [49], but it certainly is not the most recognizable manifestation of the disorder.

Strengths: standard imaging without radiation; *weaknesses:* MRI, time-consuming, expensive, limited availability, and supine patient.

Cardiac Imaging

Besides the cardiology standard techniques coronary angiography for the exclusion of coronary vessel disease and transthoracic echocardiography (TTE) as the typical tool for the assessment of cardiomyopathy, cardiac MRI has been used increasingly in patients with NMD. In particular, the early detection of cardiac manifestations in muscular dystrophies has been repeatedly reported [50]. It is recommended to be considered a sensitive method in inflammatory myopathies [51], and there are descriptions of its use in myofibrillar and metabolic myopathies. However, the exam itself can be rather stressful for the severely affected NMD patient and availability is variable. Successful identification of cardiac affection in NMD will frequently lead to device implantation (pacemaker, defibrillator), eliminating cardiac MRI as a follow-up option in these patients. Thus, for now, it seems a sensitive tool for early detection, potentially useful in the quest to rapidly assess the possibility of a cardiac cause of an NMD emergency.

Strengths: sensitive and non-invasive; *weaknesses:* time-consuming, expensive, need for prolonged supine patient position with slight thorax compression, and contraindication with implanted devices.

Histology/Cytology

Muscle Biopsy

The general rule for the muscle biopsy in an acute-onset muscle disorder found in most textbooks and reviews can be paraphrased as ‘wait four weeks before you do the biopsy, unless you think it is an inflammatory condition’. However, this mostly addresses the diagnostic work-up of rhabdomyolysis, for example [52]. The concept behind this approach is that one can guess the muscle necrosis from the CK; there will be effects from a combination of biochemical conditions; inflammatory cells will be present in any case, clearing away the tissue damage; and finally, the examiner will also be in danger of missing finer morphological clues. The critically ill

patient may also be at an increased risk of complications. While the logic of this is hard to contradict for the hereditary disorders possibly underlying rhabdomyolysis, applying this to all acute muscle conditions with a high CK cannot be recommended. Obviously, some treatment decisions cannot wait that long. Moreover, the increasing knowledge about immune-mediated necrotizing myopathies (IMNM) in the last decade has reduced the number of cases in which an autoimmune condition would not be considered.

Another argument against waiting long weeks before taking a muscle biopsy in a severely ill patient are the changes that the neuromuscular system will undergo in an immobilized patient. These changes make interpretation more difficult, particularly when systemic inflammatory conditions, organ failure, neuromuscular blocking agents, steroids, etc., enter into this. In other words, the conditions that will bring a patient to the ICU will also change the muscle morphology in a rapid and sometimes drastic way. The onset of the loss of muscle function and mass in immobility is prompt even in the healthy [53, 54], and the onset of critical illness myopathy (CIM) in permissive condition is frequently within 10 days of admission [55]. If this results in type II fibre atrophy (Fig. 2.9l) only, one would argue that this does not affect the search for another muscle condition severely. The histological picture associated with myosin loss can be impressive (Fig 2.9g–i), and it will be less easy to characterize another condition in an affected muscle sample. In addition, inflammatory infiltrates and muscle fibre necrosis, occasionally the major histopathological sign, have also been described in CIM [55–57]. Unfortunately, the myopathological characterization of CIM has not progressed as far as that of myositis/IMNM [58], so it may be hard to differentiate these processes.

Despite the variabilities of the individual patients and diagnostic settings, there seem to be groups of patients with different clinical signs and courses that call for different time points for a muscle biopsy.

Candidates for an early biopsy are patients with rapidly progressive muscle symptoms and findings that do *not* appear to follow the dynamics of an episodic condition (e.g. CK dynamic of a rhabdomyolysis episode, periodic paralysis, associated with infection, vaccination or change in medication etc.) *and* no possibility to definitely clarify the differential diagnosis by specific laboratory tests within 10 days *or* the need to start immunosuppressive medication (including steroids) if inflammation/autoimmunity is the biopsy query.

Note that steroids will markedly reduce the amount of cellular infiltration in an inflammatory myopathy in a matter of days, distorting the pattern of pathology. This will be trivial in a few cases but can be a grave problem in many others. Discontinuation of immunosuppressive treatment—including steroids—for at least 2 weeks prior to a biopsy should be the standard. If this is impossible, at least make sure that the respective pathologist is aware of this. An experienced pathologist will even be able to advise ahead of the biopsy on the relevance steroids and other treatments will have on a particular diagnostic query.

Candidates for a late muscle biopsy are patients with an episodic course (e.g. classic rhabdomyolysis) or independent intercurrent event (infection, etc.) or when the detection of histological signs of CIM is the query in weaning failure, etc.

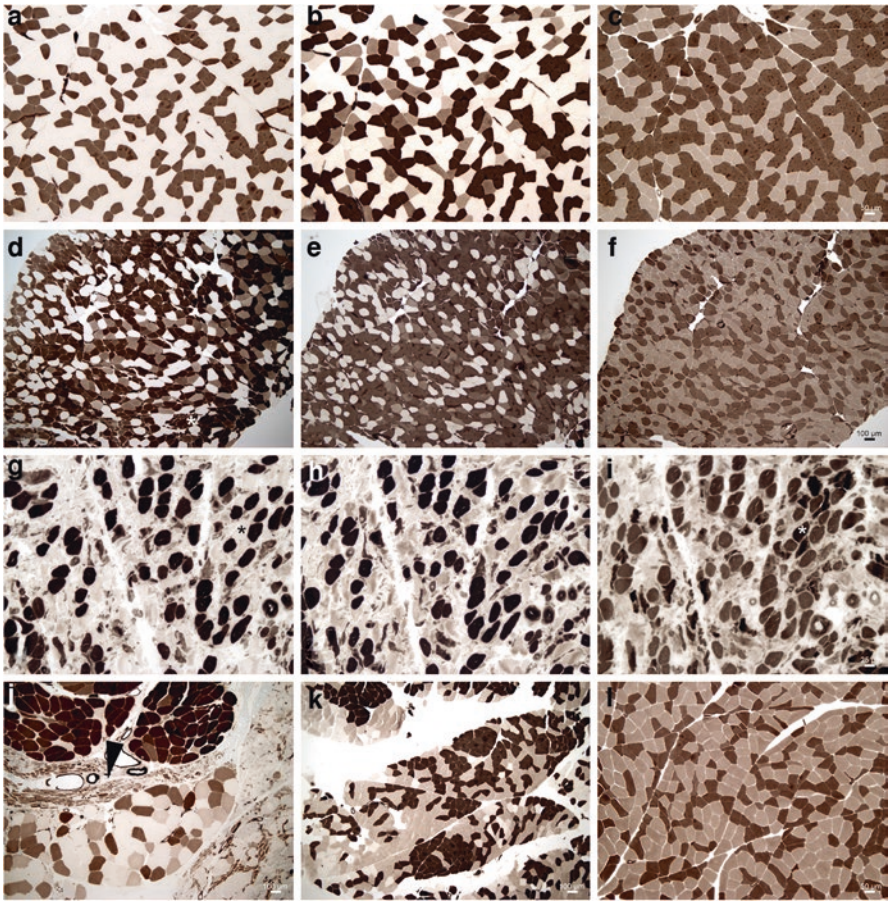


Fig. 2.9 An exercise in pattern recognition: (**a**) to (**c**) show normal checkerboard pattern of ATPases at pH 4.2 (**a**), 4.6 (**b**), and 9.4 (**c**). At pH 4.2 and 9.4, there are only two shades of stain: dark type I fibres and light type II fibres in (**a**) and vice versa in (**c**), while at pH 4.6 (**b**), type IIa (light) and type IIb (slightly darker) can be differentiated from the dark type I fibres. However, with the same reactions in (**d**–**f**), there are populations of fibres with intermediate reactivity at pH 4.2 (**d**) and 9.4 (**f**) as well, indicating pathological/'immature' fibre types. In conjunction with the absence of other signs of damage to these fibres and the small groups of atrophic fibres (one is marked by the white asterisk in (**d**)), this argues for recent denervation. In (**g**–**i**), the same reactions are shown for a biopsy with the myosin loss variant of critical illness myopathy (case 5). Many atrophic fibres have lost the (myosin) ATPase activity, most of the remaining fibres react as type I, only few type II fibre remain reactive (like the one with the white asterisk in (**i**)). (**j**) An ATPase at pH 4.2 shows chronic, continuing denervation: in the upper part, reinnervation has led to non-atrophic fibres with fibre type grouping, in the lower part, pathological fibre type without grouping, similar to (**e**). Between those parts (arrowhead) and to the right, groups and whole fascicles of atrophic fibres show denervation of previously reinnervated areas. (**k**) An ATPase at pH 4.6 shows fibre type grouping without much atrophy, indicating successful reinnervation. (**l**) An ATPase at pH 9.4 shows type II fibre atrophy as it might be seen in a milder variant of CIM, but is caused by a rheumatological disorder in this case

Obviously, in a large number of episodic conditions, histology is not the first-line diagnostic tool, but genetic and metabolic tests should be used in the meantime. Likewise, clinical and neurophysiological investigations, as well as, in some cases, a relatively rapid improvement from severe tetraparesis, will make the histological confirmation of CIM a rare necessity.

Case Vignette 5

*A woman in her late 60s was admitted to the oncology ICU with severe ALT and AST elevation. She had received allogenic stem cell transplantation in the treatment of recurrent acute myeloid leukaemia (AML) half a year earlier and had cutaneous graft versus host disease (GVHD) responding to steroids. Neurological exam showed proximal tetraparesis (MRC 2–3 lower limbs, MRC 4 upper limbs). CK was normal, but had been up to 2,000 U/l for a brief episode in the recent past, which led to discontinuation of a statin treatment. The initial question was whether this could be spreading of GVHD to liver and muscle, but then influenza A infection was detected as an alternative cause. A muscle biopsy was taken and showed the myosin-loss variant of critical illness myopathy without signs of autoimmune or viral inflammation (*Fig. 2.9g–i*).*

Learning Points

Some diseases can affect skeletal muscle directly, but they or their treatments can also contribute to the development of CIM. Potentially, these manifestations might even coexist. Histology still appears to be the most reliable way to clarify such a situation.

The principal time courses of muscle regeneration and atrophy are best known for experimental conditions, particularly in rodent models, and the transfer of this data to the clinical condition in humans is uncertain. Two weeks appear to be sufficient for a damaged rodent skeletal muscle to regenerate fully as long as innervation and vasculature remain functional [59]. Thus, the classic 4-week delay for a biopsy after rhabdomyolysis seems to fit well, even considering that human regenerative powers generally lag behind those of mice and rats. In animal neurotomy experiments, a severe loss of muscle fibre cross-sectional area is seen within a few days [60]. Transfer of these data to humans is even worse as neurotomy is not part of most peripheral nerve diseases and the metabolic rate in humans is lower than in rodents. However, one study found significantly smaller median type II fibre cross-sectional areas in patients with neurophysiological signs of critical illness myopathy on ICU day 5 [61], therefore, rapid atrophy is possible under some circumstances.

When a muscle biopsy is taken, the same rules apply to any and all muscle samples: One should choose a muscle affected to an intermediate degree, which is an 'established' biopsy muscle (i.e. preferentially vastus lateralis, biceps brachii, gastrocnemius, deltoid; if necessary tibialis anterior, biceps femoris, triceps brachii) unless there is a very good reason to pick a different site. It is not advisable to 'include' muscle for biopsy taken in some other surgical procedure, particularly not one with any other pathology close by. The myopathologist requires swift transport of a cold but unfixed and unfrozen sample of never less than 1 cm^3, in which the direction of the muscle fibres can be clearly recognized and is even, but also needs clinical and laboratory data to understand the case. The rule applies 'if you could not recognise the patient from the query, do not be surprised if you will not be able to connect the report to the case'.

Acute conditions are frequently harder to diagnose in myopathology than chronic conditions as the defining criteria often depend on the tissue changes in secondary response to ongoing damage (e.g. fibrosis, fatty replacement, reinnervation, compensatory hypertrophy) while early changes like oedema, fibre necrosis, and myophagocytosis or reactive inflammatory changes are less specific. In some samples of acute disorders, the myopathologist will have to judge internalized myonuclei, fibre-type distribution and sizes, as well as the distribution and state of fibre necrosis and regeneration against the clinical course and laboratory data to categorize the process and its relevance to the query.

Three conditions are particularly problematic.

Firstly, rapidly progressive denervation with little reinnervation. With most of the signs of chronic neurogenic damage absent (fibre-type grouping, grouped atrophy, compensatory hypertrophy), the major clue in standard stains is the dominance of atrophy and fibres with pathological fibre types over signs of fibre damage (degeneration, necrosis, etc.). Note that sometimes mitochondrial abnormalities and a bit of inflammation will cause further confusion [62].

Secondly, in some muscles with chronic denervation, 'secondary myopathic' or 'pseudomyopathic' changes occur (e.g. internalized myonuclei, fibre splitting, rimmed vacuoles, fibrosis). While individual myopathologists will accept varying degrees of this before suspecting two coexisting conditions, this is always a chronic process. Not taking the biopsy from a previously abnormal muscle (e.g. chronic radicular damage) will mostly avoid this dilemma with regard to acute disorders.

Thirdly, necrotizing myopathies can be hard to classify because fibre necrosis as the predominant or even sole histopathological feature occurs regularly in toxic, metabolic, and autoimmune conditions. It can even be seen in early stages of muscular dystrophies. Recent years have seen many detailed studies on the signs of IMNM, but unfortunately the comparisons are almost exclusively between inflammatory myopathies, that is, the value of these signs to differentiate between IMNM and other aetiologies is unknown. As most toxic and metabolic conditions leading to an acute muscle disorder have an episodic character or start with the decompensation of a metabolic process that was previously just coping, the fibre damage in these cases has a tendency to occur at more or less one time point. The damaged fibres will be in the same state across the biopsy. In contrast, necrotic fibres in

various stages of necrosis, myophagocytosis, and regeneration are a hallmark of IMNM. This is also the case in muscular dystrophies, but there is frequently a trend to focal necrotic clusters of fibres not seen in IMNM (but reported for immune checkpoint inhibitor-associated 'irMyositis' [63]). Dedicated immunohistochemistry will help with the question of IMNM versus muscular dystrophy versus irMyositis, but not so much for the toxic and metabolic causes [64]. A particular problem are patients with first decompensation of long-chain fatty acid metabolism (frequently associated with *ETFDH* mutations) as they will not show spontaneous recovery and muscle histology can show mild and unspecific changes or necrotizing myopathy or cytochrome-c-oxidase-negative fibres. Checking the acylcarnitines in plasma and treatment with high-dose riboflavin (and possibly coenzyme Q10) is recommended strongly in such cases.

Strengths: versatile testing and plenty of reference data; *weaknesses:* invasive, frequent problems to differentiate previous affections from acute pathology, time-consuming, and need for expert pathologist.

Nerve Biopsy

Nerve biopsies in emergency situations are very rare, but they will be discussed in ICU cases when the fast proof/exclusion of inflammatory damage or amyloid deposition—although various other tissues can be used in the search for systemic amyloidosis—is important for the treatment decision, for example, in the differential diagnosis to motor neuron conditions, when paraneoplastic complications are discussed or even organ transplantation. However, abnormal sural nerve biopsy in, for example, ALS has been described not to be infrequent [65]. Critical illness polyneuropathy (CIP) causes an axonal damage [56], and it is unusual to prove this by histology. The sural nerve is the typical biopsy nerve due to frequent involvement and the relatively minor deficit the patient suffers from the loss. However, sequelae are well known [66]. Other sites have been used, though more rarely, like the superficial radial nerve or the increasingly used combined muscle and nerve biopsies (superficial peroneal nerve plus peroneus brevis muscle) in the search for vasculitis [67].

Strengths: definitive diagnostic for some conditions; *weaknesses*: invasive with relatively high rate of sequelae [66], time-consuming, and need for expert pathologist.

Blood Film Examination

In a number of metabolic disorders [68] and most of the neuroacanthocytosis disorders [69], standard investigations of blood smear samples will—given experience in performance and evaluation—be a faster way to the confirmation of a diagnosis than biochemistry or genetic analysis in most places. Both vacuolated lymphocytes and

acanthocytes can be found in normal samples, so quantitative analysis is required. A few more caveats: the overall detection rate is low [68], despite this, in one study even the heterozygous carriers of Pompe disease *GAA* mutations were tested positive [70], blood samples for acanthocyte detection should be diluted with isotonic sodium chloride solution (1:1) [69], and the standard counts and cut-off values should always be observed.

Strengths: inexpensive, fast, and not particularly invasive; *weaknesses:* low overall detection rate and need for expert pathologist.

Self Assessment Questions

Elevated serum lactate may indicate several medical conditions.

1. Which of the following conditions cause lactate elevation in blood?

   (a) Mitochondrial cytopathy
   (b) Sepsis
   (c) Tissue ischaemia
   (d) All of the above (*)

2. Reduction of serum creatine kinase (CK) activity after steroid treatment in a patient with suspected inflammatory myopathy confirms the diagnosis.

   (a) True
   (b) False (*)

A CK elevation in blood may indicate a neuromuscular disease but also a cardiac problem. Measuring troponin blood levels may help to clear the differential diagnosis.

3. Troponin is only found in cardiac muscle.

   (a) True
   (b) False (*)

4. Black persons usually have higher CK than White persons.

   (a) True (*)
   (b) False

Both hyperthyroidism and hypothyroidism may lead to a myopathy.

5. What can be said about serum CK activity in these conditions? They are ….

   (a) Elevated in both hyperthyroidism and hypothyroidism
   (b) Elevated in hyperthyroidism and normal in hypothyroidism
   (c) Normal in hyperthyroidism and elevated in hypothyroidism (*)
   (d) Normal in both hyperthyroidism and hypothyroidism

6. Which of the following is considered a good activity marker in autoimmune muscle inflammation?

   (a) CK (*)
   (b) CRP
   (c) ESR
   (d) All of the above

7. Which of the following 'liver parameters' is often elevated in blood in the context of a muscle disease without liver or pancreatic problems?

   (a) Aminotransferase (*)
   (b) Amylase
   (c) Bilirubin
   (d) Gamma-GT

8. Myoglobin is a very specific marker of muscle damage.

   (a) True (*)
   (b) False

9. What can be stated about the dynamic of myoglobin in the context of muscle damage? The dynamic of myoglobin is …

   (a) Faster than the dynamic of CK (*)
   (b) Comparable to the dynamic of CK
   (c) Slower than the dynamic of CK

10. Once urine is normally coloured, there is no use to test for myoglobinuria.

    (a) True
    (b) False (*)

A 68-year-old female is diagnosed with a myopathy. For a more specific diagnosis, further blood tests have been ordered. One of the abnormal findings is a monoclonal gammopathy. Therefore, it is decided to take a muscle biopsy. (This scenario is related to the following two questions.)

1. Which of the following abnormalities can be expected in this situation?

   (a) Inclusion bodies
   (b) Lymphocytic infiltration
   (c) Nemaline rods (*)
   (d) Vacuoles

2. Which of the following deposits can be expected in this situation?

   (a) Amyloid (*)
   (b) Calcium
   (c) Fat
   (d) Glycogen

A multitude of viruses may affect skeletal muscle, thus leading to a viral myositis.

3. What is the problem with viral diagnostics in this situation?

   (a) Tests are not very specific
   (b) Tests are not very sensitive
   (c) There are too many viruses to look for (*)
   (d) The time frames of the tests are too narrow

4. Anti-titin antibodies are associated with which of the following disease?

   (a) Dermatomyositis
   (b) Inclusion body myositis
   (c) Myasthenia gravis (*)
   (d) Myasthenic syndrome

5. Anti-Hu antibodies are associated with which of the following diseases?

   (a) Rhabdomyolysis
   (b) MELAS
   (c) Neurosarcoidosis
   (d) Sensory neuropathy (*)

6. Which of the following is considered the major benefit of electrophysiological tests compared to clinical examination in the IC setting?

   (a) Their predictive value for the outcome of most neuromuscular diseases
   (b) Their sensitivity to neuromuscular pathology is better (*)
   (c) Their specificity to neuromuscular pathology is better

7. What's the problem in electrophysiological phrenic motor studies in the ICU?

   (a) They may interfere with the monitoring modules
   (b) Electrical noise of the IC can easily obscure the low responses (*)
   (c) Both are a problem
   (d) None of these is a problem

8. Phrenic conduction studies are contraindicated on the side of a central line catheter.

   (a) True (*)
   (b) False

9. At which location can the phrenic nerve be stimulated?

   (a) Posterior to the sternocleidomastoid muscle approximately 3 cm above the clavicle
   (b) Between the sternal and clavicular heads of the sternocleidomastoid just above the clavicle
   (c) On both sites (*)

10. Which of the following is the earliest abnormality in most cases of acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome)?

    (a) Denervation in needle examination
    (b) Dispersion of CMAPs
    (c) Peripheral conduction blocks in NCS
    (d) Prolonged F waves (*)

11. Which of the following is a characteristic finding at RNS in pre-synaptic myasthenic disorders?

    (a) Initial low CMAP, decreasing at 3 Hz stimulation (*)
    (b) Initial low CMAP, increasing at 3 Hz stimulation
    (c) Initial normal CMAP, decreasing at 3 Hz stimulation
    (d) Initial normal CMAP, increasing at 3 Hz stimulation

12. In which of the following disorders, myotonia-like discharges may be characteristically found in the paraspinal musculature?

    (a) Becker dystrophinopathy
    (b) Inflammatory myopathy
    (c) Myasthenic syndrome
    (d) Pompe disease (*)

13. Which of the following tests is most reliable for determining diaphragmatic weakness in the ICU setting?

    (a) Measuring the difference in VC in sitting and supine position (*)
    (b) Measuring the difference in peakflow in sitting and supine position

14. Diaphragmatic imaging to investigate the failure to wean from the ventilator is best done by MRI.

    (a) True
    (b) False (*)

15. Which of the following is the best indication for a nerve biopsy in the ICU setting? To diagnose …

    (a) A critical illness neuropathy
    (b) An inflammatory demyelinating neuropathy
    (c) A paraneoplastic neuropathy
    (d) A vasculitis neuropathy (*)

Acknowledgements Jens Reimann acknowledges gratefully Prof. Elke Hattingen for the MRI of the spinal ischaemia posing as GBS and PD Dr. Oliver Kaut for providing data he had gathered on this case. I further thank Dr. Maren Winkler, who had the right muscle slides as well as a case of porphyria with rhabdomyolysis at hand and—as always—Mrs. Karin Kappes-Horn for her brilliant histology.

Lokesh Wijesekera would like to thank Ann Harvey and Graham Cox for their help with producing the nerve conduction images and also Dr. Andrew Michell for performing part of the electrodiagnostic study in Case Vignette 3.

References

1. Brewster LM, Mairuhu G, Sturk A, van Montfrans GA. Distribution of creatine kinase in the general population: implications for statin therapy. Am Heart J. 2007;154:655–61.
2. George MD, McGill NK, Baker JF. Creatine kinase in the U.S. population: Impact of demographics, comorbidities, and body composition on the normal range. Medicine (Baltimore). 2016;95:e4344.
3. Lippi G, Schena F, Ceriotti F. Diagnostic biomarkers of muscle injury and exertional rhabdomyolysis. Clin Chem Lab Med. 2018;57:175–82.
4. Stein W. Creatinkinase (Gesamtaktivität) Creatinkinase-Isonzyme und Varianten. In: Thomas L, editor. Labor und Diagnose: Indikation und Bewertung von Laborbefunden für die medizinische Diagnostik. 5th ed. Frankfurt: TH Books; 1998. p. 88–96.
5. Black HR, Quallich H, Gareleck CB. Racial differences in serum creatine kinase levels. Am J Med. 1986;81:479–87.
6. Kenney K, Landau ME, Gonzalez RS, Hundertmark J, O'Brien K, Campbell WW. Serum creatine kinase after exercise: drawing the line between physiological response and exertional rhabdomyolysis. Muscle Nerve. 2012;45:356–62.
7. Stahl K, Rastelli E, Schoser B. A systematic review on the definition of rhabdomyolysis. J Neurol. 2020;267:877–82.
8. Schmid J, Liesinger L, Birner-Gruenberger R, Stojakovic T, Scharnagl H, Dieplinger B, et al. Elevated cardiac troponin T in patients with skeletal myopathies. J Am Coll Cardiol. 2018;71:1540–9.
9. Giannitsis E, Mueller C, Katus HA. Skeletal myopathies as a non-cardiac cause of elevations of cardiac troponin concentrations. Diagnosis (Berl). 2019;6:189–201.
10. Lim AKH. Abnormal liver function tests associated with severe rhabdomyolysis. World J Gastroenterol. 2020;26:1020–8.
11. Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. N Engl J Med. 2009;361:62–72.
12. Wakerley BR, Yuki N. Mimics and chameleons in Guillain-Barré and Miller Fisher syndromes. Pract Neurol. 2015;15:90–9.
13. Marsden JT, Peters TJ. Rhabdomyolysis in a patient with acute intermittent porphyria. Ann Clin Biochem. 2004;41:341–3.
14. Bunschoten C, Jacobs BC, Van den Bergh PYK, Cornblath DR, van Doorn PA. Progress in diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy. Lancet Neurol. 2019;18:784–94.
15. Lazzerini PE, Capecchi PL, Guideri F, Bellisai F, Selvi E, Acampa M, et al. Comparison of frequency of complex ventricular arrhythmias in patients with positive versus negative anti-Ro/SSA and connective tissue disease. Am J Cardiol. 2007;100:1029–34.
16. Sharp GC, Irvin WS, Tan EM, Gould RG, Holman HR. Mixed connective tissue disease--an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). Am J Med. 1972;52:148–59.
17. Mielnik P, Chwalinska-Sadowska H, Wiesik-Szewczyk E, Maslinski W, Olesinska M. Serum concentration of interleukin 15, interleukin 2 receptor and TNF receptor in patients with polymyositis and dermatomyositis: correlation to disease activity. Rheumatol Int. 2012;32:639–43.
18. Takahisa T, Kawaguchi Y, Hara M, Masuda I, Katsumata Y, Shinozaki M, et al. Increased ferritin predicts development and severity of acute interstitial lung disease as a complication of dermatomyositis. Rheumatology (Oxford). 2010;49:1354–60.
19. Leis AA, Stokic DS. Neuromuscular manifestations of west nile virus infection. Front Neurol. 2012;3:37.
20. Harper CM. Electrodiagnosis of endplate disease. In: Engel AG, editor. Myasthenia gravis and myasthenic disorders. Oxford: Oxford University Press; 1999. p. 65–86.
21. Taylor C. Intensive care unit acquired weakness. Anaesth Intensive Care. 2018;19:79–82.

22. Dangayach NS, Smith M, Claassen J. Electromyography and nerve conduction studies in critical care: step by step in the right direction. Intensive Care Med. 2016;42:1168–71.
23. Moss M, Yang M, Macht M, Sottile P, Gray L, McNulty M, et al. Screening for critical illness polyneuromyopathy with single nerve conduction studies. Intensive Care Med. 2014;40:683–90.
24. Latronico N, Bertolini G, Guarneri B, Botteri M, Peli E, Andreoletti S, et al. Simplified electrophysiological evaluation of peripheral nerves in critically ill patients: the Italian multicentre CRIMYNE study. Crit Care. 2007;11(1):R11.
25. Latronico N, Nattino G, Guarneri B, Fagoni N, Amantini A, Bertolini G, et al. Validation of the peroneal nerve test to diagnose critical illness polyneuropathy and myopathy in the intensive care unit: the multicentre Italian CRIMYNE-2 diagnostic accuracy study. F1000Res. 2014 Jun;11(3):127.
26. Allen DC, Arunachalam R, Mills KR. Critical illness myopathy: further evidence from muscle-fiber excitability studies of an acquired channelopathy. Muscle Nerve. 2008;37:14–22.
27. Fromageot C, Lofaso F, Annane D, Falaize L, Lejaille M, Clair B, et al. Supine fall in lung volumes in the assessment of diaphragmatic weakness in neuromuscular disorders. Arch Phys Med Rehabil. 2001;82:123–8.
28. Kamath S, Venkatanarasimha N, Walsh MA, Hughes PM. MRI appearance of muscle denervation. Skelet Radiol. 2008;37:397–404.
29. Simon NG, Noto YI, Zaidman CM. Skeletal muscle imaging in neuromuscular disease. J Clin Neurosci. 2016;33:1–10.
30. Jungbluth H. Myopathology in times of modern imaging. Neuropathol Appl Neurobiol. 2017;43:24–43.
31. West GA, Haynor DR, Goodkin R, Tsuruda JS, Bronstein AD, et al. Magnetic resonance imaging signal changes in denervated muscles after peripheral nerve injury. Neurosurgery. 1994;35:1077–85.; discussion 1085–6.
32. Yeon EK, Ryu KN, Kang HJ, Yoon SH, Park SY, Park JS. Characteristic MR image finding of squatting exercise-induced rhabdomyolysis of the thigh muscles. Br J Radiol. 2017;90:20160740.
33. Cunningham J, Sharma R, Kirzner A, Hwang S, Lefkowitz R, Greenspan D, et al. Acute myonecrosis on MRI: etiologies in an oncological cohort and assessment of interobserver variability. Skelet Radiol. 2016;45:1069–78.
34. Sein Anand Ł, Kosiak W. Sonographic appearance of rhabdomyolysis - a systematic review of the literature. Med Ultrason. 2020;22:92–6.
35. Hollister AM, Simoncini A, Sciuk A, Jordan J. High frequency ultrasound evaluation of traumatic peripheral nerve injuries. Neurol Res. 2012;34:98–103.
36. Grimm A, Décard BF, Axer H. Ultrasonography of the peripheral nervous system in the early stage of Guillain-Barré syndrome. J Peripher Nerv Syst. 2014;19:234–41.
37. Oudeman J, Eftimov F, Strijkers GJ, Schneiders JJ, Roosendaal SD, Engbersen MP, et al. Diagnostic accuracy of MRI and ultrasound in chronic immune-mediated neuropathies. Neurology. 2020;94:e62–74.
38. Fayssoil A, Behin A, Ogna A, Mompoint D, Amthor H, Clair B, et al. Diaphragm: pathophysiology and ultrasound imaging in neuromuscular disorders. J Neuromuscul Dis. 2018;5:1–10.
39. Harlaar L, Ciet P, van der Ploeg AT, Brusse E, van der Beek NAME, Wielopolski PA, et al. Imaging of respiratory muscles in neuromuscular disease: A review. Neuromuscul Disord. 2018;28:246–56.
40. Weidauer S, Nichtweiß M, Hattingen E, Berkefeld J. Spinal cord ischemia: aetiology, clinical syndromes and imaging features. Neuroradiology. 2015;57:241–57.
41. Goto Y, Nonaka I, Horai A. A mutation in tRNALeu(UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. Nature. 1990;348:651–3.
42. Yoneda M, Maeda M, Kimura H, Fujii A, Katayama K, Kuriyama M. Vasogenic edema on MELAS: a serial study with diffusion-weighted MR imaging. Neurology. 1999;53:2182–4.

43. Lefeber DJ, Schönberger J, Morava E, Guillard M, Huyben KM, Verrijp K, et al. Deficiency of Dol-P-Man synthase subunit DPM3 bridges the congenital disorders of glycosylation with the dystroglycanopathies. Am J Hum Genet. 2009;85:76–86.
44. Basu A, Horvath R, Esisi B, Birchall D, Chinnery PF. Recurrent stroke-like episodes in X-linked Charcot-Marie-Tooth disease. Neurology. 2011;77:1205–6.
45. Alkan A, Sigirci A, Kutlu R, Aslan M, Doganay S, Yakinci C. Merosin-negative congenital muscular dystrophy: diffusion-weighted imaging findings of brain. J Child Neurol. 2007;22:655–9.
46. Oliveira J, Gruber A, Cardoso M, Taipa R, Fineza I, Gonçalves A, et al. LAMA2 gene mutation update: Toward a more comprehensive picture of the laminin-α2 variome and its related phenotypes. Hum Mutat. 2018;39:1314–37.
47. Finsterer J, Zarrouk MS. Leukoencephalopathies in mitochondrial disorders: clinical and MRI findings. J Neuroimaging. 2012;22(3):e1–11.
48. Mascalchi M, Montomoli M, Guerrini R. Neuroimaging in mitochondrial disorders. Essays Biochem. 2018;62:409–21.
49. Minnerop M, Gliem C, Kornblum C. Current progress in CNS imaging of myotonic dystrophy. Front Neurol. 2018;9:646.
50. Lamacie MM, Warman-Chardon J, Crean AM, Florian A, Wahbi K. The added value of cardiac magnetic resonance in muscular dystrophies. J Neuromuscul Dis. 2019;6(4):389–99.
51. Diederichsen LP. Cardiovascular involvement in myositis. Curr Opin Rheumatol. 2017;29:598–603.
52. Nance JR, Mammen AL. Diagnostic evaluation of rhabdomyolysis. Muscle Nerve. 2015;51:793–810.
53. Kortebein P, Symons TB, Ferrando A, Paddon-Jones D, Ronsen O, Protas E, et al. Functional impact of 10 days of bed rest in healthy older adults. J Gerontol A Biol Sci Med Sci. 2008;63:1076–81.
54. Hvid LG, Suetta C, Aagaard P, Kjaer M, Frandsen U, Ørtenblad N. Four days of muscle disuse impairs single fiber contractile function in young and old healthy men. Exp Gerontol. 2013;48:154–61.
55. Helliwell TR, Wilkinson A, Griffiths RD, McClelland P, Palmer TE, Bone JM. Muscle fibre atrophy in critically ill patients is associated with the loss of myosin filaments and the presence of lysosomal enzymes and ubiquitin. Neuropathol Appl Neurobiol. 1998;24:507–17.
56. Latronico N, Fenzi F, Recupero D, Guarneri B, Tomelleri G, Tonin P, et al. Critical illness myopathy and neuropathy. Lancet. 1996;347:1579–82.
57. Derde S, Hermans G, Derese I, Güiza F, Hedström Y, Wouters PJ, et al. Muscle atrophy and preferential loss of myosin in prolonged critically ill patients. Crit Care Med. 2012;40:79–89.
58. Benveniste O, Goebel HH, Stenzel W. Biomarkers in inflammatory myopathies – an expanded definition. Front Neurol. 2019;10:554.
59. Schiaffino S, Partridge T. Skelel muscle repair and regeneration. In: Stienen GJM, editor. Advances in muscle research 3. Springer; 2008.
60. Engel AG, Stonnington HH. Trophic functions of the neuron. II. Denervation and regulation of muscle. Morphological effects of denervation of muscle. A quantitative ultrastructural study. Ann N Y Acad Sci. 1974;228:68–88.
61. Bierbrauer J, Koch S, Olbricht C, Hamati J, Lodka D, Schneider J, et al. Early type II fiber atrophy in intensive care unit patients with nonexcitable muscle membrane. Crit Care Med. 2012;40:647–50.
62. Al-Sarraj S, King A, Cleveland M, Pradat PF, Corse A, Rothstein JD, et al. Mitochondrial abnormalities and low grade inflammation are present in the skeletal muscle of a minority of patients with amyotrophic lateral sclerosis; an observational myopathology study. Acta Neuropathol Commun. 2014;2:165.
63. Touat M, Maisonobe T, Knauss S, Ben Hadj Salem O, Hervier B, Auré K, et al. Immune checkpoint inhibitor-related myositis and myocarditis in patients with cancer. Neurology. 2018;91:e985–94.

64. Stenzel W, Goebel HH, Aronica E. Review: immune-mediated necrotizing myopathies--a heterogeneous group of diseases with specific myopathological features. Neuropathol Appl Neurobiol. 2012;38(7):632–46.
65. Luigetti M, Conte A, Del Grande A, Bisogni G, Romano A, Sabatelli M. Sural nerve pathology in ALS patients: a single-centre experience. Neurol Sci. 2012;33:1095–9.
66. Hilton DA, Jacob J, Househam L, Tengah C. Complications following sural and peroneal nerve biopsies. J Neurol Neurosurg Psychiatry. 2007;78:1271–2.
67. Collins MP, Mendell JR, Periquet MI, Sahenk Z, Amato AA, Gronseth GS, et al. Superficial peroneal nerve/peroneus brevis muscle biopsy in vasculitic neuropathy. Neurology. 2000;55:636–43.
68. Anderson G, Smith VV, Malone M, Sebire NJ. Blood film examination for vacuolated lymphocytes in the diagnosis of metabolic disorders; retrospective experience of more than 2,500 cases from a single centre. J Clin Pathol. 2005;58:1305–10.
69. Storch A, Kornhass M, Schwarz J. Testing for acanthocytosis a prospective reader-blinded study in movement disorder patients. J Neurol. 2005;252:84–90.
70. Pascarella A, Terracciano C, Farina O, Lombardi L, Esposito T, Napolitano F, et al. Vacuolated PAS-positive lymphocytes as an hallmark of Pompe disease and other myopathies related to impaired autophagy. J Cell Physiol. 2018;233:5829–37.
71. Zink W, Kollmar R, Schwab S. Critical illness polyneuropathy and myopathy in the intensive care unit. Nat Rev Neurol. 2009;5:372–9.

Chapter 3
Respiratory Management in Acute Neuromuscular Disease

Maxwell Damian and Eelco F. M. Wijdicks

Case Vignette 1

A 26-year-old woman presented to the emergency department with a feeling of being out of breath (as if run up to a train) and often tingling in hands and feet. She attributed this to "bad flu" she had 6 weeks earlier and "never got over it."

On examination, she was anxious and "hyperventilating." Her examination showed some generalized weakness. Her pulse oximeter readings were normal but with occasional dips into the low 90s, which improved with a nasal cannula.

A neurologist was consulted and found generalized proximal weakness MRC 4/5, total areflexia, and no objective sensory changes. Laying her flat did make her feel very uncomfortable with return of marginal hypoxemia.

A presumptive diagnosis of Guillain–Barré syndrome (GBS) was made, and she was admitted to the ward for more tests. The following morning, her weakness had worsened and she became more dysphonic. She showed short

Supplementary Information The online version contains supplementary material available at [https://doi.org/10.1007/978-3-030-91932-0_3].

M. Damian (✉)
Cambridge University Hospitals, Cambridge, UK

Essex Cardiothoracic Centre, Basildon, UK
e-mail: msdd2@cam.ac.uk

E. F. M. Wijdicks
Neurocritical Care Services, Mayo Clinic Hospitals, Rochester, MN, USA
e-mail: wijde@mayo.edu

M. Damian, M. de Visser (eds.), *Emergencies in Neuromuscular Disorders*,
https://doi.org/10.1007/978-3-030-91932-0_3

windedness with frequent pauses in her speech. She was transferred to the ICU but initially refused ventilator assistance.

Later that day, she started using her accessory muscles and was electively intubated. She progressed to full tetraplegia and had episodes of dysautonomia (blood pressure swings and sustained tachycardia), but eventually recovered after 3 months' ICU stay and 6 months' rehabilitation to unassisted walking.

Learning Points
GBS can start quite subtly before it progresses. Respiratory weakness not always follows nadir of weakness. For once, a reflex hammer does the trick here.

Introduction

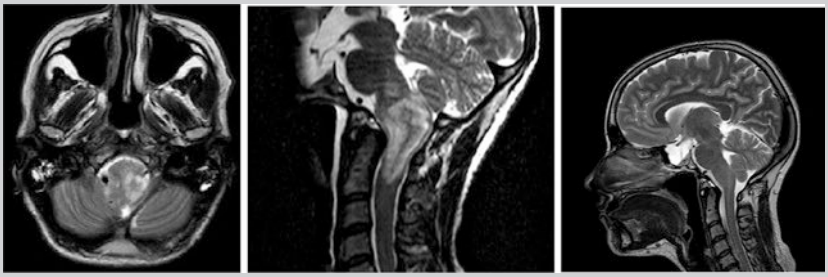
Respiratory mechanics can become impaired in rapidly evolving neuromuscular disorders. It is well established as part of many chronic disorders and a last manifestation—in those patients, respiratory failure leading to aspiration or hypercarbia is a leading cause of death. In more acute situations, the outcome is quite different. Hence, detailed understanding of respiratory physiology is key to the management of many neuromuscular emergencies. Three mechanisms (weakness of the respiratory pump, inability to open the airway tract, and a poor cough) combine in respiratory failure to create a critical condition with accelerating degrees of severity. Neurologists may see subtle findings (e.g., shallow, rapid breathing and interrupted, staccato speech) or far more obvious presentations (dysphonia, pooling secretions, and hypoxemia), but there is an expectation that each patient requires urgent action and preemptive admission to an intensive care unit, often to assist in ventilation. Respiratory mechanics involve chest wall integrity and flexibility of movement, but forces involved in breathing—pulling in air and changing lung volume—are muscles of the pharynx, larynx, diaphragm, spine, and neck. The bulbar musculature maintains the architecture of a patent airway conduit, with abdominal wall and internal intercostal muscles needed to produce an effective cough. Acute dysfunction with a neural trajectory from brain stem to muscle may change respiratory mechanics [1]. In chronic progressive disorders, factors such as a rigid spine, (kypho)scoliosis, and chest wall rigidity compound the problem, in some conditions complicated by abnormal lung parenchyma. This chapter reviews the pathophysiology, provides a practical assessment, and offers guidance in the management of acutely failing respiratory pump function.

Central Components of Mechanical Respiratory Failure

The central respiratory breathing generator resides principally in the medulla oblongata and signals to the respiratory muscles with feedback from chemoreceptors and pulmonary mechanoreceptors. Control of the autonomic rhythm of breathing is located in the bilateral respiratory group ventral to the nucleus ambiguus in the medulla oblongata [2]. Experimental studies with specific lesions strategically placed in specific neuron group have found a specific cell population for each function. The ventral respiratory group (VRG) contains inspiratory and expiratory neurons, but their function drives not only the spinal respiratory neurons innervating the intercostal and abdominal muscles but also the upper airway muscles of inspiration. Work on central respiratory generators has identified the primacy of the pre-Bötzinger complex. Inhibitory neurons within this complex have a crucial role in the generation of central apneas, including *Ondine's curse*—the name used to indicate central hypoventilation from loss of automaticity of breathing [3]. Acquired forms of *Ondine's curse* have mostly involved lesions in the respiratory centers of the medulla oblongata. Multiple cases of central hypoventilation have been described with acute stroke, brain stem tumors, infections, multiple sclerosis, and cervical cordotomy. Central respiratory chemoreceptors—responding to hypercarbia —are present in the serotonergic raphe neurons in the pons and medulla but also in the retrotrapezoid nucleus [4, 5]. The respiratory centers appear relatively immune to acute injury and to metabolic insults, and persistent abnormalities of respiratory drive and rhythm are exceptionally infrequent [6–8].

Case Vignette 2

A 32-year-old female with a history of mental health problems and nonepileptic seizures developed nausea and vomiting, leading to severe malnutrition over the course of a year. She underwent a number of gastrointestinal investigations with no significant result and was provided with a nasojejunal tube. Three months later, she was admitted to an emergency department on account of progressive general weakness becoming unable to walk over months. She was noted to be hypercapnic, and during the night became apneic and was intubated. The neurologist noted bilateral end of gaze nystagmus, general weakness, and upgoing toes on both sides. She did well on the ventilator and had adequate respiratory efforts, but weak respiratory drive was noted, requiring the backup ventilator frequency. She was extubated, but became apneic during the night and was reintubated. Her MRI scan revealed a large brain stem glioma extending from the pons to the upper cervical cord. She was tracheotomied and remained on invasive home ventilation until she died at home.



T2-weighted MRI scans of the patient's brain show a large brain stem mass (A: axial; B: sagittal). (C) The MRI done 3 years earlier was normal.

Learning Points
Ondine's curse is a disorder of abnormal respiratory drive through brain stem dysfunction.

The nucleus ambiguus innervates the dilator muscles of the soft palate, pharynx, and larynx, and adjusts ventilatory drive to respiratory muscle activity and particularly airway resistance [9]. Acute damage to the nucleus ambiguus contributes to mechanical dysfunction with the consequence of failure to manage secretions and maintain an open airway.

At a different level, spinal cord lesions affecting the mid and high cervical regions (C3–C5) above the level of the phrenic motor neurons cause complete paralysis of the muscles of both inhalation and exhalation and immediate dependence on mechanical ventilation [10]. Lesions below the level of C5 spare the nerve connections to the diaphragm, but expiratory effort and peak expiratory flow are markedly reduced by lower spinal lesion due to the involvement of the abdominal and intercostal muscles [11, 12]. In the acute phase, sympathetic nerves are interrupted and the vagus nerve predominates, resulting in increased, potentially airway-blocking tracheobronchial secretions, and unopposed parasympathetic input may facilitate bronchial airway narrowing (Fig. 3.1).

Peripheral Component of Mechanical Respiratory Failure

The diaphragm is the main muscle of inspiration. When it is paralyzed, the dome rises to an expiratory position and reduces lung volume. The respiratory muscles may not be affected alone, and weakness from acute neurological disease may also

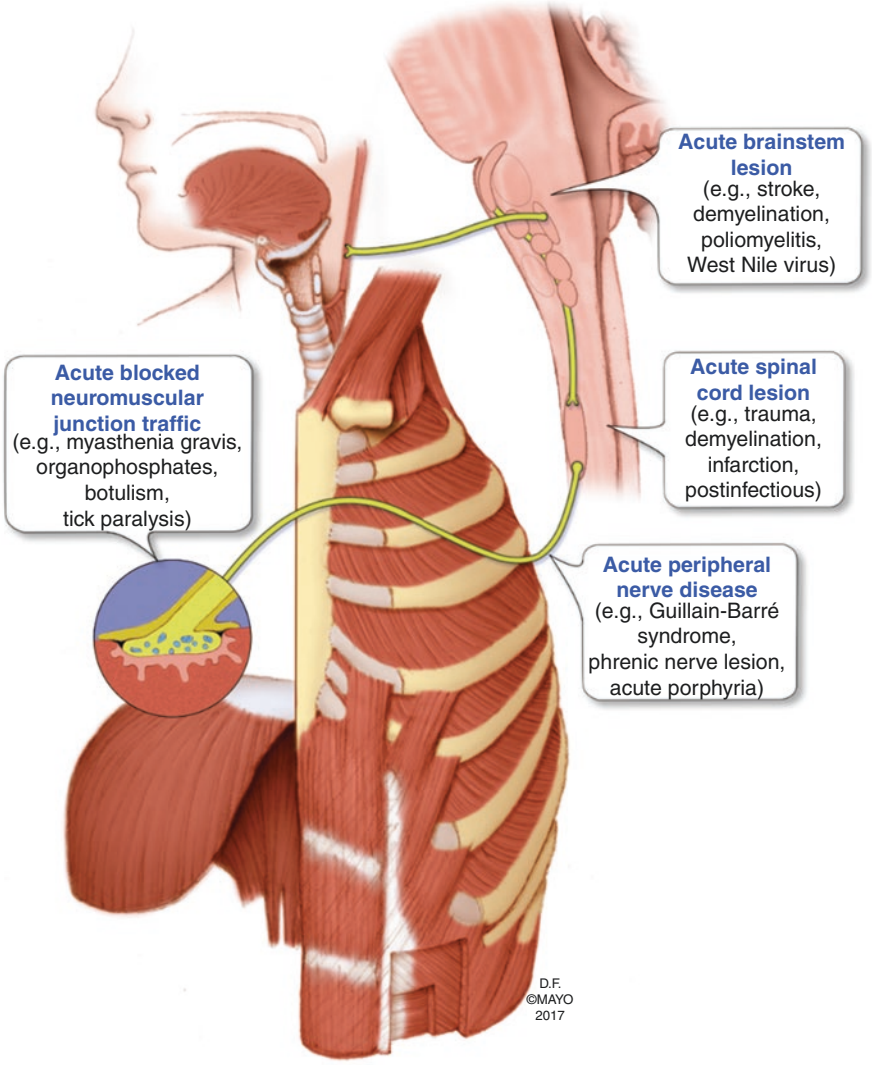


Fig. 3.1 Schematic of the neural pathways involved in respiration; the main causes of acute mechanical respiratory failure are summarized. (Figure first published in Wijdicks EFM. The neurology of acutely failing respiratory mechanics. Ann Neurol. 2017;81(4):485–494)

affect the oropharyngeal muscles involved in swallowing, palate, and larynx. Both muscle systems may be affected together, but oropharyngeal dysfunction often precedes demonstrable respiratory pump failure in central disorders [13–17]. Involvement in neuromuscular disease may be very selective, for instance, isolated diaphragmatic failure due to Pompe disease.

Case Vignette 3

A 31-year-old man presented to the respiratory physicians with a 3-year history of fatigue and was investigated for sleep apnea. He was found to have chronic neuromuscular respiratory failure, but there was no facial or limb weakness. His creatine kinase level (CK) was elevated at 1659 U/L, and his EMG was myopathic. The muscle biopsy was described as "dystrophic … no glycogen storage … but some increase in acid phosphatase." A next-generation sequencing genetic screen for limb girdle muscular dystrophies, which included common acid glucosidase alpha (GAA) gene mutations, was "negative." However, the Pompe blood spot test had been positive, and white cell testing confirmed reduced alpha glucosidase activity. Sequencing of the entire GAA gene showed a pathogenic variant in GAA c.-32-13 T > G outside the original test's region of interest, and sequence data showed a drop in coverage for GAA exon 18, which was interpreted to suggest a concomitant heterozygous deletion. The patient started enzyme substitution treatment.

Learning Points

Patients with predominantly diaphragmatic weakness must be investigated for Pompe disease: the blood spot screen is highly specific, and the clinician needs a basic understanding of strengths and limitations of all diagnostic tests. [The blood spot test is based upon a ratio calculated between the creatine (Cre) and creatinine (Crn) and the activity of acid-alpha glucosidase (GAA)]. The muscle biopsy may not always reveal typical glycogen storage and may show unspecific changes (though an increase in acid phosphatase may be a clue).

The diaphragm is responsible for the majority of the inspiratory effort through contraction and downward movement. The sternocleidomastoid and scalene muscles (innervated by cranial nerve XI and cervical-spine segments 1 and 2) and the external intercostals (innervated by thoracic spine segments) support inspiratory force; these "accessory" muscles are visibly recruited in patients with diaphragmatic failure, even in quiet breathing at rest [15, 18, 19].

During forceful inspiration, lungs expand as a result of downward contraction of the diaphragm that lengthens the chest cavity, and by elevation of the ribs through intercostal muscles that widens the chest; the actual air movement also depends on the resistance of inspiratory flow, the resistance of the chest wall and lungs, and the positive pressure at peak expiration. Expiration is mostly due to recoil of the thoracic cage and some recruitment of the internal intercostals (thoracic segments 1–12), but abdominal wall muscles (thoracic spine, segments 7–12) are also necessary to generate forceful expiration and a strong cough. The four overlapping layers

of the abdominal muscles pull the ribs and sternum down and increase intra-abdominal pressure, elevating the diaphragm during expiration. Most importantly, however, the abdominal muscles assist in coughing, and weakness in these muscles will result in failure to clear secretions. Hence, in practical terms, not only the vital capacity helps inform on likely success of weaning from the ventilator, but also the peak cough flow, by indicating whether there is a risk of failure to clear airways causing delayed chest infection.

Measurable Pathophysiology in Mechanical Respiratory Failure

With reduced tidal volume, the inspiratory time of the respiratory cycle shortens, which leads to decreased respiratory compliance, and poor lung deployment. Regional ventilation and perfusion mismatch in deflated alveoli lead to an early increase in alveolar–arterial oxygen gradient [20] with increased dead-space ventilation. The rapid breathing is the result of signals to the respiratory pattern generator from the abnormal, weak respiratory muscles, as well as an attempt to compensate for hypoxemia.

Pulse oximeter measurement, although important to detect hypoxemia, does not identify looming CO_2 retention. A normal arterial pCO_2 in a tachypneic patient may signal impending fatigue because mechanical failure prevents the patient from reducing arterial pCO_2. The arterial pCO_2 rises above normal when the diaphragm becomes adynamic (Fig. 3.2).

Pulmonary function tests have some clinical utility by providing information about inspiratory muscle strength. But it cannot be more emphasized that neuromuscular respiratory failure is a clinical diagnosis and requires a practiced skill to recognize subtleties, progression, and certainly imminent danger of respiratory arrest. Patients with diaphragmatic weakness show decreased vital capacity and pressures. Abnormal values for vital capacity usually are beneath normal baseline

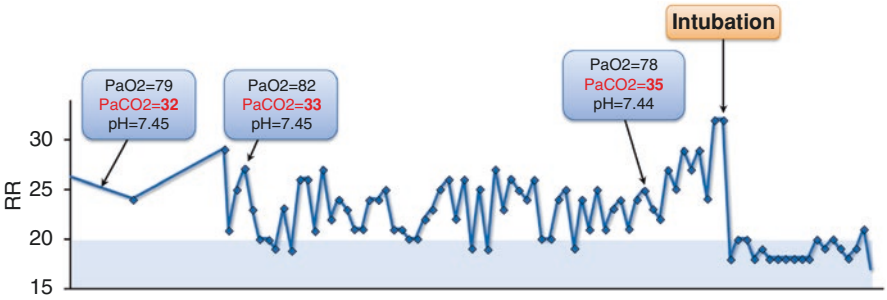


Fig. 3.2 This graph shows the significance of falsely normal pCO_2 in a tachypneic patient, meaning early diaphragmatic failure and not "blowing off" CO_2. RR = Respiratory Rate

(40–70 mL/kg or 3–5 L) by more than 50%. Maximal inspiratory pressure (PImax), is obtained at residual volume by occluding the inspiratory port of the valve (normal: −100 cm H_2O), whereas maximal expiratory pressure (PEmax) is measured at total lung volume by occluding the expiratory port (normal: 80 cm H_2O). PEmax and peak cough flow (PCF; normal: >360 L/min) are important measures of the ability to cough effectively [21]. These bedside pressure tests can now be easily obtained using handheld devices (if your hospital has them). Measurement of the sniff nasal inspiratory pressure is less commonly applied at the bedside—patients with oropharyngeal weakness have a nasal feeding tube in place that may complicate testing—but recent studies on nasal sniff pressure in Guillain–Barré syndrome suggested better correlation with worsening weakness than traditional spirometry measures, which can be partly explained by circumventing leaks from facial diplegia [22]. Nasal sniff pressures may be the preferred option in chronic conditions where the mouth seal is impaired, such as amyotrophic lateral sclerosis with progressive bulbar palsy (see Chap. 13). It remains to be seen if nasal sniff pressures are reliable in patients with acute oropharyngeal dysfunction and upper airway collapse, which may result in poorly coordinated muscle contraction and falsely low values. Falsely abnormal values of pulmonary function tests due to poor closure may also correct themselves with mask spirometry [23].

Respiratory muscle testing requires expertise in administering the test, and optimal patient cooperation needs to be ensured (see Video 1). Problems with the technique are particularly common in general medical wards, and the unstable patient who needs regular, repeated assessment is better managed through experienced staff in an HDU/ICU setting. In respiratory muscle testing of patients with myasthenia gravis, fatiguing weakness may mean that results can rapidly change, and that patients with a clear history of respiratory distress may at a single given test demonstrate falsely reassuring results (Fig. 3.3).

Clinical Recognition of Acute Respiratory Failure

As alluded to, clinical recognition must remain the gold standard for acute failure of respiratory mechanics, for which there is no alternative (this is fundamentally different from all other critical respiratory illnesses). Failure of respiratory mechanics leads to restlessness, tachycardia (>100 bpm), tachypnea (>20 per min), use of sternocleidomastoid or scalene muscles, failure to string more than a few words together in a sentence (i.e., “staccato speech”; see Supplemental material, Video 2), and asynchronous, sometimes paradoxical breathing. Even in the presence of a normal arterial blood gas, patients continue to have a sensation of breathlessness. When PaO_2 declines and $PaCO_2$ rises, patients experience “air hunger,” a result of increased respiratory drive and overstimulated chemoreceptors. Patients often have an unpleasant, frightening feeling of not catching enough air (reminiscent of the feeling after running up the stairs) and may report a struggle to breathe. It is important

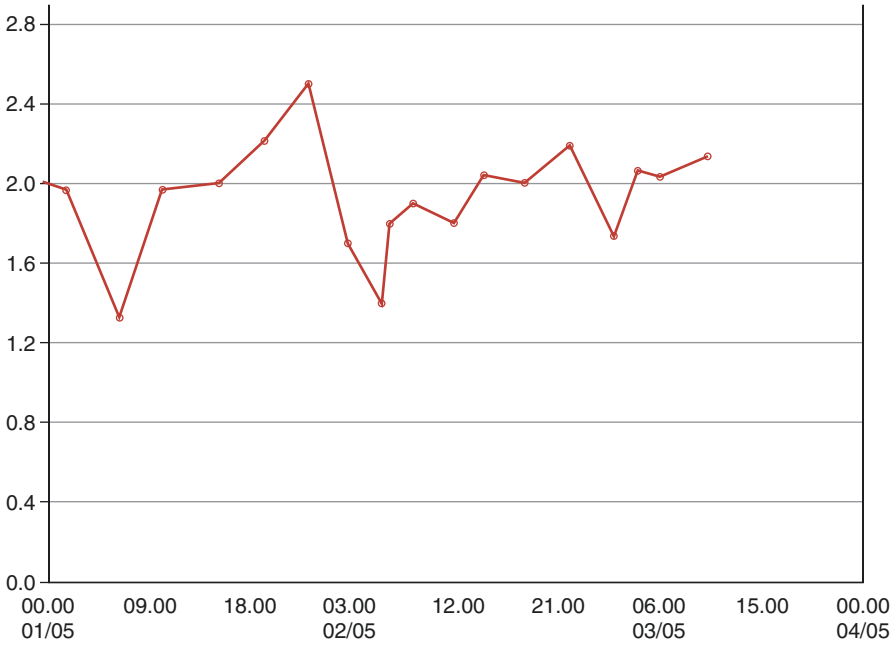


Fig. 3.3 A patient with myasthenia complained of early morning breathlessness. Serial VC measurement shows low VC shortly before pyridostigmine doses are given (on a 3× daily regimen). Her symptoms improved with more frequent dosing and controlled release pyridostigmine administered in the evening. X-axis: time; Y-axis: VC serial measurements in liters

to recognize these symptoms because it may imply the patient is in need of endotracheal intubation—and, indeed, may have been long before. In chronic neuromuscular disorders, however, the clinical signs of respiratory failure may be very subtle. Weakness of the oropharyngeal muscles leads to dysphonia and dysphagia. Gurgling mucus makes this element of mechanical failure immediately recognizable, and the patient is in real danger of asphyxiation. Physicians will find a patient not thinking clearly and falling asleep—and further obstructing the airway—when there is emerging hypercarbia better known by the right alarmist term "CO_2 narcosis " [24–26].

Thoraco-abdominal dyssynchrony may be apparent [15, 18, 19]. Normally, the abdomen and chest expand and contract in a synchronized fashion. During inspiration, downward movement of diaphragm pushes the abdominal contents down and out as the rib margins are lifted and moved out, raising both chest and abdomen. Little of this is present in patients with mechanical respiratory failure, and the movements are not coordinated, creating a "rocking horse" effect, also known as abdominal paradox (i.e., chest out, abdomen in). The degree to which dyssynchrony is present depends on the severity of respiratory muscle weakness and is most often apparent with diaphragm standstill (see Video 3).

Causes of Acute Mechanical Respiratory Failure

Acute stroke, acute demyelination, or infectious causes can all lead to acute dorsolateral medulla oblongata lesions. Poliomyelitis, still a health-care problem in some parts of the world, may cause permanent respiratory failure [27]. Now less prevalent, West Nile disease may cause lesions of the brain stem or anterior horns of the spinal cord [28, 29].

Acute traumatic spinal cord injury remains the most common cause of spinal cord-associated respiratory failure. Other causes are upper cervical cord infarction and acute cervical myelitis associated with neuromyelitis optica, which has been complicated by respiratory failure in up to 33% of cases [30, 31].

Two disorders epitomize the major manifestations of acute neuromuscular respiratory failure—myasthenia gravis and Guillain–Barré syndrome (GBS) [32]. The term myasthenic crisis is traditionally applied to myasthenia with respiratory failure requiring mechanical ventilation and purportedly occurs in 20–40% of admitted patients, not infrequently within the first 12 months of disease onset [33, 34].

In GBS, facial and oropharyngeal muscles are affected in nearly 50% of cases. Respiratory failure occurs in about 20–30% of patients and commonly within 1 week after the onset of paresthesia. The cause of GBS is a respiratory virus (most trivial Influenza viruses) or enteric bacteria (*Campylobacter*). The consequences of the Zika virus epidemic on the prevalence of GBS are not yet known, and the virus has waned. The first reported clusters of cases noted both short rapid progression and short plateau phases but comparable incidence of respiratory failure in Zika-associated GBS when compared with typical causes of GBS [35, 36]. A number of cases of GBS have been described in the recent COVID-19 pandemic caused by the SARS-CoV2 virus, but the true incidence is not yet clear and so far it has not caused outbreaks of GBS [37].

Some rare acute disorders may also cause abnormal respiratory mechanics. Phrenic nerve injury and unilateral damage may cause marked breathlessness during any form of exercise and prevent the patient from lying flat. Many cases of phrenic nerve damage are unexplained but may be due to neuralgic amyotrophy (associated with intense pain in shoulder muscles), stretch injury, or traumatic brachial plexus injury. Phrenic nerve injury may occur with compression of the brachial plexus due to tumor (commonly squamous cell lung carcinoma), aneurysm (thoracic aorta), prior chest surgery (including thymectomy for myasthenia gravis), cannulation of the subclavian or internal jugular vein, herpes zoster infection, chiropractic manipulation, or, more recently, monoclonal antibody ipilimumab targeting cytotoxic T lymphocyte antigen 4 in metastatic melanoma [38–41].

There are a number of case reports where isolated vocal cord paralysis may lead to respiratory failure in myasthenia gravis, particularly associated with anti-MuSK antibodies [42, 43].

Case Vignette 4

A 66-year-old man had been diagnosed with myasthenia gravis with mild generalized and bulbar weakness 6 years earlier [Myasthenia Gravis Foundation of America (MGFA) clinical score MGFA2B], and symptoms resolved rapidly with treatment. He was on mycophenolate mofetil alone for 5 years, then tapered it off over 6 months on account of ongoing gastrointestinal discomfort. One month later, he noticed mild recurrence, and restarted. Seen in clinic 2 months later, he was asymptomatic without evidence of fatiguing on examination, but reported having a hoarse voice on long phone calls. This was not evident in the consultation. Three days later, he was admitted to ICU in respiratory distress. His breathing improved almost immediately when intubated, and there was no myasthenic weakness in the limbs, respiratory, or facial muscles. Over the next few days, he failed several attempts at extubation due to vocal cord paralysis and severe stridor after extubation. Vocal cord function rapidly improved after intravenous immunoglobulin treatment, and he was successfully extubated.

Learning Points

Subtle indications of vocal cord dysfunction can be a serious warning sign in myasthenia, even in the absence of fatiguing in other muscles.

Consults in medical and surgical intensive care units are often about weakness in patients who have survived a critical illness. After prolonged mechanical ventilation, most patients develop severe diaphragm weakness, resulting in dyssynchrony after weaning. Recent work has found marked decrease in respiratory muscle strength within weeks of mechanical ventilation [44].

In developing countries, acute neuromuscular respiratory failure due to tetanus and botulism remains prevalent [45, 46] (see Chap. 15), but is less common in high-income societies. Unfortunately, poisoning with organophosphorus compounds from self-administration or terrorist attacks is common and often fatal. The combination of bronchoconstriction, hypersecretion, and respiratory muscle paralysis makes this a major challenge, but patients with less severe manifestations may survive with support [47].

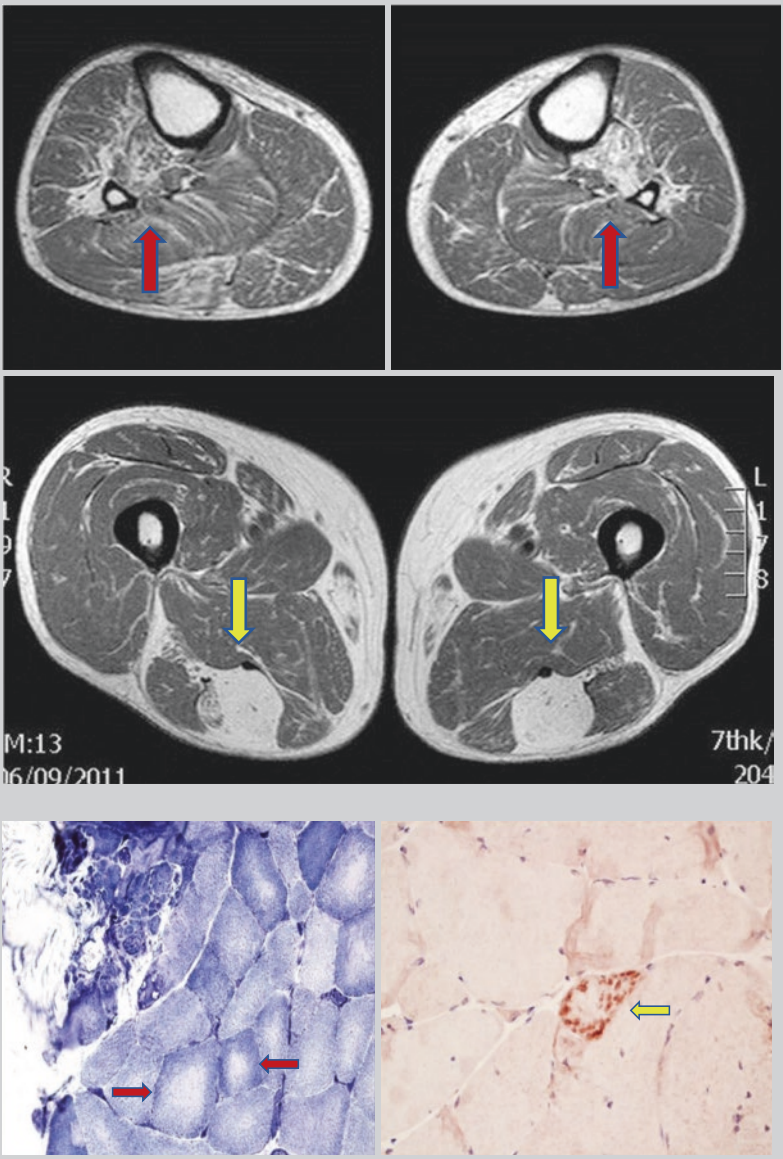
Chronic myopathies (see Chap. 1, tables) eventually will involve the oropharyngeal musculature and diaphragmatic function; common examples are the major dystrophies (Duchenne, Becker, limb-girdle), congenital myopathies such as X-linked myotubular myopathy, centronuclear myopathies, RYR1-related, and Selenoprotein

N (SEPN1 or SELENON)-related myopathies and metabolic myopathies (acid maltase deficiency or Pompe disease) [48–52]. Their presentation is rarely acute, with the exception of acute-on-chronic decompensation; gradual oropharyngeal weakness requiring tracheostomy is a more common presentation than abnormal respiratory mechanics. Titin gene mutations are a well-recognized cause of hereditary myopathy with early respiratory failure (HMERF), in which respiratory weakness is the predominant feature and disproportionate to sometimes mild distal weakness (see Case Vignette 5) [53].

Case Vignette 5

A 58-year-old previously healthy man married and went on a honeymoon trip to the Rocky Mountains. On an all-day hike at high altitude (>200 m), he developed increasing shortness of breath. He was air-evacuated and arrived at a local hospital in acute respiratory failure, where he was intubated and ventilated; he was diagnosed with Guillain–Barré syndrome (GBS) and treated with IVIG. There were no complications, but he could not be weaned from the ventilator. On repatriation to the United Kingdom, he was awake, conversant, and had no facial or proximal weakness, but he had contractures of calf muscles, which appeared atrophic and had been "very thin" for years. CK was normal, neurophysiological studies revealed a myopathic EMG, and MRI of thigh muscles showed a selective symmetric pattern of fatty degeneration of, in particular, the semitendinosus muscle. A degenerative myopathy was suspected.

MRI of muscle performed in the ICU showed symmetric but selective fatty degeneration of muscles (images: axial T1 sections through calves—above, with fatty degeneration of the posterior tibial muscles—red arrows; thigh muscles—below, showing almost complete fatty replacement of the semitendinosus on both sides—yellow arrows).



Muscle biopsy showing "rubbed-out areas" on NADH-TR stain suggesting myofibrillar disruption (left—red arrows), and accumulation of myotilin in muscles on immunohistochemistry (right—yellow arrow). The genetic analysis confirmed titinopathy with a mutation typical for hereditary myopathy with early respiratory failure type 1 (HMERF; OMIM 603689; Titin R279W mutation). The patient was ultimately weaned after 2 months to noninvasive nocturnal ventilation via *mask and was fully ambulatory.*

Learning Points
Chronic respiratory failure can be compensated for a long time, but may suddenly deteriorate with increased work of breathing.

When acute respiratory failure requiring endotracheal intubation and ventilation occurs on the basis of a chronic myopathy, there is a high chance of a successful wean off the ventilator and off tracheostomy, with the likelihood of achieving the previous level of function again. In contrast, in ALS, neuromuscular respiratory failure and aspiration pneumonia are common reasons for hospitalizations including emergency ICU admissions (see Chap. 6). However, patients with ALS who are intubated for acute respiratory failure, with or without an established diagnosis, rarely achieve independence from the ventilator. Almost all of these patients need long-term ventilatory support and the degree of respiratory support increases with time [54]. In-hospital mortality is high, and in survivors, time to death after first hospitalization is 10–20 months [55, 56].

Recurrent laryngospasm is a recognized complication of spinobulbar muscular atrophy/Kennedy disease, and may present an anesthetic risk [57]. It is also observed in ALS and in polio with bulbar involvement.

Neurophysiological and Dynamic Testing

In addition to the assessments detailed in Chap. 2, the neurophysiological investigation of neuromuscular respiratory failure phrenic nerve stimulation may be useful to differentiate between a myopathy, myasthenic syndrome, or neuropathy. The phrenic nerve is located underneath the posterior border of the sternocleidomastoid muscle and can easily be stimulated once or repetitively. The diaphragmatic compound action potential is of low amplitude but affected by the respiratory cycle [58]. Needle electromyography (EMG) of the diaphragm can also be performed (needle entry at the sixth or seventh intercostal space), although it is not performed often, out of concerns of iatrogenic pneumothorax, even though that is infrequent [59]. Diaphragmatic EMG via an esophageal electrode can be used to assess respiratory drive and is a component of neurally adjusted ventilator-assisted ventilation (NAVA) [60, 61], but its value in neuromuscular disease is unclear. Newer technology such as ultrasound imaging of the diaphragm provides dynamic information and can also improve the accuracy of testing for phrenic nerve conduction with a twitch seen on ultrasound after stimulation [62]. This may reduce false-positive results in nerve conduction studies in patients without diaphragm dysfunction [62–64]. These three modes of testing combined have great potential in ICU settings. In acute neuromuscular diseases, however, comprehensive data are not available on whether phrenic nerve and diaphragm EMG and ultrasound predict future intubation or a successful weaning trial. Dynamic MRI is available but has not been tested other than in

chronic muscular disease [65, 66]. Its short acquisition times (<30 min) may make it a potentially useful tool, particularly combined with imaging of chest wall muscles but limited availability, and problems around patients with impaired respiratory function tolerating the scan limit its current use [67, 68].

ICU Level of Care

Any respiratory distress signal requires intensive care admission. Pooling of secretions can make the supine position immediately dangerous. Vomiting with repeated (weak) coughing carries the risk of massive aspiration with acute marked hypoxemia. In acute, high-cervical spinal cord lesions, intubation and mechanical ventilation are urgent.

Oxygen administration should be used judiciously to achieve oxygen saturation between 90 and 95%, but prolonged O_2 administration may potentially cause CO_2 retention in patients with neuromuscular respiratory failure, resulting in hypercapnic coma or respiratory arrest [69, 70]. High-flow, nasal-cannula oxygen, which has been considered an alternative to BiPAP ventilation, provides 50 L/min and an FIO_2 of 1.0 through large-bore binasal prongs [71] but must be used judiciously to avoid rapid hypercarbia. Mechanical ventilation—intubation or noninvasive—must be strongly considered in any patient with respiratory failure and oxygen desaturations rather than trying to circumvent the problem with supplemental oxygen.

In GBS, the time between onset of weakness and hospital admission, the presence of facial weakness or oropharyngeal dysfunction, and the severity of limb weakness assessed by the Medical Research Council sum score all predict the need for intubation [72–74]. This confirms the clinical impression that difficulty in clearing secretions in patients with a rapid-onset weakness (<3 days after onset) indicates a high risk of respiratory failure. In less severely affected patients, management of secretions is important and requires frequent suctioning. If the weak patient can reach the mouth with a Yankauer suction tip, the plastic suction tip with a large opening and bulbous head allows effective suction without tissue injury. Secretions can also be managed with anticholinergics such as scopolamine patch and tricyclic antidepressant, both of which will produce an effect within hours [75]. However, with progression of symptoms, the benefit of these measures is temporary.

As far as timing of ICU admission and intubation is concerned, several clinical decisions come into play. Most conditions favor immediate intubation, particularly when the patient appears in distress. These are patients with clear clinical signs such as inability to cough up secretions, tachypnea, sweating, hemodynamic instability, and abnormal arterial blood gas with hypoxemia or early hypercapnia. Other situations are far less clear on presentation but may be equally life threatening. Any patient with increased work to breathe or other more subtle signs such as restlessness, anxiety, sternocleidomastoid muscle contractions, nasal flaring (contraction of dilator muscle of external nares), and mouth opening should be preemptively intubated rather than guided by a pulmonary function test threshold. Patients with an

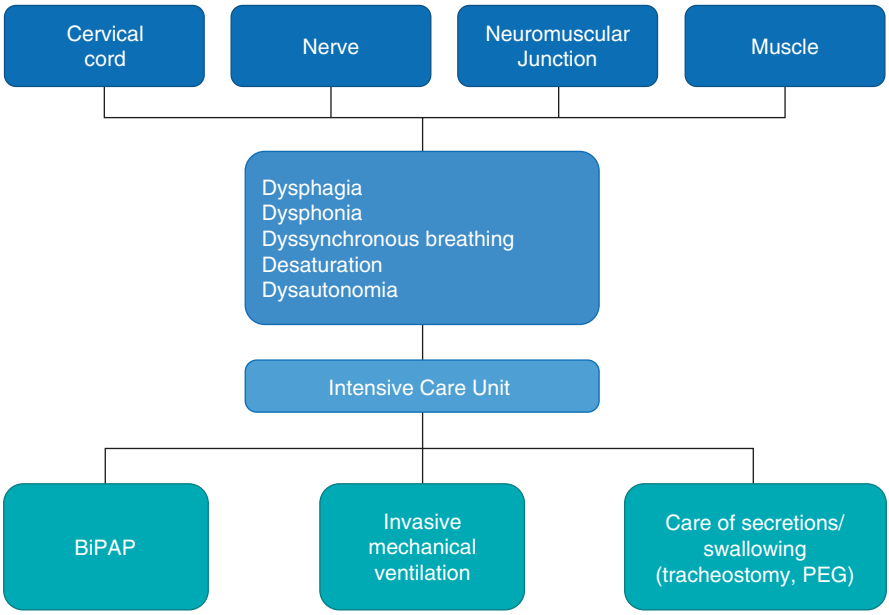


Fig. 3.4 Factors influencing the decision to admit to the ICU and the choice of management (the "5Ds"—dysphagia; dysphonia; dyssynchronous breathing; desaturation; dysautonomia are the clinical distress signals that suggest the need for ICU admission)

increasing oxygen demand despite corrected hypoxemia are a second group where ICU admission is prudent. A third category of patients are those with progressive symptoms and worsening pulmonary function tests, but without frank respiratory distress, and this presents a practical dilemma. Knowledge of the expected progression of certain neurological disorders may affect the decision on ICU admission (Fig. 3.4).

The recent appearance of oropharyngeal weakness and dysphonia with incremental limb weakness (even if mild) is often reason enough to protect the patient from sudden respiratory arrest by early intubation. Any decline in pulmonary function tests when serial measurements are available has equivalent value, but these volitional tests cannot be interpreted without careful bedside evaluation. A reasonable guideline is a continuous decline or a vital capacity reaching 10–15 mL/kg or 1 L. Inspiratory and expiratory pressures do decline but not necessarily in parallel. An additional PImax or PEmax decline 30–50% from baseline value should seriously concern clinicians. In GBS, we have found VC < 20 mL/kg, PImax < −30 cm H_2O, and PEmax <40 cm H_2O ("20/30/40 rule") may guide practitioners [72]. At these levels, sighing or deep inhalation is reduced, leading to atelectasis and hypoxemia. In chronic neuromuscular disorders with gradually developing weakness of respiratory muscles, it is less clear what results signify a risk of acute failure. Mouth pressures (see also Chap. 4) are less commonly used for respiratory monitoring in muscular dystrophies in most countries, but a recent systematic study indicates that

they may provide clinically useful information in addition to VC [76]. Similarly, the role and timing of noninvasive mechanical ventilation in less affected patients with acutely failing respiratory mechanics have not been clearly established. The major objective of noninvasive ventilation, most often provided as bilevel positive airway pressure (BiPAP), is to maintain adequate gas exchange while avoiding intubation. In recently extubated patients, BiPAP may spare them from reintubation. Limitations of BiPAP include discomfort from the close-fitting mask, failure to rest and sleep, leaks, gastric distention, and risk of aspiration. Noninvasive ventilators provide pressure support ventilation with a preset inspiratory pressure to assist in spontaneous breathing efforts. Many devices also provide pressure control ventilation that provides time-cycled preset inspiratory and expiratory pressures and even adjustable inspiratory and expiratory ratios. Additional modes could permit the patient to trigger, and there can be a selective backup rate. Typical settings for BiPAP are an inspiratory positive airway pressure (IPAP) of 10 cm H_2O (range, 5–25 cm H_2O) and an expiratory positive airway pressure (EPAP) of 5 cm H_2O (range, 0–30 cm H_2O). This will then result in a pressure support of about 10 cm H_2O. A backup rate should be set at 12–16 breaths per minute [77].

BiPAP is useful for patients with acute respiratory failure due to myasthenia gravis, ALS presenting acutely, and chronic muscular disorders (such as immune-mediated necrotizing myopathy evolving over months, or acute decompensation of chronic myopathies through chest infection or intercurrent illness) reaching a tipping point with respiratory involvement. BiPAP is unreliable in GBS, where diaphragmatic failure is often too severe to be treated with pressure support alone, and many patients continue to use accessory muscles despite being on BiPAP. However, BiPAP may considerably benefit patients with myasthenia gravis exacerbation and respiratory failure. BiPAP can be used during plasma exchange, which often improves muscle weakness fairly rapidly. It may be necessary to reduce the dose of pyridostigmine, but the drug cannot be completely withheld. (This is in contrast to patients who are intubated and on a mechanical ventilator, where the drug should be discontinued for the period of ventilation because of hypersalivation.) BiPAP is not successful in patients with profound cholinergic symptoms due to hypersecretion and airways blockage. Clinical evaluation of the patient and judgment of patient's comfort is the best guide when using BiPAP, so a relatively unimpaired level of consciousness is necessary.

Tracheostomy

The need for tracheostomy reflects the need for long-term mechanical ventilation. In many patients, tracheal secretions are better managed with a tracheostomy in place. Tracheostomy is strongly encouraged after 2 weeks to avoid the uncommon—but severe—tracheomalacia and post-intubation tracheal stenosis. Most patients with high cervical traumatic injury require an early tracheostomy to reduce respiratory complications [78, 79]. In many acute neuromuscular diseases and other

critical illnesses, timing of the tracheostomy is controversial with little impact on mortality and some reduction of ventilator-associated pneumonia when performed within 2 weeks [80]. GBS patients unable to lift their arms from the bed or patients with electrophysiological evidence of axonal degeneration at 1 week likely need prolonged mechanical ventilation—in these patients, tracheostomy should be considered early [81]. Many patients need tracheostomy placement despite early plasma exchange or IVIG treatment [82]. In myasthenia gravis, weaning and extubation are expected soon after initiation of immunomodulation, and tracheostomy can be postponed. Some cases of vocal cord paralysis and urgent tracheostomy in myasthenia gravis are on record (see above) [83]. Tracheostomy can be controversial in chronic muscle disease due to fears of permanently depriving the patient of a voice if the tracheostoma cannot be reversed, but in our experience this is a very rare occurrence, except in bulbar ALS.

Liberating the Patient from Mechanical Ventilation

Several preconditions must be considered before even attempting to wean patients from the ventilator. Mechanical ventilation can be prolonged in GBS, of short term in MG and permanent in acute spinal cord disorders. Patients with C2- to C3-level spinal injury may recover diaphragmatic function [11, 84]. But the chances of recovering fully independent breathing decrease to less than 5% in patients with complete high tetraplegia and certainly beyond a year [85]. (In a later phase, respiratory muscle pacing in stable, ventilator-dependent tetraplegia has shown promise particularly with microsurgical nerve transfer [86, 87]). The experience with weaning from the ventilator in the presence of inflammatory, demyelinating, or postinfectious myelitis is limited, and recovery potential is not exactly known and depends on the degree of injury and recovery; in one circumstance with acute cervical cord inflammation, we were able to wean a patient from the ventilator following administration of high-dose corticosteroids [88]. After intubation, however, respiratory function parameters in GBS often continue to fall, and pressures and volumes may become unmeasurable. However, in GBS, one should anticipate weeks to months on the ventilator [89, 90].

Weaning from mechanical ventilation should be undertaken as early as possible because of the significant complications associated with prolonged intubation and to prevent unnecessary early tracheotomy in patients ready to wean. The process can be initiated once VC reaches 10–15 mL/kg and spontaneous tidal volumes of 7 mL/kg are attained. In GBS, PImax exceeding −50 cm H_2O and VC improvement by 4 mL/kg from pre-intubation to pre-extubation were associated with successful extubation, but measurement of pulmonary function tests is dependent on patient effort and difficulty while still intubated, and these volitional measurements should not be seen as a definitive threshold. No single value is a predictor of extubation success [91].

Generally, in acute neuromuscular disorders, weaning from mechanical ventilation should be guided by improvement in diaphragm strength as documented by values on serial pulmonary function tests. Diaphragmatic weakness may reverse before limb weakness; thus, recovery of extremity muscle strength should not exclusively dictate the timing of weaning. In some patients with persistent limb weakness, spontaneous pressure support trials have been tolerated well as judged by lack of fatigue, lack of increased work of breathing, and maintaining oxygenation.

GBS patients on mechanical ventilation can anticipate a prolonged ICU stay. Still, many mechanically ventilated patients subsequently regain the ability to walk independently; about 75% walk again up to 2 years after onset [89]. Mortality in GBS has been estimated at 3% but doubles in long-term mechanically ventilated patients and may even approach 10–20% in elderly patients [89]. Patients may succumb from ventilator-associated pneumonia when it progresses to sepsis. Better ICU care and respiratory rehabilitation have greatly improved these percentages, but preexisting illness (in particular, prior COPD) remains a major disadvantage.

In myasthenia gravis, one important priority is to achieve satisfactory treatment of the myasthenic symptoms. In addition, the patient should have no major pulmonary problem and no evidence of clinically significant atelectasis, pleural effusion, or marked difficulty in handling secretions [92]. Secretion volume, whether the patient is comfortable with a T-piece trial, and a completely normal chest X-ray are good predictors of successful extubation in any patient with acute neuromuscular respiratory failure [93]. Pulmonary function tests can predict weaning to a certain extent but are far from reliable. The maximal expiratory pressure that reflects coughing up of secretions and thus abdominal musculature strength might be the best predictor of successful weaning. In myasthenia gravis, pyridostigmine is discontinued during mechanical ventilation. The optimal timing of reintroducing pyridostigmine is not known. Some neurologists start pyridostigmine in a lower dose around the time of extubation to optimize oropharyngeal and diaphragmatic strength. Careful monitoring for increased secretions after reintroduction of pyridostigmine is imperative.

Case Vignette 6

A 74-year-old man was diagnosed with myasthenia gravis (MG) featuring mild bulbar symptoms. He had a history of diabetes and pulmonary tuberculosis (TB) last active 39 years earlier. MG was well controlled with low-dose steroids for 5 years. He then rapidly developed dysphagia and aspiration; no trigger was identified. Despite starting IVIG, his condition deteriorated and he required intubation 5 days after admission. Aspiration pneumonia was promptly treated, but despite plasma exchanges he was slow to wean and required tracheotomy after two failed extubations due to inadequate airway protection and episodic confusion. He required BiPAP for 55 days, but then weaned respiratory support and was transferred to a rehabilitation unit in the hospital. Trials of tracheostoma cuff deflation started on day 67. Initially,

these could only be tolerated for a few minutes because of copious secretion buildup. Pyridostigmine was discontinued without increased weakness, but hyoscine patches and glycopyrrolate did not help, and subglottic secretions posed an immediate aspiration risk. His further course was complicated by episodes of confusion and a hip fracture sustained during physiotherapy. After 4 weeks' TB eradication therapy, mycophenolate mofetil was started. Secretions only slightly improved by day 155, and trials with deflated cuff remained short. After discussion with the patient and his family, a decision was taken to remove the tracheostomy canule under the rationale that the tube itself might be causing secretions by irritation of the trachea. This decision was not uncontroversial in the team.

After removing the tube, secretions rapidly decreased. The patient was discharged to his home and has remained stable and self-caring in the 8 months since discharge.

Learning Points
Weaning from the ventilator and tracheotomy is influenced by multiple factors, including premorbidity and mental state, but can be successful even in high-risk patients.

Weaning methods may vary, and the relative benefits of different weaning protocols in neuromuscular disease have not been conclusively established. However, we strongly believe that having a clear pathway to weaning agreed by the team is essential. Too often weaning is delayed when different ICU teams use a varying approach, and one shift rolls back on progress made in the preceding period, or when targets set are either too demanding, or too unambitious. Weaning may be prolonged in acute neuromuscular disorders because of reduced hypercapnic response from reduced chemoreceptor sensitivity due to presumed autonomic involvement [94]. Extubation failure may harm the patient physiologically, but prolonged ventilation also harms patients. The weaning process cannot realistically start without stable, sufficient lung and cardiac function, adequate control of infection, a sufficient level of consciousness to produce a good cough, and the absence of delirium. A possible early weaning approach includes reducing the synchronized intermittent mandatory ventilation rate. Patients may be switched to pressure support ventilation (PSV) and the level decreased. After the patient is disconnected from the ventilator, one method employs a T-shaped tube connected to the endotracheal tube and opens to the atmosphere at the other end to provide oxygen supplementation. These so-called "T-piece trials" for 30 min or a trial with a CPAP of 0 cm Hg may determine whether respiratory mechanics are sufficient, but oropharyngeal weakness may still be present, and inability to assess the upper airway may result in failure to wean [95].

Summary

There remain major gaps in our knowledge and unexplored aspects of understanding failing respiratory mechanics and how best to assess and manage this condition in acute neurology. This is undoubtedly a reflection of the rarity of the disorders described and no registry of cases—simple or complex. Recommendations for future research directions are (1) better development of diagnostic tests measuring respiratory control and breathing instability, and (2) systematic evaluation of intubation criteria and modes of mechanical ventilation in a number of different disease entities.

Self Assessment Questions

1. Which of the following types of speech is most indicative of imminent respiratory failure?

   (a) Scanning speech
   (b) Slurred speech
   (c) Spastic speech
   (d) Staccato speech (*)

2. Which of the following muscles are predominantly involved in pulling in air?

   (a) Abdominal wall muscles
   (b) Diaphragm muscles (*)
   (c) Internal intercostal muscles

3. Which of the following muscles are most involved in producing an effective cough?

   (a) Abdominal wall muscles (*)
   (b) Diaphragm muscles
   (c) Palatal muscles

Central components of mechanical respiration mainly reside in the medulla oblongata.

4. Which of the following parts of the CNS contain chemoreceptors responding to hypercarbia?

   (a) The intermediolateral spinal nucleus
   (b) The pontine serotonergic raphe neurons (*)
   (c) The mesencephalic periaqueductal gray
   (d) The hypothalamic dorsomedial nuclei

5. The respiratory centers appear relatively immune to metabolic insults.

   (a) True (*)
   (b) False

6. Which of the following respiratory functions may be affected due to a spinal cord lesion below the level of C5?

   (a) Expiratory effort (*)
   (b) Inspiratory flow
   (c) Maintaining an open airway

7. Which of the following problems, potentially leading to respiratory problems, is most likely to occur in the acute phase of a spinal cord lesion below the level of C5?

   (a) Bronchial dilation
   (b) Laryngospasm
   (c) Tracheobronchial hypersecretion (*)

8. Which muscles are first affected in case of myogenic respiratory failure due to central disorders?

   (a) Oropharyngeal muscles (*)
   (b) Respiratory muscles

9. Which muscles are visibly recruited in order to maintain respiration in patients with diaphragmatic failure?

   (a) Abdominal wall muscles
   (b) Platysma muscles
   (c) Scalenic muscles (*)

10. Which of the following devices is most helpful in a medium care (high dependency) unit for monitoring patients with the Guillain–Barré syndrome in a supine lying position?

    (a) Blood pressure monitor
    (b) ECG monitor (*)
    (c) Handheld spirometer
    (d) Pulse oximeter

11. Nowadays clinical recognition remains the gold standard for acute failure of respiratory mechanisms

    (a) True (*)
    (b) False

12. Which of the following symptoms is most indicative of failure of respiratory mechanisms in a patient with an imminent myasthenic crisis?

    (a) Increasing dysarthria
    (b) Miosis

(c) Pale appearance
(d) Restlessness (*)

13. Which of the following symptoms is indicating slowly progressive respiratory failure in chronic neuromuscular disorders?

(a) Blue appearance in skin
(b) Dry mouth
(c) Gurgling mucus (*)
(d) Insomnia

14. Which of the following symptoms may more than the others herald respiratory failure in myasthenia gravis?

(a) Hoarseness (*)
(b) Hypernasal speech
(c) Lispling
(d) Rhinolalia aperta

15. Which of the following symptoms or signs is the most significant problem after prolonged ventilation of a neuromuscular patient?

(a) Bronchoconstriction
(b) Diaphragm weakness (*)
(c) Sensitivity to viral infections
(d) Uncontrollable coughing

16. Which of the following symptoms fits most with poisoning with organophosphorus compounds?

(a) Bradycardia
(b) Bronchoconstriction (*)
(c) Sweating
(d) Xerostomia

17. Which of the following factors may particularly precipitate deterioration of chronic respiratory failure?

(a) Abnormal exertion (*)
(b) Air journey
(c) Psychological distress
(d) Tropical heat

18. In patients with chronic myopathy with acute respiratory failure requiring endotracheal intubation and ventilation, there is a high chance of a successful wean off the ventilator.

(a) True (*)
(b) False

19. Patients with ALS who are intubated for acute respiratory failure rarely achieve independence from the ventilator.

    (a) True (*)
    (b) False

A patient with a chronic myopathy is referred to a local hospital because of respiratory distress attributed to a viral infection. He gets oxygen by a nasal cannula and is monitored in a general ward. After a few hours, a respiratory arrest occurred.

20. What is the most probable diagnosis?

    (a) Cardiac failure
    (b) Hypercapnic coma (*)
    (c) Pulmonary embolism
    (d) Rhabdomyolysis

21. Which of the following factors predicts the need for intubation of a Guillain–Barré syndrome patient more than the others?

    (a) Blood pressure fluctuations
    (b) Cardiac arrhythmia
    (c) Facial weakness (*)
    (d) Proximal leg muscle involvement

22. Which of the following deserves most attention in neuromuscular patients with imminent respiratory failure?

    (a) Clearing secretions (*)
    (b) Keeping constant room humidity
    (c) Maintaining a horizontal position
    (d) Nursing in a room without other patients

23. Which of the following symptoms indicates the need for endotracheal intubation in an unstable neuromuscular patient?

    (a) Facial signs of distress
    (b) Masticatory spasms
    (c) Nasal flaring (*)
    (d) Difficulty swallowing

BiPAP may be used in respiratory distress to avoid endotracheal intubation.

24. In which of the following neuromuscular diseases, BiPAP may be a reliable support?

    (a) Guillain–Barré syndrome
    (b) Myasthenia gravis (*)
    (c) Pompe disease
    (d) All of these

25. Which of the following is a contraindication for BiPAP?

(a) Bronchial hypersecretion (*)
(b) Dental symptoms
(c) Profuse sweating
(d) Tachycardia

26. In which Guillain–Barré syndrome patients, early tracheostomy should be considered? In patients with…

(a) Autonomic instability
(b) Axonal degeneration (*)
(c) Facial weakness
(d) Full paraplegia

27. The critical VC for the decision intubation of weaning from ventilation is situated within the range of ……

(a) 5–10 mL/kg body weight
(b) 10–15 mL/kg body weight (*)
(c) 15–20 mL/kg body weight
(d) 20–25 mL/kg body weight

28. Mechanical respiratory failure is reliably excluded if PaO_2 and $PaCO_2$ are normal.

(a) True
(b) False (*)

29. Invasive ventilation is contraindicated in acute respiratory failure in patients with a limb-girdle muscular dystrophy because most of these cannot be weaned from artificial ventilation anymore.

(a) True
(b) False (*)

30. Guillain–Barré syndrome can safely be managed in the general ward as long as blood gases remain normal.

(a) True
(b) False (*)

31. Measurement of vital capacity allows adequate respiratory assessment in clinical settings as long as there is sufficient facial muscle strength.

(a) True
(b) False (*)

32. There is a contraindication for tracheostomy in patients with respiratory failure due to chronic neuromuscular disease.

(a) True
(b) False (*)

33. Tracheotomy in patients with Guillain–Barré syndrome should be deferred more than 2 weeks after intubation if they are treated with IVIG.

    (a) True
    (b) False (*)

34. Weaning can often be successful in spite of multiple extubation attempts.

    (a) True (*)
    (b) False

References

1. Bolton CF, Chen R, Wijdicks EFM, Zifko UA. Neurology of breathing. Amsterdam: Elsevier; 2004.
2. Smith JC, Abdala AP, Borgmann A, Rybak IA, Paton JF. Brainstem respiratory networks: building blocks and microcircuits. Trends Neurosci. 2013;36:152–62.
3. Severinghaus JW, Mitchell RA. Ondine's curse – failure of respiratory center automaticity while awake. Clin Res. 1962;10:122.
4. Mulkey DK, Rosin DL, West G, Takakura AC, Moreira TS, Bayliss DA, et al. Serotonergic neurons activate chemosensitive retrotrapezoid nucleus neurons by a ph-independent mechanism. J Neurosci. 2007;27:14128–38.
5. Teran FA, Massey CA, Richerson GB. Serotonin neurons and central respiratory chemoreception: where are we now? Prog Brain Res. 2014;209:207–33.
6. Terao S, Miura N, Osano Y, Noda A, Sobue G. Rapidly progressive fatal respiratory failure (ondine's curse) in the lateral medullary syndrome. J Stroke Cerebrovasc Dis. 2004;13:41–4.
7. Mendoza M, Latorre JG. Pearls and oy-sters: reversible Ondine's curse in a case of lateral medullary infarction. Neurology. 2013;80:e13–6.
8. Bogousslavsky J, Khurana R, Deruaz JP, Hornung JP, Regli F, Janzer R, et al. Respiratory failure and unilateral caudal brainstem infarction. Ann Neurol. 1990;28:668–73.
9. Guyenet PG, Bayliss DA. Neural control of breathing and CO2 homeostasis. Neuron. 2015;87:946–61.
10. Mathru M, Esch O, Lang J, Herbert ME, Chaljub G, Goodacre B, et al. Magnetic resonance imaging of the upper airway. Effects of propofol anesthesia and nasal continuous positive airway pressure in humans. Anesthesiology. 1996;84:273–9.
11. McKinley WO. Late return of diaphragm function in a ventilator-dependent patient with a high cervical tetraplegia: case report, and interactive review. Spinal Cord. 1996;34:626–9.
12. Hassid VJ, Schinco MA, Tepas JJ, Griffen MM, Murphy TL, Frykberg ER, et al. Definitive establishment of airway control is critical for optimal outcome in lower cervical spinal cord injury. J Trauma. 2008;65:1328–32.
13. Burakgazi AZ, Hoke A. Respiratory muscle weakness in peripheral neuropathies. J Peripher Nerv Syst. 2010;15:307–13.
14. Carr AS, Hoeritzauer AI, Kee R, Kinney M, Campbell J, Hutchinson A, et al. Acute neuromuscular respiratory failure: a population-based study of aetiology and outcome in Northern Ireland. Postgrad Med J. 2014;90:201–4.
15. Derenne JP, Macklem PT, Roussos C. The respiratory muscles: mechanics, control, and pathophysiology. Am Rev Respir Dis. 1978;118:119–33.
16. Hughes RA, Bihari D. Acute neuromuscular respiratory paralysis. J Neurol Neurosurg Psychiatry. 1993;56:334–43.
17. Laghi F, Tobin MJ. Disorders of the respiratory muscles. Am J Respir Crit Care Med. 2003;168:10–48.

18. Derenne JP, Macklem PT, Roussos C. The respiratory muscles: mechanics, control, and pathophysiology. Part 2. Am Rev Respir Dis. 1978;118:373–90.
19. Derenne JP, Macklem PT, Roussos C. The respiratory muscles: mechanics, control, and pathophysiology. Part III. Am Rev Respir Dis. 1978;118:581–601.
20. Loh L, Hughes JM, Davis JN. Gas exchange problems in bilateral diaphragm paralysis. Bull Eur Physiopathol Respir. 1979;15(Suppl):137–43.
21. Kelling JS, DiMarco AF, Gottfried SB, Altose MD. Respiratory responses to ventilatory loading following low cervical spinal cord injury. J Appl Physiol. 1985;1985(59):1752–6.
22. Walterspacher S, Kirchberger A, Lambeck J, Walker DJ, Schworer A, Niesen WD, et al. Respiratory muscle assessment in acute Guillain-Barré syndrome. Lung. 2016;194:821–8.
23. Kramer CL, McCullough M, Wijdicks EF. Teaching video neuroimages: how to unmask respiratory strength confounded by facial diplegia. Neurology. 2015;84:e57–8.
24. Cohen CA, Zagelbaum G, Gross D, Roussos C, Macklem PT. Clinical manifestations of inspiratory muscle fatigue. Am J Med. 1982;73:308–16.
25. Galtrey CM, Faulkner M, Wren DR. How it feels to experience three different causes of respiratory failure. Pract Neurol. 2012;12:49–54.
26. Wijdicks EFM. Short of breath, short of air, short of mechanics. Pract Neurol. 2002;2:208–13.
27. Polio PR. Terror and the immunological worldview. Glob Public Health. 2016:1–22.
28. Sejvar JJ. Clinical manifestations and outcomes of West Nile virus infection. Viruses. 2014;6:606–23.
29. Tso G, Kaldas K, Springer J, Barot N, Kamangar N. West Nile meningoencephalitis presenting as isolated bulbar palsy with hypercapnic respiratory failure: case report and literature review. J Intensive Care Med. 2016;31:285–7.
30. Howard RS, Thorpe J, Barker R, Revesz T, Hirsch N, Miller D, et al. Respiratory insufficiency due to high anterior cervical cord infarction. J Neurol Neurosurg Psychiatry. 1998;64:358–61.
31. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology. 1999;53:1107–14.
32. Cabrera Serrano M, Rabinstein AA. Causes and outcomes of acute neuromuscular respiratory failure. Arch Neurol. 2010;67:1089–94.
33. Thomas CE, Mayer SA, Gungor Y, Swarup R, Webster EA, Chang I, et al. Myasthenic crisis: clinical features, mortality, complications, and risk factors for prolonged intubation. Neurology. 1997;48:1253–60.
34. Alshekhlee A, Miles JD, Katirji B, Preston DC, Kaminski HJ. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in us hospitals. Neurology. 2009;72:1548–54.
35. Cao-Lormeau VM, Blake A, Mons S, Lastere S, Roche C, Vanhomwegen J, et al. Guillain-Barré syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. Lancet. 2016;387:1531–9.
36. Parra B, Lizarazo J, Jimenez-Arango JA, Zea-Vera AF, Gonzalez-Manrique G, Vargas J, et al. Guillain-Barré syndrome associated with Zika virus infection in Colombia. N Engl J Med. 2016;375:1513–23.
37. Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. Lancet Neurol 2020;S1474-4422(20)30221–0.
38. Ahmed R, McNamara S, Gandevia S, Halmagyi GM. Paradoxical abdominal wall movement in bilateral diaphragmatic paralysis. Pract Neurol. 2012;12:184–6.
39. Gokcen HB, Erdogan S, Kara K, Ersozlu S, Ozturk C. Bilateral diaphragm paralysis due to phrenic nerve palsy after two-level cervical corpectomy. Spine J. 2016;16:e431–2.
40. Jinnur P, Lim KG. Severe acute orthopnea: Ipilimumab-induced bilateral phrenic nerve neuropathy. Lung. 2015;193:611–3.
41. John S, Tavee J. Bilateral diaphragmatic paralysis due to cervical chiropractic manipulation. Neurologist. 2015;19:65–7.
42. Jiménez Caballero PE, Fermin Marrero JA, Trigo Bragado I, Casado NI. Vocal cord paralysis as a manifestation of myasthenia gravis with anti-MuSK antibodies. Neurologia. 2014;29(4):253–4.

43. Hara K, Mashima T, Matsuda A, et al. Vocal cord paralysis in myasthenia gravis with anti-MuSK antibodies. Neurology. 2007;68:621–2.
44. Tobin MJ, Laghi F, Jubran A. Narrative review: ventilator-induced respiratory muscle weakness. Ann Intern Med. 2010;153:240–5.
45. Cherington M. Clinical spectrum of botulism. Muscle Nerve. 1998;21:701–10.
46. Woldeamanuel YW, Andemeskel AT, Kyei K, Woldeamanuel MW, Woldeamanuel W. Case fatality of adult tetanus in africa: systematic review and meta-analysis. J Neurol Sci. 2016;368:292–9.
47. Hulse EJ, Davies JO, Simpson AJ, Sciuto AM, Eddleston M. Respiratory complications of organophosphorus nerve agent and insecticide poisoning. Implications for respiratory and critical care. Am J Respir Crit Care Med. 2014;190:1342–54.
48. Fromageot C, Lofaso F, Annane D, Falaize L, Lejaille M, Clair B, et al. Supine fall in lung volumes in the assessment of diaphragmatic weakness in neuromuscular disorders. Arch Phys Med Rehabil. 2001;82:123–8.
49. Newsom-Davis J. The respiratory system in muscular dystrophy. Br Med Bull. 1980;36:135–8.
50. Poppe M, Bourke J, Eagle M, Frosk P, Wrogemann K, Greenberg C, et al. Cardiac and respiratory failure in limb-girdle muscular dystrophy 2i. Ann Neurol. 2004;56:738–41.
51. Santos DB, Boussaid G, Stojkovic T, Orlikowski D, Letilly N, Behin A, et al. Respiratory muscle dysfunction in facioscapulohumeral muscular dystrophy. Neuromuscul Disord. 2015;25:632–9.
52. Shahrizaila N, Kinnear WJ, Wills AJ. Respiratory involvement in inherited primary muscle conditions. J Neurol Neurosurg Psychiatry. 2006;77:1108–15.
53. Palmio J, Evilä A, Chapon F, et al. Hereditary myopathy with early respiratory failure: occurrence in various populations. J Neurol Neurosurg Psychiatry. 2014;85:345–53.
54. Bradley MD, Orrell RW, Clarke J, et al. Outcome of ventilatory support for acute respiratory failure in motor neurone disease. J Neurol Neurosurg Psychiatry. 2002;72:752–6.
55. Lechtzin N, Wiener CM, Clawson L, Chaudhry V, Diette GB. Hospitalization in amyotrophic lateral sclerosis: causes, costs, and outcomes. Neurology. 2001;56:753–7.
56. Pisa FE, Logroscino G, Giacomelli Battiston P, Barbone F. Hospitalizations due to respiratory failure in patients with amyotrophic lateral sclerosis and their impact on survival: a population-based cohort study. BMC Pulm Med. 2016;16:136.
57. Sperfeld AD, Hanemann CO, Ludolph AC, Kassubek J. Laryngospasm: an underdiagnosed symptom of X-linked spinobulbar muscular atrophy. Neurology. 2005;64(4):753–4.
58. Boon AJ, O'Gorman C. Ultrasound in the assessment of respiration. J Clin Neurophysiol. 2016;33:112–9.
59. Gechev A, Kane NM, Koltzenburg M, Rao DG, van der Star R. Potential risks of iatrogenic complications of nerve conduction studies (NCS) and electromyography (EMG). Clin Neurophysiol Pract. 2016;1:62–6.
60. Sun QW, Li XC, Lin ZM, et al. Assessment of respiratory drive with esophageal diaphragmatic electromyography in patients with acute respiratory distress syndrome treated with prone position ventilation. J Thorac Dis. 2019;11:4188–96.
61. Schmidt M, Kindler F, Cecchini J, et al. Neurally adjusted ventilatory assist and proportional assist ventilation both improve patient-ventilator interaction. Crit Care. 2015;19:56.
62. Johnson NE, Utz M, Patrick E, Rheinwald N, Downs M, Dilek N, et al. Visualization of the diaphragm muscle with ultrasound improves diagnostic accuracy of phrenic nerve conduction studies. Muscle Nerve. 2014;49:669–75.
63. Boon AJ, Alsharif KI, Harper CM, Smith J. Ultrasound-guided needle EMG of the diaphragm: technique description and case report. Muscle Nerve. 2008;38:1623–6.
64. Boon AJ, Harper CJ, Ghahfarokhi LS, Strommen JA, Watson JC, Sorenson EJ. Two-dimensional ultrasound imaging of the diaphragm: quantitative values in normal subjects. Muscle Nerve. 2013;47:884–9.

65. Mogalle K, Perez-Rovira A, Ciet P, Wens SC, van Doorn PA, Tiddens HA, et al. Quantification of diaphragm mechanics in Pompe disease using dynamic 3d MRI. PLoS One. 2016;11:e0158912.
66. Wens SC, Ciet P, Perez-Rovira A, Logie K, Salamon E, Wielopolski P, et al. Lung MRI and impairment of diaphragmatic function in Pompe disease. BMC Pulm Med. 2015;15:54.
67. Barnard AM, Lott DJ, Batra A, et al. Imaging respiratory muscle quality and function in Duchenne muscular dystrophy. J Neurol. 2019;266(11):2752–63.
68. Mankodi A, Kovacs W, Norato G, et al. Respiratory magnetic resonance imaging biomarkers in Duchenne muscular dystrophy. Ann Clin Transl Neurol. 2017;4:655–62. Published 28 Jul 2017.
69. Gay PC, Edmonds LC. Severe hypercapnia after low-flow oxygen therapy in patients with neuromuscular disease and diaphragmatic dysfunction. Mayo Clin Proc. 1995;70:327–30.
70. O'Driscoll BR, Howard LS, Davison AG, British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. Thorax. 2008;63(Suppl 6):vi1–68.
71. Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med. 2015;372:2185–96.
72. Lawn ND, Fletcher DD, Henderson RD, Wolter TD, Wijdicks EF. Anticipating mechanical ventilation in guillain-barre syndrome. Arch Neurol. 2001;58:893–8.
73. Sharshar T, Chevret S, Bourdain F, Raphael JC. French cooperative group on plasma exchange in Guillain-Barre S. early predictors of mechanical ventilation in Guillain-Barré syndrome. Crit Care Med. 2003;31:278–83.
74. Walgaard C, Lingsma HF, Ruts L, Drenthen J, van Koningsveld R, Garssen MJ, et al. Prediction of respiratory insufficiency in Guillain-Barré syndrome. Ann Neurol. 2010;67:781–7.
75. Penttila J, Syvalahti E, Hinkka S, Kuusela T, Scheinin H. The effects of amitriptyline, citalopram and reboxetine on autonomic nervous system. A randomised placebo-controlled study on healthy volunteers. Psychopharmacology (Berl). 2001;154:343–9.
76. Wenninger S, Stahl K, Wirner C, et al. Utility of maximum inspiratory and expiratory pressures as a screening method for respiratory insufficiency in slowly progressive neuromuscular disorders. Neuromuscul Disord. 2020;30:640–8.
77. Mehta S, Hill NS. Noninvasive ventilation. Am J Respir Crit Care Med. 2001;163:540–77.
78. Tanaka J, Yugue I, Shiba K, Maeyama A, Naito M. A study of risk factors for tracheostomy in patients with a cervical spinal cord injury. Spine (Phila Pa 1976). 2016;41:764–71.
79. Yugue I, Okada S, Ueta T, Maeda T, Mori E, Kawano O, et al. Analysis of the risk factors for tracheostomy in traumatic cervical spinal cord injury. Spine. 2012;37:E1633–8.
80. Siempos II, Ntaidou TK, Filippidis FT, Choi AM. Effect of early versus late or no tracheostomy on mortality and pneumonia of critically ill patients receiving mechanical ventilation: a systematic review and meta-analysis. Lancet Respir Med. 2015;3:150–8.
81. Walgaard C, Lingsma HF, van Doorn PA, van der Jagt M, Steyerberg EW, Jacobs BC. Tracheostomy or not: prediction of prolonged mechanical ventilation in Guillain-Barré syndrome. Neurocrit Care. 2017;26:6–13.
82. Fairley JW, Hughes M. Acute stridor due to bilateral vocal fold paralysis as a presenting sign of myasthenia gravis. J Laryngol Otol. 1992;106:737–8.
83. Khan MK, Powell SM, Hartley C, Cleland P. Myasthenia gravis presenting as acute vocal cord paresis. BMJ Case Rep. 2010;2010:bcr10.2009.2371.
84. Oo T, Watt JW, Soni BM, Sett PK. Delayed diaphragm recovery in 12 patients after high cervical spinal cord injury. A retrospective review of the diaphragm status of 107 patients ventilated after acute spinal cord injury. Spinal Cord. 1999;37:117–22.
85. Brown R, DiMarco AF, Hoit JD, Garshick E. Respiratory dysfunction and management in spinal cord injury. Respir Care. 2006;51:853–68. discussion 869–70
86. Kaufman MR, Elkwood AI, Aboharb F, Cece J, Brown D, Rezzadeh K, et al. Diaphragmatic reinnervation in ventilator-dependent patients with cervical spinal cord injury and concomitant

phrenic nerve lesions using simultaneous nerve transfers and implantable neurostimulators. J Reconstr Microsurg. 2015;31:391–5.
87. Posluszny JA Jr, Onders R, Kerwin AJ, Weinstein MS, Stein DM, Knight J, et al. Multicenter review of diaphragm pacing in spinal cord injury: successful not only in weaning from ventilators but also in bridging to independent respiration. J Trauma Acute Care Surg. 2014;76:303–9. discussion 309–10
88. Pittock SJ, Rodriguez M, Wijdicks EF. Rapid weaning from mechanical ventilator in acute cervical cord multiple sclerosis lesion after steroids. Anesth Analg. 2001;93:1550–1.
89. Fletcher DD, Lawn ND, Wolter TD, Wijdicks EF. Long-term outcome in patients with Guillain-Barré syndrome requiring mechanical ventilation. Neurology. 2000;54:2311–5.
90. Henderson RD, Lawn ND, Fletcher DD, McClelland RL, Wijdicks EF. The morbidity of Guillain-Barré syndrome admitted to the intensive care unit. Neurology. 2003;60:17–21.
91. Lawn ND, Wijdicks EF. Post-intubation pulmonary function test in Guillain-Barré syndrome. Muscle Nerve. 2000;23:613–6.
92. Seneviratne J, Mandrekar J, Wijdicks EF, Rabinstein AA. Predictors of extubation failure in myasthenic crisis. Arch Neurol. 2008;65:929–33.
93. Rabinstein AA, Mueller-Kronast N. Risk of extubation failure in patients with myasthenic crisis. Neurocrit Care. 2005;3:213–5.
94. Rialp G, Raurich JM, Llompart-Pou JA, Ayestaran I, Ibanez J. Central respiratory drive in patients with neuromuscular diseases. Respir Care. 2013;58:450–7.
95. Sklar MC, Burns K, Rittayamai N, Lanys A, Rauseo M, Chen L, et al. Effort to breathe with various spontaneous breathing trial techniques. A physiological meta-analysis. Am J Respir Crit Care Med. 2017;195:1477–85.

Chapter 4
Management of Respiratory Emergencies in Chronic Neuromuscular Disease

Michael A. Gaytant and Peter J. Wijkstra

Introduction

Neuromuscular disease (NMD) can affect all major respiratory muscles, ultimately leading to respiratory failure. This is the most common cause of morbidity and mortality in patients with chronic NMD [1–3]. When these patients develop chronic respiratory failure, long-term mechanical ventilation (MV) is the main therapeutic intervention to support their respiratory muscle function, increasing life expectancy and health-related quality of life [4–7].

There are four components that may contribute to the occurrence of respiratory failure [1]:

1. Due to weakness of the facial, oropharyngeal, and laryngeal muscles, the upper airways can be compromised and thus interfere with swallowing and secretion clearance, which can lead to aspiration. Weakness of these muscles can also result in mechanical obstruction of the upper airway, particularly in the supine position.
2. Weakness of the muscles of inspiration (the diaphragm, intercostals, and accessory muscles) may lead to inadequate lung expansion, which can result in microatelectasis. This results in ventilation/perfusion mismatch, and subsequently to hypoxemia and compensatory tachypnea, with small tidal volumes, which in

M. A. Gaytant (✉)
Department of Pulmonary Diseases and Home Mechanical Ventilation, University Medical Center Utrecht, Utrecht, the Netherlands
e-mail: m.a.gaytant@umcutrecht.nl

P. J. Wijkstra
Department of Pulmonary Diseases and Home Mechanical Ventilation, University Medical Center Groningen, Groningen, the Netherlands
e-mail: p.j.wijkstra@umcg.nl

M. Damian, M. de Visser (eds.), *Emergencies in Neuromuscular Disorders*,
https://doi.org/10.1007/978-3-030-91932-0_4

turn will exacerbate the atelectasis. This reduces the compliance of the respiratory system and increases the mechanical load on already weak respiratory muscles.
3. Due to weakness of the expiratory muscles, cough and secretion clearance will be inadequate, resulting in an increasing risk of aspiration and pneumonia.
4. Complications like pneumonia may further increase the ventilator demands on an already failing respiratory system.

We can distinguish NMD with rapidly progressive muscle weakness and those that manifest with slowly progressive muscle weakness. The former are represented, among others, by amyotrophic lateral sclerosis (ALS) and spinal muscular atrophies (SMA) (see Chap. 6). We will not address myasthenic syndromes since that will be dealt with in Chap. 9. Relatively rapid progression of limb muscle weakness is observed in Duchenne muscular dystrophy (DMD), leading to loss of ambulation during or before adolescence with subsequent involvement of the respiratory muscles. Until the introduction of assisted ventilation, most patients died between 15 and 20 years of age from respiratory failure. Life span has increased by at least 10 years since the introduction of ventilatory support [5, 6].

In other myopathies, such as Becker muscular dystrophy, facioscapulohumeral muscular dystrophy, limb-girdle muscular dystrophies, and myotonic dystrophy type 1, there is a slowly progressive reduction in respiratory muscular function.

The patients initially suffer from nocturnal respiratory failure and recurrent respiratory infections. Due to progression of their disease, this results in daytime hypercapnia and eventually leads to death [5, 6, 8]. Long-term MV delivered either invasively or noninvasively [noninvasive positive pressure ventilation (NIPPV)] is the main therapeutic intervention to support these patients in their respiratory muscle function and increase life expectancy and health-related quality of life.

However, these patients are at high risk of developing acute exacerbations of respiratory failure. This chapter will focus on acute-on-chronic respiratory failure in patients with chronic neuromuscular disease (Table 4.1), further illustrated by two case vignettes.

Table 4.1 Neuromuscular diseases affecting respiratory function

1. *Motor neuron diseases*
• Amyotrophic lateral sclerosis (ALS)
• Poliomyelitis, post-polio syndrome
• Spinal muscular atrophy (SMA)
• Spinobulbar muscular atrophy (Kennedy disease)
2. *Peripheral neuropathies*
• Guillain–Barré syndrome
• Chronic inflammatory demyelinating polyneuropathy (CIDP)
• Hereditary motor and sensory neuropathies (HMSN)
3. *Disorders of neuromuscular junction*
• Myasthenia gravis
• Congenital myasthenic syndromes

Table 4.1 (continued)

4. *Myopathies*
• Idiopathic inflammatory myopathies (IIM), particularly immune-mediated necrotizing myopathy, and IIM associated with interstitial lung disease, such as anti-MDA5-associated dermatomyositis and anti-synthetase syndrome
• Muscular dystrophies, e.g., Duchenne and Becker muscular dystrophy, facioscapulohumeral muscular dystrophy, limb-girdle muscular dystrophies, distal myopathies, and myotonic dystrophy type 1
• Congenital myopathies, e.g., central core disease, myotubular myopathy, nemaline myopathy
• Congenital muscular dystrophies (CMD), e.g., Ullrich's congenital muscular dystrophy (CMD), merosin-deficient CMD, alpha-dystroglycanopathies
• Metabolic myopathies, e.g., mitochondrial myopathies and Pompe disease
• Myofibrillar myopathies

Respiratory Muscle Weakness Due to Neuromuscular Disease

Respiratory muscle weakness due to neuromuscular disease may include weakness of the inspiratory, expiratory, and upper airway muscles. This can lead to insufficient ventilation and ineffective cough.

Insufficient Ventilation

The principal cause of insufficient ventilation is weakness of the inspiratory muscles: diaphragm, external intercostals, scaleni, sternocleidomastoids, and trapezii. Due to progressive weakness of the inspiratory muscles and increasing elastic load by reduced lung and thorax compliance, the vital capacity (VC) will decline progressively and work of breathing will increase. The consequence is decruitment of alveolar units and formation of micro-atelectasis causing ventilation/perfusion mismatch, leading to hypoxemia [9–13]. Due to the decrease in tidal volume, respiratory frequency will increase in an effort to compensate for the diminished tidal volume and maintain alveolar ventilation. Eventually, the tidal volume may fall to such a degree that increased respiratory rate is insufficient to maintain alveolar ventilation, resulting in alveolar hypoventilation, leading to hypercapnia [14].

Bulbar Dysfunction

Bulbar dysfunction is due to weakness of the facial, oropharyngeal, and laryngeal muscles (bulbar muscles). This weakness can affect the ability to speak, swallow, and clear airway secretions, leading to an increased risk of aspiration [14]. In

addition, NMD may also be associated with obstructive or central sleep-disordered breathing, particularly during rapid eye movement sleep (REM), which may result in severe alveolar hypoventilation, leading to sustained oxygen desaturation and hypercapnia [15, 16].

Patients with NMD usually experience mild to moderate bulbar dysfunction, but in some it can be severe, for example, ALS (especially, the bulbar palsy variant), SMA types 1 and 2, Kennedy syndrome (spinobulbar muscular atrophy), Guillain–Barré syndrome, myasthenia gravis and congenital myasthenic syndromes, oculopharyngeal muscular dystrophy, various congenital myopathies, and some idiopathic inflammatory myopathies.

Ineffective Cough

An effective cough consists of three sequential phases [17]:

- Inspiratory phase consisting of a rapid and large tidal volume inspiration. The increased lung volume lengthens the expiratory muscles, allowing them to generate more positive intrathoracic pressure and greater expiratory flow during the subsequent phases.
- Compressive phase: Glottic closure (by the upper airway adductor muscles) occurs at the onset of active expiratory muscle contraction. This results in a dramatic increase in positive intrathoracic pressure (up to 300 cm H_2O).
- Expiratory phase: The glottis opens after approximately 0.2 s. This allows for high peak expiratory flow (approximately 12 L/s) due to the sudden release of pressurized gas and dynamic airway compression. The high gas velocity in the compressed airways creates a shearing force that dislodges mucus adhering to airway walls.

An effective cough requires all three phases to generate sufficient intrathoracic pressures and obtain high peak expiratory flows [18]. An ineffective cough is most often due to expiratory muscle weakness combined with inadequate lung inflation that prevents effective coughing and airway clearance, altering airway resistance and increasing the risk of developing atelectasis and pneumonia [18, 19]. An ineffective cough can also occur due to isolated vocal cord palsy, compounding aspiration.

Evaluation

Patients with neuromuscular disease who are at risk of developing respiratory insufficiency, including those in whom there are no overt clinical signs of respiratory failure, should undergo objective physiological testing to confirm respiratory muscle weakness, and thus identify patients who need ventilatory support, and also those with ineffective cough.

Respiratory Muscle Weakness

Respiratory muscle strength can be assessed noninvasively by measuring the maximal inspiratory pressure (MIP or PImax), maximal expiratory pressure (MEP or PEmax), and maximal sniff nasal inspiratory pressure (SNIP). SNIP is also a noninvasive test of inspiratory muscle strength but without using a mouthpiece (see video https://youtu.be/9bQgY2ZaiLk). So, this is particularly helpful for patients who have facial weakness [20, 21].

MIP and SNIP reflect the strength of the diaphragm and other inspiratory muscles, while MEP reflects the strength of the abdominal muscles and other expiratory muscles.

These tests are simple and quick, and high adequate values can exclude clinically significant weakness of the respiratory muscles. They do, however, require technical expertise and experience to be reliable, especially in the presence of orofacial weakness or reduced patient effort. For example, a normal MIP and/or SNIP reliably excludes inspiratory muscle weakness, but a low MIP can be caused by submaximal patient effort or poor technique. When a low MIP is recorded, the additional measurement of SNIP is helpful to confirm suspected weakness.

The combination of MIP, SNIP, and MEP measurements can localize respiratory muscle weakness. A low MIP and SNIP but a normal MEP suggest isolated inspiratory muscle weakness (usually diaphragmatic), while a low MIP, SNIP, and MEP suggest generalized skeletal muscle weakness. To increase diagnostic accuracy for inspiratory muscle weakness, it is advised to perform multiple tests [22].

MIP values of less than −70 cm H_2O for women and −80 cm H_2O for men practically tend to exclude clinically relevant inspiratory muscle weakness [20]. A MIP below one-third of normal predicts hypercapnic respiratory failure [23].

A SNIP of 35% of normal very likely predicts ventilatory failure in ALS and a MEP less than 60 cm H_2O predicts a weak cough with difficulty clearing secretions [23–26].

The vital capacity [VC, or in some studies slow vital capacity (SVC)] and the forced vital capacity (FVC) are alternatives to MIP and MEP. VC and FVC are the maximum volumes of gas that can be expelled from full inspiration. The difference between the two measurements is that FVC is measured when the patient is exhaling with maximal speed and effort. Therefore, the results of FVC are directly related to the degree of obstruction and affected by coexisting obstructive airway disease.

Diaphragmatic Function

The diaphragm is the main respiratory muscle during inspiration and accounts for 70% of the inspired air volume during regular breathing [27]. In patients with NMD, diaphragmatic function is often impaired, leading to a restrictive respiratory pattern [28]. There are several techniques that can analyze the function of the diaphragm

like fluoroscopy and chest X-ray, which are nonspecific and expose the patient to ionizing radiation [29].

The change in vital capacity from the seated to supine position can be used to screen for diaphragmatic dysfunction. In case of restrictive respiratory disease, VC will be worse in the supine position. Measuring the percent change in VC when moving from the seated to supine position has been adopted as a screening test for diaphragmatic dysfunction. Diaphragmatic weakness is suggested by a decrease in the supine VC of more than 10%. Unilateral diaphragmatic paralysis is usually associated with a decrease in VC of 15–25%, and in bilateral diaphragmatic paralysis there is a decrease in supine VC of approximately 50% [30–32].

However, some patients are unable to tolerate the supine position. The ratio of MEP to MIP (MEP/MIP) has similar sensitivity and specificity in predicting isolated diaphragmatic weakness to the change in VC in going from the upright to supine position. This ratio may be useful in patients who cannot tolerate the supine position [33].

The reference exam for determining diaphragmatic function still is transdiaphragmatic pressure measurement, but this method is invasive and technically challenging [34]. Assessment of the phrenic nerve conduction is another option but requires some expertise. Another test to assess the inspiratory muscle function is measurement of diaphragmatic thickness by ultrasound. This is a noninvasive, radiation-free, accurate, reproducible, and safe assessment of diaphragmatic anatomy and function [33–35].

Cough Assessment

An ineffective cough can lead to aspiration, retention of secretions, pneumonia, and respiratory failure [36]. Ineffective cough can be identified by several tests.

Peak cough flow (PCF) is measured by the highest cough flow obtained after instructing the patient to inspire fully by taking a deep breath and cough forcibly through a mask or mouthpiece attached to a peak flow meter [37].

A PCF of <270 L/min is associated with higher risk for acute respiratory failure and higher respiratory morbidity in case of a respiratory tract infection. If PCF is <160 L/min, cough is ineffective and respiratory infections are likely, especially in those with bulbar weakness. The assessment of the MEP can also give an indication of the cough strength. A MEP less than 60 cm H_2O suggests an ineffective cough [38, 39].

Symptoms and Signs of Respiratory Failure

The reduction in inspiratory and expiratory muscle strength leads to chronic respiratory failure, as well as potentially life-threatening problems. The related symptoms will be increasing generalized weakness, dysphagia, dyspnea on exertion and at

rest, fatigue, and daytime sleepiness. Clinical signs of respiratory failure are rapid shallow breathing, tachycardia, a weak cough, use of accessory muscles, abdominal paradox, orthopnea, single-breath count and staccato speech, and cough after swallowing [8].

Regular assessment for clinical signs of respiratory muscle fatigue and objective monitoring of VC, MIP, and MEP are essential to determine the appropriate timing of starting mechanical ventilation.

Management of Acute Respiratory Failure

The timely identification of patients who have a high risk of respiratory failure is crucial and requires timely provision of inspiratory and expiratory aids as early as needed to prevent acute respiratory failure. In this part, we will elaborate on what to do if acute respiratory failure (ARF) develops. Firstly, we will focus on the inspiratory aids, both noninvasive and invasive mechanical ventilation, and secondly on expiratory aids like air stacking and coughing machine.

Mechanical Ventilation

In case of ARF, it has been suggested that mechanical ventilation should be considered if the patients show one of the following symptoms/signs: (1) dyspnea, (2) lethargy, or (3) acute respiratory acidosis (pH < 7.35 and $PaCO_2$ > 45 mmHg) [40]. It is preferred to start with noninvasive positive pressure ventilation (NIPPV); however, if patients are already using nocturnal NIPPV, it may be extended to daytime as well (24 h if needed). Of note, if NIPPV is indicated, it should be initiated as soon as possible. Delays in NIPPV implementation result in deterioration and increase the likelihood of NIPPV failure [41]. In most situations, NIPPV is initiated in the emergency department or the intensive care unit (Case Vignette 1), a specialized respiratory or high-dependency unit, but can also successfully be used in the general ward setting. However, knowledge and experience in NIPPV by an experienced staff is critical to its success. The presence of bedside experts who can provide comfortable interfaces with minimal air leaks, choose the appropriate initial settings, and give the support to patients who are in distress is crucial.

Case Vignette 1

A 73-year-old former professional soccer player had undiagnosed progressive muscle weakness for a few months, before his admission to ICU because of respiratory insufficiency ($PaCO_2$ 70 mmHg). The months before admission he had complained about progressive loss of muscle strength, initially in his

hands and arms. In the weeks before admission, he had difficulty climbing stairs, disturbed night rest due to orthopnea, and sleepiness during daytime. In the days before admission, he suffered from dyspnea on exertion and at rest. At that moment, he did not have swallowing problems.

He was diagnosed with ALS on the basis of diaphragmatic weakness and signs of involvement of the lower motor neuron on EMG. Severe respiratory insufficiency (pCO_2 77 mmHg; pH 7.36; pO_2 55 mmHg; actual bicarbonate 37.4 mmol/L; base excess 11.9 mmol/L) urged the initiation of noninvasive ventilation. Due to increasing $PaCO_2$ levels (up to 102 mmHg), noninvasive ventilation (NIV) failed and led to intubation. His wish was to continue the ventilation, and therefore, he was tracheotomized.

One month later, a PEG was placed because of severe swallowing problems and aspiration. Because his home situation did not allow management of invasive ventilation, he was transferred to a nursing home with ventilation facilities.

He died 2 years later.

Learning Points

Acute-on-chronic respiratory failure is an important indication of NIPPV. Since bulbar symptoms were absent, in this case NIPPV was initiated instead of initial intubation. However, NIPPV failed and the patient had to be intubated. Because of progressive bulbar problems, tracheostomy was eventually unavoidable.

The other learning point is the awareness that in 10% of the cases respiratory failure may be the first symptom of a motor neuron disease.

Interfaces

NIPPV during ARF can be delivered through several types of interfaces, and the most common are the following:

Oronasal mask—It includes the nose and mouth and is most commonly used in patients with acute respiratory failure.

Nasal mask—Just covering the nose and may be an alternative for those who do not tolerate an oronasal mask. However, the downside is that a large air leak through the mouth might occur and that a chin strap is necessary.

Total face mask—It includes the eyes, nose, and mouth. Although this mask is superior in terms of maximizing the NIPPV delivered and minimizing air leaks, it is often poorly tolerated.

Helmet—The advantage is that it allows patients to talk, read, and drink through a straw, while minimizing complications such as skin necrosis, gastric distension, and eye irritation.

Mouthpiece—This device can be inserted into the mouth and is commonly used in patients who need 24 h NIPPV; it can be used as an alternative to a face mask.

NIPPV: Initial Settings and Practical Aspects

The selection of initial settings depends upon the specific mode, resource availability, clinician and staff expertise, and patient tolerance. Next to mask fitting, success of NIPPV depends on the adjustment of settings and mode to ensure patient comfort and tolerance. If the experienced staff takes the time at bedside to provide patient education and reassurance during the initial trial of NIPPV, it adds to the success. In most situations, one can start with pressure support mode in the spontaneous/timed (S/T) setting with a low backup rate of around 10 breaths/minute. In this setting, all breaths are supported and an escape of a minimum respiratory rate is provided if the patients are not breathing themselves. The inspiratory positive airway pressure (IPAP) may be titrated upward as tolerated, usually in increments of 2 cm H_2O. Close attention needs to be paid during titration aimed at less dyspnea, a decrease in respiratory rate, an increased tidal volume, and good patient–ventilator synchrony. If an adequate tidal volume is provided, this will reduce the labor of breathing and will increase the alveolar ventilation, leading to a reduction of hypercapnia.

Depending on the airway obstruction, especially in patients with ALS, expiratory positive airway pressure has to be provided as well. While one may start with an expiratory positive airway pressure (EPAP) of 5 cm H_2O, it is sometimes necessary to increase it to 10 cm H_2O. However, one has to take into account that if the IPAP remains the same the delivered tidal volume will be reduced.

In case of a low saturation, it is tempting to add oxygen; however, in NMD patients, low saturation is often the result of retention of secretions. In that case, coughing techniques like air stacking or the use of cough machines are far more effective.

However, one should be careful to apply NIPPV in patients having swallowing difficulty and uncontrollable secretions despite expiratory aids. In these patients, invasive ventilation might be the first choice. In a recent systematic review aimed at comparing the efficacy of noninvasive ventilation with invasive ventilation with survival as primary outcome, however, not one single randomized trial was found [42]. Despite the fact that no RCTs are available, two studies are interesting in this respect.

Vianello et al. performed a prospective analysis of short-term outcomes of 14 patients with ARF receiving NIPPV and compared this with 14 matched historical controls receiving ventilator support via endotracheal intubation (ETI) [40]. Seven

patients who were ventilated noninvasively also had a cricothyroid mini-tracheostomy (CM) as they were unable to clear bronchial secretions. The authors found a lower intrahospital mortality and less treatment failure in the NIPPV group compared to the ETI group (2 vs. 8 and 4 vs. 11 patients, respectively). The duration in the ICU was also shorter in the NIPPV group (14 vs. 48 days). The mini-tracheostomy was well tolerated, and no significant side effects were noted. While these results support the extended use of NIPPV in combination with CM in ARF, some factors are limiting its use. Due to the inability to protect the upper airway, two patients had to be excluded from NIPPV. In addition, seven patients needed a cricothyroid mini-tracheostomy because secretions could not be cleared effectively. As dysphagia is a common problem in these patients, one has to check this before one starts with NIPPV.

A Japanese study also showed some limitations in applying NIPPV in ARF [43]. They studied 27 NMD patients who initially received NIPPV to manage end-stage ARF. After 24 h, all but one (ALS) received NIPPV. After 3 days, five patients had to switch from NIPPV to invasive ventilation, and this concerned a higher proportion of patients with ALS. Therefore, the authors concluded that patients with ALS have to be monitored intensively to determine when NIPPV is not sufficient anymore.

Air Stacking and Mechanical In- and Exsufflation

Overall, the common thought is that NIPPV is the first choice of treatment of acute-on-chronic respiratory failure in patients with a neuromuscular disease. However, NIPPV as the sole ventilatory support is mostly not enough and coughing techniques must be added as sputum mobilization is crucial in these patients [44]. In an excellent overview article, Chatwin et al. presented all available airway clearance techniques [45]. Air stacking (AS) and mechanical insufflation and exsufflation (M I-E) are the most used techniques that will be discussed in more detail.

Air stacking increases inspiratory capacity by providing a series of breaths in without the patient breathing out in between. Mostly it starts by instructing the patient to take a deep breath, and then the inspiratory capacity is augmented by a series of breaths supported by a one-way valve bag without breathing out until they are full with air. Once the patient is close to their total lung capacity, they are instructed to cough combined with manual assisted compression (MAC) of the chest or abdomen. In the chronic situation, it is suggested to start with air stacking if the PCF is <270 L/min and/or FVC < 50% of predicted as this is considered the lower limit for effective secretion mobilization in patients older than 12 years [45]. Air stacking with MAC will lead to an increase in the PCF, which will improve the mobilization of sputum. If patients are experienced in applying air stacking every day in the chronic situation, it can easily be used in the acute situation in case more

sputum is produced. Ishikawa et al. found that the combination of MAC and air stacking is significantly more effective than air stacking alone [46]. In a study of 28 DMD patients, mean PCFs at baseline, with chest compression, after air stacking and with the use of the combined technique were 171 ± 67, 231 ± 81, 225 ± 80, and 292 ± 86 L/min, respectively. This shows that a combination of techniques might be more effective in sputum mobilization. Regarding efficacy, air stacking only increases the lung volume by recruiting more lung areas. By contrast, the MI-E generates a deep insufflation by positive pressure (+ 30 to +40 cm H_2O), followed immediately by a forced exsufflation with a deep expiratory pressure (−30 to −40 cm H_2O). The MI-E can be applied via a full-face mask or via the endotracheal or tracheostomy tube with the cuff inflated. It has been shown that the cough flow rates generated by the MI-E are much higher than those generated by manual coughing techniques [47]. Especially in cases of acute respiratory failure and too much sputum, air stacking might not generate enough power to mobilize the sputum and MI-E is much more effective (Case Vignette 2).

Case Vignette 2

A 22-year-old man with Duchenne muscular dystrophy was presented at the ER with difficulty coughing and dyspnea. Since 2 days, he had fever (39º C) and the GP already started with antibiotics the day before presentation. History-taking disclosed that at that time he needed his noninvasive ventilation continuously, while he normally used this only during the night. Auscultation of the lungs revealed in- and expiratory rhonchi, and the X-ray showed an infiltrate in the left lower lobe. Blood testing showed high CRP and leukocytosis, and the blood gas, while using the ventilator, showed a normal $PaCO_2$ but a low saturation (85%). He was admitted to the hospital with a diagnosis of pneumonia with sputum retention due to impaired muscle strength because of his muscle disease. Antibiotics were continued, and the physical therapist started with mechanical insufflation and exsufflation (M I-E) to mobilize the sputum as air stacking was not effective. We started with an inspiratory pressure of +20 H_2O and an expiratory pressure of −20 cm H_2O, and this procedure was repeated every 3 h. Gradually the pressures could be increased to +40 and −40 and the sputum could be mobilized effectively. After 2 days, the patient improved, the quantity of the sputum decreased, and the number of hours on NIPPV could be reduced to 12 h/day. The frequency of the M I-E could be reduced to 3 times a day and air stacking could be reintroduced. After 5 days, we stopped the coughing machine and air stacking was performed three times a day, just like before admission. After 7 days, the patient could leave the hospital, using the ventilator only during the night, while air stacking was continued three times a day.

Learning Points
Patients with NMD who are already using nocturnal NIV and develop acute respiratory failure with sputum retention can be effectively treated with MI-E combined with increasing the number of hours on NIV. In this way, invasive ventilatory support at the ICU can be prevented.

Vianello et al. investigated the combined effect of MI-E and conventional chest physical treatments in 11 neuromuscular disease patients with respiratory tract infections and mucus encumbrance and compared this with chest physical treatment alone in 16 patients [48]. Treatment failure defined as mini-tracheostomy was significantly lower in the MI-E group compared to conventional treatment alone (2/11 vs. 10/16 cases). Bronchoscopy should only be considered in patients with persistent atelectasis if all noninvasive coughing techniques have been shown to be unsuccessful.

Conclusion

This chapter provides important information about what to do in case of acute respiratory failure in patients with chronic neuromuscular disease. As especially their ventilatory capacity is limited, one should not only focus on oxygenation but also on ventilation, that is, CO_2 assessment. Sometimes ventilatory support has to be started, and if patients are already on chronic NIPPV, this must be continued after adjustments to the settings. As impaired sputum mobilization is the other main problem of these patients, airway clearance techniques have to be started immediately as well. It is obvious that both therapies are equally important as both reduce work of breathing leading to less dyspnea, being very important for their quality of life.

Self Assessment Questions

1. Which factor mainly exacerbates atelectasis in neuromuscular diseases? Weakness of …

   (a) Bulbar musculature
   (b) Inspiration muscles (*)
   (c) Expiratory muscles

2. Patients with bulbar weakness—even if isolated—in the context of a neuromuscular disorder should be asked for daily excessive sleepiness. This is because of the possibility of …

(a) CO_2-accumulation during daytime
(b) Overloading speech and swallow musculature
(c) Hypoxemia because of multiple micro-atelectases
(d) Obstructive sleep apnea syndrome (*)

3. *Central* sleep-disordered breathing may be associated with neuromuscular disorders.

(a) True (*)
(b) False

4. Ineffective cough in neuromuscular disease is most often due to ……

(a) Bulbar muscle weakness
(b) Muscle weakness during expiration (*)
(c) Muscle weakness during inspiration

5. Which muscles are mainly tested by the sniff nasal inspiratory pressure test?

(a) Chest wall muscles
(b) Diaphragm (*)
(c) Facial muscles
(d) Pharyngeal muscles

6. Which muscles are mainly tested by the maximal expiratory pressure test?

(a) Abdominal muscles (*)
(b) Diaphragm
(c) Facial muscles
(d) Pharyngeal muscles

7. Which parameter(s) is(are) measured with a forced vital capacity test?

(a) Obstruction
(b) Restriction
(c) Both a and b (*)

Several muscles are involved in inspiration, the diaphragm being one of them.

8. How can the diaphragm function be estimated separately from the other muscles? By comparing VC ….

(a) With SNIP and MIP
(b) In seated and supine position (*)
(c) Before and after a heavy meal
(d) With and without bronchodilators

9. The diaphragm function may also be estimated by combining two lung function parameters. Which ones?

(a) MEP and MIP (*)
(b) MIP and VC

(c) VC and forced expiratory volume in 1 s
(d) VC and peak expiratory flow

10. Cough assessment may be done by measuring peak cough flow or by …..

(a) Forced expiratory volume in 1 s/forced vital capacity
(b) Maximal expiratory pressure (*)
(c) Maximal expiratory pressure/maximal inspiratory pressure

11. Which of the following symptoms is related to chronic respiratory failure?

(a) Constipation
(b) Dysphagia (*)
(c) Halitosis
(d) Hiccup

12. Which of the following is an important problem in noninvasive positive pressure ventilation (NIPPV) with an oronasal mask?

(a) Gastric distension (*)
(b) Middle ear inflation
(c) Mouth to nose air regurgitation
(d) Sinus infections

13. Which type of interfaces is mostly used if 24 h NIPPV is needed?

(a) Helmet
(b) Mouthpiece (*)
(c) Nasal mask
(d) Total face mask

14. The need for expiratory positive airway pressure depends on the existence of airway obstruction.

(a) True (*)
(b) False

15. Invasive ventilation may be the first choice instead of NIPPV in patients with ……

(a) An atopic constitution
(b) Dryish airways
(c) Hypertension
(d) Swallowing problems (*)

16. What's the use of air stacking techniques in NIPPV?

(a) Circumvention of obstructive airway problems
(b) Increasing the effectivity of inhaled oxygen
(c) Prevention of CO_2 accumulation
(d) Removing airway secretions (*)

17. Vocal cord paralysis is the main cause of weak cough in NMDs.

(a) True
(b) False (*)

18. Monitoring with a combination of measurement of oxygen saturation and vital capacity provides adequate information on respiratory muscle function.

(a) True
(b) False (*)

19. Close monitoring of PaO_2 best informs on the indication of NIPPV.

(a) True
(b) False (*)

20. Cricothyroid mini-tracheostomy may extend the use of noninvasive ventilation when secretion control is difficult.

(a) True (*)
(b) False

21. "Air stacking" is dangerous in acute-on-chronic respiratory failure.

(a) True
(b) False (*)

22. Mechanical insufflation-exsufflation is more effective than air stacking in acute-on-chronic respiratory failure.

(a) True (*)
(b) False

References

1. Mehta S. Neuromuscular disease causing acute respiratory failure. Respir Care. 2006;51:1016–21.
2. Hill NS. Neuromuscular disease in respiratory and critical care medicine. Respir Care. 2006;51:1065–71.
3. Perrin C, Unterborn JN, Ambrosio CD, et al. Pulmonary complications of chronic neuromuscular diseases and their management. Muscle Nerve. 2004;29:5–27.
4. Annane D, Orlikowski D, Chevret S, et al. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. Cochrane Database Syst. 2007;17:CD001941 Rev.
5. Eagle M, Baudouin S, Chandler C, et al. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscul Disord. 2002;12(10):926–9.
6. ATS Consensus Statement. Respiratory care of the patient with duchenne muscular dystrophy. Am J Respir Crit Care Med. 2004;170:456–65.
7. Lloyd Owen SJ, Donaldson GC, Ambrosino N, et al. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. Eur Respir J. 2005;25:1025–31.
8. Ambrosino N, Carpene N, Gherardi M. Chronic respiratory care for neuromuscular diseases in adults. Eur Respir J. 2009;34:444–51.

9. Gozal D. Pulmonary manifestations of neuromuscular disease with special reference to Duchenne muscular dystrophy and spinal muscular atrophy. Pediatr Pulmonol. 2000;29:141–50.
10. Bach JR. Progressive neuromuscular and degenerative diseases. In: Ambrosino N, Goldstein RS, editors. Ventilatory support for chronic respiratory failure. New York: Informa Healthcare Pub; 2008. p. 445–55.
11. Vitacca M, Clini E, Facchetti D, et al. Breathing pattern and respiratory mechanics in patients with amyotrophic lateral sclerosis. Eur Respir J. 1997;10:1614–21.
12. Polkey MI, Lyall RA, Moxham J, et al. Respiratory aspects of neurological disease. J Neurol Neurosurg Psychiatry. 1999;66:5–15.
13. Polkey MI, Lyall RA, Green M, et al. Expiratory muscle function in amyotrophic lateral sclerosis. Am J Respir Crit Care Med. 1998;158:734–41.
14. Racca F, Del Sorbo L, Mongini T, et al. Respiratory management of acute respiratory failure in neuromuscular diseases. Minerva Anestesiol. 2010;76:51–62.
15. Culebras A. Sleep and neuromuscular disorders. Neurol Clin. 2005;23:1209–23.
16. Shneerson JM, Simonds AK. Noninvasive ventilation for chest wall and neuromuscular disorders. Eur Respir J. 2002;20:480–7.
17. McCool FD, Leith DE. Pathophysiology of cough. Clin Chest Med. 1987;8:189.
18. Bach JR. Update and perspective on noninvasive respiratory muscle aids: part 2. The expiratory aids. Chest. 1994;105:1538–44.
19. Benditt JO. Management of pulmonary complications in neuromuscular disease. Phys Med Rehabil Clin N Am. 1998;9:167–85.
20. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002;166:518–624.
21. Héritier F, Rahm F, Pasche P, et al. Sniff nasal inspiratory pressure. A noninvasive assessment of inspiratory muscle strength. Am J Respir Crit Care Med. 1994;150:1678–83.
22. Steier J, Kaul S, Kaul S, et al. The value of multiple tests of respiratory muscle strength. Thorax. 2007;62:975–80.
23. Lyall RA, Donaldson N, Polkey MI, et al. Respiratory muscle strength and ventilatory failure in amyotrophic lateral sclerosis. Brain. 2001;124:2000–13.
24. Morgan RK, McNally S, Alexander M, et al. Use of Sniff nasal-inspiratory force to predict survival in amyotrophic lateral sclerosis. Am J Respir Crit Care Med. 2005;171:269–74.
25. Man WD, Kyroussis D, Fleming TA, et al. Cough gastric pressure and maximum expiratory mouth pressure in humans. Am J Respir Crit Care Med. 2003;168:714–7.
26. Szeinberg A, Tabachnik E, Rashed N, et al. Cough capacity in patients with muscular dystrophy. Chest. 1988;94:1232–5.
27. Mead J, Loring SH. Analysis of volume displacement and length changes of the diaphragm during breathing. J Appl Physiol Respir Environ Exerc Physiol. 1982;53(3):750–5.
28. Bushby K, Finkel R, Birnkrant DJ, et al. DMD care considerations working group. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. Lancet Neurol. 2010;9(2):177–89.
29. Chavhan GB, Babyn PS, Cohen RA, et al. Multimodality imaging of the pediatric diaphragm: anatomy and pathologic conditions. Radiographics. 2010;30(7):1797–817.
30. Mier--Jedrzejowicz A, Brophy C, Moxham J, et al. Assessment of diaphragm weakness. Am Rev Respir Dis. 1988;137:877–83.
31. van Alfen N, Doorduin J, van Rosmalen M, et al. Phrenic neuropathy and diaphragm dysfunction in neuralgic amyotrophy. Neurology. 2018;91(9):e843–9.
32. Lechtzin N, Wiener CM, Shade DM, et al. Spirometry in the supine position improves the detection of diaphragmatic weakness in patients with amyotrophic lateral sclerosis. Chest. 2002;121(2):436–42.
33. Koo P, Oyieng'o DO, Gartman EJ, et al. The maximal expiratory-to-inspiratory pressure ratio and supine vital capacity as screening tests for diaphragm dysfunction. Lung. 2017;195:29–35.
34. McCool FD, Tzelepis GE. Dysfunction of the diaphragm. N Engl J Med. 2012;366(10):932–42.

35. Wait JL, Nahormek PA, Yost WT, et al. Diaphragmatic thickness-lung volume relationship in vivo. J Appl Physiol. 1989;67(4):1560–8.
36. Finder JD, Birnkrant D, Carl J, et al. Respiratory care of the patient with Duchenne muscular dystrophy: ATS consensus statement. Am J Respir Crit Care Med 2004; 170:456–465.
37. Bach JR, Saporito LR. Criteria for extubation and tracheostomy tube removal for patients with ventilatory failure. A different approach to weaning. Chest. 1996;110:1566–71.
38. Voulgaris A, Antoniadou M, Agrafiotis, et al. Respiratory involvement in patients with neuromuscular diseases: a narrative review. Pulm Med. 2019:2734054.
39. Bach JR, Ishikawa Y, Kim H. Prevention of pulmonary morbidity for patients with Duchenne muscular dystrophy. Chest. 1997;112:1024–8.
40. Vianello A, Bevilacqua M, Arcaro G, et al. Non-invasive ventilatory approach to treatment of acute respiratory failure in neuromuscular disorders. A comparison with endotracheal intubation. Intensive Care Med. 2000;26:384–90.
41. Nava S, Navalesi P, Conti G.Nava S, et al. Time of non-invasive ventilation. Intensive Care Med 2006; 32:361–370
42. Luo F, Annnane D, Orlikowsky, et al. Invasive versus non-invasive ventilation for acute respiratory failure in neuromuscular disease and chest wall disorders. Cochrane Database Syst Rev. 2017;12(12):CD008380.
43. Kataoka H, Nanaura H, Kinugawa K, et al. Risk of unsuccessful noninvasive ventilation for acute respiratory failure in heterogeneous neuromuscular diseases: a retrospective study. Neurol Int. 2017;9:6904.
44. Racca F, Del Sorbo L, Mongini T, Vianello A, Ranieri VM, Racca F, et al. Respiratory management of acute respiratory failure in neuromuscular diseases. Minerva Anestesiol. 2010;76:51–62.
45. Chatwin M, Toussaint M, Gonçalves MR, et al. Airway clearance techniques in neuromuscular disorders: a state of the art review. Respir Med. 2018;136:98–110.
46. Ishikawa Y, Bach JR, Komaroff E, et al. Cough augmentation in Duchenne muscular dystrophy. Am J Phys Med Rehabil. 2008;87(9):726–30.
47. Chatwin M, Ross E, Hart N, et al. Cough augmentation with mechanical insufflation/exsufflation in patients with neuromuscular weakness. Eur Respir J. 2003;21:502–8.
48. Vianello A, Corrado A, Arcaro G, et al. Mechanical insufflation-exsufflation improves outcomes for neuromuscular disease patients with respiratory tract infections. Am J Phys Med Rehabil Actions. 2005;84:83–8.

Chapter 5
Weaning from the Ventilator and Long-Term Respiratory Support

Susana Quijano-Roy, Blaise Mbieleu, Jean Bergounioux, and Helene Prigent

S. Quijano-Roy (✉)
Service de Neurologie Pédiatrique et Réanimation, DMU Santé Enfant Adolescent (SEA)
Hôpital Raymond Poincaré, APHP Université Paris-Saclay, Garches, France

Unité Neuromusculaire de l'Enfant, Centre de Référence Maladies Neuromusculaires
Nord-Est Ile de France (Filière FILNEMUS), Paris, France

UMR U1179 (INSERM/UVSQ) Handicap neuromusculaire: Physiopathologie, Biothérapie et
Pharmacologie appliquées (END-ICAP), Versailles, Montigny-le-Bretonneux, France

Garches-Necker-Mondor-Hendaye Consortium (GNMH), Reference Center on
Neuromuscular Diseases for the European Network (Euro-NMD), Paris, France
e-mail: susana.quijano-roy@aphp.fr

B. Mbieleu
Service de Neurologie Pédiatrique et Réanimation, DMU Santé Enfant Adolescent (SEA)
Hôpital Raymond Poincaré, APHP Université Paris-Saclay, Garches, France

Unité Neuromusculaire de l'Enfant, Centre de Référence Maladies Neuromusculaires
Nord-Est Ile de France (Filière FILNEMUS), Paris, France

Garches-Necker-Mondor-Hendaye Consortium (GNMH), Reference Center on
Neuromuscular Diseases for the European Network (Euro-NMD), Paris, France
e-mail: blaise.mbieleu@aphp.fr

J. Bergounioux
Service de Neurologie Pédiatrique et Réanimation, DMU Santé Enfant Adolescent (SEA)
Hôpital Raymond Poincaré, APHP Université Paris-Saclay, Garches, France

UMR U1179 (INSERM/UVSQ) Handicap neuromusculaire: Physiopathologie, Biothérapie et
Pharmacologie appliquées (END-ICAP), Versailles, Montigny-le-Bretonneux, France
e-mail: jean.bergounioux@aphp.fr

H. Prigent
UMR U1179 (INSERM/UVSQ) Handicap neuromusculaire: Physiopathologie, Biothérapie et
Pharmacologie appliquées (END-ICAP), Versailles, Montigny-le-Bretonneux, France

Garches-Necker-Mondor-Hendaye Consortium (GNMH), Reference Center on
Neuromuscular Diseases for the European Network (Euro-NMD), Paris, France

Service de Physiologie et Explorations Fonctionnelles, DMU Handicap et locomoteur,
Hôpital Raymond Poincaré, APHP Université Paris-Saclay, Garches, France
e-mail: helene.prigent@aphp.fr

M. Damian, M. de Visser (eds.), *Emergencies in Neuromuscular Disorders*,
https://doi.org/10.1007/978-3-030-91932-0_5

Current Concepts on Long-Term Ventilation of Neuromuscular Patients

Respiratory failure is estimated to be found in 42% of NMDs [1] and may result from different mechanisms [2, 3]. Inspiratory muscle weakness leads to failure of the respiratory pump and alveolar ventilation, indicated by hypercapnia [3]. While this mechanism is prevailing in neuromuscular respiratory failure and remains the main indication of long-term support ventilation, it can also be associated with expiratory muscle weakness, leading to cough failure. Cough inefficiency exposes patients to an increased risk of infection and acute respiratory failure [3, 4]. Moreover, upper airway weakness can also complicate neuromuscular diseases contributing not only to increased cough failure and exposure to aspiration risk (and therefore to infection and acute respiratory failure) but also to a higher prevalence of obstructive apnea in patients already at risk of sleep-disordered breathing. Finally, respiratory drive and CO_2 response may also be progressively impaired along with compromised respiratory muscles [5, 6]. This highlights that, while mechanical ventilation is the first-line treatment in neuromuscular respiratory failure, identifying precisely the type of respiratory muscle weakness presented by a patient is needed to allow for an adequate management. For instance, cough assistance techniques may be required, in addition to ventilation, in order to compensate cough weakness [7, 8]. Likewise, the presence of obstructive apnea or hypopnea may necessitate adaptation of ventilation parameters.

Respiratory failure is disease-specific and dependent on involvement of respiratory muscles. While all Duchenne muscular dystrophy (DMD) [8, 9] and Pompe disease patients will require ventilation in due course, this holds for less than 5% of facioscapulohumeral dystrophy patients [10]. This symptomatic treatment's purpose is to support the dysfunction of the respiratory pump and correct the hypoventilation by providing a mechanical assistance. Ventilation has improved the survival of NMD patients with respiratory failure not only in case of slowly progressive disease, such as DMD [11–13], but also in very rapidly evolving respiratory failure, such as amyotrophic lateral sclerosis (ALS) [14–16].

Evidence of alveolar hypoventilation is the main reason for starting ventilation. For a long time, general criteria were used to decide the initiation of ventilation: symptoms associated with vital capacity below 50% of predicted value or inspiratory maximal pressure below 60 cm H_2O or hypercapnia defined as $PaCO_2$ above 45 mmHg or nocturnal O_2 desaturation below 90% for more than 5 min [17]. Over the past two decades, increasing knowledge of NMDs has led to better identification of specific clinical presentations and consequently specific criteria for initiating treatment that should be tailored if possible for each disease. Thus, in DMD, vital capacity below 20% of predicted value has proven to be predictive of hypercapnia [18] while preventive ventilation, initiated solely on pulmonary function results, has not improved survival [19]. This evidence has led to more specific criteria for DMD patients [9]. By contrast, in ALS, early introduction of ventilation has been associated with improved survival probably due to the rapid deterioration of respiratory

function [14, 20]. Therefore, in order to appropriately introduce this treatment, close monitoring of respiratory function (including pulmonary function test and sleep studies) is essential in NMD patients. A number of tests, invasive and noninvasive techniques, volitional and nonvolitional, provide objective measurements that will detect the need for respiratory assistance and help determine the need for intubation, choose ventilator settings, or decide the optimal moment for intubation, respectively [21–24].

Considerations of Respiratory Management in Children

Many infantile-onset neuromuscular diseases show bulbar, proximal, or axial involvement associated with respiratory failure (spinal muscular atrophy, myopathies, myasthenic syndromes). On the other hand, diseases associated with muscle weakness of distal limbs (distal myopathies, Charcot–Marie–Tooth neuropathies) are either not frequent in children or do not show significant respiratory complications. An exception is represented by spinal muscular atrophy with respiratory distress (SMARD), a rare distal neuropathy that is associated with diaphragmatic involvement and is often lethal in infancy [25].

In any case, a high suspicion of respiratory dysfunction has to be retained in children with NMDs, and regularly and systematically searched for. As in adults, sleep studies and spirometric measurements in supine and sitting positions are of great help to assess respiratory muscle function [26]. Volitional studies such as FVC or inspiratory and expiratory pressures will not be reliable in young children or noncooperative patients, although they may at least allow estimating a basal respiratory function while crying [27]. Peak cough flow or sniff nasal inspiratory pressure (SNIP) is easier to obtain from young children [28, 29]. The use of a nasobuccal mask to perform spirometric measures is recommended to prevent air leak or insufficient mouth strength or limited cooperation [30, 31].

Respiratory difficulties observed clinically or described by the parents give important clues. Acute respiratory failure signs prior to the imminent failure may not be very evident in young children, who present hypomotility, tachypnea, walking or feeding refusal, weak cry or voice or staccato speech, discomfort breathing lying flat (intolerance to decubitus), or profuse sweating [32]. If not treated, somnolence, loss of consciousness or coma, and cardiorespiratory arrest may occur. This may be the case in a myasthenic crisis, although the most frequent setting of acute respiratory failure in a child with a neuromuscular disease is secondary to a pulmonary infection. In case of hypoxia, cough assistance and/or ventilatory support should be promptly initiated (but not oxygen mask alone) depending on the respiratory effort and the gas exchange monitoring [33].

Most often, a chronic and progressive restrictive insufficiency develops over time. In these cases, respiratory failure may be difficult to diagnose. Abnormalities will initially only be detected during sleep (hypercapnia, apneas, or hypopneas) and will remain transitory, being compensated by an increased breathing rate

(tachypnea) or by frequent night awakenings. Subtle signs and symptoms will be progressively identified also during the day (unexplained loss of weight, tiredness due to poor sleep, morning headaches, sleepiness, fatigue). It is in this period of "hidden" or minor symptoms when the risk of life-threatening complications is higher because they may occur unexpectedly [32]. Any sign of overexertion or inhibition of respiratory function (infections, fever, exercise, anesthesia, sedation) may lead to acute respiratory failure or trigger a multisystemic failure (cor pulmonale) and end fatally. Of note, the use of inhaled equimolar mixture of oxygen and nitrous oxide (Kalinox® or MEOPA = "Mélange équimolaire d'oxygène et protoxyde d'azote" in French) in children with neuromuscular disease may trigger acute respiratory failure, particularly in those who have diaphragmatic weakness, unless a mechanical ventilatory support is provided with monitoring of vital signs and ICU availability [34]. Also, using oral sedative and muscle relaxant drugs in young children should be discouraged.

Non-neuromuscular causes of respiratory failure should be suspected in children suffering from a neuromuscular disease with abnormal sleep studies while respiratory function is normal or relatively preserved. Obstructive apneas in the pediatric patient are often due to enlarged tonsils or anatomical deformities (facial or maxillary abnormalities, retrognathia, Pierre–Robin sequence, macroglossia). Central respiratory failure may also occur due to central nervous system abnormalities, including brain stem and cervical spinal cord or upper motoneuron dysfunction. In the presence of central apneas, an arrest of respiratory drive in sleep (Ondine Syndrome) should be ruled out by molecular analysis of the PHOX2B gene [35].

Patterns of Respiratory Muscle Dysfunction and Spinal and Thoracic Complications in Neuromuscular Diseases

Table 5.1 shows the characteristics and profiles of the main neuromuscular disorders with impact on the respiratory function, including their cardiac and spinal complications. Insufficiency of the intercostal muscles with spared diaphragm drive is typical of spinal muscular atrophy and is associated with impaired breathing and pulmonary function (FCV) in the patient while sitting in an upright position, compared to supine [36, 37]. In contrast, selective diaphragmatic failure is more often observed in myopathies and myasthenic syndromes, and in this case, patients show intolerance of the supine position, whereas their pulmonary function will be better in a sitting or upright position than in supine [38, 39]. Selective weakness of abdominal muscles (e.g., early feature in Duchenne boys) may lead to reduced expiratory volumes and ability to cough [40, 41]. Inspiratory and expiratory volumes are also severely impaired when thoracic stiffness develops due to intercostal muscles contractures, which is a quite frequent complication in the course of many neuromuscular diseases, particularly those with early onset or phenotypes associated with contractures (arthrogrypotic syndromes, congenital muscular dystrophies and

Table 5.1 Patterns of respiratory muscle involvement, spinal and thoracic complications, and correlation with motor function in genetic neuromuscular diseases with respiratory muscle involvement

Disease	Bulbar hypotonia	Selective diaphragmatic weakness	Intercostals (ex)/insp) weakness	Abdominal muscle dysfunction	Spinal kyphosis	Thoracic lordosis	Spinal and thoracic stiffness	Motor and respiratory correlation	Cardiac disease
Spinal muscular atrophy	++/+++	–	+++ (early)	+++	++	+/–	++	Yes	–
Duchenne–Becker dystrophy	+ (late)	++ (late)	+	++ (early)	+	+	+ (late)	Yes	Cardiomyopathy
Myasthenic syndromes (genetic) and myasthenia gravis	+++	+++ (fatigue)	+ (fatigue)	++ (fatigue)	+/–	+/–	+/– (late)	No (ventilation in walkers)	–
Congenital muscular dystrophies									
• COL6-myopathy	–	+++	+	++	+++	–	+++	Yes	–
• Merosin deficiency	+	+	+++	++	–	+++	+++	Yes	–
• SEPN1-myopathy	–	+++	+	+	–	+++	+++	No (ventilation in walkers)	–
• Dystroglycanopathy	–	++ (late)	+	++ (early)	+/–	+/–	+ (late)	Yes	+
• Laminopathy (*LMNA*)	–	–	++	–	–	+++	+++	Yes	+++ (dysrhythmia, cardiomyopathy)
Myotonic dystrophy	+	+/–	+/–	+/–	–	–	–	No (ventilation in walkers)	++ (dysrhythmias))
Congenital myopathies									
• Nemaline (*NEB, ACTA1*)	++/+++	+++	–	++	+/–	++	++ (late)	No (ventilation in walkers)	–

(continued)

Table 5.1 (continued)

Disease	Bulbar hypotonia	Selective diaphragmatic weakness	Intercostals (ex)/insp) weakness	Abdominal muscle dysfunction	Spinal kyphosis	Thoracic lordosis	Spinal and thoracic stiffness	Motor and respiratory correlation	Cardiac disease
• Core myopathy (*RYR1*)	−	−	−	−	+/−	+/−	+/−	+ Yes (ventilation in severe cases)	−
• Centronuclear/ myotubular	++/+++	++/ +++	+	++	+/−	+		No (ventilation in walkers)	−
Emery–Dreifuss muscular dystrophy	−	−	++	−	−	++/+++	++	Yes	+++ (dysrhythmias, cardiomyopathy)
Pompe disease									+++
• Infantile	++/+++	+++	+	++	+/−	++	−	Variable	Myocardiopath
• Juvenile and late onset	+	+++	+	++	+/−	+	+	No (ventilation in walkers)	−
Limb-girdle muscular dystrophies	+ (late)	++ (late)	+	++ (early)	+	+	+ (late)	Yes	+/++ Cardiomyopathy
Facioscapulohumeral dystrophy	−	−	−	++	−	−	−	Yes	−
SMARD	+ /−	+++	+	−	−	−	−	Yes	−

myopathies, spinal muscular atrophy) [42–44]. As a general rule, rigidity of the spine [rigid spine syndromes (RSS)] or flat thorax in a child or adult with a neuromuscular disorder should prompt a search for respiratory failure [38, 45, 46].

In most diseases, the severity of respiratory dysfunction is correlated with the severity of motor disabilities, and ventilatory support is needed only in nonambulant patients. This is not the case in specific disease entities, particularly SEPN1-myopathy, and juvenile Pompe disease [47–50], where the respiratory dysfunction is out of proportion. Also, it can happen in an ambulant patient with a rapidly progressive scoliosis.

Profound decrease in respiratory function presenting in the course of a few weeks or months in a child affected with a chronic neuromuscular disorder, particularly myopathies with early contractures, should prompt a thorough assessment, including pulmonary and spinal radiological tests (lateral views on X-rays, thoracic CT scan) to search for a pulmonary collapse (atelectasis) or a bronchial obstruction by the spinal deformity. Airway obstruction by the vertebral bodies is more likely to happen in those diseases associated with a thoracic lordotic deformity rather than in those with dorsal kyphosis. A severe scoliosis may also lead to lung collapse by compression of the pulmonary tissue against the thoracic cage [32] (Fig. 5.1).

Finally, it is important not to forget a systematic cardiac function assessment during follow-up either to identify a primary cardiac involvement or to detect a secondary involvement due to respiratory chronic failure (pulmonary hypertension).

The arrival of new specific therapies in infantile fatal diseases has changed the standards of respiratory care in these diseases to more proactive management whenever the indication of a therapeutic drug is validated. Since respiratory failure remains the leading cause of morbidity and mortality in patients with NMDs [1], the initiation of ventilatory support in specialized centers when there is a risk of restrictive respiratory failure may be instituted as a comfort or preventive intervention for the patients, and not a sign of aggravation of the disease itself [46].

- In infantile Pompe disease with respiratory failure, the early initiation of NIV makes it possible to start the enzyme replacement therapy and eventually over time to reduce the level of ventilation.
- Patients with SMA types 1 and 2 develop a bell-shaped thoracic deformity and pectus excavatum attributed to intercostal muscle involvement and relative diaphragm sparing [54]. The initiation of early ventilatory support or daily hyperinsufflation sessions by IPPB (Fig. 5.2) improves respiratory function prognosis [55–57].
- In DMD, scoliosis frequently presents in the second decade of life after loss of walking ability due to paravertebral muscle weakness [58]. Pressure relievers should be started early, followed by NIV when vital capacity drops to less than 1–1.5 l [9].
- In some CMDs, the spinal deformity can lead to bronchial compression, responsible for a ventilation disorder, requiring urgent orthopedic treatment in order not to lead to an almost complete and irreversible amputation of one lobe or several pulmonary lobes [32] (Fig. 5.1).

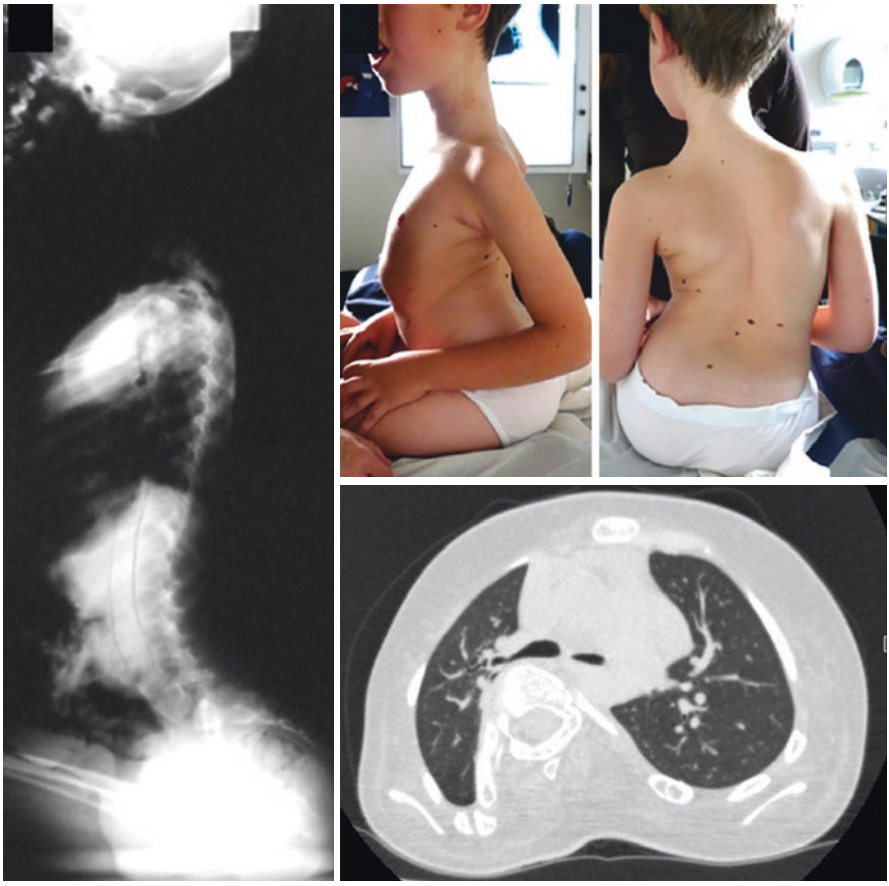


Fig. 5.1 In some CMDs, the spinal deformity can lead to bronchial compression, responsible for a ventilation disorder, requiring urgent orthopedic treatment in order not to lead to an almost complete and irreversible amputation of one lobe or several pulmonary lobes. In the figure, a patient with a LAMA2 congenital muscular dystrophy (merosin-deficient CMD, MDC1A). Thoracic lordosis was initially treated by a Garches brace [51]. However, at age 11 years vertebral bodies compressed the right bronchus, reducing severely pulmonary volumes. Mini-invasive fusionless surgery [52, 53] and intensive hyperinsufflation therapy by alpha 300 device daily allowed improvement of FVC in the postoperative period. At age 21, the patient maintains >500 ml and is treated by nocturnal NIV (never required tracheostomy)

Setting Up and Follow-Up of Home Ventilation in an Adult with a Neuromuscular Disease

Hypoventilation in neuromuscular disease often first presents at night during sleep, particularly during REM stage [59–62]. Sleep studies can be used to evaluate sleep-disordered breathing, detecting first expression of nocturnal alveolar ventilation, before baseline values of daytime Pa_{CO2} reach 45 mmHg. They also allow the

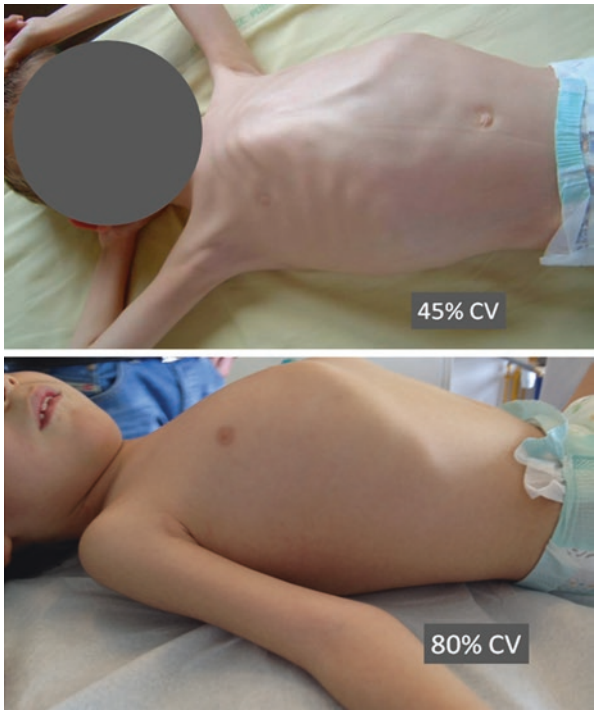


Fig. 5.2 Patients with SMA types 1 and 2 develop a bell-shaped thoracic deformity and pectus excavatum attributed to intercostal muscle involvement and relative diaphragm sparing [54]. The initiation of proactive ventilatory support or IPPB improves thoraco-pulmonary growth. On the upper view, in a 6-year-old boy suffering from SMA type 2 without proactive treatment, thorax is reduced and hypoplastic. On the lower view, a 6-year-old boy with SMA type 2 treated daily by IPPB (and abdominal belt) from diagnosis at 10 months

evaluation of associated apnea (obstructive or central), which will influence the parameters of treatment. A base excess of at least 4 mEq/l may also correlate with sleep hypoventilation [63, 64]. Recurrent infections associated with cough weakness may also necessitate ventilation support. Finally, long-term ventilation may also be needed following an acute respiratory failure episode complicated by persistent hypercapnic respiratory failure ("acute-on-chronic").

Noninvasive ventilation (NIV) is the first-line mode of treatment [8, 9, 65, 66]. The main purpose of mechanical ventilation is to correct hypoventilation. Nocturnal NIV treatment for NMD has been reported to improve symptoms (fatigue, dyspnea, daytime hypersomnolence, and morning headaches) as well as gas exchange [67]. Volume-controlled ventilation was the first mode used in the neuromuscular population as it was initially the only ventilation mode available for long-term ventilation. But the development and improvement of pressure-controlled or pressure-support modes over the past three decades have led to an increasing use, and they have become the preferred mode upon ventilation initiation [68, 69]. Generating a flow curve closer to spontaneous breathing cycles, they are more comfortable during the initiation period even though the delivered volume is not fixed [70]. Over time, volume-controlled ventilation use has been mainly limited to ventilator-dependent patients [71]. While there is only weak evidence comparing both modes, they are both efficient in correcting hypoventilation [72, 73].

Ventilatory inspiratory support needs to be titrated in order to generate tidal volumes close to 8–10 ml/kg and to normalize Pa_{CO2} values [9, 65, 67]. Expiratory pressure will depend on the presence of apneic events shown in the initial sleep studies. Back-up respiratory rate will be adjusted to the severity of respiratory failure and the level of dependency of the patient. Monitoring of blood gases will be necessary to assert ventilation efficiency. Overnight transcutaneous capnography or, at least, oximetry is also useful in monitoring ventilation efficiency at home and its capacity to normalize nocturnal ventilation [74–77]. These monitoring tools may replace a full laboratory polysomnogram, which brings more information but is less accessible. Built-in monitoring programs of ventilation devices are also useful in the evaluation of ventilation efficiency and patient–ventilator synchronization; their study may help to adjust ventilation parameters [78–80]. However, in case of persistent hypoventilation despite actions to correct ventilation efficiency, full sleep studies may be required to study the underlying mechanisms leading to ventilation failure, which may be, for instance, leaks, insufficient support, or persistent obstruction [78, 81].

Different types of interfaces can be considered, although nasal masks are usually preferred upon treatment initiation, especially in patients with severe motor dysfunction [65]. Facial masks can also be used, especially in case of important mouth leaks, compromising ventilation efficiency; however, recent evidence suggests that they may promote an increase in apneic events [82, 83] and should not be used in patients without upper limbs mobility. In the latter, the patient may not be able to take the mask off in the event of vomiting or intense cough, and this carries a risk of asphyxia.

In case of persistent hypoventilation, for patients who have elevated Pa_{CO2} despite adequate nocturnal therapy, dyspnea during daytime, and/or hypoxemia due to recurrent respiratory infections, daytime ventilatory support may be needed in order to increase treatment duration [66, 84, 85]. The use of mouthpiece ventilation has been an important alternative in ventilation interfaces, providing efficient ventilation and allowing prolonged efficient ventilation during daytime [85, 86]. The availability of various NIV interfaces has enabled the use of NIV in patients, delaying and even avoiding tracheostomy and invasive ventilation [87]. Over the course of the past two decades, the indications for invasive ventilation have declined and have become restricted to failure of NIV, inability to wean invasive ventilation and to situations where bulbar dysfunction impairs NIV modalities or when uncontrolled aspiration is occurring [9, 88]. NIV is unanimously considered the first-line treatment of NMDs with respiratory failure.

Initiating Home Ventilation at the Pediatric Age

The ventilation of children with NMD is different from that of adults in various aspects. Close monitoring of respiratory function and sleep assessment is, as in adults, the standard of care. Early recognition of sleep breathing disorders and

initiation of NIV can also improve their quality of life and prolong survival [46, 89–91].

However, ventilation in the child is complex for different reasons. The child is a dynamic body due to growth, and therefore, even for the same disease, clinical pictures and solutions can be very different depending on the age, the period of the disease, and its severity. Any paralytic impairment of the respiratory muscles before 4 years of age (i.e., during the period of alveolar multiplication) will lead to pulmonary hypoplasia. It is therefore necessary to be preventive in congenital pathologies. Growth of the pulmonary tree continues until the second decade by increasing the diameter of alveoli and bronchi [92, 93]. As a result, proactive ventilation (e.g., in spinal muscular atrophy) or daily sessions of thoraco-pulmonary expansion by intermittent positive pressure breathing therapy (IPPB alpha 300 device or similar) are beneficial in short and long term in children with congenital diseases [91, 94]. This is particularly true in cases of flat and stiff thoracic cage due to intercostal muscles contractures, such as congenital muscular dystrophies or spinal muscular atrophy [32] (Fig. 5.2). The use of insufflators is also beneficial to increase coughing [56, 95]. Bulbar weakness, gastrointestinal dysfunction, and abdominal weakness or reduced tone are very frequent in infants and lead to cough deficit, gastroesophageal reflux, and swallowing disorder (hypersialorrhea leading to aspiration), which make it difficult to initiate noninvasive ventilation. Recurrent upper airway infections during the first years of life also lead to upper airway obstruction. Finally, development of pulmonary hypotrophy, scoliosis, and stiffness of the thoracic cage may further complicate ventilatory assistance. The need for relatively high inspiratory pressures, particularly in the presence of abdominal muscle weakness, may cause abdominal discomfort due to air leaking to the digestive tube, requiring abdominal wall support by an elastic belt [94]. Gastrostomy or enteral nutrition by nasogastric tube can also hamper adequate ventilation. As mentioned above, nasobuccal masks are not recommended in young children or if the upper limb function is severely impaired due to the risk of aspiration if they cannot take off the mask in the event of vomiting.

The development of new turbine ventilator machines with different modes, technology, and monitoring comparable to resuscitation ventilators, even if the interfaces especially in young children remain limited, facilitates ventilation at an early stage. The development of instrumental decluttering tools is also an essential aid in the respiratory care of children with neuromuscular diseases. The objective of the respiratory management of children with neuromuscular disorders is threefold: (1) ventilatory support, (2) increased cough, and (3) recruitment of lung volume. The ventilatory support assists the function of weak respiratory muscles and stabilizes gas exchange; increased coughing improves cough flow and promotes the elimination of secretions; and lung volume recruitment aims to avoid functional decline due to atelectasis and contractures of the chest wall [96, 97]. Ventilation by tracheostomy was the standard treatment for patients with prolonged or complete dependence on ventilation and for those whose decluttering was impaired due to weak cough. However, the combination of nasal or oral ventilation with cough-increasing

strategies has made this option obsolete for the majority of cases, except for those with advanced bulbar disease [International consensus]; [21].

It should be noted that in children the NIV is generally set with pressure modes because it allows a better compensation for air leaks. However, it is essential to have an exhaled tidal volume monitoring that should reach 8–12 ml/kg or use pressure modes with the possibility of setting a guaranteed volume. Leaks should also be monitored and stabilized.

In acute respiratory failure in patients with NMD, NIV and aggressive management of secretions with cough assistance should be initiated. Importantly, NIV should be considered in patients with NMD who present with acute illness and tachypnea (respiratory rate >20/min), even in the absence of hypercapnia, especially in those with known VC < 1 l [98, 99]. Adequate hydration should be ensured and the clinician should have a low threshold for administration of antibiotics, especially when there is a high likelihood of underlying lung infection [100]. The role of NIV associated with mechanical in-exsufflator (MI-E) was investigated in a prospective, uncontrolled study of 16 children with NMD and acute respiratory failure treated in a pediatric intensive care unit [101]. However, where there is failure of NIV and secretion management strategies (e.g., due to severe upper airway obstruction, craniofacial abnormalities, or impaired consciousness), timely invasive ventilation should not be delayed.

Weaning an Adult from Ventilation

Weaning from mechanical ventilation is the process of transition to spontaneous ventilation, either from invasive ventilation (intubation, tracheostomy) or from non-invasive ventilation. Concerning endotracheal ventilation, successful weaning is defined as the ability to maintain spontaneous ventilation for at least 48 h without the need for reintubation and invasive mechanical ventilation [102, 103]. The decision to progress to extubation is more challenging in neuromuscular patients with advanced respiratory muscle weakness as the underlying disease may impair the patients' ability to sustain the effort of spontaneous breathing [104, 105]. Weaning failure may lead to a need for prolonged mechanical ventilation (more than 21 days depending on the study) inducing significant mortality and morbidity and in some patients to tracheostomy for long-term ventilation. In up to 25% of NMD patients, long-term ventilation is necessary after an acute respiratory failure event [106].

Several techniques have been proposed in the weaning process; however, neuromuscular patients have usually been excluded from the main studies of weaning protocols as they are considered by definition high-risk patients for weaning failure. The two main protocols currently used are conducted as follows [102, 107–110]:

- "T"-piece trials, in which the patients breathe spontaneously through a T-shaped tube connected to an endotracheal tube (orotracheal or tracheostomy) and only receive supplemental oxygen if necessary.

- Decreasing pressure support ventilation that uses progressively lower levels of inspiratory pressure support until it reaches 5–8 cm H_2O at which level extubation can be attempted.

T-piece trials can be considered periods that allow respiratory muscle training as ventilation is completely discontinued, while pressure support ventilation maintains support of the respiratory muscles. Numerous trials have studied these weaning protocols; protocolized weaning strategies may lead to better outcomes as they allow sedation reduction [111, 112]. However, the superiority of either technique remains a subject of discussion. A meta-analysis showed a slight superiority of the pressure ventilation technique [107], which was recommended as first-line strategy in 2017 [102, 108]. However, a recent randomized trial supports better success with T-piece trials [113]. The interesting information for NMD patients is that T-piece trials may be more sensitive in identifying subjects with high weaning failure risk, which might suggest that it would be an interesting technique to evaluate NMDs patients. However, robust evidence in this population is lacking to support a specific strategy.

In neuromuscular disorders, underlying respiratory muscle weakness may lead to the introduction of long-term ventilation following an acute respiratory failure. Therefore, in this situation, weaning might mean weaning of invasive techniques of ventilation rather than weaning of any form of ventilation. Strategies involving the systematic use of NIV in the process of weaning have been increasingly proposed in patients at high risk of extubation failure [87], and NIV seems indicated in patients with hypercapnic respiratory failure [66, 114–117]. But more evidence for specific neuromuscular diseases is needed to warrant this approach [21, 118].

Finally, the ability of the patient to protect his or her airway from excessive secretions by effective cough needs to be evaluated, including the quality of cough with airway suctioning, the amount of secretions, and the frequency of suctioning. Preserved cough efficiency, evaluated prior to extubation, is associated with a higher weaning success [119, 120]. In NMD patients, cough assistance techniques, such as in-exsufflation, may be introduced after extubation to ensure weaning success [104].

Weaning a Child with Neuromuscular Disease

The extubation of a child with neuromuscular disease is a complex process. Knowledge of the patterns of respiratory muscle failure and fatigability may help ICU teams to tailor the withdrawal protocol for different types and severities of neuromuscular disorders (diseases with predominant diaphragmatic failure vs. intercostal muscles, myasthenic patients, metabolic myopathies).

Weaning a child follows well-defined care algorithms. Intubated babies must be assessed daily for extubation criteria. In contrast to adults, the T-tube test is not feasible in young children because the intubation tube's gauges are too small and generate too much resistance to airflow during tube ventilation. This test is therefore

replaced by a low-pressure support test, which consists of administering a ventilation pressure that is necessary and sufficient to compensate for these resistances related to the intubation catheter. The pressure regime is considered to have been reached for an inspiratory pressure around 10 cm H_2O of mercury and an expiratory pressure around 3 mm of mercury. If these tests are performed, the extubation failure rate is 13%; when these tests are not performed, it is 40% [121].

To prevent weaning failure, the clinician has to take into account several considerations. The natural course of a lung infection in a healthy child may take weeks or months in healing. Complications related to hospitalization and mechanical ventilation have additional negative effects. Indeed, as is known in adult studies, diaphragmatic strength decreases by 30% after 5–6 days of mechanical ventilation [122]. The muscle force decreases by 15–25% after 14 days of bed rest [123]. Undernutrition is also a concern, and assessment of growth in neuromuscular children is hampered due to the absence of standardized growth charts for different disorders, but this aspect is of major importance [124]. Therefore, a longer recovery time is expected in children with NMD, necessary to cope with the maintenance of adequate respiratory function. Certain neuromuscular diseases are more at risk [congenital, myopathies with thoracic cage stiffness, diaphragmatic weakness, myasthenia, metabolic myopathies (Pompe, mitochondrial diseases)]. To facilitate weaning, noninvasive ventilation is often used as a "bridge." This helps to reduce fatigability and compensate weakness of the respiratory muscles. Low vital capacity and inability to cough may last for many weeks, and the ventilatory assistance will allow waiting for this slow recovery. To treat bronchial secretion stocking and congestion, specialized decluttering devices such as the Cough-Assist® or Intrapulmonary Percussive devices (IPV; Percussionaire®) [125, 126] are available. These devices generate alternating positive and negative flows, allowing efficient clearance of the airways, often requiring additional manual maneuvers. Their handling requires a certain amount of experience, but parents and caregivers may be trained by teams used to the chronic management of children with restrictive respiratory insufficiency. Bulbar weakness is present in many of these disorders, adding congestion and hypersalivation due to abnormal control of the oropharyngeal muscles. To treat this complication, inclined or lateral positioning is used to drain secretions; atropine derivatives may help but requires close monitoring.

For all these reasons, it is preferable that children at risk of complex extubation in the context of neuromuscular disease are referred to a specialized service [127]. Noninvasive support may be maintained in some cases on a long-term basis. This is particularly true in congenital disorders with frequent respiratory infections or bulbar weakness because reducing the number of pulmonary infections and hospitalizations will contribute to the child's well-being. Moreover, therapeutic developments in congenital diseases (SMA, myopathies) may warrant more proactive respiratory management in these disorders, including early noninvasive ventilation and intensive coughing and respiratory physiotherapy techniques [128].

Cardiac dysfunction is a relatively rare event in children. Heart failure may hinder extubation in certain myopathies such as Duchenne muscular dystrophy, myotonic dystrophy, or laminopathies (L-CMD, Emery–Dreifuss MD) [129]. As in

adult patients, the use of inotropic treatment to control cardiac output for extubation may be considered [130].

Whenever weaning of invasive endotracheal ventilation is not achieved in a reasonable time, tracheotomy has to be discussed: ethical limitations may be a consideration in this situation. The proportion of patients undergoing tracheostomy varies largely depending on the populations studied and the local experience of the team (2.1–6.6% of patients hospitalized in multipurpose adult medical intensive care units [131]; the average time to tracheostomy is 14.4 days [132]). In young children, however, tracheostomy is not without risk of tracheal tube obstruction due to thick or dry mucous plug, displacement, or early surgical complications [133]. Also, the social impact is important because few long-stay centers or schools easily accommodate tracheotomized children. The decision must therefore also be made together with the child and her/his family [134].

As mentioned, ventilatory withdrawal can be a long-term undertaking. The lung is a slow-healing organ, and the physical recovery necessary for its functioning may also take several months or even more than a year. It is in this context and in view of the high costs of hospitalization in intensive care units that ventilatory weaning units were created. The first unit of this type for adults was inaugurated at Bethesda Hospital in the United States in 1979. The aim is to accompany patients toward partial or complete respiratory autonomy using noninvasive ventilation and progressive exercise rehabilitation. These units have become widespread in view of the generalization of resuscitation units and the progress of mechanical ventilation. Progress in pediatric ventilation and the management of patients with neuromuscular diseases recently led to the opening of such units also for pediatric patients. The evidence is still limited, but the success rates of these units might be higher than those presented by the adult services [135].

Case Vignette 1

A 9-year-old girl affected with a myopathy with contractures diagnosed as an Ullrich congenital muscular dystrophy (CMD) consulted our neuromuscular center. She had never walked and had developed a progressive and rigid scoliosis. Spinal surgery was indicated in the next months, in a center with experience in Duchenne muscular dystrophy and spinal muscular atrophy, and the surgical team sent the patient to inquire about additional specific care and management indications. Weight was in P10 and had not changed in the last year. The child looked healthy. Last year's sleep study showed a mean O_2 saturation of 95% and pCO_2 of 48 mmHg. Spirometry 6 months ago showed FVC 550 ml (42%). No nocturnal ventilation had been considered so far due to the lack of oxygen fall and relative good pulmonary function, weight, and general state.

Ullrich CMD due to mutations in one of the three COL6 genes (COL6A1, A2, or A3) is a myopathy with contractures and distal hyperlaxity. The most severe complications are orthopedic and respiratory. In the nonambulant

children, there is a progressive restrictive respiratory insufficiency and spinal kyphoscoliosis associated with thoracic stiffness. Remarkably, Ullrich CMD is characterized by specific involvement of the diaphragm [39]. *Even without any clinical or complementary sign of diaphragmatic failure or nocturnal hypoventilation at this moment, our advice would be to start nocturnal noninvasive ventilation before surgery because with the low pulmonary function a nocturnal ventilation is very likely to be required in the postoperative period (proactive recommendation). This way the patient will be in a better respiratory condition and used to sleep with a mask and respiratory support, and weaning will be sooner and easier.*

Question

What are the most important questions and tests to perform in order to give appropriate advice?

Answer

The main tests to perform are a spirometry in upright and supine position and a capillary blood sample to explore pCO_2 and bicarbonate compensation [90].

Parents' interview: It is important to ask about asthenia and anorexia, headaches, sweating during sleep, and insomnia. The child has never eaten very much, parents report sweating at night and difficulties sleeping in the last months, and some headaches in the last weeks.

Complementary tests:

FVC in upright position: 490 ml; FVC in supine position: 370 ml (fall of more than 20%); capillary blood gas: pCO_2 5.9 kPa; Bic 28

Interpretation: The sleep study 6 months ago was already suggestive of nocturnal hypoventilation ($pCO_2 > 45$ mmHg), and today's tests and history confirm the clear signs of diaphragmatic failure (fall of FVC over 20% in the supine position), borderline diurnal hypercapnia, and very likely nocturnal hypoventilation (high bicarbonate, renal retention to compensate respiratory acidosis).

Conclusion: The child should start nocturnal ventilation in the next coming weeks and should not have surgery until nocturnal ventilation is effectively used for several months to achieve optimal respiratory muscle management, reduce the infectious and respiratory complications, and facilitate postoperative weaning from invasive ventilation.

Considerations on ventilatory support parameters in Ullrich CMD: Due to stiff thorax, compliance in this disease is decreased and high inspiratory pressures and frequencies will probably be necessary (author comments: over 15 cm H_2O; frequency 20/min). An abdominal belt will improve tolerance and efficacy of the ventilation, reducing air leak toward the gastrointestinal tube.

Self Assessment Questions

1. What proportion of neuromuscular diseases features respiratory failure? About ….

   (a) 10%
   (b) 20%
   (c) 30%
   (d) 40% (*)

2. Which of the following mechanisms is the most prevalent problem in NMD patients with respiratory problems?

   (a) Expiratory insufficiency leading to cough failure
   (b) Inspiratory insufficiency leading to inhalation failure (*)
   (c) Swallowing problems leading to aspiration and obstructive apnea

3. How are the criteria for initiating ventilatory support in NMD nowadays set?

   (a) There are no standard settings, every patient is judged individually
   (b) Standard settings are available for specific clinical situations (*)
   (c) General criteria for ventilatory support are now available and in use

4. Which of the following tests is most easily obtained for testing inspiratory capacity in young children?

   (a) Forced vital capacity
   (b) Inspiratory pressure measurement
   (c) Sniff nasal inspiratory pressure (*)

5. Which of the following tests is most reliable for testing expiratory capacity in young children?

   (a) Expiratory pressure measurement
   (b) Forced expiratory volume
   (c) Peak cough flow (*)

6. Which of the following is a hidden symptom of progressive restrictive insufficiency?

   (a) Inability to fall asleep
   (b) Morning headache (*)
   (c) Unexplained gain of weight

7. In which of the following diseases, insufficiency of intercostal muscles with preserved diaphragm drive is observed?

   (a) Myasthenia
   (b) Myopathic syndromes
   (c) Spinal muscle atrophy (*)

8. In the majority, but not in all NMDs, ventilatory support is needed only in non-ambulant patients.

   (a) True (*)
   (b) False

9. Spinal deformities play an important role in respiratory function disturbances.

   (a) True (*)
   (b) False

10. Spinal deformities leading to respiratory insufficiency may occur in neuromuscular disease. In which types?

    (a) Only in myogenic types
    (b) Only in neurogenic types
    (c) In both (*)

11. Early start of noninvasive ventilation may reduce the level of ventilation over time.

    (a) True (*)
    (b) False

12. Sleep studies are useful to evaluate sleep-disordered breathing. In NMD, these are particularly useful in what stage of the disease?

    (a) In the initial stage (*)
    (b) In the advanced stage

13. What can be stated about facial masks as an interface for noninvasive ventilation?

    (a) They may promote an increase in apneic events (*)
    (b) They are not suitable in patients with mouth leaks
    (c) They are especially suitable for patients without upper limb mobility

14. Which of the following interfaces is especially suitable for prolonged efficient ventilation during daytime?

    (a) A helmet
    (b) A face mask
    (c) A mouthpiece (*)
    (d) A nasal mask

15. In which situation, invasive ventilation is preferred above noninvasive ventilation?

    (a) In nonambulant patients
    (b) In case of impaired bulbar function (*)
    (c) In case of reduced upper limb motility

16. What is important in artificial ventilation in the child?

    (a) It should be delayed as much as possible for the sake of mental development
    (b) It should be started at an early stage to prevent pulmonary hypoplasia (*)

17. Ventilation by tracheostomy is still the standard treatment for children with a need for prolonged dependence on ventilation to enhance recruitment of lung volume.

    (a) True
    (b) False (*)

18. Which of the following statements about weaning from invasive mechanical ventilation in NMD is true?

    (a) Weaning should be started as soon as possible to avoid chronic ventilation
    (b) Weaning failure may lead to a need for prolonged mechanical ventilation and increase in mortality (*)
    (c) Weaning is often impossible, more than half of the patients will need long-term ventilation once they are intubated

19. Which effect can be the most significant with mechanical ventilation for 1 week?

    (a) Development of obstructive lung disease
    (b) Increasing diaphragmatic weakness (*)
    (c) Reduction in cardiac capacity
    (d) Decrease in renal function

20. The recovery period after mechanical ventilation is usually longer in children than in adults with an NMD

    (a) True (*)
    (b) False

21. “Preventive” ventilation can be beneficial, particularly where respiratory insufficiency develops rapidly, for instance, in amyotrophic lateral sclerosis.

    (a) True (*)
    (b) False

22. Some neuropathies with distal weakness may cause early respiratory failure.

    (a) True (*)
    (b) False

23. Genetic diagnosis is important for calculating the risk of respiratory failure in NMD.

    (a) True (*)
    (b) False

24. Air leak to the digestive tract in noninvasive ventilation may be counteracted by abdominal wall support.

    (a) True (*)
    (b) False

25. Which of the following measurements is crucial to maintain noninvasive ventilation?

    (a) Early detection of ENT infections
    (b) Improving secretion management (*)
    (c) Management of obstructive pulmonary disease
    (d) Prevention of gastric reflux

26. T-piece trials for weaning of mechanical ventilation are particularly useful in young children.

    (a) True
    (b) False (*)

27. Cardiomyopathy may complicate extubation.

    (a) True (*)
    (b) False

References

1. Perrin C, Unterborn JN, Ambrosio CD, Hill NS. Pulmonary complications of chronic neuromuscular diseases and their management. Muscle Nerve. 2004;29(1):5–27.
2. Aboussouan LS. Sleep-disordered breathing in neuromuscular disease. Am J Respir Crit Care Med. 2015;191(9):979–89.
3. Benditt J, Boitano L. Pulmonary issues in patients with chronic neuromuscular disease. Am J Respir Crit Care Med. 2013;187(10):1046–55.
4. Boitano Louis J. Management of airway clearance in neuromuscular disease. Respir Care. 2006;51(8):913–22. discussion 922-4
5. Contal O, Janssens JP, Dury M, Delguste P, Aubert G, Rodenstein D. Sleep in ventilatory failure in restrictive thoracic disorders. Effects of treatment with non invasive ventilation. Sleep Med. 2011;12(4):373–7.
6. Nickol AH, Hart N, Hopkinson NS, Moxham J, Simonds A, Polkey MI. Mechanisms of improvement of respiratory failure in patients with restrictive thoracic disease treated with non-invasive ventilation. Thorax. 2005;60(9):754–60.
7. Bach JR. Noninvasive respiratory management of patients with neuromuscular disease. Ann Rehabil Med. 2017;41(4):519–38.
8. Chatwin M, Toussaint M, Gonçalves MR, Sheers N, Mellies U, Gonzales-Bermejo J, Sancho J, Fauroux B, Andersen T, Hov B, Nygren-Bonnier M, Lacombe M, Pernet K, Kampelmacher M, Devaux C, Kinnett K, Sheehan D, Rao F, Villanova M, Berlowitz D, Morrow BM. Airway clearance techniques in neuromuscular disorders: a state of the art review. Respir Med. 2018;136:98–110.
9. Birnkrant DJ, Bushby K, Bann CM, Alman BA, Apkon SD, Blackwell A, Case LE, Cripe L, Hadjiyannakis S, Olson AK, Sheehan DW, Bolen J, Weber DR, Ward LM, DMD Care

Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. Lancet Neurol. 2018;17(4):347–61.
10. Santos DB, Boussaid G, Stojkovic T, Orlikowski D, Letilly N, Behin A, Butel S, Lofaso F, Prigent H. Respiratory muscle dysfunction in facioscapulohumeral muscular dystrophy. Neuromuscul Disord. 2015;25(8):632–9.
11. Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscul Disord. 2002;12:926–9.
12. Kieny P, Chollet S, Delalande P, Le Fort M, Magot A, Pereon Y, Perrouin Verbe B. Evolution of life expectancy of patients with Duchenne muscular dystrophy at AFM Yolaine de Kepper centre between 1981 and 2011. Ann Phys Rehabil Med. 2013;56(6):443–54.
13. Ishikawa Y, Miura R, Ishikava Y, Aoyagi T, Ogata H, Hamada S, Minami R. Duchenne muscular dystrophy: survival by cardio-respiratory interventions. Neuromuscul Disord. 2011;21(1):47–51.
14. Aboussouan LS, Khan SU, Meeker DP, Stelmach K, Mitsumoto H. Effect of noninvasive positive-pressure ventilation on survival in amyotrophic lateral sclerosis [see comments]. Ann Intern Med. 1997;127:450–3.
15. Bourke SC, Bullock RE, Williams TL, Shaw PJ, Gibson GJ. Noninvasive ventilation in ALS: indications and effect on quality of life. Neurology. 2003;61:171–7.
16. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. Lancet Neurol. 2006;5:140–7.
17. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation—a consensus conference report. Chest. 1999;116(2):521–534.
18. Toussaint M, Steens M, Soudon P. Lung function accurately predicts hypercapnia in patients with Duchenne muscular dystrophy. Chest. 2007;131(2):368–75.
19. Raphael JC, Chevret S, Chastang C, Bouvet F. Randomised trial of preventive nasal ventilation in Duchenne muscular dystrophy. French Multicentre Cooperative Group on home mechanical ventilation assistance in Duchenne de Boulogne muscular dystrophy. Lancet. 1994;343(8913):1600–4.
20. Carratù P, Spicuzza L, Cassano A, Maniscalco M, Gadaleta F, Lacedonia D, Scoditti C, Boniello E, Di Maria G, Resta O. Early treatment with non-invasive positive pressure ventilation prolongs survival in Amyotrophic Lateral Sclerosis patients with nocturnal respiratory insufficiency. Orphanet J Rare Dis. 2009;4:10.
21. Bach JR, Goncalves MR, Hamdani I, Winck JC. Extubation of patients with neuromuscular weakness: a new management paradigm. Chest. 2010;137:1033–9.
22. Fauroux B, Quijano-Roy S, Desguerre I, Khirani S. The value of respiratory muscle testing in children with neuromuscular disease. Chest. 2015;147(2):552–9.
23. Lofaso F, Prigent H, Orlikowski D, Trebbia G, Lejaille M, Falaize L, Louis A, Ruquet M, Raphaël JC. Neuromuscular diseases in adults: which respiratory muscle explorations for what type of management? Rev Mal Respir. 2005;22(1 Pt 2):2S78–85.
24. Nicot F, Hart N, Forin V, Boulé M, Clément A, Polkey MI, Lofaso F, Fauroux B. Respiratory muscle testing: a valuable tool for children with neuromuscular disorders. Am J Respir Crit Care Med. 2006;174(1):67–74.
25. Viguier A, Lauwers-Cances V, Cintas P, Manel V, Peudenier S, Desguerre I, Quijano-Roy S, Vanhulle C, Fradin M, Isapof A, Jokic M, Mathieu-Dramard M, Dieterich K, Petit F, Magdelaine C, Giuliano F, Gras D, Haye D, Nizon M, Magen M, Bieth E, Cances C. Spinal muscular atrophy with respiratory distress type 1: a multicenter retrospective study. Neuromuscul Disord. 2019;29(2):114–26.
26. Fromageot C, Lofaso F, Annane D, Falaize L, Lejaille M, Clair B, Gajdos P, Raphaël JC. Supine fall in lung volumes in the assessment of diaphragmatic weakness in neuromuscular disorders. Arch Phys Med Rehabil. 2001;82(1):123–8.

27. Shardonofsky FR, Perez-Chada D, Milic-Emili J. Airway pressures during crying: an index of respiratory muscle strength in infants with neuromuscular disease. Pediatr Pulmonol. 1991;10:172–7.
28. Fauroux B, Aubertin G, Clément A, Lofaso F, Bonora M. Which tests may predict the need for noninvasive ventilation in children with neuromuscular disease? Respir Med. 2009;103(4):574–81.
29. Marcelino AA, Fregonezi GA, Lira MGA, de Oliveira LM, Araújo PRS, Parreira VF, de Andrade AD, Resqueti V. Reference values of sniff nasal inspiratory pressure in healthy children. Pediatr Pulmonol. 2020;55(2):496–502.
30. Banerjee SK, Davies M, Sharples L, Smith I. The role of facemask spirometry in motor neuron disease. Thorax. 2013;68:385–6.
31. Wohlgemuth M, van der Kooi EL, Hendriks JC, Padberg GW, Folgering HT. Face mask spirometry and respiratory pressures in normal subjects. Eur Respir J. 2003;22(6):1001–6.
32. Rutkowski A, Chatwin M, Koumbourlis A, Fauroux B, Simonds A. CMD Respiratory Physiology Consortium. 203rd ENMC international workshop: respiratory pathophysiology in congenital muscle disorders: implications for pro-active care and clinical research 13-15 December, 2013, Naarden, The Netherlands. Neuromuscul Disord. 2015;25(4):353–8.
33. Kneyber MCJ, de Luca D, Calderini E, Jarreau PH, Javouhey E, Lopez-Herce J, Hammer J, Macrae D, Markhorst DG, Medina A, Pons-Odena M, Racca F, Wolf G, Biban P, Brierley J, Rimensberger PC. Recommendations for mechanical ventilation of critically ill children from the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC); section respiratory failure of the European Society for Paediatric and Neonatal Intensive Care. Intensive Care Med. 2017;43(12):1764–80.
34. Fauroux B, Cordingley J, Hart N, Clément A, Moxham J, Lofaso F, Polkey MI. Depression of diaphragm contractility by nitrous oxide in humans. Anesth Analg. 2002;94(2):340–5. table of contents
35. Maloney MA, Kun SS, Keens TG, Perez IA. Congenital central hypoventilation syndrome: diagnosis and management. Expert Rev Respir Med. 2018;12(4):283–92.
36. Perez A, Mulot R, Vardon G, Barois A, Gallego J. Thoracoabdominal pattern of breathing in neuromuscular disorders. Chest. 1996;110:454–61.
37. Gómez-García de la Banda M, Amaddeo A, Khirani S, Pruvost S, Barnerias C, Dabaj I, Bénézit A, Durigneux J, Carlier RY, Desguerre I, Quijano-Roy S, Fauroux B. Assessment of respiratory muscles and motor function in children with SMA treated by nusinersen. Pediatr Pulmonol. 2021;56(1):299–306.
38. Caggiano S, Khirani S, Dabaj I, Cavassa E, Amaddeo A, Arroyo JO, Desguerre I, Richard P, Cutrera R, Ferreiro A, Estournet B, Quijano-Roy S, Fauroux B. Diaphragmatic dysfunction in SEPN1-related myopathy. Neuromuscul Disord. 2017;27(8):747–55.
39. Quijano-Roy S, Khirani S, Colella M, Ramirez A, Aloui S, Wehbi S, de Becdelievre A, Carlier RY, Allamand V, Richard P, Azzi V, Estournet B, Fauroux B. Diaphragmatic dysfunction in Collagen VI myopathies. Neuromuscul Disord. 2014;24(2):125–33.
40. Lo Mauro A, D'Angelo MG, Romei M. Abdominal volume contribution to tidal volume as an early indicator of respiratory impairment in Duchenne muscular dystrophy. Eur Respir J. 2010;35:1118–25.
41. Mayer OH, Finkel RS, Rummey C, Benton MJ, Glanzman AM, Flickinger J, Lindström BM, Meier T. Characterization of pulmonary function in Duchenne muscular dystrophy. Pediatr Pulmonol. 2015;50(5):487–94.
42. Fauroux B, Amaddeo A, Quijano-Roy S, Barnerias C, Desguerre I, Khirani S. Respiratory insight to congenital muscular dystrophies and congenital myopathies and its relation to clinical trial. Neuromuscul Disord. 2018 Sep;28(9):731–40.
43. Khirani S, Amaddeo A, Fauroux B. Cough, sniff and maximal static pressure patterns in spinal muscular atrophy. Respir Physiol Neurobiol. 2020;271:103308.
44. Khirani S, Colella M, Caldarelli V, Aubertin G, Boulé M, Forin V, Ramirez A, Fauroux B. Longitudinal course of lung function and respiratory muscle strength in spinal muscular atrophy type 2 and 3. Eur J Paediatr Neurol. 2013;17(6):552–60.

45. Ras GJ, van Staden M, Schultz C, Stübgen JP, Lotz BP, van der Merwe C. Respiratory manifestations of rigid spine syndrome. Am J Respir Crit Care Med. 1994;150(2):540–6.
46. Shneerson JM, Simonds AK. Noninvasive ventilation for chest wall and neuromuscular disorders. Eur Respir J. 2002;20(2):480–7.
47. Bönnemann CG, Wang CH, Quijano-Roy S, Deconinck N, Bertini E, Ferreiro A, Muntoni F, Sewry C, Béroud C, Mathews KD, Moore SA, Bellini J, Rutkowski A, North KN, Members of International Standard of Care Committee for Congenital Muscular Dystrophies. Diagnostic approach to the congenital muscular dystrophies. Neuromuscul Disord. 2014;24(4):289–311.
48. North KN, Wang CH, Clarke N, Jungbluth H, Vainzof M, Dowling JJ, Amburgey K, Quijano-Roy S, Beggs AH, Sewry C, Laing NG, Bönnemann CG, International Standard of Care Committee for Congenital Myopathies. Approach to the diagnosis of congenital myopathies. Neuromuscul Disord. 2014;24(2):97–116.
49. Prigent H, Orlikowski D, Laforêt P, Letilly N, Falaize L, Pellegrini N, Annane D, Raphael JC, Lofaso F. Supine volume drop and diaphragmatic function in adults with Pompe disease. Eur Respir J. 2012;39(6):1545–6.
50. Villar-Quiles RN, von der Hagen M, Métay C, Gonzalez V, Donkervoort S, Bertini E, Castiglioni C, Chaigne D, Colomer J, Cuadrado ML, de Visser M, Desguerre I, Eymard B, Goemans N, Kaindl A, Lagrue E, Lütschg J, Malfatti E, Mayer M, Merlini L, Orlikowski D, Reuner U, Salih MA, Schlotter-Weigel B, Stoetter M, Straub V, Topaloglu H, Urtizberea JA, van der Kooi A, Wilichowski E, Romero NB, Fardeau M, Bönnemann CG, Estournet B, Richard P, Quijano-Roy S, Schara U, Ferreiro A. The clinical, histologic, and genotypic spectrum of SEPN1-related myopathy: a case series. Neurology. 2020;95(11):e1512–27.
51. Morillon S, Thumerelle C, Cuisset JM, Santos C, Matran R, Deschildre A. Effect of thoracic bracing on lung function in children with neuromuscular disease. Ann Readapt Med Phys. 2007;50(8):645–50.
52. Miladi L, Gaume M, Khouri N, Johnson M, Topouchian V, Glorion C. Minimally invasive surgery for neuromuscular scoliosis: results and complications in a series of one hundred patients. Spine (Phila Pa 1976). 2018;43(16):E968–75.
53. Odent T, Ilharreborde B, Miladi L, Khouri N, Violas P, Ouellet J, Cunin V, Kieffer J, Kharrat K, Accadbled F, Scoliosis Study Group (Groupe d'étude de la scoliose); French Society of Pediatric Orthopedics (SOFOP). Fusionless surgery in early-onset scoliosis. Orthop Traumatol Surg Res. 2015;101(6 Suppl):S281–8.
54. Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. Muscle Nerve. 2015;51(2):157–67.
55. Fauroux B, Guillemot N, Aubertin G, Nathan N, Labit A, Clément A, Lofaso F. Physiologic benefits of mechanical insufflation-exsufflation in children with neuromuscular diseases. Chest. 2008;133(1):161–8.
56. Lacombe M, Del Amo CL, Boré A, Chapeau D, Horvat E, Vaugier I, Lejaille M, Orlikowski D, Prigent H, Lofaso F. Comparison of three cough-augmentation techniques in neuromuscular patients: mechanical insufflation combined with manually assisted cough, insufflation-exsufflation alone and insufflation-exsufflation combined with manually assisted cough. Respiration. 2014;88(3):215–22.
57. Bourdin G, Guérin C, Leray V, Delannoy B, Debord S, Bayle F, Germain M, Richard JC. Comparison of Alpha 200 and Cough Assist as intermittent positive pressure breathing devices: a bench study. Respir Care. 2012;57(7):1129–36.
58. Finder JD. A 2009 perspective on the 2004 American Thoracic Society statement, respiratory care of the patient with Duchenne muscular dystrophy. Pediatrics. 2009;123(4):S239–41.
59. Culebras A. Sleep disorders and neuromuscular disease. Semin Neurol. 2005;25(1):33–8.
60. Labanowski M, Schmidt-Nowara W, Guilleminault C. Sleep and neuromuscular disease: frequency of sleep-disordered breathing in a neuromuscular disease clinic population. Neurology. 1996;47(5):1173–80.
61. Ragette R, Mellies U, Schwake C, Voit T, Teschler H. Patterns and predictors of sleep disordered breathing in primary myopathies. Thorax. 2002;57(8):724–8.

62. Bourke SC, Gibson GJ. Sleep and breathing in neuromuscular disease. Eur Respir J. 2002;19(6):1194–201.
63. Hukins CADR, Hillman. Daytime predictors of sleep hypoventilation in Duchenne muscular dystrophy. Am J Respir Crit Care Med. 2000;161(1):166–70.
64. Mellies U, Ragette R, Schwake C, Boehm H, VoitH T, Teschler. Daytime predictors of sleep disordered breathing in children and adolescents with neuromuscular disorders. Neuromuscul Disord. 2003;13(2):123–8.
65. Hess DR. Noninvasive ventilation in neuromuscular disease: equipment and application. Respir Care. 2006;51(8):896–911. discussion 911–2
66. Hess DR. The growing role of noninvasive ventilation in patients requiring prolonged mechanical ventilation. Respir Care. 2012;57(6):900–18. discussion 918–20
67. Mehta S, Hill NS. Noninvasive ventilation. Am J Respir Crit Care Med. 2001;163: 540–77.
68. Cantero C, Adler D, Pasquina P, Uldry C, Egger B, Prella M, Younossian AB, Soccal PM, Pépin JL, Janssens JP. Long-term noninvasive ventilation in the geneva lake area: indications, prevalence, and modalities. Chest. 2020;158(1):279–91.
69. Janssens JP, Sophie Derivaz S, Breitenstein E, De Muralt BB, Fitting JW, Chevrolet JC, Rochat T. Changing patterns in long-term noninvasive. Ventilation: a 7-year prospective study in the Geneva Lake area. Chest. 2003 Jan;123(1):67–79.
70. Rabec C, Rodenstein D, Leger P, Rouault S, Perrin C, Gonzalez-Bermejo J, SomnoNIV Group. Ventilator modes and settings during non-invasive ventilation: effects on respiratory events and implications for their identification. Thorax. 2011;66(2):170–8.
71. Lofaso F, Prigent H, Tiffreau V, Menoury N, Toussaint M, Monnier AF, Stremler N, Devaux C, Leroux K, Orlikowski D, Mauri C, Pin I, Sacconi S, Pereira C, Pépin JL, Fauroux B, Association Française Contre les Myopathies Research Group. Long-term mechanical ventilation equipment for neuromuscular patients: meeting the expectations of patients and prescribers. Respir Care. 2014 Jan;59(1):97–106.
72. Annane D, Orlikowski D, Chevret S. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. Cochrane Database Syst Rev. 2014;12:CD001941.
73. Sancho J, Servera E, Morelot-Panzini C, Salachas F, Similowski T, Gonzalez-Bermejo J. Non-invasive ventilation effectiveness and the effect of ventilatory mode on survival in ALS patients. Amyotroph lateral Scler frontotemporal Degener. 2014;15(1–2): 55–61.
74. Georges M, Nguyen-Baranoff D, Griffon L, Foignot C, Bonniaud P, Camus P, Pepin JL, Rabec C. Usefulness of transcutaneous PCO2 to assess nocturnal hypoventilation in restrictive lung disorders. Respirology. 2016;21(7):1300–6.
75. Janssens JP, Borel JC, Pépin JL, SomnoNIV Group. Nocturnal monitoring of home noninvasive ventilation: the contribution of simple tools such as pulse oximetry, capnography, built-in ventilator software and autonomic markers of sleep fragmentation. Thorax. 2011;66(5):438–45.
76. Nardi J, Prigent H, Adala A, Bohic M, Lebargy F, Quera-Salva MA, Orlikowski D, Lofaso F. Nocturnal oximetry and transcutaneous carbon dioxide in home-ventilated neuromuscular patients. Respir Care. 2012;57(9):1425–30.
77. Nardi J, Prigent H, Garnier B, Lebargy F, Quera-Salva MA, Orlikowski D, Lofaso F. Efficiency of invasive mechanical ventilation during sleep in Duchenne muscular dystrophy. Sleep Med. 2012;13(8):1056–65.
78. Gonzalez-Bermejo J, Janssens JP, Rabec C, Perrin C, Lofaso F, Langevin B, Carlucci A, Lujan M, SomnoNIV Group. Framework for patient-ventilator asynchrony during long-term non-invasive ventilation. Thorax. 2019;74(7):715–7.
79. Pasquina P, Adler D, Farr P, Bourqui P, Bridevaux PO, Janssens JP. What does built-in software of home ventilators tell us? An observational study of 150 patients on home ventilation. Respiration. 2012;83(4):293–9.

80. Rabec C, Georges M, Kabeya NK, Baudouin N, Massin F, Reybet-Degat O, Camus P. Evaluating noninvasive ventilation using a monitoring system coupled to a ventilator: a bench-to-bedside study. Eur Respir J. 2009;34:902–13.
81. Gonzalez-Bermejo J, Perrin C, Janssens JP, Pepin JL, Mroue G, Léger P, Langevin B, Rouault S, Rabec C, Rodenstein D, SomnoNIV Group. Proposal for a systematic analysis of polygraphy or polysomnography for identifying and scoring abnormal events occurring during non-invasive ventilation. Thorax. 2012;67(6):546–52.
82. Borel JC, Tamisier R, Sonia Dias-Domingos S, Sapene M, Martin F, Stach B, Grillet Y, Muir JF, Levy P, Series F, Pepin JL, On behalf of the Scientific Council of the Sleep Registry of the French Federation of Pneumology (OSFP). Type of mask may impact on continuous positive airway pressure adherence in apneic patients. PLoS One. 2013;8(5):e64382. Published online 2013 May 15
83. de Andrade RGS, Schmeling Piccin V, Nascimento JA, Madeiro Leite Viana F, Rodrigues Genta P, Lorenzi-Filho G. Impact of the type of mask on the effectiveness of and adherence to continuous positive airway pressure treatment for obstructive sleep apnea. J Bras Pneumol. 2014;40(6):658–68.
84. Benditt JO. Full-time noninvasive ventilation: possible and desirable. Respir Care. 2006;51:1005–12. discussion 1012–1005
85. Toussaint M, Steens M, Wasteels G, Soudon P. Diurnal ventilation via mouthpiece: survival in end-stage Duchenne patients. Eur Respir J. 2006;28:549–55.
86. Nardi J, Leroux K, Orlikowski D, Prigent H, Lofaso F. Home monitoring of daytime mouthpiece ventilation effectiveness in patients with neuromuscular disease. Chron Respir Dis. 2016;13(1):67–74.
87. Esteban A, Frutos-Vivar F, Ferguson ND, Arabi Y, Apezteguia C, Gonzalez M, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med. 2004;350:2452–60.
88. Boussaïd G, Lofaso F, Santos DB, Vaugier I, Pottier S, Prigent H, Bahrami S, Orlikowski D. Impact of invasive ventilation on survival when non-invasive ventilation is ineffective in patients with Duchenne muscular dystrophy: a prospective cohort. Respir Med. 2016;115:26–32.
89. Fauroux B, Khirani S, Griffon L, Teng T, Lanzeray A, Amaddeo A. Non-invasive ventilation in children with neuromuscular disease. Front Pediatr. 2020;8:482.
90. Khirani S, Dabaj I, Amaddeo A, Ramirez A, Quijano-Roy S, Fauroux B. The value of respiratory muscle testing in a child with congenital muscular dystrophy. Respirol Case Rep. 2014;2(3):95–8.
91. Simonds AK. Nasal intermittent positive pressure ventilation in neuromuscular and chest wall disease. Monaldi Arch Chest Dis. 1993;48(2):165–8.
92. Davies G, Reid L. Growth of the alveoli and pulmonary arteries in childhood. Thorax. 1970;25(6):669–81.
93. Dunnill MS. The problem of lung growth. Thorax. 1982;37(8):561–3.
94. Guérin C, Vincent B, Petitjean T, Lecam P, Luizet C, Rabilloud M, Richard JC. The short-term effects of intermittent positive pressure breathing treatments on ventilation in patients with neuromuscular disease. Respir Care. 2010;55(7):866–72.
95. Pascoe JE, Sawnani H, Mayer OH, McConnell K, McDonough JM, White C, Rutkowski AM, Amin RS, Modi AC. Adherence and barriers to hyperinsufflation in children with congenital muscular dystrophy. Pediatr Pulmonol. 2017;52(7):939–45.
96. Bach JR, Mahajan K, Lipa B, Saporito L, Goncalves M, Komaroff E. Lung insufflation capacity in neuromuscular disease. Am J Phys Med Rehabil. 2008;87(9):720–5.
97. Molgat-Seon Y, Hannan LM, Dominelli PB, et al. Lung volume recruitment acutely increases respiratory system compliance in individuals with severe respiratory muscle weakness. ERJ Open Res. 2017;3(1):00135.
98. Davidson AC, Banham S, Elliott M, et al. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax. 2016;71(Suppl 2):i1–i35.

99. Racca F, Del Sorbo L, Mongini T, Vianello A, Ranieri VM. Respiratory management of acute respiratory failure in neuromuscular diseases. Minerva Anestesiol. 2010;76(1):51–62.
100. Simonds AK. Ventilator support in children with neuromuscular diseases. In: Sterni LM, Carroll JL, editors. Caring for the ventilator dependent child: a clinical guide. New York: Springer; 2016. p. 283–98.
101. Chen TK, Hsu J-H, Wu J-R, et al. Combined noninvasive ventilation and mechanical in-exsufflator in the treatment of pediatric acute neuromuscular respiratory failure. Pediatr Pulmonol. 2014;49(6):589–96.
102. Girard TD, Alhazzani W, Kress JP, Ouellette DR, Schmidt GA, Truwit JD, Burns SM, Epstein SK, Esteban A, Fan E, Ferrer M, Fraser GL, Gong MN, Hough CL, Mehta S, Nanchal R, Patel S, Pawlik AJ, Schweickert WD, Sessler CN, Strøm T, Wilson KC, Morris PE, ATS/CHEST Ad Hoc Committee on Liberation from Mechanical Ventilation in Adults. An Official American Thoracic Society/American College of Chest Physicians Clinical Practice Guideline: Liberation from Mechanical Ventilation in Critically Ill Adults. Rehabilitation protocols, ventilator liberation protocols, and cuff leak tests. Am J Respir Crit Care Med. 2017;195(1):120–33.
103. MacIntyre NR, Cook DJ, Ely EW Jr, Epstein SK, Fink JB, Heffner JE, et al. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. Chest. 2001;120(6 Suppl):375s–95s.
104. Bach JR, Saporito LR. Criteria for extubation and tracheostomy tube removal for patients with ventilatory failure. A different approach to weaning. Chest. 1996;110(6):1566–71.
105. Mehta S. Neuromuscular disease causing acute respiratory failure. Respir Care. 2006;51:1016–21.
106. Laub M, Berg S, Midgren B. Symptoms, clinical and physiological findings motivating home mechanical ventilation in patients with neuromuscular diseases. J Rehabil Med. 2006;38(4):250–4.
107. Ladeira Magdaline T, Vital Flavia MR, Andriolo Regis B, Andriolo Brenda NG, Atallah Alvaro N, Peccin MS. Pressure support versus T-tube for weaning from mechanical ventilation in adults. Cochrane Database Syst Rev. 2014;5:0527.
108. Ouellette DR, Patel S, Girard TD, Morris PE, Schmidt GA, Truwit JD, Alhazzani W, Burns SM, Epstein SK, Esteban A, Fan E, Ferrer M, Fraser GL, Gong MN, Hough CL, Mehta S, Nanchal R, Pawlik AJ, Schweickert WD, Sessler CN, Strøm T, Kress JP. Liberation from mechanical ventilation in critically ill adults: an official American College of Chest Physicians/American Thoracic Society clinical practice guideline: inspiratory pressure augmentation during spontaneous breathing trials, protocols minimizing sedation, and noninvasive ventilation immediately after extubation. Chest. 2017;151(1):166–80.
109. Ou-Yang LJ, Chen PH, Jhou HJ, Su VY, Lee CH. Proportional assist ventilation versus pressure support ventilation for weaning from mechanical ventilation in adults: a meta-analysis and trial sequential analysis. Crit Care. 2020;24(1):556.
110. Sklar MC, Burns K, Rittayamai N, et al. Effort to breathe with various spontaneous breathing trial techniques. A physiologic meta-analysis. Am J Respir Crit Care Med. 2017;195:1477–85.
111. Blackwood B, Burns KE, Cardwell CR, O'Halloran P. Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients. Cochrane Database Syst Rev. 2014;11:CD006904.
112. Ely EW, Baker AM, Dunagan DP, Burke HL, Smith AC, Kelly PT, Johnson MM, Browder RW, Bowton DL, Haponik EF. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med. 1996;335(25):1864–9.
113. Subirà C, Hernández G, Vázquez A, Rodríguez-García R, González-Castro A, García C, Rubio O, Ventura L, López A, de la Torre MC, Keough E, Arauzo V, Hermosa C, Sánchez C, Tizón A, Tenza E, Laborda C, Cabañes S, Lacueva V, Del Mar FM, Arnau A, Fernández R. Effect of pressure support vs t-piece ventilation strategies during spontaneous breathing

trials on successful extubation among patients receiving mechanical ventilation: a randomized clinical trial. JAMA. 2019;321(22):2175–82.
114. Burns KE, Adhikari NK, Keenan SP, Meade M. Use of non-invasive ventilation to wean critically ill adults off invasive ventilation: meta-analysis and systematic review. BMJ. 2009;338:b1574.
115. Girault C, Bubenheim M, Abroug F, Diehl JL, Elatrous S, Beuret P, Richecoeur J, L'Her E, Hilbert G, Capellier G, Rabbat A, Besbes M, Guérin C, Guiot P, Bénichou J, Bonmarchand G, VENISE Trial Group. Noninvasive ventilation and weaning in patients with chronic hypercapnic respiratory failure: a randomized multicenter trial. Am J Respir Crit Care Med. 2011;184(6):672–9.
116. Nava S, Gregoretti C, Fanfulla F, Squadrone E, Grassi M, Carlucci A, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med. 2005;33:2465–70.
117. Perkins GD, Mistry D, Gates S, Gao F, Snelson C, Hart N, Camporota L, Varley J, Carle C, Paramasivam E, Hoddell B, McAuley DF, Walsh TS, Blackwood B, Rose L, Lamb SE, Petrou S, Young D, Lall R, Breathe Collaborators. Effect of protocolized weaning with early extubation to noninvasive ventilation vs invasive weaning on time to liberation from mechanical ventilation among patients with respiratory failure: the breathe randomized clinical trial. JAMA. 2018;320(18):1881–8.
118. Kim SM, Kang S-W, Choi Y-C, et al. Successful extubation after weaning failure by noninvasive ventilation in patients with neuromuscular disease: case series. Ann Rehabil Med. 2017;41:450–5.
119. Gobert F, Yonis H, Tapponnier R, Fernandez R, Labaune MA, Burle JF, Barbier J, Vincent B, Cleyet M, Richard JC, Guérin C. Predicting extubation outcome by cough peak flow measured using a built-in ventilator flow meter. Respir Care. 2017;62(12):1505–19.
120. Terzi N, Lofaso F, Masson R, Beuret P, Normand H, Dumanowski E, Falaize L, Sauneuf B, Daubin C, Brunet J, Annane D, Parienti JJ, Orlikowski D. Physiological predictors of respiratory and cough assistance needs after extubation. Ann Intensive Care. 2018;8(1):18.
121. Saura P, Blanch L, Mestre J, Vallés J, Artigas A, Fernández R. Clinical consequences of the implementation of a weaning protocol. Intensive Care Med. 1996;22(10): 1052–6.
122. Umbrello M, Formenti P. Ultrasonographic assessment of diaphragm function in critically Ill subjects. Respir Care. 2016;61(4):542–55. Curr Opin Anaesthesiol 29(2):150–7
123. Doorduin J, van der Hoeven JG, Heunks LM. The differential diagnosis for failure to wean from mechanical ventilation. Curr Opin Anaesthesiol. 2016;29(2):150–7.
124. Baranello G, De Amicis R, Arnoldi MT, Zanin R, Mastella C, Masson R, Leone A, Alberti K, Foppiani A, Battezzati A, Bertoli S. Evaluation of body composition as a potential biomarker in spinal muscular atrophy. Muscle Nerve. 2020;61(4):530–4.
125. Riffard G, Toussaint M. Indications for intrapulmonary percussive ventilation (IPV): a review of the literature. Rev Mal Respir. 2012;29(2):178–90.
126. Toussaint M, Guillet MC, Paternotte S, Soudon P, Haan J. Intrapulmonary effects of setting parameters in portable intrapulmonary percussive ventilation devices. Respir Care. 2012;57(5):735–42.
127. Chen J-HH. Noninvasive ventilation and mechanical insufflator-exsufflator for acute respiratory failure in children with neuromuscular disorders. Front Pediatr. 2020;8:593282.
128. Paul GR, Gushue C, Kotha K, Shell R. The respiratory impact of novel therapies for spinal muscular atrophy. Pediatr Pulmonol. 2021;56(4):721–8.
129. Heller F, Dabaj I, Mah JK, Bergounioux J, Essid A, Bönnemann CG, Rutkowski A, Bonne G, Quijano-Roy S, Wahbi K. Cardiac manifestations of congenital LMNA-related muscular dystrophy in children: three case reports and recommendations for care. Cardiol Young. 2017;27(6):1076–82.
130. Sumanaru D, Josseran L, Essid A, Mbieleu B, Haegy I, Bergounioux J. Acute heart failure in a patient with Duchenne muscular dystrophy. Pediatr Cardiol. 2019;40(3):668–70.

131. Edwards JD, Houtrow AJ, Lucas AR, Miller RL, Keens TG, Panitch HB, Dudley RA. Children and young adults who received tracheostomies or were initiated on long-term ventilation in PICUs. Pediatr Crit Care Med. 2016;17(8):e324–34.
132. Terragni P, Faggiano C, Martin EL, Ranieri VM. Tracheostomy in mechanical ventilation. Semin Respir Crit Care Med. 2014;35(4):482–91.
133. Gergin O, Adil EA, Kawai K, Watters K, Moritz E, Rahbar R. Indications of pediatric tracheostomy over the last 30 years: has anything changed? Int J Pediatr Otorhinolaryngol. 2016;87:144–7.
134. Rul B, Carnevale F, Estournet B, Rudler M, Hervé C. Tracheotomy and children with spinal muscular atrophy type 1: ethical considerations in the French context. Nurs Ethics. 2012;19(3):408–18.
135. Pilcher DV, Bailey MJ, Treacher DF, Hamid S, Williams AJ, Davidson AC. Outcomes, cost and long term survival of patients referred to a regional weaning centre. Thorax. 2005;60(3):187–92.

Chapter 6
Emergencies in Motor Neuron Diseases

Laurent Servais and Philip Van Damme

Introduction

Motor neuron disorders consist of a group of diseases primarily affecting the upper motor neurons in the motor cortex and/or the lower motor neurons in the brain stem nuclei and ventral horn of the spinal cord. Degeneration of lower motor neurons leads to loss of innervation of skeletal muscles, which is clinically manifested by muscle weakness, muscle atrophy, fasciculations, reduced muscle tone, and hyporeflexia. Dysfunction of upper motor neurons gives rise to loss of coordinated movements, slowing of movements, hyperreflexia, and increased muscle tone. Depending on the speed of disease progression and the involvement of bulbar and respiratory muscles, life expectancy in patients with motor neuron disorders can be severely reduced.

In children, the most common motor neuron disorder is 5q-spinal muscular atrophy (SMA). 5q-SMA results in the loss of functional SMN protein, which is encoded by the *SMN1* gene located on the long arm of chromosome 5 [1, 2]. It is an autosomal-recessive disease affecting around 1 in 9000–10,000 newborns. About 95% of patients have a homozygous deletion in the *SMN1* gene, and a heterozygous

L. Servais (✉)
Department of Paediatrics, MDUK Neuromuscular Centre, University of Oxford, Oxford, UK

Division of Child Neurology, Department of Pediatrics, Neuromuscular Reference Center, University Hospital Liège and University of Liège, Liège, Belgium
e-mail: laurent.servais@paediatrics.ox.ac.uk

P. Van Damme (✉)
Department of Neurosciences, Experimental Neurology, and Leuven Brain Institute (LBI), KU Leuven—University of Leuven, Leuven, Belgium

Laboratory of Neurobiology, VIB, Center for Brain and Disease Research, Leuven, Belgium

Department of Neurology, University Hospitals Leuven, Leuven, Belgium
e-mail: philip.vandamme@uzleuven.be

M. Damian, M. de Visser (eds.), *Emergencies in Neuromuscular Disorders*,
https://doi.org/10.1007/978-3-030-91932-0_6

deletion and a point mutation account for only 5% of cases. Humans also express the *SMN2* gene that can be present in multiple copies. *SMN2* differs from *SMN1* only by five nucleotides, of which a critical C to T substitution in exon 7 affects the alternative splicing of the RNA so that exon 7 is excluded from most SMN2 mRNA transcripts. However, a small amount of functional protein is expressed from *SMN2*, which explains the correlation between SMN2 copy numbers and phenotype [1, 2].

Spinal and bulbar motor neurons of the anterior horns are especially sensitive to the lack of SMN protein, leading to the characteristic features of hypotonia, muscle weakness, and areflexia in SMA.

On the most severe end of the spectrum (SMA0) are patients with symptom onset during fetal development or at birth, with contractures, respiratory insufficiency, and a very limited life expectancy. The most frequent form, SMA1, is characterized by the onset of symptoms before the age of 6 months and limited life expectancy in the absence of supportive treatment. Most patients with SMA1 have either two or three copies of *SMN2*. Patients who develop symptoms after the acquisition of the sitting position but not the autonomous ambulation constitute the SMA2 group and harbor two, three, or four copies of *SMN2*. Patients with SMA3 are able to achieve independent ambulation, although a large proportion of them will subsequently lose this function over time. A very limited number of patients start having symptoms in adulthood and are referred to as SMA4, most with four or more copies of *SMN2*. Across the disease severity, SMA is associated with a significant burden [3]. There are also different forms of non-5q-related SMA, caused by a growing list of genes [4].

A rare but notable form of motor neuron disease in children is the Brown–Vialetto Van Laere syndrome that is caused by a mutation in the riboflavin transporter and is associated with bulbospinal atrophy syndrome and deafness. This form is important to recognize as it can be treated with a high dose of riboflavin [5].

In adults, the most common motor neuron disorder is amyotrophic lateral sclerosis (ALS) [6]. ALS is characterized by the loss of upper and lower motor neurons, giving rise to progressive muscle weakness and wasting. ALS has a relatively low prevalence (4–10/100,000), although the lifetime risk to attract ALS is estimated to be 1/400 [7]. The incidence ranges from 1.75 to 3 per 100,000 persons per year [8]. The disease is more prevalent in males, at least in spinal onset ALS [9]. The age at onset is variable, ranging from 16 to above 85 years of age, but the 45–75 age group has the highest risk to develop ALS.

In the majority (~85%) of patients, the cause of ALS remains enigmatic. In about 10%, there is a family history of ALS, suggestive of a monogenetic form of ALS with high penetrance. In 90% of patients, there are no affected relatives and such patients can be classified as having sporadic ALS. Even in such patients, the heritability of ALS is estimated to be around 60% [10]. The genetic landscape of sporadic ALS is complex. Most likely, both monogenetic subtypes of ALS with reduced penetrance, genetic risk factors, and environmental factors contribute to the risk of sporadic ALS.

The most frequent monogenetic causes of ALS are all inherited in an autosomal-dominant manner. Mutations in the *chromosome 9 open reading frame 72* (*C9orf72*) are responsible for 30–50% of familial ALS, but also encountered in ~7% of sporadic ALS [11–13]. Such mutations are also frequently encountered in patients with frontotemporal dementia (FTD) or in patients with ALS-FTD. FTD is a

neurodegenerative disorder primarily affecting the frontal and anterior temporal lobes, which has overlapping clinical, genetic, and neuropathological features with ALS [14]. Mutations in the *superoxide dismutase 1* gene (*SOD1*) are responsible for 20% of familial cases. Mutations in the genes encoding TAR DNA-binding protein 43 (*TARDBP*) and fused in sarcoma (*FUS*) are responsible for 3–5% of familial cases [15]. At the neuropathological level, patients with mutations in the genes encoding SOD1, TDP-43, and FUS display intraneuronal ubiquitin-positive aggregates of these respective disease proteins. The majority of ALS patients (including patients with sporadic ALS and patients with *C9orf72* mutations) have TDP-43 pathological lesions in the brain and spinal cord [16].

Patients with ALS typically have a focal onset of disease manifestations, which occurs in the bulbar muscles (in about 1/3 of the patients, called "bulbar ALS") or in the limb muscles (in about 2/3 of patients, called "spinal ALS," Fig. 6.1). Bulbar ALS can present with progressive dysarthria, dysphagia, and/or dysphonia. Spinal

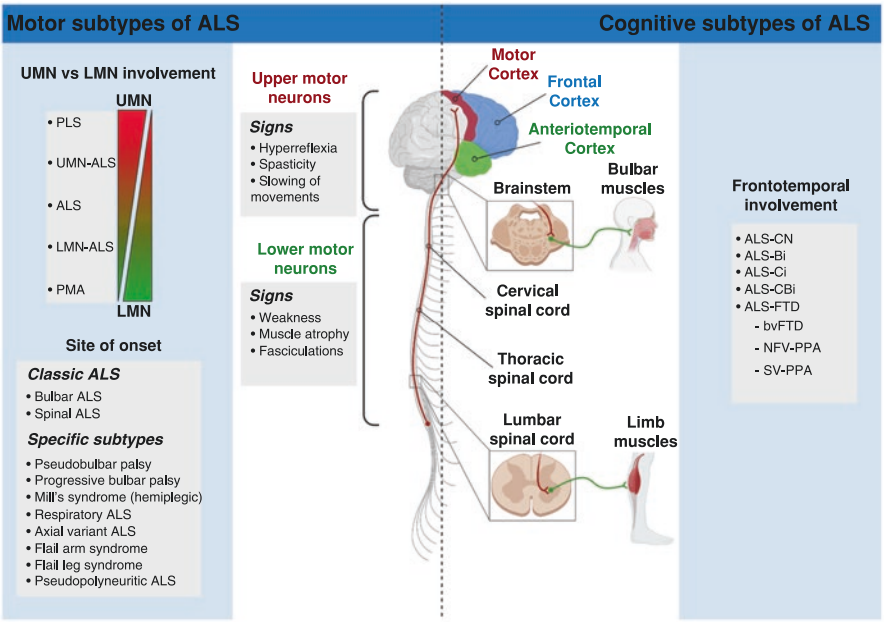


Fig. 6.1 Core features and phenotypic presentations of ALS. The central part of the figure depicts the neuroanatomical aspects of ALS and the signs associated with a loss of upper motor neurons in the motor cortex and of lower motor neurons in the brain stem nuclei and the ventral horn of the spinal cord. The left part of the figure describes different motor subtypes of ALS, which can be classified according to the site of onset, and the relative amount of upper versus lower motor neuron involvement. The right part of the figure shows the different cognitive subtypes of ALS. *ALS-Bi* ALS with behavioral impairment, *ALS-CBi* ALS with cognitive and behavioral impairment, *ALS-Ci* ALS with cognitive impairment, *ALS-CN* ALS cognitively normal, *ALS-FTD* ALS with frontotemporal dementia, *bvFTD* behavioral variant FTD, *LMN* lower motor neuron, *LMN-ALS* LMN predominant ALS, *NFV-PPA* nonfluent variant of primary progressive aphasia, *PLS* primary lateral sclerosis, *PMA* progressive muscular atrophy, *SV-PPA* semantic variant of primary progressive aphasia, *UMN* upper motor neuron, *UMN-ALS* UMN predominant ALS. Adapted from [6]

ALS patients generally have a unilateral distal limb (hand or distal leg) weakness at disease onset. After disease onset, ALS has a tendency to lead to progressive impairment in the region of onset, but also to spread to neighboring body regions [17, 18]. The median survival after disease onset is only 3 years, mostly due to dysfunction of bulbar muscles and respiratory muscles. Negative predictors of survival include older age at onset, bulbar onset, a short diagnostic delay, a reduced forced vital capacity, pronounced weight loss, widespread disease at first presentation, the presence of a *C9orf72* mutation, and the presence of concomitant frontotemporal dysfunction or frank frontotemporal dementia [19, 20].

The diagnosis of ALS relies on clinical judgment and can be made in patients with progressive muscle weakness in whom no alternative cause for the signs and symptoms of the patient can be identified. The original El Escorial criteria have been amended twice (revised El Escorial criteria, Awaji algorithm) to increase the sensitivity [21–24]. These criteria link the diagnostic certainty to the spreading of the disease, with disease manifestations in one, two, or three body regions, and allow categorizing patients as having possible, probable, or definite ALS, respectively. Recently, a simplified set of clinical diagnostic criteria has been proposed that allows making a diagnosis of ALS if combined signs of upper and lower motor neuron dysfunction are present in one body region or if signs of lower motor neuron involvement are present in at least two body regions [25]. It is important to discriminate ALS from diseases that can present with symptoms mimicking ALS. Bulbar weakness, including tongue atrophy, can be seen in Kennedy disease (bulbospinal muscular atrophy, an X-linked recessive disorder caused by an expansion of a CAG repeat in the *androgen receptor* gene [26]) or in myasthenia gravis with anti-MuSK (muscle-specific kinase) antibodies [27]. In both conditions, there can be limb weakness as well, but there will be no upper motor neuron features. Focal distal weakness in the upper or lower limb without upper motor neuron involvement can also be the first disease manifestation of multifocal motor neuropathy or inclusion body myositis. Therefore, electrodiagnostic testing is not only important for the confirmation of the diagnosis of ALS, but also to exclude other conditions that can present with muscle weakness.

There are no effective treatments available for ALS. Riluzole is the only drug that is approved by both the EMA and FDA, but has a limited effect (of 2–3 months) on survival [28]. Intermittent intravenous administration of edaravone was shown to have a mild effect on functional decline in selected people with ALS, but has only been approved by the FDA, not by the EMA [29]. Multidisciplinary care consisting of nutritional and respiratory support and the management of disease-related symptoms remains the cornerstone of the treatment of patients with ALS.

Although ALS is a well-recognized clinical entity that can be readily diagnosed in most patients, there is a large degree of heterogeneity in clinical disease presentations (Fig. 6.1). Classic ALS, the prototypical disease phenotype, has a very broad range of age at onset, disease progression rates, and survival time. This phenotypic variability poses challenges for the planning of care, but also for the design of clinical trials. In addition to motor impairment, at least 50% of ALS patients also suffer

from variable cognitive and behavioral problems (Fig. 6.1). In about 10% of patients, the diagnosis of FTD can be made. The most common form of FTD associated with ALS is behavioral variant FTD. The nonfluent and semantic variant of primary progressive aphasia is much rarer. In 30–40% of patients, an intermediate cognitive phenotype with milder behavioral, executive or language impairments is present [30].

Apart from typical ALS, rarer forms of motor neuron disease exist, which can be classified according to the relative involvement of upper versus lower motor neuron involvement and the variability in the site of symptom onset [6]. Primary lateral sclerosis (PLS) is a more slowly progressive pure upper motor neuron disorder. Progressive muscular atrophy (PMA) is a pure lower motor neuron disorder, which has a disease course that resembles ALS. Intermediate variants with predominant upper or lower motor neuron involvement can be labeled as upper motor neuron predominant and lower motor neuron predominant ALS, respectively, although there is no consensus on how to diagnose these subtypes.

As mentioned above, in classic ALS, the disease mostly starts in distal limb muscles or in bulbar muscles. Rarer sites of onset include respiratory onset ALS (with respiratory insufficiency as the manifesting symptom), axial variant ALS (with paravertebral weakness and stooped posture as the first manifestation of disease), flail arm syndrome, and flail leg syndrome. In pseudopolyneuritic ALS, there is a rather symmetrical distal onset of weakness in lower and upper limbs.

Pseudobulbar palsy is a rare slowly progressive upper motor neuron bulbar variant of motor neuron disease, whereas progressive bulbar palsy patients have a bulbar onset lower motor neuron variant of ALS. Mill's syndrome (a hemiplegic variant) is a rare slowly progressive upper motor neuron predominant form of motor neuron disease that causes unilateral spasticity and weakness. It is important to recognize these variations in ALS disease presentations as they have different life expectancies [31].

Emergencies in Spinal Muscular Atrophy

Diagnosis

The first emergency in SMA is the diagnostic. Indeed, there are today three drugs that have been approved by the EMA and FDA [32–36]. A constant finding across the different programs is that disease duration is the main prognosis factor of treatment efficacy [34, 37–39], which has prompted several newborn screening programs in different regions of the EU [40–42], in Australia [43], and the United States [44]. Studies of biomarkers of motor neuron destruction have largely confirmed that initiating a disease-modifying treatment is an emergency [45].

Clinical Vignette 1

An otherwise healthy 3-month-old girl presented with truncal hypotonia, decreased spontaneous movements, and loss of head control. She is the third child of nonrelated parents, and her siblings are healthy. The parents quickly noticed their daughter's unusual loss of motor acquisition as they could easily compare this with the development of their other children. The baby was born in Southern Belgium, where SMA is screened at birth; nevertheless, the pediatrician noticed the typical phenotype of SMA1, including proximal and axial weakness, bright eyes, weakness more severe at the lower limb level, areflexia, and tongue fasciculations.

The patient was promptly referred to the Neuromuscular Center. Given the fact that she was screened negative for a homozygous deletion of exon 7, the sequencing of the SMN1 gene was immediately prescribed, and the diagnostic of SMA1 due to a heterozygous SMN1 deletion and a point mutation on the second allele was confirmed within 10 days. Standards of care were initiated during this period of time. Nusinersen treatment was initiated 2 days after the confirmation of diagnosis, and the patient presented with a positive motor evolution since she acquired the sitting position at the age of 13 months. She is on a prophylactic noninvasive ventilation at night, is immunized against respiratory syncytial virus, and benefits from chest and motor physiotherapy and multidisciplinary follow-ups.

Learning Points

This clinical vignette illustrates how clinical diagnosis is important even in the context of newborn screening. Newborn screening detects homozygous deletion in 100% of cases, but cannot detect point mutation. The awareness of the first-line pediatrician prompted immediate diagnosis and treatment initiation, which contributed to the good clinical outcome.

Choking

Choking is a frequent issue in SMA 1 and, to a lesser extent, SMA2 [46]. The consequences of choking are amplified by inability or reduced power in coughing. Given the high frequency of choking events in daily life, parents should be trained and equipped to support airway clearance, such as with oral suctioning devices, manual chest therapy methods, and, if possible, with a cough insufflator/exsufflator such as Cough Assist® or VitalCough® [47]. In the context of an acute respiratory failure in a patient with SMA, airways clearance should always be considered a top priority in therapeutic management.

Respiratory Emergency

Emergencies that result from an acute respiratory event are frequently caused by a complex combination of choking, inability to cough, poor respiratory clearance, and infection, leading to hypercapnia and respiratory failure [48]. This applies especially to patients with SMA type 1 and, to a certain extent, patients with type 2. Management should always consider the implication of the different mechanisms and include

(a) Protection of respiratory airways (proclive position, oral aspiration, decreasing or suspending oral alimentation, and ultimately, oral or nasopharyngeal intubation).
(b) Improved airways clearance, including intensive chest physiotherapy with a cough insufflator/exsufflator.
(c) Treatment of infection with large spectrum IV antibiotics.
(d) Treatment of respiratory failure through noninvasive ventilation using bilevel positive airway pressure. The ventilatory support, including the FiO_2, should be evaluated on the global gas exchange profile rather than on the oxygen saturation level. In all cases, passive oxygen or continuous positive airway pressure should be avoided.

Parents should be aware that intubation may result in long-term or definitive dependence on invasive ventilation, and therefore, its indication should be carefully selected and discussed from an ethical perspective.

Overall, implementation of standards of care, including chest physiotherapy, parents' training, careful evaluation of swallowing, immunization using palivizumab through 24 months, and annual influenza vaccination after 6 months of age, may allow for a decrease in the incidence of such events [47].

Clinical Vignette 2

A 7-month-old baby with SMA1 (onset of symptoms at the age of 2 months) traveled with his parents to Belgium from his native country as they wished for him to be included in a clinical trial. They had not had previous contact with the principal investigator. The child's weight was 5 kg, and his height was 68 cm. Standards of care had not yet been implemented, the baby had not yet been immunized, no vaccination had been performed, and the parents had not been trained for oral suction or chest physiotherapy. The baby was breastfed, and meals took up to 90 min, with frequent pauses and choking episodes.

In the waiting room, he presented with acute respiratory failure, a respiratory rate up to 85/min, severe intercostal retraction, and clear cyanosis. After careful oral and pharyngeal aspiration and airways clearing maneuvers, the child was initially ventilated through a bag valve mask that allows for an

improvement of the clinical cyanosis. A chest X-ray demonstrated acute condensation in the right middle lobe and additional condensation in the lower right lobe. Amoxicilline-Acide Clavulanique 100 mg/kg/day and intense physiotherapy plus noninvasive ventilation were initiated.

After the initial stabilization of the patient, the parents were invited for a discussion through a translator with the principal investigator of the trial in which they had hoped their child could be involved, and the ICU doctor. The clinicians explained that the baby was unfortunately not within the inclusion criteria of the clinical trial, and that in the case of acute failure, there was a high risk of the need for invasive ventilation, and then for long-term/definitive invasive ventilation that could not be reversed by any disease-modifying therapy. The parents were invited for a second discussion during which they expressed that they preferred to avoid invasive resuscitation, but asked that the doctors "do anything they can until intubation is needed."

The child deceased peacefully in the arms of his parents 3 days later. In a follow-up discussion, the parents expressed that feeling that they had done "everything they could" for their child was helpful for them in the mourning process.

Learning Points

The innovative clinical trials that have been conducted over the last several years as well as early access programs have prompted many parents of children with SMA to travel to countries where they can hope to be part of these programs. Unfortunately, this is sometimes associated with a misunderstanding of the reasonable expectations that can be raised from an innovative medication in a postsymptomatic patient and the inclusion process in a clinical trial. Traveling with an SMA1 baby can be extremely dangerous, and basic standards of care, including parents training to perform oral suction and airways clearance maneuvers, should be initiated before traveling. Patients should also be evaluated before traveling; not only to estimate the risk, but also the benefit of such travel.

Parents should be clearly informed of the risk of irreversibility of intubation, regardless of the disease-modifying treatment that is initiated.

Metabolic Management During Emergency/Surgical Procedures

Patients with SMA present with impaired lipid metabolism [49, 50], which may be the combined consequence of muscle wasting [51] and SMN protein absence in peripheral tissue as has been recently suggested [52]. It is thus recommended to

adequately support patients with fluids, ions, and glucose who undergo elective (such as gastrostomy placement) or acute (such as femoral osteotomies) surgery, or during routine illness such as gastroenteritis [47].

Fractures

Fractures constitute a common issue in spinal muscular atrophy [53, 54]. Although fractures are also very common in other pediatric conditions that cause severe immobility, such as cerebral palsy [55], it has been recently suggested that fractures could also result from the absence of SMN protein in bone tissues [53].

Fractures appear more frequently in the upper leg region, followed by lower leg and ankle fractures [56]. In ambulant patients, the incidence of fracture of upper extremities increases with the risk of falls; the distribution of fractures in SMA type IIIa differs slightly, with a higher prevalence for fractures in upper extremities [56].

Osteosynthesis should be discussed with regard to the bone mineralization that is needed to ensure proper early remobilization and functional treatment after surgery, and should be driven by functional considerations.

Conservative treatment is likely to result in subsequent severe muscle atrophy, and thus could be considered when there is little functional hope (for instance, femoral fractures in a nonsitter patient) or with severe demineralization [57]. Demineralization can, to a certain extent, be limited by a proper application of preventive measures (calcium and vitamin D intake, mobilization, bisphosphonate treatment in primary or secondary prevention), and functional considerations should now be envisaged in the context of the change of patients' trajectory when treated by disease-modifying treatments [58].

Emergencies in Amyotrophic Lateral Sclerosis

Most emergencies in patients with amyotrophic lateral sclerosis are related to worsening bulbar and respiratory muscle weakness. Swallowing problems can give rise to reduced caloric intake and weight loss, but also to choking and aspiration pneumonia. Respiratory muscle weakness can present with shortness of breath upon physical activity or at rest, but can also induce nocturnal hypercapnia, which can be life-threatening. Vocal cord dysfunction can present with laryngospasm or stridor, which can be frightening to patients. Other medical emergencies that are related to immobility, especially of the lower limbs, include deep venous thrombosis and pulmonary embolus.

While the management of patients with ALS is geared toward anticipating the problems associated with disease progression and informing the patients about possible interventions in a timely manner, it is not always possible to avoid emergency situations and acute hospital admissions. On such occasions, it is extremely helpful to have advance life directives available that can guide decision-making. However,

in some cases, unexpected sudden worsening may occur and some patients change their view on treatment options along the disease trajectory. It is therefore always important to involve the patient and their close relatives in a process of joint decision-making, whenever this is possible. In this process, the stage of the disease and the disease progression rate (which is related to the specific disease phenotype) are important to consider as well.

Respiratory Failure

Respiratory failure is the leading cause of death in patients with ALS [59]. Early manifestations of emergent respiratory muscle weakness include morning headaches, frequent nocturnal awakenings, poor appetite, and daytime fatigue. Shortness of breath upon exertion or talking and orthopnea are manifest symptoms of respiratory insufficiency. The most widely used treatment for respiratory muscle weakness is noninvasive ventilation, which has been shown to prolong survival and improve the quality of life in patients with ALS [60, 61]. In patients with bulbar weakness, noninvasive ventilation is less well tolerated, in part due to oral and pharyngeal secretions [62]. Noninvasive ventilation can also improve the daytime sleepiness, the quality of sleep, and can result in an improved appetite and weight gain [63, 64].

Several methods are used to monitor the respiratory function in patients with ALS, such as upright and supine forced vital capacity, slow vital capacity, sniff nasal pressure, percutaneous nocturnal oximetry and/or capnography, or arterial blood gasses [65, 66]. Although there are no trials that convincingly demonstrate that early initiation of noninvasive ventilation results in a better outcome, it is important to monitor the patient's respiratory symptoms, signs and respiratory tests, and discuss the therapeutic options in due time.

If patients do not wish to be ventilated, this should be documented in advance life directives. Ideally, a management plan should be in place before the respiratory complications occur. However, respiratory failure cannot always be anticipated (as described in Clinical Vignette 1) because some patients postpone the decision about ventilation, have an unexpected rapid decline in respiratory function, or show respiratory distress when they first present.

Clinical Vignette 3

A 51-year-old patient was diagnosed with ALS after presenting at the emergency department, 4 months after the initial occurrence of swallowing problems. During this period, more than 20 kg of weight was lost and the swallowing problems were rapidly followed by muscle weakness in both upper limbs.

On clinical examination, a clear dysarthria was present. Examination of the cranial nerves revealed some facial weakness and profound weakness and atrophy of the tongue with an exaggerated jaw reflex. In the upper limbs, a distal weakness was present, with atrophy of the thenar and hypothenar muscles on both sides, and reflexes were jerky. Electrodiagnostic testing revealed signs of lower motor neuron degeneration with fibrillation potentials and sharp waves in the bulbar, thoracic, and cervical regions. The forced vital capacity was 66% of the expected value, but no symptoms of respiratory failure were present. Treatment with riluzole was initiated, and because swallowing had become hazardous, the patient agreed to undergo an urgent gastrostomy tube insertion. The initiation of enteral nutrition went well, and a multidisciplinary follow-up 1 month later was planned upon discharge.

However, only 3 weeks later the patient was again admitted to the emergency department due to dyspnea, exhaustion, and reduced consciousness. The patient had a respiratory failure with hypercapnia ($PaCO_2$ of 51 mmHg, which quickly evolved to levels of 107 mmHg). There were no signs of a respiratory tract infection. Noninvasive ventilation was started in an acute emergency setting, but nevertheless could be successfully initiated.

The hypercapnia recovered, and the patient became alert and communicative again. Given the rapid disease progression and the rapidly reduced quality of life, the patient expressed that he no longer wished to be ventilated. Palliative care was administered, and the respiratory support stopped after thorough discussions with the patient and the family. The patient peacefully died 1 day later, only 5 months after disease onset.

Learning Points

In this clinical vignette, a pure respiratory pump failure caused the respiratory symptoms of the patient. The disease progression was so rapid that there was no time to discuss the therapeutic options in depth before the respiratory failure set in. In many cases, the presence of secretions, silent or clinically apparent aspiration or pulmonary infections, may further complicate the patient's state. Depending on the clinical picture (including the disease stage and the age and comorbidities of the patient) and the wishes of the patient and the family, more invasive therapies may be considered. Infections can be treated with antibiotics, secretions with anticholinergics, or if needed bronchial aspirations. In most cases, it is possible to avoid intubation of patients after discussing the different treatment options with the patient and caregivers.

Choking

Although most patients in the terminal stage of ALS die peacefully, some patients exhibit distress in the dying process, which can be related to breathing difficulty, anxiety, pain, insomnia, or choking [59]. Acute asphyxia due to severe choking is rare. Swallowing and nutritional management are geared toward avoiding choking and optimizing caloric intake. Simple measures, such as a change in body position, compensatory techniques, and dietary changes, can reduce the risk of choking in patients with swallowing problems [67]. However, patients do not always follow the advice given to them. Therefore, it can be helpful to teach the primary caregivers how to perform a Heimlich maneuver, which can be used in the event of severe choking. This maneuver consists of an abdominal thrust that can be life-saving in case of an upper airway obstruction caused by a foreign body (e.g., a piece of meat that was too large to swallow) [68].

Risks of Gastrostomy Tube Placement

In patients with severe dysphagia, loss of body weight, episodes of aspiration, and aspiration pneumonia reduce the quality of life and increase the risk of mortality. Gastrostomy feeding is recommended to provide long-term nutritional support and reduce the risks of aspiration [69]. However, the placement of a gastrostomy may become hazardous in patients in an advanced stage of the disease, especially if the respiratory function is impaired. Gastrostomy-related mortality can be linked to the procedure, refeeding syndrome, or postoperative respiratory failure. The 30-day mortality rate after a gastrostomy seems independent from the method of gastrostomy placement, and ranges from about 1% to 4% [70, 71]. Observational studies suggest a survival benefit of enteral feeding, especially in patients with less pronounced weight loss [70, 71].

For all of these reasons, guidelines generally recommend gastrostomy for patients with severe dysphagia, but a forced vital capacity of greater than 50% of the predicted value [69, 72]. To mitigate the risks of respiratory failure during and after gastrostomy insertion, noninvasive ventilation can be initiated prior to the procedure in patients with signs or symptoms of emerging respiratory impairment. Most patients with respiratory impairment can safely undergo a percutaneous endoscopic gastrostomy under mild sedation (e.g., midazolam or propofol) when ventilated during the procedure using noninvasive ventilation via either a nasal mask or a special endoscopic mask (with an opening that allows the insertion of the endoscope) [73–75].

Intensive monitoring of the nutritional and respiratory status of ALS patients is important to determine the optimal moment for initiation of noninvasive ventilation and gastrostomy placement, and thus to avoid emergency complication of gastrostomy placement. However, some patients decline the use of noninvasive ventilation

or do not tolerate the treatment, but may still want to be fed by enteral nutrition. In such cases, a difficult decision has to be taken after discussing with the patient the risks of the gastrostomy placement and the lack of therapeutic options in case of respiratory complications after the procedure.

Laryngospasm and Stridor

Vocal cord dysfunction is a rare presentation of ALS, but commonly develops during the course of the disease. At some point, most patients experience hoarseness, reduced vocal volume, or changed voice quality. On laryngological examination, reduced vocal cord closure can be noted [76]. In addition, a reduced laryngeal adductor reflex may also contribute to the aspiration risk [77]. Glottic narrowing, on the contrary, can cause laryngospasms and stridor in ALS; this can be caused by abductor paresis, but paradoxical inspiratory adduction of the vocal cords has also been reported in ALS [78, 79].

Glottic narrowing and bouts of glottic closure are life-threatening events. In laryngospasm, patients experience attacks of sudden dyspnea or suffocation, which are often accompanied by inspiratory stridor. These attacks are usually self-limiting and last only a few seconds, but they are frightening to patients and their caregivers. Laryngospasm has been reported in 2% of ALS patients, although higher frequencies have been observed if specifically asked for [80]. They can be triggered by laryngeal secretions, coughing, smoke, cold air, or gastroesophageal reflux [81]. In the case of reflux, antireflux therapy can be attempted. Nonpharmacological measures (such as a rapid change to an upright position with fixation of the arms to stabilize the body, breathing through the nose, swallowing repetitively, and breathing with slow exhalation through lips) can help many patients to handle the attacks [81]. Benzodiazepines can be used to reduce the frequency of episodes of laryngospasm.

Stridor is caused by turbulence during breathing (usually inspiratory) through a narrowed glottis. It is a rare symptom in ALS, but it can cause pronounced distress, most often at night. Very few reports about stridor in ALS exist. The exact prevalence is not known, and no guidelines on the management of stridor exist. In case of severe therapy-resistant vocal cord dysfunction, more invasive treatment strategies, such as cordotomy or tracheostomy, can be considered.

Clinical Vignette 4

A 58-year-old patient was diagnosed with bulbar ALS after developing progressive dysarthria and dysphagia a few months earlier. A clinical examination showed pronounced tongue weakness with tongue atrophy and fasciculations, and an exaggerated jaw jerk. Some facial weakness was also

noted. Muscle strength in the limbs was normal, although some fasciculations in the upper limbs were present. The reflexes were rather weak, and the plantar responses were downgoing. Needle EMG displayed fasciculations and chronic neurogenic changes in the tongue and the orbicularis oris muscle, as well as in the biceps and triceps. The diagnosis of ALS was made and therapy with riluzole initiated. The forced vital capacity was good (121% of predicted).

The bulbar symptoms progressed rapidly, and the patient became anarthric within 6 months after disease onset. Because of sialorrhea, a treatment with oxybutynine was started. The patient later developed uncontrolled laughing, which was treated with dextromethorphan hydrobromide/quinidine sulfate.

Two years after disease onset, the patient experienced inspiratory stridor, which was especially bothersome at night and made sleeping difficult. By this point, the patient had lost more than 10% of her body weight and could only eat mixed food. The strength of her limbs was reduced, but the patient was still capable of independently performing most daily activities. There was dyspnea upon exertion, but the patient reported no orthopnea or morning headaches. A spirometry could no longer be performed, but the patient had normal arterial blood gas values. A laryngoscopy showed immobile vocal cords in the paramedian position. The difficult situation of emerging respiratory insufficiency, swallowing problems with insufficient caloric intake, and risk of aspiration in combination with inspiratory stridor was discussed in a multidisciplinary manner involving both the patient and her primary caregiver. Noninvasive ventilation was thought to be difficult (severe bulbar dysfunction, vocal cord dysfunction) and was not opted for by the patient. A gastrostomy was proposed, but was not favored by the patient.

A posterior cordotomy was then considered in a palliative setting to mitigate the disabling stridor that prevented the patient from sleeping. Because this intervention would increase the risk of aspiration, it was agreed that it would be better to perform this only if a gastrostomy was inserted as well. The option of purely palliative care was also discussed. As the patient suffered considerably from the stridor (especially at night), a joint decision to perform a posterior cordotomy after gastrostomy insertion was taken, accepting the risks of general anesthesia. The surgery went well and the patient could quickly return home without stridor and was able to sleep again. Due to disease progression, the patient died at home 4 months later.

Learning Points

This case description illustrates how difficult it can be to make a clinical decision in patients with severe and disabling stridor. As there are no studies on different treatment options for stridor, the risks and benefits of interventions such as a cordotomy can only be weighed and discussed in

a multidisciplinary setting. Occasionally, an invasive procedure can dramatically increase the patient's comfort. The period of benefit after the intervention was relatively short in this case, but it was nevertheless valued as worthwhile by the patient.

Deep Venous Thrombosis and Pulmonary Embolus

Immobility is an important risk factor for deep venous thrombosis (DVT) and pulmonary embolus (PE). Patients with ALS have an increased risk to develop a DVT [82, 83]. A prospective observational study with intensive screening for the presence of DVT or PE [84] estimated the annual incidence to be 11%. In subjects with significant leg weakness, the number was even higher (35%), suggesting that it is much more common than previously thought. In patients with ALS, a PE is a life-threatening event; however, the frequency of PE causing death in patients with ALS has not been studied in detail. PE is clinically recognized as the cause of death in about 2% of patients [85], although a postmortem study has suggested that a PE is present in 8% of deceased patients. Patients who develop a clinically apparent DVT or PE can be treated according to general treatment guidelines. A diagnosis of ALS should not necessarily change the therapeutic attitude, at least in early disease stages. When considering treatments with anticoagulation, the risk of falls and the patient's life expectancy should be taken into account. There are no ALS-specific guidelines for the use of anticoagulants and the decision will always have to be tailored to the individual patient's history (Clinical Vignette 3).

Clinical Vignette 5

A diagnosis of ALS was made in a 52-year-old member of a family with a known G94C mutation of the superoxide dismutase 1 gene (SOD1) due to weakness of the toes of the left foot with brisk reflexes and denervation of intrinsic foot muscles on needle EMG. The patient gradually developed progressive muscle weakness and atrophy in the legs, and after 4 years, this was followed by bilateral distal muscle weakness and atrophy in the upper limbs. The patient became wheelchair-dependent for longer distances 9 years after disease onset, but was still able to walk short distances with a walker.

At the age of 62, the patient experienced a sudden shortness of breath while using the walker and was transferred to hospital after becoming acutely unwell. In hospital, the patient collapsed. A saddle embolus was suspected, and therefore an acute cardiac intervention with removal of thrombus material from both pulmonary arteries was carried out. The patient recovered well and was started on oral anticoagulants. The patient's forced vital capacity started to decline 12 years after disease onset, and swallowing problems

emerged 13 years after disease onset. The patient declined life-prolonging interventions such as noninvasive ventilation and eventually died 21 years after disease onset, more than 10 years after the successful treatment of the saddle embolus.

Learning Points
As demonstrated by this case, invasive life-saving therapies may be justified in selected cases with ALS. The decision-making around treatments for acute DVT and PE remains complex, with little evidence to rely on. Despite the increased risk to develop DVT and PE, pharmacological prophylaxis is not routinely recommended in patients with ALS [86]. There are no studies that show that primary prevention of DVT or PE is effective, has a good risk/benefit balance, or extends survival of patients with ALS. Further studies are needed to explore if certain subgroups of ALS patients would benefit from prophylaxis for DVT.

Concluding Remarks

One of the objectives of the management of patients with ALS and SMA is to anticipate complications of disease progression in order to avoid emergency situations and undesired hospital admissions. Advance life directives resulting from early discussions about possible life-prolonging interventions and the way potential complications should be managed are an important aspect of the management plan. However, not all emergency situations can be avoided. The decision-making process in such emergency settings is challenging for the multidisciplinary team and patients alike; involving a combination of medical, social, cultural, and ethical factors and requiring in-depth discussions with the patient and caregivers. There are no randomized controlled trials that can help us to guide such decisions, and large differences in common practices exist between different neuromuscular centers and different countries.

The appropriate response to an emergency situation can vary significantly in different circumstances, ranging from an acute invasive intervention to palliative care. In the decision-making process, the disease phenotypes, disease stage, risks of the intervention, patient's wishes, and social situation of the patient should all be balanced; under optimal conditions, the patient/family should be actively involved. In the context of SMA, the anticipated trajectory of patients treated with innovative disease-modifying treatment should also be considered. There is no conclusive evidence regarding the effectiveness and optimal timing of treatments for any of the emergencies discussed in this chapter. Further research is therefore needed in order to guide the difficult and complex decisions that must often be made.

Self Assessment Questions

1. How is the division of SMA in types 1–4 defined?

   (a) By the age at onset.
   (b) By the patient's ability to sit and walk. (*)
   (c) By the locus of the genetic defect.
   (d) By the number of SMN2-copies.

2. A rare form of motor neuron disease can be treated by a vitamin. Which vitamin?

   (a) Cobalamin.
   (b) Folic acid.
   (c) Pyridoxine.
   (d) Riboflavin. (*)
   (e) Thiamin.

3. In what percentage of the patients with ALS the cause remains enigmatic? In about….

   (a) 40%
   (b) 55%
   (c) 70%
   (d) 85% (*)

Amyotrophic lateral sclerosis is associated with some degenerative diseases of the central nervous system.

4. Which association is most frequently encountered? An association with…

   (a) Frontotemporal dementia. (*)
   (b) Late onset ataxia.
   (c) Parkinson's disease.
   (d) Progressive supranuclear palsy.

5. Which gene is most frequently involved in hereditary ALS?

   (a) CACNA1A
   (b) Notch3
   (c) SMN2
   (d) C9orf72 (*)

6. What percentage of the ALS patients starts with bulbar symptoms? About……

   (a) 2%
   (b) 5%
   (c) 20%
   (d) 33% (*)

7. Which of the following is a negative predictor of survival in ALS?

   (a) Bulbar onset. (*)
   (b) Male gender.
   (c) Painful cramps.
   (d) Younger age at onset.

A 45-year-old male developed left lower limb weakness in the course of two years. At examination proximal leg weakness and a discrete foot drop were found at the left side. No pyramidal signs, low to absent muscle stretch reflexes, and no sensory deficits. At EMG examination changes of chronic denervation were found, mainly in the proximal muscles, in several territories of peripheral nerves. The same was found in the right hip extensor which was clinically normal. Conduction studies were normal. MRI showed no spinal or pelvic abnormalities. CK was about 600 U/l (UNL 200). The diagnosis of motor neuron disease was made. Half a year later, the right leg became symptomatic as well. One year later, he felt the weakness extending to both upper limbs, voice became trembling and his speech unclear. Gradually his blood sugar metabolism became dysregulated. Physical examination at the age of 48 years: male breast development, normal external genitalia, slurred speech, tongue muscle atrophy, facial and perioral fasciculations. Weakness and atrophy of the proximal muscles of both legs. Upper limbs normal apart from tremors in both his hands. Areflexia, no sensory symptoms. No pyramidal, extrapyramidal, or cerebellar symptoms.

On inquiry no other family members were affected with these symptoms. Nevertheless genetic testing showed that there was an abnormal expansion of CAG repeats in exon 1 of the androgen receptor gene on the X-chromosome.

8. Which diagnosis is most likely in this case?

   (a) Hereditary ALS.
   (b) Progressive spinal muscle atrophy.
   (c) Spinal muscle atrophy type 4.
   (d) X-linked bulbospinal neuronopathy. (*)

9. How many ALS patients do have cognitive and behavioral problems in one way or another? About…

   (a) 2%
   (b) 5%
   (c) 20%
   (d) 50% (*)

A 40-year-old female complains of slowly progressive weakness of her right leg. Symptoms started one year ago. She had been operated upon a mamma carcinoma 10 years ago and subsequently was treated with chemotherapy. She was considered tumor-free. Climbing stairs becomes more and more difficult and she feels her right foot is dragging. At clinical examination there is weakness in her iliopsoas muscle and in a lesser degree in her quadriceps. Hip adductors on the right side may be

somewhat weakened as well, hip extensors and abductor muscles were normal. No foot drop was noted and there were no sensory abnormalities. Muscle stretch reflexes were absent in her legs, only the left knee reflex was preserved. Upper limb reflexes were low. At a first EMG no conduction abnormalities were found. Signs of denervation were present in her left leg both proximally and distally and not restricted to distinct peripheral nerve areas. MRI of her spine, pelvis, and abdomen showed no abnormalities. In spite of second opinions in two other academic centers (with new EMG-investigations) no diagnosis was made and a wait-and-see policy was accepted. In course of time, she felt more weakness in both feet and in her right shoulder. After 3 years, a 5th EMG showed progression of denervation signs and a conduction block in her left tibial nerve which was clinically unaffected.

10. Which diagnosis is most likely here?

    (a) Motor neuropathy post chemotherapy.
    (b) Multifocal motor neuropathy with conduction blocks. (*)
    (c) Paraneoplastic motor neuron disease.
    (d) Progressive spinal muscle atrophy.

11. Which of the following statements is true for SMA 1?

    (a) BiPAP is not an option.
    (b) Choking is a frequent issue. (*)
    (c) Intubation is usually reversible.
    (d) Without therapy about only 10–20% will be able to walk.

12. Which of the following complications is the most important issue in SMA?

    (a) Bone fractures. (*)
    (b) Obstructive lung disease.
    (c) Thyroid dysfunction.
    (d) Varicosis.

13. Which of the following ENT-problems is most likely to herald ALS?

    (a) Clogged ears.
    (b) Hoarseness. (*)
    (c) Nasal sniffing.
    (d) Tinnitus.

14. Which symptom is an early manifestation of respiratory muscle weakness?

    (a) Chest pain.
    (b) Headache at awakening. (*)
    (c) Irregular heart beating.
    (d) Regurgitation.

15. What may hamper non-invasive ventilation the most?

    (a) Bulbar weakness. (*)
    (b) Frequent nocturnal awakenings.

(c) Malnutrition.
(d) Profuse fasciculations.

16. Nocturnal non-invasive ventilation improves alertness of ALS patients by day.

(a) True. (*)
(b) False.

17. Nocturnal non-invasive ventilation improves appetite and thus weight gain in ALS patients.

(a) True. (*)
(b) False.

18. Acute asphyxia due to severe choking is a frequent problem in ALS.

(a) True.
(b) False. (*)

19. Invasive ventilation is the preferred treatment for respiratory muscle weakness in ALS.

(a) True.
(b) False. (*)

20. Placement of a gastrostomy should preferably be done before the respiratory function is severely impaired.

(a) True. (*)
(b) False.

21. Non-invasive ventilation during placement of a gastrostomy is an option for patients with ALS and respiratory impairment.

(a) True. (*)
(b) False.

22. Which of the following problems may occur most frequently in the context of ALS?

(a) Esophageal achalasia.
(b) Gastric reflux.
(c) Laryngospasm. (*)
(d) Uncontrollable hiccup.

23. Which of the following treatments is most effective for prevention of stridor in ALS?

(a) Benzodiazepines.
(b) Consumption of milk products.
(c) Posterior cordotomy. (*)
(d) Quinidine sulphate.

24. Current guidelines recommend preventive use of anti-coagulants in ALS patients with significant leg weakness.

    (a) True.
    (b) False. (*)

References

1. Lefebvre S, Burglen L, Frezal J, Munnich A, Melki J. The role of the SMN gene in proximal spinal muscular atrophy. Hum Mol Genet. 1998;7(10):1531–6. PubMed PMID: 9735373. Epub 1998/09/15
2. Lefebvre S, Burlet P, Liu Q, Bertrandy S, Clermont O, Munnich A, et al. Correlation between severity and SMN protein level in spinal muscular atrophy. Nat Genet. 1997;16(3):265–9. PubMed PMID: 9207792. Epub 1997/07/01
3. Chabanon A, Seferian AM, Daron A, Pereon Y, Cances C, Vuillerot C, et al. Prospective and longitudinal natural history study of patients with Type 2 and 3 spinal muscular atrophy: Baseline data NatHis-SMA study. PLoS One. 2018;13(7):e0201004. PubMed PMID: 30048507.
4. Darras BT. Spinal muscular atrophies. Pediatr Clin North Am. 2015;62(3):743–66. PubMed PMID: 26022173. Epub 2015/05/30
5. Woodcock IR, Menezes MP, Coleman L, Yaplito-Lee J, Peters H, White SM, et al. Genetic, radiologic, and clinical variability in Brown-Vialetto-van Laere syndrome. Semin Pediatr Neurol. 2018;26:2–9. PubMed PMID: 29961509. Epub 2018/07/03
6. Masrori P, Van Damme P. Amyotrophic lateral sclerosis: a clinical review. Eur J Neurol. 2020;11. PubMed PMID: 32526057. Pubmed Central PMCID: 7540334
7. Johnston CA, Stanton BR, Turner MR, Gray R, Blunt AH, Butt D, et al. Amyotrophic lateral sclerosis in an urban setting: a population based study of inner city London. J Neurol. 2006;253(12):1642–3. PubMed PMID: 17219036. Epub 2007/01/16
8. Collaborators GBDMND. Global, regional, and national burden of motor neuron diseases 1990-2016: a systematic analysis for the global burden of disease study 2016. Lancet Neurol. 2018;17(12):1083–97. PubMed PMID: 30409709. Pubmed Central PMCID: 6234315
9. Manjaly ZR, Scott KM, Abhinav K, Wijesekera L, Ganesalingam J, Goldstein LH, et al. The sex ratio in amyotrophic lateral sclerosis: a population based study. Amyotroph Lateral Scler. 2010;11(5):439–42. PubMed PMID: 20225930. Pubmed Central PMCID: PMC6485484. Epub 2010/03/17
10. Al-Chalabi A, Fang F, Hanby MF, Leigh PN, Shaw CE, Ye W, et al. An estimate of amyotrophic lateral sclerosis heritability using twin data. J Neurol Neurosurg Psychiatry. 2010;81(12):1324–6. PubMed PMID: 20861059. Pubmed Central PMCID: 2988617
11. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. Neuron. 2011;72(2):245–56. PubMed PMID: 21944778. Pubmed Central PMCID: 3202986. Epub 2011/09/29. eng
12. Renton AE, Majounie E, Waite A, Simon-Sanchez J, Rollinson S, Gibbs JR, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. Neuron. 2011;72(2):257–68. PubMed PMID: 21944779. Pubmed Central PMCID: PMC3200438. Epub 2011/09/29
13. Debray S, Race V, Crabbe V, Herdewyn S, Matthijs G, Goris A, et al. Frequency of C9orf72 repeat expansions in amyotrophic lateral sclerosis: a Belgian cohort study. Neurobiol Aging. 2013;34(12):2890.e7–e12. PubMed PMID: 23870417

14. Phukan J, Pender NP, Hardiman O. Cognitive impairment in amyotrophic lateral sclerosis. Lancet Neurol. 2007;6(11):994–1003. PubMed PMID: 17945153
15. Renton AE, Chio A, Traynor BJ. State of play in amyotrophic lateral sclerosis genetics. Nat Neurosci. 2014;17(1):17–23. PubMed PMID: 24369373. Pubmed Central PMCID: PMC4544832. Epub 2013/12/27
16. Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science. 2006;314(5796):130–3. PubMed PMID: 17023659. Epub 2006/10/07
17. Ravits JM, La Spada AR. ALS motor phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration. Neurology. 2009;73(10):805–11. PubMed PMID: 19738176. Pubmed Central PMCID: 2739608
18. Gromicho M, Figueiral M, Uysal H, Grosskreutz J, Kuzma-Kozakiewicz M, Pinto S, et al. Spreading in ALS: the relative impact of upper and lower motor neuron involvement. Ann Clin Transl Neurol. 2020;7(7):1181–92. PubMed PMID: 32558369. Pubmed Central PMCID: PMC7359118. Epub 2020/06/20
19. Chio A, Logroscino G, Hardiman O, Swingler R, Mitchell D, Beghi E, et al. Prognostic factors in ALS: a critical review. Amyotroph Lateral Scler. 2009;10(5–6):310–23. PubMed PMID: 19922118. Pubmed Central PMCID: PMC3515205. Epub 2009/11/20
20. Govaarts R, Beeldman E, Kampelmacher MJ, van Tol MJ, van den Berg LH, van der Kooi AJ, et al. The frontotemporal syndrome of ALS is associated with poor survival. J Neurol. 2016;263(12):2476–83. PubMed PMID: 27671483. Pubmed Central PMCID: 5110703
21. Brooks BR. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical limits of amyotrophic lateral sclerosis" workshop contributors. J Neurol Sci. 1994;124 Suppl:96–107. PubMed PMID: 7807156. Epub 1994/07/01.
22. Brooks BR, Miller RG, Swash M, Munsat TL. World Federation of Neurology Research Group on motor neuron D. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1(5):293–9. PubMed PMID: 11464847. Epub 2001/07/24
23. de Carvalho M, Dengler R, Eisen A, England JD, Kaji R, Kimura J, et al. Electrodiagnostic criteria for diagnosis of ALS. Clin Neurophysiol. 2008;119(3):497–503. PubMed PMID: 18164242. Epub 2008/01/01. eng
24. Schrooten M, Smetcoren C, Robberecht W, Van Damme P. Benefit of the Awaji diagnostic algorithm for amyotrophic lateral sclerosis: a prospective study. Ann Neurol. 2011;70(1):79–83. PubMed PMID: 21437935. Epub 2011/03/26. eng
25. Upadhyay V, Katz M, Kiernan M, Henderson R. Review of the revised amyotrophic lateral sclerosis diagnostic criteria. Clin Neurophysiol. 2020;131(8):1767–8. PubMed PMID: 32504937
26. Hashizume A, Fischbeck KH, Pennuto M, Fratta P, Katsuno M. Disease mechanism, biomarker and therapeutics for spinal and bulbar muscular atrophy (SBMA). J Neurol Neurosurg Psychiatry. 2020;91(10):1085–91. PubMed PMID: 32934110
27. Huijbers MG, Niks EH, Klooster R, de Visser M, Kuks JB, Veldink JH, et al. Myasthenia gravis with muscle specific kinase antibodies mimicking amyotrophic lateral sclerosis. Neuromuscul Disord. 2016;26(6):350–3. PubMed PMID: 27133662
28. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole Study Group. N Engl J Med. 1994;330(9):585–91. PubMed PMID: 8302340. Epub 1994/03/03
29. Writing G, Edaravone ALSSG. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017;16(7):505–12. PubMed PMID: 28522181. Epub 2017/05/20
30. Strong MJ, Abrahams S, Goldstein LH, Woolley S, McLaughlin P, Snowden J, et al. Amyotrophic lateral sclerosis—frontotemporal spectrum disorder (ALS-FTSD): revised

diagnostic criteria. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18(3–4):153–74. PubMed PMID: 28054827
31. Chio A, Calvo A, Moglia C, Mazzini L, Mora G, group Ps. Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. J Neurol Neurosurg Psychiatry. 2011;82(7):740–6. PubMed PMID: 21402743. Epub 2011/03/16
32. Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. N Engl J Med. 2017;377(18):1713–22. PubMed PMID: 29091557. Epub 2017/11/02
33. Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med. 2018;378(7):625–35. PubMed PMID: 29443664. Epub 2018/02/15
34. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med. 2017;377(18):1723–32. PubMed PMID: 29091570. Epub 2017/11/02
35. Naryshkin NA, Weetall M, Dakka A, Narasimhan J, Zhao X, Feng Z, et al. Motor neuron disease. SMN2 splicing modifiers improve motor function and longevity in mice with spinal muscular atrophy. Science. 2014;345(6197):688–93. PubMed PMID: 25104390. Epub 2014/08/12
36. Ramdas S, Servais L. New treatments in spinal muscular atrophy: an overview of currently available data. Expert Opin Pharmacother. 2020;21(3):307–15. PubMed PMID: 31973611. Epub 2020/01/25
37. Dangouloff T, Servais L. Clinical evidence supporting early treatment of patients with spinal muscular atrophy: current perspectives. Ther Clin Risk Manag. 2019;15:1153–61. PubMed PMID: 31632042. Pubmed Central PMCID: PMC6778729. Epub 2019/10/22
38. Pane M, Coratti G, Sansone VA, Messina S, Bruno C, Catteruccia M, et al. Nusinersen in type 1 spinal muscular atrophy: twelve-month real-world data. Ann Neurol. 2019;86(3):443–51. PubMed PMID: 31228281. Epub 2019/06/23
39. Aragon-Gawinska K, Seferian AM, Daron A, Gargaun E, Vuillerot C, Cances C, et al. Nusinersen in patients older than 7 months with spinal muscular atrophy type 1: a cohort study. Neurology. 2018;91(14):e1312–e8. PubMed PMID: 30158155. Epub 2018/08/31
40. Boemer F, Caberg JH, Dideberg V, Dardenne D, Bours V, Hiligsmann M, et al. Newborn screening for SMA in southern Belgium. Neuromuscul Disord. 2019;29(5):343–9. PubMed PMID: 31030938. Epub 2019/04/30
41. Vill K, Kolbel H, Schwartz O, Blaschek A, Olgemoller B, Harms E, et al. One year of newborn screening for SMA—results of a German pilot project. J Neuromuscul Dis. 2019;6(4):503–15. PubMed PMID: 31594245. Pubmed Central PMCID: PMC6918901. Epub 2019/10/09
42. Dangouloff T, Burghes A, Tizzano EF, Servais L, Group NSS. 244th ENMC international workshop: newborn screening in spinal muscular atrophy May 10-12, 2019, Hoofdorp, The Netherlands. Neuromuscul Disord. 2020;30(1):93–103. PubMed PMID: 31882184. Epub 2019/12/29
43. Kariyawasam DST, Russell JS, Wiley V, Alexander IE, Farrar MA. The implementation of newborn screening for spinal muscular atrophy: the Australian experience. Genet Med. 2020;22(3):557–65. PubMed PMID: 31607747. Epub 2019/10/15
44. Kay DM, Stevens CF, Parker A, Saavedra-Matiz CA Sack V, Chung WK, et al. Implementation of population-based newborn screening reveals low incidence of spinal muscular atrophy. Genet Med. 2020. PubMed PMID: 32418989. Epub 2020/05/19.
45. Darras BT, Crawford TO, Finkel RS, Mercuri E, De Vivo DC, Oskoui M, et al. Neurofilament as a potential biomarker for spinal muscular atrophy. Ann Clin Transl Neurol. 2019;6(5):932–44. PubMed PMID: 31139691. Epub 2019/05/30
46. van der Heul AMB, Wijngaarde CA, Wadman RI, Asselman F, van den Aardweg MTA, Bartels B, et al. Bulbar problems self-reported by children and adults with spinal muscular atrophy. J Neuromuscul Dis. 2019;6(3):361–8. PubMed PMID: 31476167. Epub 2019/09/03
47. Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, et al. Diagnosis and management of spinal muscular atrophy: part 2: pulmonary and acute care; medications,

supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord. 2018;28(3):197–207. PubMed PMID: 29305137. Epub 2018/01/07
48. Hull J, Aniapravan R, Chan E, Chatwin M, Forton J, Gallagher J, et al. British Thoracic Society guideline for respiratory management of children with neuromuscular weakness. Thorax. 2012;67(Suppl 1):i1–40. PubMed PMID: 22730428. Epub 2012/06/29
49. Zolkipli Z, Sherlock M, Biggar WD, Taylor G, Hutchison JS, Peliowski A, et al. Abnormal fatty acid metabolism in spinal muscular atrophy may predispose to perioperative risks. Eur J Paediatr Neurol. 2012;16(5):549–53. PubMed PMID: 22264649. Epub 2012/01/24
50. Crawford TO, Sladky JT, Hurko O, Besner-Johnston A, Kelley RI. Abnormal fatty acid metabolism in childhood spinal muscular atrophy. Ann Neurol. 1999;45(3):337–43. PubMed PMID: 10072048. Epub 1999/03/11
51. Orngreen MC, Zacho M, Hebert A, Laub M, Vissing J. Patients with severe muscle wasting are prone to develop hypoglycemia during fasting. Neurology. 2003;61(7):997–1000. PubMed PMID: 14557579. Epub 2003/10/15
52. Deguise MO, Baranello G, Mastella C, Beauvais A, Michaud J, Leone A, et al. Abnormal fatty acid metabolism is a core component of spinal muscular atrophy. Ann Clin Transl Neurol. 2019;6(8):1519–32. PubMed PMID: 31402618. Pubmed Central PMCID: PMC6689695. Epub 2019/08/14
53. Baranello G, Vai S, Broggi F, Masson R, Arnoldi MT, Zanin R, et al. Evolution of bone mineral density, bone metabolism and fragility fractures in spinal muscular atrophy (SMA) types 2 and 3. Neuromuscul Disord. 2019;29(7):525–32. PubMed PMID: 31266719. Epub 2019/07/04
54. Wasserman HM, Hornung LN, Stenger PJ, Rutter MM, Wong BL, Rybalsky I, et al. Low bone mineral density and fractures are highly prevalent in pediatric patients with spinal muscular atrophy regardless of disease severity. Neuromuscul Disord. 2017;27(4):331–7. PubMed PMID: 28258940. Pubmed Central PMCID: PMC6448139. Epub 2017/03/05
55. Martinez de Zabarte Fernandez JM, Ros Arnal I, Pena Segura JL, Garcia Romero R, Rodriguez Martinez G. Bone health impairment in patients with cerebral palsy. Arch Osteoporos. 2020;15(1):91. PubMed PMID: 32556612. Epub 2020/06/20.
56. Fujak A, Kopschina C, Forst R, Gras F, Mueller LA, Forst J. Fractures in proximal spinal muscular atrophy. Arch Orthop Trauma Surg. 2010;130(6):775–80. PubMed PMID: 20364429. Epub 2010/04/07
57. Haaker G, Fujak A. Proximal spinal muscular atrophy: current orthopedic perspective. Appl Clin Genet. 2013;6(11):113–20. PubMed PMID: 24399883. Pubmed Central PMCID: PMC3876556. Epub 2014/01/09
58. Gidaro T, Servais L. Nusinersen treatment of spinal muscular atrophy: current knowledge and existing gaps. Dev Med Child Neurol. 2019;61(1):19–24. PubMed PMID: 30221755. Epub 2018/09/18
59. Mandler RN, Anderson FA Jr, Miller RG, Clawson L, Cudkowicz M, Del Bene M, et al. The ALS patient care database: insights into end-of-life care in ALS. Amyotroph Lateral Scler Other Motor Neuron Disord. 2001;2(4):203–8. PubMed PMID: 11958732
60. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. Lancet Neurol. 2006;5(2):140–7. PubMed PMID: 16426990. Epub 2006/01/24. eng
61. Jackson CE, Rosenfeld J, Moore DH, Bryan WW, Barohn RJ, Wrench M, et al. A preliminary evaluation of a prospective study of pulmonary function studies and symptoms of hypoventilation in ALS/MND patients. J Neurol Sci. 2001;191(1–2):75–8. PubMed PMID: 11676995
62. Lo Coco D, Marchese S, Pesco MC, La Bella V, Piccoli F, Lo CA. Noninvasive positive-pressure ventilation in ALS: predictors of tolerance and survival. Neurology. 2006;67(5):761–5. PubMed PMID: 16899545
63. Vrijsen B, Testelmans D, Belge C, Robberecht W, Van Damme P, Buyse B. Non-invasive ventilation in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2013;14(2):85–95. PubMed PMID: 23286745
64. Vrijsen B, Buyse B, Belge C, Robberecht W, Van Damme P, Decramer M, et al. Noninvasive ventilation improves sleep in amyotrophic lateral sclerosis: a prospective polysomnographic

study. J Clin Sleep Med. 2015;11(5):559–66. PubMed PMID: 25766713. Pubmed Central PMCID: 4410930
65. Lechtzin N, Cudkowicz ME, de Carvalho M, Genge A, Hardiman O, Mitsumoto H, et al. Respiratory measures in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener. 2018;19(5–6):321–30. PubMed PMID: 29566571
66. de Carvalho M, Swash M, Pinto S. Diaphragmatic neurophysiology and respiratory markers in ALS. Front Neurol. 2019;10:143. PubMed PMID: 30846968. Pubmed Central PMCID: 6393326
67. Kuhnlein P, Gdynia HJ, Sperfeld AD, Lindner-Pfleghar B, Ludolph AC, Prosiegel M, et al. Diagnosis and treatment of bulbar symptoms in amyotrophic lateral sclerosis. Nat Clin Pract Neurol. 2008;4(7):366–74. PubMed PMID: 18560390
68. Ojeda Rodriguez JA, Ladd M, Brandis D. Abdominal Thrust Maneuver (Heimlich). StatPearls Treasure Island (FL) 2020.
69. Diagnosis ETFo, Management of Amyotrophic Lateral S, Andersen PM, Abrahams S, Borasio GD, de Carvalho M, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)—revised report of an EFNS task force. Eur J Neurol. 2012;19(3):360–75. PubMed PMID: 21914052
70. Dorst J, Dupuis L, Petri S, Kollewe K, Abdulla S, Wolf J, et al. Percutaneous endoscopic gastrostomy in amyotrophic lateral sclerosis: a prospective observational study. J Neurol. 2015;262(4):849–58. PubMed PMID: 25618254
71. ProGas Study G. Gastrostomy in patients with amyotrophic lateral sclerosis (ProGas): a prospective cohort study. Lancet Neurol. 2015;14(7):702–9. PubMed PMID: 26027943. Pubmed Central PMCID: 4578147
72. Miller RG, Jackson CE, Kasarskis EJ, England JD, Forshew D, Johnston W, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the quality standards Subcommittee of the American Academy of Neurology. Neurology. 2009;73(15):1218–26. PubMed PMID: 19822872. Pubmed Central PMCID: PMC2764727. Epub 2009/10/14
73. Strijbos D, Hofstede J, Keszthelyi D, Masclee AAM, Gilissen LPL. Percutaneous endoscopic gastrostomy under conscious sedation in patients with amyotrophic lateral sclerosis is safe: an observational study. Eur J Gastroenterol Hepatol. 2017;29(11):1303–8. PubMed PMID: 28877087
74. Banfi P, Volpato E, Valota C, D'Ascenzo S, Alunno CB, Lax A, et al. Use of noninvasive ventilation during feeding tube placement. Respir Care. 2017;62(11):1474–84. PubMed PMID: 28807987
75. Czell D, Bauer M, Binek J, Schoch OD, Weber M. Outcomes of percutaneous endoscopic gastrostomy tube insertion in respiratory impaired amyotrophic lateral sclerosis patients under noninvasive ventilation. Respir Care. 2013;58(5):838–44. PubMed PMID: 23107129
76. Tomik J, Tomik B, Partyka D, Skladzien J, Szczudlik A. Profile of laryngological abnormalities in patients with amyotrophic lateral sclerosis. J Laryngol Otol. 2007;121(11):1064–9. PubMed PMID: 17319997
77. Shock LA, Gallemore BC, Hinkel CJ, Szewczyk MM, Hopewell BL, Allen MJ, et al. Improving the utility of laryngeal adductor reflex testing: a translational tale of mice and men. Otolaryngol Head Neck Surg. 2015;153(1):94–101. PubMed PMID: 25832829
78. van der Graaff MM, Grolman W, Westermann EJ, Boogaardt HC, Koelman H, van der Kooi AJ, et al. Vocal cord dysfunction in amyotrophic lateral sclerosis: four cases and a review of the literature. Arch Neurol. 2009;66(11):1329–33. PubMed PMID: 19901163
79. Hillel A, Dray T, Miller R, Yorkston K, Konikow N, Strande E, et al. Presentation of ALS to the otolaryngologist/head and neck surgeon: getting to the neurologist. Neurology. 1999;53(8 Suppl 5):S22–5. discussion S35-6. PubMed PMID: 10560633
80. Forshew DA, Bromberg MB. A survey of clinicians' practice in the symptomatic treatment of ALS. Amyotroph Lateral Scler Other Motor Neuron Disord. 2003;4(4):258–63. PubMed PMID: 14753660
81. Jackson CE, McVey AL, Rudnicki S, Dimachkie MM, Barohn RJ. Symptom management and end-of-life care in amyotrophic lateral sclerosis. Neurol Clin. 2015;33(4):889–908. PubMed PMID: 26515628. Pubmed Central PMCID: 5031364

82. Kimura F. Increased incidence of deep venous thrombosis in ALS. Neurology. 2007;68(23):2046–7. author reply 7. PubMed PMID: 17548561
83. Qureshi MM, Cudkowicz ME, Zhang H, Raynor E. Increased incidence of deep venous thrombosis in ALS. Neurology. 2007;68(1):76–7. PubMed PMID: 17200499
84. Gladman M, Dehaan M, Pinto H, Geerts W, Zinman L. Venous thromboembolism in amyotrophic lateral sclerosis: a prospective study. Neurology. 2014;82(19):1674–7. PubMed PMID: 24727309
85. Gil J, Funalot B, Verschueren A, Danel-Brunaud V, Camu W, Vandenberghe N, et al. Causes of death amongst French patients with amyotrophic lateral sclerosis: a prospective study. Eur J Neurol. 2008;15(11):1245–51. PubMed PMID: 18973614
86. Forrest K, O'Rourke P, McCombe P, Henderson R. Venous thromboembolism in amyotrophic lateral sclerosis: should we consider routine prophylactic anticoagulation? Amyotroph Lateral Scler Frontotemporal Degener. 2015;16(3–4):280–1. PubMed PMID: 25482368

Chapter 7
Emergencies in Peripheral Neuropathies

Alejandro A. Rabinstein

Introduction

Diseases of peripheral nerves can be caused by a variety of factors, including immune reactions to infections, drugs, or cancer, and damage from toxic exposures, direct infection of the nerves, malignant infiltration, or vasculitis among others. Although uncommonly, peripheral nerve disorders can be sometimes so severe that they result in medical emergencies. The most serious emergency from peripheral neuropathies is neuromuscular respiratory failure. Among these emergency presentations, the most frequent by far is the clinical entity known as Guillain-Barré syndrome (GBS), though arguably a different eponym could be more historically correct [1, 2]. This syndrome is typically caused by an acute inflammatory polyradiculoneuropathy but the immune trigger may vary. Because of its prominent representation among acute neuropathies seen in the ICU, GBS will be the main focus of this chapter.

Overall, this chapter summarizes current knowledge on peripheral nerve disorders that may cause medical emergencies and also offers practical advice from my personal experience. Various aspects of the chapter (such as differential diagnosis of acute weakness and evaluation of neuromuscular respiratory failure) are expounded in other chapters of the book and therefore discussed in less detail here.

A. A. Rabinstein (✉)
Mayo Clinic, Rochester, MN, USA
e-mail: rabinstein.alejandro@mayo.edu

M. Damian, M. de Visser (eds.), *Emergencies in Neuromuscular Disorders*,
https://doi.org/10.1007/978-3-030-91932-0_7

Guillain-Barré Syndrome

GBS is a relatively infrequent diagnosis, but clinicians should be aware of it because of its potential for causing major medical complications, which may become life-threatening. Although its most common presentation is often quite characteristic, atypical features are not exceptional and recognition is often delayed in clinical practice. There are some pervasive misunderstandings about several aspects of the syndrome that play a role not only in early misdiagnosis but also in suboptimal identification and management of complications. Throughout the chapter, I will point out these pitfalls and highlight ways to prevent them.

Epidemiology

GBS is the most common cause of acute flaccid paralysis in adults, with an estimated incidence of 1–2 per 100,000 people per year in Western countries [3]. The incidence in Asia may be higher and seasonal fluctuations have been reported in Bangladesh and China [4]. GBS gets more frequent with age, [3] but individuals of all ages can be affected from very early childhood [5]. Incidence rates have increased markedly in association with some epidemics, as seen a few years ago during the rapid spread of the Zika virus in South and Central America [6]. A sharp increase in cases of GBS also occurred in 1976 in relation to a specific type of swine influenza vaccine and to a much lesser degree in association with H1N1 monovalent influenza vaccination in 2009, but otherwise the risk of GBS after vaccination for preventable infectious diseases, including influenza is very low [7, 8]. Most recently, cases of GBS have been diagnosed in patients with SARS-CoV2 infection and after their recovery from the respiratory disease (COVID-19). However a large national study of the UK population as well as in Singapore showed a decreased incidence of GBS during 8 the pandemic and failed to find a definitive link between GBS and COVID-19 infection [9, 10]. An association between first-dose ChAdOx1 nCoV-19COVID-19 vaccination (AstraZeneca) and GBS excess was reported, albeit the cause for this association is currently unclear, and excess risk remains comparable to previous vaccine-associated GBS [11].

Pathophysiology

GBS is provoked by an immune reaction against Schwann cells or axonal antigens that result in demyelinating or axonal damage. The target of the immune injury determines the type of GBS. The most common type is demyelinating (acute inflammatory demyelinating polyradiculoneuropathy [AIDP]), but axonal forms also occur (acute motor axonal neuropathy [AMAN] and acute motor sensory axonal neuropathy [AMSAN]). The precise antigenic targets in AIDP are not elucidated, but gangliosides are the target of axonal damage mediated by auto-antibodies and

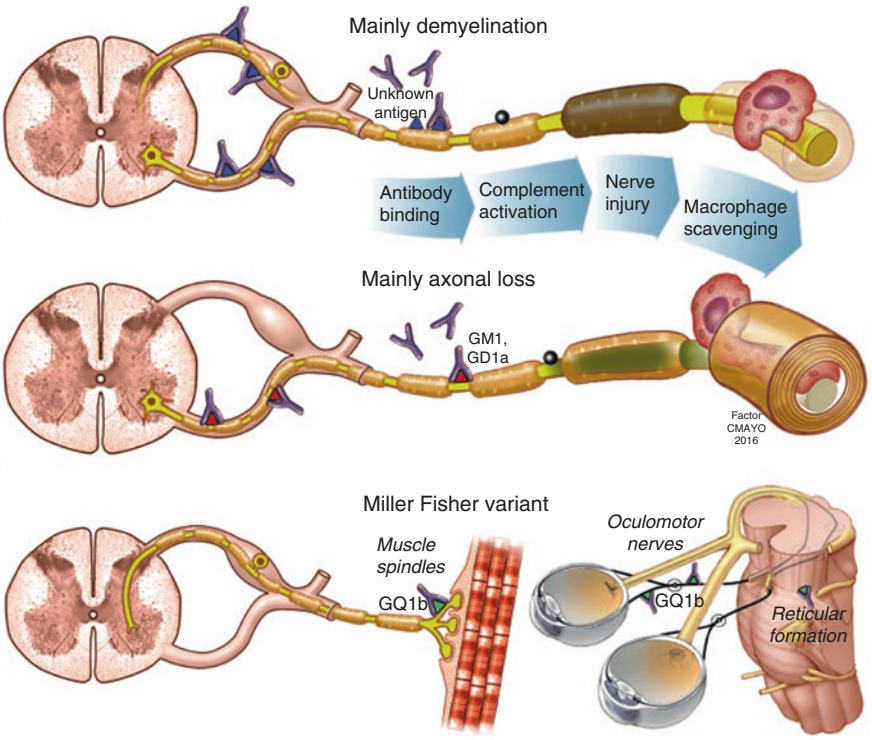


Fig. 7.1 Illustration of the pathogenesis of the various types of GBS. Reproduced with permission from Wijdicks and Klein [1]

complement [12]. Gangliosides (especially GQ1b) are also the target antigen in the Miller Fisher variants of GBS (Fig. 7.1) [13].

The immune reaction is generated most often by an infectious agent. Respiratory or gastrointestinal symptoms are reported by approximately two-thirds of patients with GBS, though documented infections are less common [14]. Associations supported by solid case-control studies have been established for *Campylobacter jejuni*, cytomegalovirus, hepatitis E virus, *Mycoplasma pneumoniae*, Epstein–Barr virus, and Zika virus [6, 14–16]. GBS may also be triggered by influenza infection [7]. While seasonal vaccinations (particularly to prevent influenza) might trigger GBS, the attributable risk is exceedingly small and most likely lower than the risk of GBS being precipitated by influenza infection – thus making the vaccine protective against GBS [7, 12].

The strongest and best understood association is with *C. jejuni*. The increased risk of GBS after *C. jejuni* gastrointestinal infection is mediated by molecular mimicry between bacterial lipo-oligosaccharides and gangliosides in peripheral nerves that leads to the production of cross-reacting antibodies in susceptible individuals [12, 17]. These anti-ganglioside antibodies provoke complement activation with subsequent complement attack to the nodes of Ranvier and development of axonal damage. This mechanism explains why *C. jejuni* infection is particularly associated

with axonal forms of GBS [18] who often have detectable serum antibodies against various gangliosides (GM1a, GM1b, GD1a, and GalNac-GD1a) [12].

Surgery and cancer have been proposed as alternative precipitants of GBS. Evidence supporting the association of surgery with GBS is scant and weak. The evidence for an association of GBS with cancer is more convincing, but GBS fails to fulfill criteria for a paraneoplastic disorder [19]. Drugs used to treat cancer (especially platinum-based chemotherapy and checkpoint inhibitors) [20, 21] or autoimmune conditions (tumor necrosis factor-alpha antagonists) [22] have also been associated with the emergence of GBS. It is, however, possible that those cases of GBS ascribed to less common or more questionable precipitants could actually be related to undiagnosed preceding infection.

Clinical Presentation

Although the principal symptom of GBS is weakness, lumbar pain and leg paresthesias often precede it [23]. Weakness progresses rapidly but it is not sudden. Characteristically it affects first the legs and then arms, which leads to the common description of an ascending pattern; however, it is important to know that the weakness in the legs does not usually start distally but it is rather first noticed in the major proximal muscle groups. Weakness is typically bilateral, though initially it can be asymmetric. Areflexia is one of the hallmarks of the disease. Yet, some patients (particularly with axonal forms of GBS) may initially have retained reflexes or even hyperreflexia [24]. Despite the presence of paresthesias and neuropathic pain, sensory deficits on examination are usually absent or very mild.

Facial, oropharyngeal, and ocular weakness typically occur after all limbs are already weak and it is seen in more severe cases. Any pattern of ophthalmoparesis is possible and the worst cases produce complete internal and external ophthalmoplegia. Weakness of laryngeal muscles may follow and these patients develop problems with phonation and have high risk of aspiration. Ventilatory muscles are generally the last ones to be affected. Weak cough is caused by weakness of expiratory muscles (internal intercostal, abdominal). Diaphragmatic weakness is manifested by shallow breathing, inability to complete sentences with a single breath, use of accessory inspiratory muscles (sternocleidomastoid, external intercostal, scalene), and, when most severe, paradoxical breathing pattern (i.e. inward rather than the normal outward movement of the abdomen during inspiration). It is important to remember that diaphragmatic failure can develop quite suddenly; thus, very close monitoring of ventilatory muscle strength is essential in patients with GBS who are experiencing rapid progression of their weakness (see also Chap. 3).

Dysautonomia is prevalent (38% in our experience) and it can manifest with multiple symptoms [25]. It is caused by the involvement of autonomic fibers and it can provoke cardiac arrhythmias (tachycardia or bradycardia), labile blood pressure (hypertension or hypotension), fever, gastroparesis, adynamic ileus, and bladder retention. Vagal dysfunction can produce baroreflex failure, but patients with GBS

have sympathetic overdrive (presumably because sympathetic fibers are less myelinated and therefore more vulnerable than parasympathetic fibers). Dysautonomia is more severe in patients with quadriparesis and respiratory failure, but it often presents before the maximum degree of weakness has been reached [25]. Though rarely, posterior reversible encephalopathy syndrome can occur after extreme blood pressure fluctuations [25]. Complications from dysautonomia can be serious and even life-threatening [26].

Pain can be refractory and disabling. The severity of pain directly correlates with the severity of weakness [23]. Neuropathic and nociceptive pain may coexist. Neuropathic pain tends to be radiculopathic, but may only affect the distal legs. It is commonly associated with marked allodynia to the point that patients may not be able to tolerate any skin contact in the affected areas – this may preclude the use of intermittent pneumatic compression devices. Young children often present with poorly localized pain, which may make the diagnosis particularly challenging [27].

GBS is a monophasic disease. Maximal weakness is most frequently reached within the first 2 weeks and almost always occurs within 4 weeks [28, 29]. Respiratory failure can occur in approximately 25% of patients with typical GBS [30, 31]. A shorter interval between the onset of symptoms and hospital admission, more severe appendicular weakness (as measured by the MRC sum score) and presence of bulbar or facial weakness are associated with a higher risk of requiring mechanical ventilation within the first week of hospitalization and these factors have been integrated into the Erasmus GBS Respiratory Insufficiency Score (EGRIS) [30].

Variants of GBS

The best-known variant of GBS is the Miller Fisher syndrome characterized by ophthalmoparesis, ataxia and areflexia [32]. Some of these patients can develop limb weakness, but it is usually mild. Other variants include pure motor, pure sensory, paraparetic, pharyngeal–cervical–brachial, and bilateral facial palsy with paresthesias [16]. Bickerstaff brainstem encephalitis is a syndrome that shares some features with the Miller Fisher syndrome (including serum IgG against GQ1b and antecedent *C. jejuni* infection). It presents with acute encephalopathy, ophthalmoplegia, and ataxia; patients may have varying degrees of weakness [33].

Diagnosis and Diagnostic Investigations

The diagnosis of GBS is eminently clinical, but it can be supported by electrophysiological findings and cerebrospinal fluid abnormalities (Table 7.1). Different sets of diagnostic criteria have been proposed [28, 29]. It should be noted that these criteria were developed for research purposes and therefore should be applied with caution in clinical practice, particularly because they are not very useful at the time of initial

Table 7.1 Clinical diagnosis of GBS

Feature	Argue for GBS	Possible	Argue against GBS
Weakness	Weakness in legs, then arms, and mostly symmetric	Weakness in arms first and mostly symmetric	Frankly asymmetric weakness[a]
Cranial nerve involvement	Present upon progression, mostly symmetric	Present at onset, mostly symmetric	Asymmetric
Pain	Back or limb pain can be severe	Back or limb pain at onset	Abdominal pain at onset headache at onset
Sensory findings	Mild sensory signs (if present)	Moderate sensory signs (AMSAN)	Severe and predominant sensory deficits Sensory level
Reflexes	Areflexia	Hyperreflexia (generalized) in early phase	Frankly asymmetric reflexes, persistent hyperreflexia, clonus, or extensor plantar responses
Dysautonomia	Present upon progression	Present early	Present before weakness Fever at onset
Respiratory failure	Present upon progression	Present early (in most severe cases)	Present at onset
Progression to nadir	In less than 2 weeks	In 2–4 weeks	Beyond 4 weeks
CSF	High protein without high nucleated cells	Normal protein Nucleated cells 5–50 per mm^3	Nucleated cells greater than 50 per mm^3

[a]Absence of limb weakness is inconsistent with the typical variant of GBS, but possible with the Miller Fisher variant

evaluation when not all manifestations of the disease may be present. The main clinical criteria required for the diagnosis of GBS are progressive weakness in more than one limb and hyporeflexia/areflexia in arms and legs. Supportive features include progression of weakness for no longer than 1 month (recrudescence after 8 weeks should be considered indicative of acute-onset chronic inflammatory demyelinating polyradiculoneuropathy), relatively symmetric weakness initially affecting the legs more than the arms, mild or absent sensory symptoms and signs, cranial nerve involvement (especially of both facial nerves), autonomic dysfunction, and back or limb pain.

Electrophysiology serves to differentiate between demyelinating (AIDP) (Fig. 7.2) and axonal (AMAN, AMSAN) (Fig. 7.3) forms of the disease and to exclude alternative diagnoses. It can confirm the diagnosis of GBS but its sensitivity is limited during the first 1–2 weeks [34]. Different electrophysiological criteria have been published ([34–36]; see Chap. 2). They categorize the findings into demyelinating, axonal, inexcitable nerves and equivocal. Specific criteria for definition of primary demyelinating versus primary axonal forms vary, but they agree on the general principles [34]. It is advisable to test at least four motor nerves, three sensory nerves, F waves, and H reflexes [31]. The electrophysiological signs of AIDP on nerve conduction studies include prolonged F wave latency (the earliest

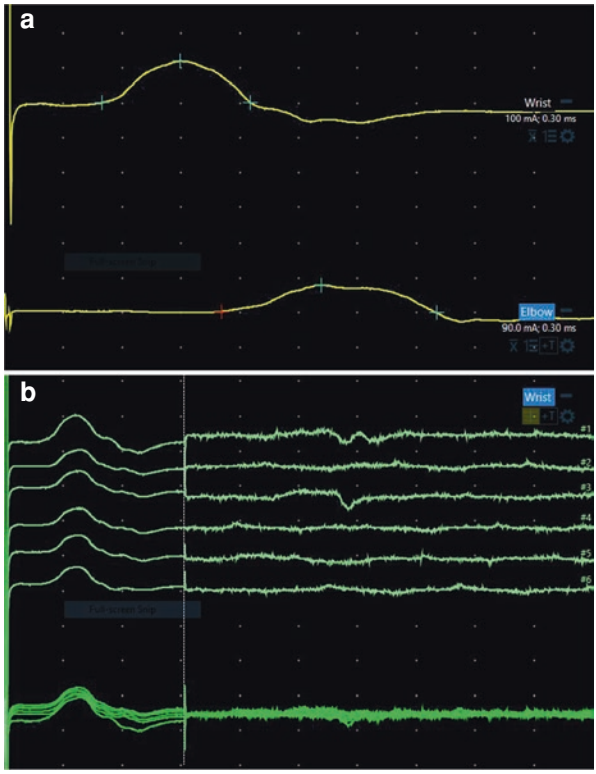


Fig. 7.2 Nerve conduction studies of a patient with AIDP. (**a**) Median motor stimulation showing slow conduction velocity and prolonged distal latency. (**b**) Absence of F waves after median nerve stimulation

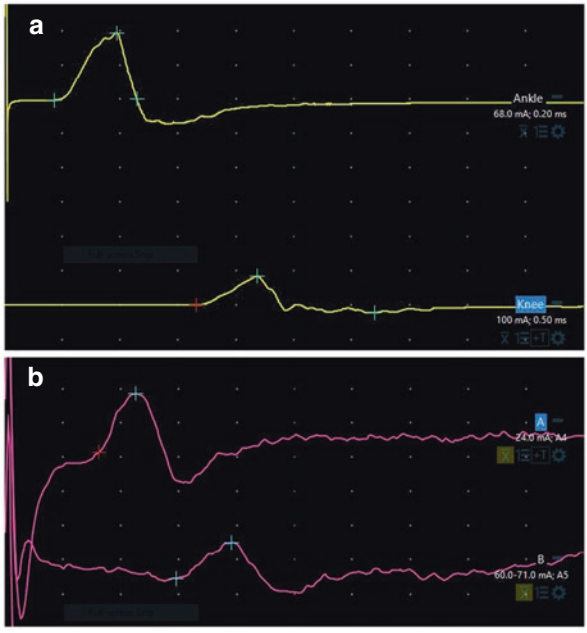


Fig. 7.3 Nerve conduction studies of a patient with AMAN. (**a**) Tibial motor stimulation showing low amplitude compound muscle action potential. (**b**) Preserved sural nerve sensory action potential

sign), prolonged distal latencies, increased temporal dispersion, and slow motor nerve conduction velocities. Sparing of the sural sensory nerve action potential is common. Conduction blocks usually appear at a later stage. In AMAN, the amplitudes of motor nerve action potentials are reduced, generally with the absence of demyelinating features. These patients can have transient conduction slowing or block (known as reversible conduction failure) [37]. Sensory amplitudes may also be reduced in AMSAN variant.

Cerebrospinal fluid analysis is most useful to exclude alternative diagnoses (such as infections and malignancy). Increased protein content without associated pleocytosis (albumino-cytological dissociation) is the characteristic abnormality in GBS. Yet, this finding is not specific to GBS and protein elevation may be delayed by a few days (present within 3 days of the onset of weakness in 50% of cases and in more than 80% after the first week, though some patients may never develop any substantial proteinorrhachia) [12]. Thus, proof of albumino-cytological dissociation is not required to make the diagnosis of GBS [12, 28, 29]. Presence of pleocytosis (especially >50 cells per mm^3) should be considered highly atypical for GBS and prompt investigations for other etiologies that could produce inflammation of the spinal nerve roots [12, 29].

Blood tests should be used sparingly to exclude other causes of generalized weakness. Electrolyte disturbances (such as extreme hypokalemia or hypophosphatemia) can mimic GBS and should be excluded. Serology for infections (such as West Nile virus, cytomegalovirus, HIV) may be indicated when the diagnosis is questioned and especially relevant when cerebrospinal fluid shows pleocytosis. Testing for infections known to trigger GBS (e.g., C. jejuni or hepatitis E) is generally not necessary. Antiganglioside antibodies can be supportive of the diagnosis when present (GM1 and GD1a for AMAN and GQ1b for Miller Fisher syndrome), but their absence carries no diagnostic implications and they do not need to be tested routinely.

MRI of the spine with contrast can show enhancement of multiple nerve roots. Similarly, nerve root enlargement may be visible with ultrasound. These findings are present early and can be helpful to assist with localization. However, they lack specificity as they can be seen with other causes of nerve root inflammation.

Differential Diagnosis

The differential diagnosis of acute, rapidly progressive flaccid paralysis in adults includes myopathies (acquired after critical illness, rhabdomyolysis, myositis, toxic necrotizing myopathies, and relatively acute presentations of acid maltase deficiency or muscular dystrophy), neuromuscular transmission disorders (myasthenia gravis, prolonged neuromuscular block, botulism, organophosphate poisoning, Lambert-Eaton syndrome, tick paralysis, envenomation), other neuropathies (discussed in the next section), and spinal cord and anterior horn cell diseases (amyotrophic lateral sclerosis, West Nile virus infection, polio and post-polio syndrome, transverse myelitis, spinal cord infarction, spinal cord compression).

Acute spinal cord compression should be considered in patients presenting with acute quadriparesis or paraparesis and sphincter dysfunction and without cranial nerve involvement. Careful history and physical examination should habitually distinguish GBS from non-neuropathic disorders. Nerve conduction studies with needle electromyography and cerebrospinal fluid analysis may be useful when GBS presentation is atypical. Emergency spine MRI is necessary when spinal cord compression is deemed possible.

Therapeutic Management

Initial Evaluation in the Emergency Department

The immediate priorities of GBS evaluation in the Emergency Department include exclusion of other acute disorders that could require different forms of emergency treatment and assessment of the severity of the presentation to ensure adequate triage of the patient (i.e. general wards vs ICU). In addition to careful history and physical examination, these objectives require a chest X-ray, electrocardiogram, and serum chemistry (including sodium, potassium, magnesium, phosphorus, and calcium). Clinicians should have a very low threshold to obtain arterial blood gases even if pulse oximetry is normal (always remembering that a pCO_2 within normal range indicates hypoventilation in a patient who is tachypneic and should therefore have a low pCO_2). Conducting a baseline measurement of vital capacity and respiratory pressures either in the Emergency Department or shortly after admission is advisable [38].

Exclusion of cardiopulmonary disease is crucially important. Cardiopulmonary disorders can be pre-existent, particularly in older patients, or result from early complications of GBS, such as aspiration, hypoventilation, or dysautonomia. Pneumonia, atelectasis, arrhythmias, and hemodynamic instability are possible and their presence demands closer monitoring.

Severe or rapidly progressive weakness, involvement of oropharyngeal muscles, weak cough, signs of diaphragmatic insufficiency, manifestations of dysautonomia, and any serious cardiopulmonary complications should be considered indications for admission to the ICU. If the patient is initially admitted to the general ward, development of these features should prompt transfer to the ICU.

Management in the Intensive Care Unit

Close monitoring in the ICU should include frequent physical examinations, cardiac telemetry, continuous pulse oximetry, and serial measurements of ventilatory function with beside spirometry (vital capacity, maximal inspiratory pressure, and maximal expiratory pressure). When appropriate, patients should also have follow-up chest X-rays and blood gases.

Tracheal intubation and mechanical ventilation should not be delayed in patients with GBS and respiratory failure. Intubation should always be considered in the presence of paradoxical breathing pattern, particularly when associated with poor cough, and poor or worsening vital capacity and respiratory pressures. A forced vital capacity lower than 20 ml/kg, a maximal inspiratory pressure lower than 30 cm H_2O, and a maximal expiratory pressure lower than 40 cm H_2O (the "20/30/40 rule") or a reduction in any of these values greater than 30% on serial measurements are associated with progression to respiratory failure and the need for intubation [39]. Of note, noninvasive ventilation is not a safe strategy in patients with GBS. Once these patients start to develop ventilatory muscle weakness, the weakness usually progresses and sometimes it does so very rapidly. Thus, patients who may appear to be initially tolerating a trial of noninvasive ventilation may decline suddenly and necessitate emergency intubation, which can be especially dangerous when dysautonomia is present [40, 41]. In addition, trying to temporize with noninvasive ventilation is not a useful practice because once the maximum degree of weakness is established, it typically does not begin to improve until days, if not weeks, later.

Patients with neuromuscular respiratory failure from GBS often need prolonged ventilation. Consequently, tracheostomy is often necessary. Prolonged ventilatory requirements should be expected in patients who cannot lift their arms or fail to show improvement in bedside respiratory function tests after a week of mechanical ventilation [42, 43]. Risk factors for prolonged ventilation include older age, inexcitable nerves or axonal pattern on EMG, dysautonomia, and pulmonary disease [42, 44]. The optimal timing of tracheostomy is not well defined, but delaying tracheostomy beyond the second week of mechanical ventilation has been associated with a greater risk of pulmonary complications [45].

The acute clinical course of GBS can be plagued with systemic complications, such as pneumonia (aspiration or ventilator-associated), atelectasis, mucous plugging, hypertension (even causing posterior reversible encephalopathy syndrome) [25], hypotension, tachy- or bradyarrhythmias, gastroparesis, adynamic ileus (sometimes so severe that it requires therapeutic colonoscopy or even colostomy), bladder dysfunction (retention or incontinence), central fever, infections, and complications from prolonged immobility (venous thromboembolism, compression neuropathies, pressure sores, heterotopic ossifications). Patients with GBS may develop hyponatremia from the syndrome of inappropriate secretion of antidiuretic hormone [46]. Therefore, serial monitoring of serum sodium is recommended and free water restriction should be implemented if hyponatremia ensues.

Supportive care should be intensive and meticulous, including pulmonary toileting, enteral nutrition, frequent body rotation and mobilization with physical therapy, and prevention of deep venous thrombosis and gastric ulcers. Patients with GBS also need psychological support; they should be reminded that they will get better. Sedative drugs that may induce delirium (such as benzodiazepines) should be avoided. Treatment of pain is essential. Nociceptive pain can be treated with regular analgesics, but opioids should be used very sparingly, if at all, because they can induce or exacerbate adynamic ileus. More importantly, treatment for neuropathic pain should be initiated and this type of pain predominates and is the most distressing. Gabapentin or pregabalin are good options. Duloxetine represents an excellent alternative because it can also help symptoms of depression. Otherwise, medication

use should be minimized in patients with GBS because many medications can worsen the signs of dysautonomia. For instance, beta-blockers, neostigmine, and metoclopramide can produce very severe bradyarrhythmias. When any of these drugs are used, atropine should be kept at the bedside.

Immunomodulatory Therapy

Plasma exchange and intravenous immunoglobulin (IVIG) are similarly effective in improving disability at 4 weeks, reducing the rate of prolonged mechanical ventilation, and hastening the recovery of independent ambulation [47]. Either of these treatments is indicated for patients who cannot walk more than 10 m without aid and should ideally be started within 2 weeks of symptom onset [48]. Plasma exchange has been conclusively proven beneficial in trials against supportive treatment only [49]. IVIG has been consistently shown equivalent to plasma exchange in trials comparing the two therapies [50].

Plasma exchange is thought to work by removing autoantibodies and complements. A full course of plasma exchange usually consists of five sessions (250 ml plasma/kg of body weight each) over alternating days, though exchanges in consecutive days can be safely conducted in some patients. Four exchanges are better than two but six are not better than 4 [49]. IVIG is thought to work by neutralizing pathogenic antibodies and inhibiting Fc-mediated activation of immune cells and antibody-mediated complement activation. The full dose of IVIG is 2 g/kg (administered as 0.4 g/kg daily for 5 consecutive days). Plasma exchange requires placement of a large-bore central venous catheter. Both treatments are usually well tolerated, but possible adverse events and individual patient factors (such as comorbidities) need to be taken into consideration when selecting which option to prefer (Table 7.2).

Table 7.2 Possible adverse events from PLEX and IVIG [38]

Plasma exchange	Intravenous Immunoglobulin
Venous catheter-related Infection Pneumothorax Local hematoma	Infusion-related Headache Shivering Myalgias
Hemodynamic instability (hypotension)[a]	Chest pain
Hemoconcentration	Hyperviscosity (risk of thrombosis, including arterial events)[b]
Coagulopathy (mild)[a]	Aseptic meningitis
Hypocalcemia	Acute kidney injury[b]
Removal of highly protein-bound drugs	Anaphylaxis (if IgA deficiency)
Transfusion reaction (including TRALI)	Transfusion reaction (including TRALI)

TRALI, transfusion-related acute lung injury

[a] Plasma exchange may be preferred in patients with advanced vascular disease or impairment of renal function

[b] IVIG may be preferred in patients who are hypotensive, hemodynamically unstable, or coagulopathic

Corticosteroids are not beneficial in GBS and they increase the risk of diabetes requiring insulin [51]. Therefore, corticosteroids should not be used for the treatment of GBS. Around one in five patients fail to improve, continue to worsen, or decline after initial improvement (treatment-related fluctuation) after the administration of plasma exchange or IVIG. The combination of plasma exchange followed by IVIG is not more effective than either treatment alone [52]. Repeating the same treatment is sometimes pursued in practice [53]. Lesser increase in serum IgG concentration 2 weeks after IVIG treatment has been associated with poorer recovery and guiding a second course of IVIG by IgG response has been proposed [54]. Yet, the evidence to support repeating plasma exchange or IVIG remains anecdotal and prospective non-randomized data has not shown benefit from a second course of IVIG [55]. A randomized, controlled trial (SIDS-GBS trial) has examined whether a second course of IVIG can help GBS patients with poor prognosis and its results did not provide evidence for that; moreover, it entails a risk of serious adverse events [56].

Novel immune therapies are also being investigated. Eculizumab, a complement factor 5 inhibitor, has been shown to be generally well tolerated as add-on therapy to IVIG in two phase 2 trials of patients with GBS [57, 58] and one of them suggested a possible benefit [58]. Further research on this agent is ongoing.

Prognosis

Improvement over time is the norm in GBS. That said, even with optimal care, severe GBS can be fatal (mortality rate 3–5% in the hospital and up to 10–20% over the following 6–12 months among patients requiring prolonged ventilation) [59–62]. Multiple factors may affect prognosis in patients with GBS, including older age, shorter interval between the onset of weakness and admission to the hospital, greater severity of weakness at nadir, preceding diarrhea (typically associated with AMAN), nerve inexcitability, severe conduction blocks or very reduced amplitude of distal compound muscle action potentials on electrophysiological studies, and some chemical biomarkers (such as serum hypoalbuminemia, various serum interleukins, and IgG1 subclass of anti-GM1 antibodies) [63–65].

Rates of independent ambulation at 6 months may exceed 80% among patients with GBS at large, but they are less than 20% among patients who are still ventilated after 2 months [60]. Chances of independent ambulation at 6 months can be estimated using the Erasmus GBS outcome score (EGOS); this score integrates age, preceding diarrhea, and the degree of disability at 2 weeks [66]. A modified version of this score (mEGOS) replaces the degree of disability at 2 weeks with the severity of weakness at 1 week (Table 7.3) [67]. Axonal forms of GBS are usually associated with a worse prognosis, but a minority of the patients may experience a rapid recovery because of the resolution of transient conduction block without axonal damage [68].

Table 7.3 Modified Erasmus GBS outcome score (mEGOS) [67]

Factor	Categories	Score
Age at onset (years)	≤40 41–60 >60	0 0.5 1
Diarrhea (within previous 4 weeks)	Absent Present	0 1
Medical Research Council sum score	51–60 41–50 31–40 0–30	0 3 6 9
mEGOS		1–12

Prolonged mechanical ventilation is associated with worse prognosis, but meaningful functional recovery is possible even among patients who remain ventilator-dependent for months; in such cases, recovery may continue over years [60, 69]. Fatigue, persistent weakness, pain, and anxiety/depression are common complaints even in the long term [70]. GBS recurrence is very rare and when it seemingly happens it is necessary to exclude chronic inflammatory polyradiculoneuropathy [71].

Case Vignette 1

A 34 years old, 20-week pregnant woman presented with rapid onset of leg weakness progressing to the arms within 3 days. By the end of the first week, she was severely quadriparetic, had bifacial weakness, and was intubated because of development of paradoxical breathing pattern and worsening vital capacity and inspiratory and expiratory pressure on bedside spirometry. Nerve conduction studies revealed a clear axonal pattern. She continued to worsen despite early treatment with IVIG and a second course was therefore administered with no noticeable changes. She underwent tracheostomy and percutaneous gastrostomy. During the acute phase, she has severe neuropathic pain, labile blood pressure, refractory ileus, and protracted urinary retention. She could be liberated from mechanical ventilation after 6 weeks. Her son was delivered by C-section at term with no complications. She regained the ability to ambulate independently at 6 months. Fatigue and neuropathic pain in the legs were still present after 1 year, but much improved by 20 months. Three years later she was fully functional and had delivered another healthy child.

Learning Points

Recovery from GBS can be very slow and protracted, but patients should be constantly reassured that it will happen. Symptoms may continue to improve even after a whole year from onset and therefore the full extent of recovery cannot be considered to be reached until the patient has either achieved full resolution of the symptoms or has remained unchanged for many weeks. Until then, rehabilitation efforts should be aggressively pursued.

Other Peripheral Neuropathy Emergencies

Several other peripheral nerve disorders may present emergently, sometimes resembling the semiological presentation of GBS. A list of these entities is presented in Table 7.4.

Checkpoint inhibitors, a class of immune agents now frequently used for the treatment of advanced or metastatic cancer, can induce severe peripheral nerve dysfunction [21]. Presentations vary, but GBS-like presentations are possible [72]. Cranial neuropathies and autonomic involvement are possible. CSF may or may not show inflammatory cells. The neuropathy usually responds to immunosuppression, and early administration of corticosteroids can be quite effective [72].

Case Vignette 2

A 58-years-old woman with metastatic melanoma under treatment with nivolumab developed rapid onset of diplopia and bilateral arm weakness and paresthesias. Examination revealed bilateral ophthalmoparesis, mild bilateral facial weakness, and predominantly proximal weakness in both arms without objective weakness of the legs. Electrophysiological studies were consistent with a demyelinating polyradiculoneuropathy and CSF showed albuminocytological dissociation and cytological examination was negative. MRI of the spine revealed very faint enhancement of cervical nerve roots. Nivolumab was discontinued and she was treated with intravenous methylprednisolone and a 5-day course of IVIG with good response.

Learning Points

Checkpoint inhibitors, such as the programmed death-1 receptor agent nivolumab, can induce acute neuropathies that may mimic GBS. Their recognition is important because worsening may occur with persistent use of the inciting agent. These neuropathies generally respond well to intravenous corticosteroids and additional immunomodulatory or immunosuppressant therapy.

Table 7.4 Peripheral neuropathy emergencies other than AIDP/AMAN

Drug-induced (e.g. biological agents, chemotherapy)
Vasculitis
Infections (e.g. cytomegalovirus)
Malignant infiltration (especially lymphoma)
Paraneoplastic neuropathies
Critical illness polyneuropathy
Toxins/venoms (e.g. tetradotoxin)
Porphyria
Heavy metals (e.g. arsenic, thallium)
Phrenic nerve injury

Chemotherapy, particularly platinum-based, typically produces sensory neuropathies, but rarely it can cause polyradiculoneuropathies that may be indistinguishable from GBS [20]. Electrophysiological findings may show axonal or demyelinating features. CSF examination is important to exclude malignant infiltration or infection. Good recovery is possible with the typical management discussed in the GBS section of this chapter [20].

Cytomegalovirus infection can directly cause severe polyradiculoneuropathies, in addition to triggering immune-mediated AIDP in other instances. Positive PCR for CMV in the CSF with pleocytosis (frequently with polymorphonuclear preponderance) and extensive enhancement of roots (and often of the cord) validate the diagnosis of CMV infection with direct involvement of these structures and warrant treatment with intravenous ganciclovir [73, 74]. The risk of CMV polyradiculitis is particularly increased in patients with AIDS [75]. Herpes zoster virus may also rarely cause cases of myeloradiculitis [76].

Critical illness neuropathy is a common complication in patients admitted to the ICU with multiorgan failure, particularly from sepsis, who require prolonged ventilation [77]. Weakness can be severe and it is often related to a combination of axonal neuropathy and myopathy with myosin loss. Cranial nerves and autonomic fibers are characteristically not involved [38]. Recovery is slow and may be incomplete, but improvement is the norm.

Malignant infiltration of multiple nerve roots, especially from B-cell lymphoma, may present as a neuromuscular emergency. Neurolymphomatosis is usually more focal and asymmetric than GBS, but the most aggressive cases may mimic GBS [78]. CSF analysis and nerve biopsy can clarify the diagnosis in such cases. MRI neurography and PET-CT are very useful imaging modalities for diagnosis, staging, and assessment of treatment response [79, 80]. (Fig. 7.4) Consideration of malignant infiltration in atypical cases of GBS (even in the absence of a known diagnosis of malignancy) is therefore important because delayed diagnosis may result in ominous prognosis [81].

Systemic vasculitis can very rarely present as a peripheral neuropathy emergency. Acute cases have been described with Behçet disease, Sjögren syndrome, and granulomatous angiitis with eosinophilia among others [82–84]. Associated features and nerve biopsy facilitate reaching the correct diagnosis. Postsurgical acute lumbosacral radiculoplexopathies from microvasculitis can occur in patients with diabetes mellitus [85].

Some heavy metal poisonings can injure severely peripheral nerves, in particular arsenic and thallium. Acute arsenic intoxication presents with abdominal pain, vomiting, and diarrhea within 1–2 weeks of the exposure; the typical peripheral nerve involvement is predominantly sensory with burning pain and ataxia, but extreme poisoning may produce severe weakness and autonomic changes [86]. While axonal changes are most often seen with arsenic neuropathy, early demyelinating features have been described [82]. Thallium intoxication can also cause acute neuropathy in association with gastrointestinal symptoms, and the characteristic delayed alopecia. A painful sensory neuropathy is most frequent, [87] but weakness with an ascending pattern has been exceptionally reported in very severe cases. Such cases also tend to manifest cognitive and behavioral changes and may develop abnormal movements and optic neuritis [82].

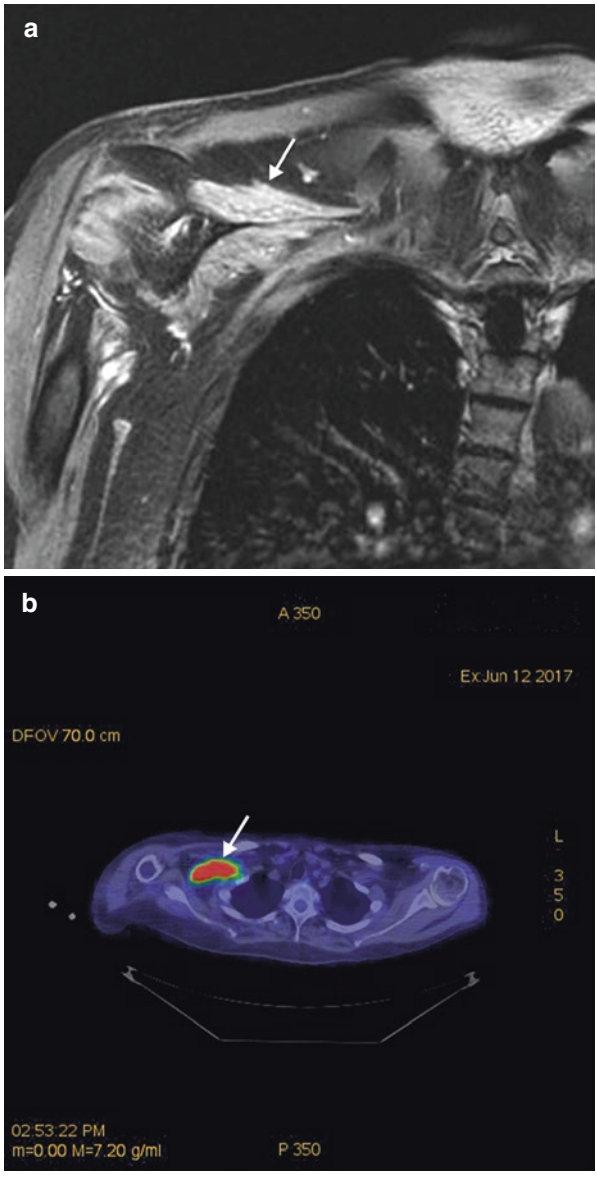


Fig. 7.4 (**a**) Coronal T2FS (left) and T1FS (right) postgadolinium MRI images of the right brachial plexus demonstrating diffuse T2 hyperintensity, enlargement, and enhancement involving most of the visualized right brachial plexus. (**b**) Coronal PET CT showing intense hypermetabolic activity along the right brachial plexus. Modified with permission from Mustafa et al. [80]

Self Assessment Questions

1. Which of the following viral infections is most likely to produce a Guillain-Barré like syndrome?

   (a) Covid-19 infection
   (b) Herpes 2 infection
   (c) West-Nile infection
   (d) Zika infection (*)

2. Which of the following hepatitis infections has been associated with acute inflammatory demyelinating polyradiculoneuropathy?

   (a) Hepatitis A
   (b) Hepatitis B
   (c) Hepatitis C
   (d) Hepatitis E (*)

3. Which diagnosis should be considered in case of a Guillain-Barré syndrome in combination with interstitional infiltrates on plain radiographs?

   (a) Campylobacter infection
   (b) Mycoplasma infection (*)
   (c) Neuroborreliosis
   (d) Tuberculosis

4. Which protein structures are most likely involved in an acute inflammatory demyelinating polyradiculoneuropathy?

   (a) Cereboside glycoproteins
   (b) Ganglioside glycoproteins (*)
   (c) Myelin-associated glycoproteins
   (d) Myelin oligodendrocyte glycoprotein

5. Which of the following drugs may cause a neuropathy mimicking GBS?

   (a) Checkpoint inhibitors (*)
   (b) Chloroquine Phosphates
   (c) Folic acid antagonists
   (d) Macrolide antibiotics

6. Which of the following ocular syndromes is most likely in GBS?

   (a) External ophthalmoplegia (*)
   (b) Internuclear ophthalmoplegia
   (c) One-and-a-half syndrome
   (d) Optic neuritis

7. Which of the following manifestations should cast doubt on the diagnosis GBS?

   (a) Extensor planter responses (*)
   (b) Internal ophthalmoplegia
   (c) Radicular pain
   (d) Urine bladder retention

8. Which of the following syndromes may be considered as a GBS-variant?

   (a) Acute demyelinating encephalomyelitis
   (b) Bickerstaff brainstem encephalitis (*)
   (c) Posterior reversible encephalopathy syndrome
   (d) Rasmussen encephalitis

9. Which antibody is associated with Miller Fisher syndrome?

   (a) Anti-Aquaporine 4
   (b) Anti-CV2
   (c) Anti-GQ1b (*)
   (d) Anti-Ma2

10. Which of the following is a characteristic symptom in Miller-Fisher Syndrome?

    (a) Ataxia (*)
    (b) Insomnia
    (c) Myoclonus
    (d) Nuchal rigidity

11. Which of the following CSF findings is acceptable for the diagnosis GBS?

    (a) Elevated pressure on the initial tap
    (b) Normal protein content (*)
    (c) Persistent signs of intrathecal Ig-synthesis
    (d) Pleiocytosis with about 100 cells per mm^3

12. What is the (increased) risk of delaying tracheostomy beyond the second week of mechanical ventilation?

    (a) Bronchopneumonia (*)
    (b) Cardiac failure
    (c) Renal failure
    (d) Spinal cord infarction

13. Which of the following complications is most likely in GBS?

    (a) Adynamic ileus (*)
    (b) Hepatic failure
    (c) Hypothyroidism
    (d) Lower body varicosis

Serial monitoring of serum electrolytes is recommended in patients with GBS.

14. Which one should be monitored in the first place?

    (a) Chloride
    (b) Magnesium
    (c) Potassium
    (d) Sodium (*)

15. What is true for IVIG in GBS?

    (a) It is as effective as plasma exchange (*)
    (b) Steroid treatment after the first course improves the prognosis
    (c) Patients not improving within 14 days should have a second course
    (d) The effectivity is increased if given in combination with plasma exchange

16. What is the overall mortality rate in GBS patients staying in the hospital?

    (a) About 4% (*)
    (b) About 8%
    (c) About 16%

17. What's the rate of independent ambulation 1 year after the onset of GBS?

    (a) 30%
    (b) 50%
    (c) 70%
    (d) >80% (*)

References

1. Wijdicks EF, Klein CJ. Guillain-Barre syndrome. Mayo Clin Proc. 2017;92(3):467–79.
2. Goodfellow JA, Willison HJ. Guillain-Barre syndrome: a century of progress. Nat Rev Neurol. 2016;12(12):723–31.
3. Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barre syndrome: a systematic review and meta-analysis. Neuroepidemiology. 2011;36(2):123–33.
4. McGrogan A, Madle GC, Seaman HE, de Vries CS. The epidemiology of Guillain-Barre syndrome worldwide. A systematic literature review. Neuroepidemiology. 2009;32(2):150–63.
5. Korinthenberg R, Trollmann R, Felderhoff-Muser U, Bernert G, Hackenberg A, Hufnagel M, et al. Diagnosis and treatment of Guillain-Barre syndrome in childhood and adolescence: an evidence- and consensus-based guideline. Eur J Paediatr Neurol. 2020;25:5–16.
6. Krauer F, Riesen M, Reveiz L, Oladapo OT, Martinez-Vega R, Porgo TV, et al. Zika virus infection as a cause of congenital brain abnormalities and Guillain-Barre syndrome: systematic review. PLoS Med. 2017;14(1):e1002203.
7. Vellozzi C, Iqbal S, Broder K. Guillain-Barre syndrome, influenza, and influenza vaccination: the epidemiologic evidence. Clin Infect Dis. 2014;58(8):1149–55.
8. Principi N, Esposito S. Vaccine-preventable diseases, vaccines and Guillain-Barre' syndrome. Vaccine. 2019;37(37):5544–50.
9. Keddie S, Pakpoor J, Mousele C, et al. Epidemiological and cohort study finds no association between COVID-19 and Guillain-Barré syndrome. Brain. 2021;144(2):682–93.
10. Umapathi T, Er B, Koh JS, Goh YH, Chua L. Guillain-Barré syndrome decreases in Singapore during the COVID-19 pandemic. J Peripher Nerv Syst. 2021;26(2):235–36.

11. Keh RYS, Scanlon S, Datta-Nemdharry P, Donegan K, Cavanagh S, Foster M, Skelland D, Palmer J, Machado PM, Keddie S, Carr AS, Lunn MP; BPNS/ABN COVID-19 Vaccine GBS Study Group. COVID-19 vaccination and Guillain-Barré syndrome: analyses using the National Immunoglobulin Database. Brain. 2022:awac067.
12. van den Berg B, Walgaard C, Drenthen J, Fokke C, Jacobs BC, van Doorn PA. Guillain-Barre syndrome: pathogenesis, diagnosis, treatment and prognosis. Nat Rev Neurol. 2014;10(8):469–82.
13. Chiba A, Kusunoki S, Shimizu T, Kanazawa I. Serum IgG antibody to ganglioside GQ1b is a possible marker of Miller fisher syndrome. Ann Neurol. 1992;31(6):677–9.
14. Jacobs BC, Rothbarth PH, van der Meche FG, Herbrink P, Schmitz PI, de Klerk MA, et al. The spectrum of antecedent infections in Guillain-Barre syndrome: a case-control study. Neurology. 1998;51(4):1110–5.
15. Liu H, Ma Y. Hepatitis E virus-associated Guillain-Barre syndrome: revision of the literature. Brain Behav. 2020;10(1):e01496.
16. Leonhard SE, Mandarakas MR, Gondim FAA, Bateman K, Ferreira MLB, Cornblath DR, et al. Diagnosis and management of Guillain-Barre syndrome in ten steps. Nat Rev Neurol. 2019;15(11):671–83.
17. Yuki N. Ganglioside mimicry and peripheral nerve disease. Muscle Nerve. 2007;35(6):691–711.
18. Drenthen J, Yuki N, Meulstee J, Maathuis EM, van Doorn PA, Visser GH, et al. Guillain-Barre syndrome subtypes related to campylobacter infection. J Neurol Neurosurg Psychiatry. 2011;82(3):300–5.
19. Vigliani MC, Magistrello M, Polo P, Mutani R, Chio A, Piemonte, et al. Risk of cancer in patients with Guillain-Barre syndrome (GBS). A population-based study. J Neurol. 2004;251(3):321–6.
20. Pappa E, Berzero G, Herlin B, Ricard D, Tafani C, Devic P, et al. Guillain-Barre syndrome during platinum-based chemotherapy: a case series and review of the literature. Oncologist. 2020;25(1):e194–e7.
21. Haugh AM, Probasco JC, Johnson DB. Neurologic complications of immune checkpoint inhibitors. Expert Opin Drug Saf. 2020;19(4):479–88.
22. Stubgen JP. Tumor necrosis factor-alpha antagonists and neuropathy. Muscle Nerve. 2008;37(3):281–92.
23. Ruts L, Drenthen J, Jongen JL, Hop WC, Visser GH, Jacobs BC, et al. Pain in Guillain-Barre syndrome: a long-term follow-up study. Neurology. 2010;75(16):1439–47.
24. Uncini A, Notturno F, Kuwabara S. Hyper-reflexia in Guillain-Barre syndrome: systematic review. J Neurol Neurosurg Psychiatry. 2020;91(3):278–84.
25. Chakraborty T, Kramer CL, Wijdicks EFM, Rabinstein AA. Dysautonomia in Guillain-Barre syndrome: prevalence, clinical spectrum, and outcomes. Neurocrit Care. 2020;32(1):113–20.
26. Zaeem Z, Siddiqi ZA, Zochodne DW. Autonomic involvement in Guillain-Barre syndrome: an update. Clin Auton Res. 2019;29(3):289–99.
27. Korinthenberg R, Schessl J, Kirschner J. Clinical presentation and course of childhood Guillain-Barre syndrome: a prospective multicentre study. Neuropediatrics. 2007;38(1):10–7.
28. Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barre syndrome. Ann Neurol. 1990;27(Suppl):S21–4.
29. Fokke C, van den Berg B, Drenthen J, Walgaard C, van Doorn PA, Jacobs BC. Diagnosis of Guillain-Barre syndrome and validation of Brighton criteria. Brain. 2014;137(Pt 1):33–43.
30. Walgaard C, Lingsma HF, Ruts L, Drenthen J, van Koningsveld R, Garssen MJ, et al. Prediction of respiratory insufficiency in Guillain-Barre syndrome. Ann Neurol. 2010;67(6):781–7.
31. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. Lancet. 2016;388(10045):717–27.
32. Wakerley BR, Uncini A, Yuki N, Group GBSC, Group GBSC. Guillain-Barre and Miller fisher syndromes--new diagnostic classification. Nat Rev Neurol. 2014;10(9):537–44.
33. Ito M, Kuwabara S, Odaka M, Misawa S, Koga M, Hirata K, et al. Bickerstaff's brainstem encephalitis and fisher syndrome form a continuous spectrum: clinical analysis of 581 cases. J Neurol. 2008;255(5):674–82.

34. Uncini A, Kuwabara S. The electrodiagnosis of Guillain-Barre syndrome subtypes: where do we stand? Clin Neurophysiol. 2018;129(12):2586–93.
35. Rajabally YA, Durand MC, Mitchell J, Orlikowski D, Nicolas G. Electrophysiological diagnosis of Guillain-Barre syndrome subtype: could a single study suffice? J Neurol Neurosurg Psychiatry. 2015;86(1):115–9.
36. Hadden RD, Cornblath DR, Hughes RA, Zielasek J, Hartung HP, Toyka KV, et al. Electrophysiological classification of Guillain-Barre syndrome: clinical associations and outcome. Plasma exchange/Sandoglobulin Guillain-Barre syndrome trial group. Ann Neurol. 1998;44(5):780–8.
37. Kokubun N, Nishibayashi M, Uncini A, Odaka M, Hirata K, Yuki N. Conduction block in acute motor axonal neuropathy. Brain. 2010;133(10):2897–908.
38. Rabinstein AA. Acute neuromuscular respiratory failure. Continuum (Minneap Minn). 2015;21(5 Neurocritical Care):1324–45.
39. Lawn ND, Fletcher DD, Henderson RD, Wolter TD, Wijdicks EF. Anticipating mechanical ventilation in Guillain-Barre syndrome. Arch Neurol. 2001;58(6):893–8.
40. Wijdicks EF, Roy TK. BiPAP in early guillain-barre syndrome may fail. Can J Neurol Sci. 2006;33(1):105–6.
41. Wijdicks EF, Henderson RD, McClelland RL. Emergency intubation for respiratory failure in Guillain-Barre syndrome. Arch Neurol. 2003;60(7):947–8.
42. Walgaard C, Lingsma HF, van Doorn PA, van der Jagt M, Steyerberg EW, Jacobs BC. Tracheostomy or not: prediction of prolonged mechanical ventilation in Guillain-Barre syndrome. Neurocrit Care. 2017;26(1):6–13.
43. Lawn ND, Wijdicks EF. Post-intubation pulmonary function test in Guillain-Barre syndrome. Muscle Nerve. 2000;23(4):613–6.
44. Nguyen TN, Badjatia N, Malhotra A, Gibbons FK, Qureshi MM, Greenberg SA. Factors predicting extubation success in patients with Guillain-Barre syndrome. Neurocrit Care. 2006;5(3):230–4.
45. Ali MI, Fernandez-Perez ER, Pendem S, Brown DR, Wijdicks EF, Gajic O. Mechanical ventilation in patients with Guillain-Barre syndrome. Respir Care. 2006;51(12):1403–7.
46. Saifudheen K, Jose J, Gafoor VA, Musthafa M. Guillain-Barre syndrome and SIADH. Neurology. 2011;76(8):701–4.
47. Hughes RA, Swan AV, Raphael JC, Annane D, van Koningsveld R, van Doorn PA. Immunotherapy for Guillain-Barre syndrome: a systematic review. Brain. 2007;130(Pt 9):2245–57.
48. Yuki N, Hartung HP. Guillain-Barre syndrome. N Engl J Med. 2012;366(24):2294–304.
49. Chevret S, Hughes RA, Annane D. Plasma exchange for Guillain-Barre syndrome. Cochrane Database Syst Rev. 2017;2:CD001798.
50. Hughes RA, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barre syndrome. Cochrane Database Syst Rev. 2014;9:CD002063.
51. Hughes RA, Brassington R, Gunn AA, van Doorn PA. Corticosteroids for Guillain-Barre syndrome. Cochrane Database Syst Rev. 2016;10:CD001446.
52. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barre syndrome. Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group. Lancet. 1997;349(9047):225–30.
53. Verboon C, Doets AY, Galassi G, Davidson A, Waheed W, Pereon Y, et al. Current treatment practice of Guillain-Barre syndrome. Neurology. 2019;93(1):e59–76.
54. Kuitwaard K, de Gelder J, Tio-Gillen AP, Hop WC, van Gelder T, van Toorenenbergen AW, et al. Pharmacokinetics of intravenous immunoglobulin and outcome in Guillain-Barre syndrome. Ann Neurol. 2009;66(5):597–603.
55. Verboon C, van den Berg B, Cornblath DR, Venema E, Gorson KC, Lunn MP, et al. Original research: second IVIg course in Guillain-Barre syndrome with poor prognosis: the non-randomised ISID study. J Neurol Neurosurg Psychiatry. 2020;91(2):113–21.
56. Walgaard C, Jacobs BC, Lingsma HF, Steyerberg EW, Van den Berg B, Doets AY, et al. Second intravenous immunoglobulin dose in patients with Guillain-Barre syndrome patients with poor

prognosis (SID-GBS trial): a double-blind randomized, placebo-controlled. Lancet Neurol 2021;20:275–83.
57. Davidson AI, Halstead SK, Goodfellow JA, Chavada G, Mallik A, Overell J, et al. Inhibition of complement in Guillain-Barre syndrome: the ICA-GBS study. J Peripher Nerv Syst. 2017;22(1):4–12.
58. Misawa S, Kuwabara S, Sato Y, Yamaguchi N, Nagashima K, Katayama K, et al. Safety and efficacy of eculizumab in Guillain-Barre syndrome: a multicentre, double-blind, randomised phase 2 trial. Lancet Neurol. 2018;17(6):519–29.
59. Witsch J, Galldiks N, Bender A, Kollmar R, Bosel J, Hobohm C, et al. Long-term outcome in patients with Guillain-Barre syndrome requiring mechanical ventilation. J Neurol. 2013;260(5):1367–74.
60. van den Berg B, Storm EF, Garssen MJP, Blomkwist-Markens PH, Jacobs BC. Clinical outcome of Guillain-Barre syndrome after prolonged mechanical ventilation. J Neurol Neurosurg Psychiatry. 2018;89(9):949–54.
61. van den Berg B, Bunschoten C, van Doorn PA, Jacobs BC. Mortality in Guillain-Barre syndrome. Neurology. 2013;80(18):1650–4.
62. Fletcher DD, Lawn ND, Wolter TD, Wijdicks EF. Long-term outcome in patients with Guillain-Barre syndrome requiring mechanical ventilation. Neurology. 2000;54(12):2311–5.
63. Rajabally YA, Uncini A. Outcome and its predictors in Guillain-Barre syndrome. J Neurol Neurosurg Psychiatry. 2012;83(7):711–8.
64. Verma R, Chaudhari TS, Raut TP, Garg RK. Clinico-electrophysiological profile and predictors of functional outcome in Guillain-Barre syndrome (GBS). J Neurol Sci. 2013;335(1–2):105–11.
65. Fokkink WR, Walgaard C, Kuitwaard K, Tio-Gillen AP, van Doorn PA, Jacobs BC. Association of albumin Levels with outcome in intravenous immunoglobulin-treated Guillain-Barre syndrome. JAMA Neurol. 2017;74(2):189–96.
66. van Koningsveld R, Steyerberg EW, Hughes RAC, Swan AV, van Doorn PA, Jacobs BC. A clinical prognostic scoring system for Guillain-Barré syndrome. Lancet Neurol. 2007;6(7):589–94.
67. Walgaard C, Lingsma HF, Ruts L, van Doorn PA, Steyerberg EW, Jacobs BC. Early recognition of poor prognosis in Guillain-Barre syndrome. Neurology. 2011;76(11):968–75.
68. Kuwabara S, Mori M, Ogawara K, Hattori T, Yuki N. Indicators of rapid clinical recovery in Guillain-Barre syndrome. J Neurol Neurosurg Psychiatry. 2001;70(4):560–2.
69. Dhar R, Stitt L, Hahn AF. The morbidity and outcome of patients with Guillain-Barre syndrome admitted to the intensive care unit. J Neurol Sci. 2008;264(1–2):121–8.
70. Merkies IS, Kieseier BC. Fatigue, pain, anxiety and depression in Guillain-Barre syndrome and chronic inflammatory demyelinating Polyradiculoneuropathy. Eur Neurol. 2016;75(3–4):199–206.
71. Ruts L, Drenthen J, Jacobs BC, van Doorn PA, Dutch GBSSG. Distinguishing acute-onset CIDP from fluctuating Guillain-Barre syndrome: a prospective study. Neurology. 2010;74(21):1680–6.
72. Dubey D, David WS, Amato AA, Reynolds KL, Clement NF, Chute DF, et al. Varied phenotypes and management of immune checkpoint inhibitor-associated neuropathies. Neurology. 2019;93(11):e1093–e103.
73. Miller RF, Fox JD, Thomas P, Waite JC, Sharvell Y, Gazzard BG, et al. Acute lumbosacral polyradiculopathy due to cytomegalovirus in advanced HIV disease: CSF findings in 17 patients. J Neurol Neurosurg Psychiatry. 1996;61(5):456–60.
74. Talpos D, Tien RD, Hesselink JR. Magnetic resonance imaging of AIDS-related polyradiculopathy. Neurology. 1991;41(12):1995–7.
75. Thongpooswan S, Chyn E, Alfishawy M, Restrepo E, Berman C, Ahmed K, et al. Polyradiculopathy and gastroparesis due to cytomegalovirus infection in AIDS: a case report and review of literature. Am J Case Rep. 2015;16:801–4.
76. Staikov I, Neykov N, Marinovic B, Lipozencic J, Tsankov N. Herpes zoster as a systemic disease. Clin Dermatol. 2014;32(3):424–9.

77. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med. 2014;370(17):1626–35.
78. Briani C, Visentin A, Campagnolo M, Salvalaggio A, Ferrari S, Cavallaro T, et al. Peripheral nervous system involvement in lymphomas. J Peripher Nerv Syst. 2019;24(1):5–18.
79. Bourque PR, Sampaio ML, Warman-Chardon J, Samaan S, Torres C. Neurolymphomatosis of the lumbosacral plexus and its branches: case series and literature review. BMC Cancer. 2019;19(1):1149.
80. Mustafa R, Klein CJ, Martinez-Thompson J, Johnson AC, Engelstad JK, Spinner RJ, et al. Recurrent brachial neuritis attacks in presentation of B-cell lymphoma. Mayo Clin Proc Innov Qual Outcomes. 2018;2(4):382–6.
81. Gwathmey KG. Plexus and peripheral nerve metastasis. Handb Clin Neurol. 2018;149:257–79.
82. Levin KH. Variants and mimics of Guillain Barre syndrome. Neurologist. 2004;10(2):61–74.
83. Benzakour M, Moudatir M, Echchilali K, Kitane Y, Alaoui FZ, Elkabli H. Acute polyradiculoneuritis revealing Behcet's disease. Rev Neurol (Paris). 2018;174(7–8):573–5.
84. Mellgren SI, Goransson LG, Omdal R. Primary Sjogren's syndrome associated neuropathy. Can J Neurol Sci. 2007;34(3):280–7.
85. Dyck PJ, Thaisetthawatkul P. Lumbosacral plexopathy. Continuum (Minneap Minn). 2014;20(5 Peripheral Nervous System Disorders):1343–58.
86. Mathew L, Vale A, Adcock JE. Arsenical peripheral neuropathy. Pract Neurol. 2010;10(1):34–8.
87. Kuo HC, Huang CC, Tsai YT, Chu CC, Hsieh ST, Chu NS. Acute painful neuropathy in thallium poisoning. Neurology. 2005;65(2):302–4.

Chapter 8
Infectious Diseases of the Peripheral Nerve and Spinal Cord

Varun Sethi and Hadi Manji

Introduction

Disorders of the peripheral nervous system can involve the spinal cord, peripheral nerve, neuromuscular junction and muscle, i.e. what is traditionally taught to be the 'lower motor neuron'. The aim of this chapter is to describe infectious neurological emergencies limited to this aspect of the nervous system.

Neuroinfectious syndromes can be caused by viruses, bacteria, fungi, protozoa or helminths and may lead to significant morbidity and mortality. An early diagnosis and prompt initiation of treatment remain paramount in achieving a good outcome. A systematic and methodical approach with a detailed history and neurological examination enables accurate neurological localisation and helps to formulate a microbiological differential diagnosis [1]. As the causative pathogens are likely to be influenced by host and environmental characteristics, a meticulous travel and immigration history from endemic geographical areas is essential (see Fig. 8.1, Table 8.1). A thorough social history should include hobbies, for example, golf or cross country running which may expose individuals to tick bites, information regarding sexual contacts and recreational drug use, which may imply risk factors for human immunodeficiency virus (HIV), hepatitis and syphilis. In addition, awareness that different populations might have an increased susceptibility to specific infections as a result of co-morbidities or acquired immunosuppression, due to disease or treatment must be teased out in a detailed historical account.

The underlying pathophysiological mechanisms of injury [4] may be due to a direct neurotropic effect of the organism—for example, in polio, Zika and West Nile infection there is destruction of the anterior horn cell. Other mechanisms include

V. Sethi
Imperial College Health Trust, London, UK
e-mail: varun.sethi@nhs.net

H. Manji (✉)
National Hospital for Neurology and Neurosurgery, London, UK

M. Damian, M. de Visser (eds.), *Emergencies in Neuromuscular Disorders*,
https://doi.org/10.1007/978-3-030-91932-0_8

Fig. 8.1 World map of Endemic infections. Reproduced with permission from [2, 3]

Table 1 Travel history in a returning traveller with neurological disorder

Detailed itineary. Include stopovers. Multiple holidays. Apart from tropics ask about breaks to Europe	See case 3
Medical history	HIV, cancer, diabetes mellitus, post-transplant, splenectomy
Drugs	Corticosteroids, antibiotics (partially treated infection), immunosuppressants
Vaccinations and malaria prophylaxis	Do not protect completely
Undercooked meat, cheese, unclean water, unpasteurised milk, poor hygiene (faecal-oral), raw fish, amphibians, snakes	Hepatitis E, toxoplasmosis, listeria, *Campylobacter jejuni*, brucellosis, neurocysticercosis, gnathostomiasis, angiostrongyliasis, sparganosis
Fresh water exposure (swimming, rafting, floods)	Schistosomiasis, leptospirosis
Injections, transfusions, intravenous drug users, tattoos	HIV, hepatitis B and C, malaria
Sexual contacts	HIV, hepatitis A, B, C, syphilis, Zika, herpes infections
Mosquito bites	Malaria, dengue fever, chikungunya, Zika, Japanese B, West Nile virus, Rift Valley fever
Tick bites	Borrelia, tickborne encephalitis
Flies	Trypanosomiasis
Animal bites	Rabies, cat-scratch fever
Visiting relatives and friends	Tuberculosis
Skin contact with soil	Melioidosis, botulism

overactivation of the immune system and/or secondary antibody activation—the so-called para-infectious or post-infectious syndromes as it occurs in Guillain-Barré syndrome after infection with *Campylobacter jejuni*. A secondary vasculitis results in damage to peripheral nerves as a consequence, for example, of herpes zoster, HIV, hepatitis B and C infections. Inflammation within the dorsal root ganglia with secondary bystander neuronal damage is the postulated mechanism in HIV-associated sensory neuropathy. In leprosy, direct invasion with an associated inflammatory response results in nerve destruction. Neurological dysfunction with serious consequences also occurs as a result of toxin production as in botulism, diphtheria and tetanus.

Neurological emergencies develop in these situations largely due to compromise of respiratory and or cardiac function. This may result from autonomic dysfunction, brain stem involvement, neuromuscular weakness or a myocarditis. In addition, a reduced level of consciousness leading to coma may result from a variety of reasons including sepsis, metabolic derangements or drug side effects. It is however also important to be cognizant of the concept that ‘time is tissue’, a phrase often used in the context of cerebrovascular accidents. This is critical when it comes to involvement of the spinal cord and peripheral nerve. Therefore, although often the clinical presentation may not be life-threatening per se, for example, in infectious radiculoneuropathy or myelitis, nevertheless these conditions are emergencies and need to be managed as such in order to avoid the spiralling cascade of secondary complications.

Various organisms are implicated in diseases of the peripheral nervous system (Table 8.2), in particular, viruses with frequent clinical implications include retroviruses such as HIV, HTLV1 and 2, herpes viruses including HSV1, HSV2 and VZV (all neurotropic and residing in neural ganglia), CMV, EBV, Flaviviruses including West Nile and Zika virus, hepatitis B and C virus and the rabies virus. Significant bacterial infections include Spirochetes such as *Borrelia burgdorferi* (Lyme disease) and *Treponema pallidum* (syphilis). Other bacteria causing neurological complications include *C. jejuni*, *Corynebacterium diphtheriae*, *Brucella* and *Clostridium* species as well as the mycobacteria tuberculosis and *Mycobacterium leprae*. Parasitic infections such as Trypanosoma, malaria and schistosomiasis must also be considered in relevant differential diagnoses [4].

Table 8.2 Infections and neuromuscular complications

Viruses			
	Herpes viruses		
		HSV 1 and 2	Myelitis, radiculopathy, peripheral nerve vasculitis.
		HVZ	Myelitis, radiculopathy, peripheral nerve vasculitis
		EBV	GBS
		CMV	GBS, radiculopathy, peripheral nerve vasculitis in immunocompromised host
	Retrovirus		
		HIV 1 and 2	GBS (seroconversion), peripheral neuropathy, radiculopathy, peripheral nerve vasculitis
		HTLV1	Peripheral neuropathy, myelitis
	Flavivirus		
		West Nile	Myelitis (Anterior Horn Cell)
		Japanese B	Myelitis (Anterior Horn Cell)
		Zika	Peripheral neuropathy, GBS
	Hepatitis		
		B, C, E	GBS, PN vasculitis, brachial and lumbosacral neuritis
	Rabies		Peripheral neuropathy, myelitis
	SARS-Cov-2		GBS, myelitis
	Enterovirus		
		Polio	Myelitis (Anterior Horn Cell)
Bacteria			
	Borrelia		Myelitis, radiculopathy
	Treponema pallidum (syphilis)		Myelitis, radiculopathy
	Clostridium botulinum		Neuromuscular junction (botulism)
	Clostridium tetani (tetanus)		Spinal cord and autonomic nervous system
	Campylobacter jejuni		GBS
	Mycobacteria		
		Tuberculosis	Tuberculoma, myelitis, radiculopathy, arachnoiditis
		Leprae	Peripheral neuropathy, vasculitis
	Brucella		myelitis, radiculopathy
	Listeria		myelitis, arachnoiditis
Protozoa			
	Malaria		GBS
	Trypanosoma		GBS
Helminths			
	Schistosomiasis		Myelitis

Localisation by Site of Involvement

The symptoms and clinical signs vary with the site of involvement. Different areas of the neuroaxis may be involved together or sequentially. Close monitoring for bulbar symptoms and involvement of respiratory muscles is imperative in these situations. This is especially applicable to patients with Guillain-Barré Syndrome (GBS). Neuro-anatomically, the most common neuromuscular presentations are with a radiculoneuropathy (GBS), myelitis, mononeuritis multiplex due to vasculitis or a motor neuropathy/neuronopathy.

Cranial Nerves

A basal meningitis with involvement of lower cranial nerves presenting with facial weakness and sensorineural deafness may be the initial presentation of an infectious disease. Cranial nerve deficits can be a part of a presentation that is multifocal, raising the possibility of a more disseminated process as seen in tuberculosis (TB), syphilis and Lyme disease. Botulism may also present with facial weakness and progress to limb weakness mimicking GBS. Cephalic tetanus may occasionally present with facial and ocular muscle weakness.

Lyme disease, caused by *B. burgdorferi*, can present with cranial nerve deficits (III, V, VI, VII and VIII). The VIIth cranial nerve seems especially vulnerable, and the diagnostic probability is increased if the involvement is bilateral; other differentials of bilateral facial palsy include HIV. Leprosy may cause a partial facial palsy involving only the frontalis muscle, orbicularis oculi or buccinator. Bilateral cranial nerve deficits with ophthalmoplegia and facial palsy in association with descending weakness should alert the clinician to the possibility of botulism [5, 6].

Spinal Cord

Myelopathy in the context of an infection can be either due to direct infection or as a result of a para-infectious or post-infectious autoimmune process. The clinical syndrome can be variable with motor and sensory deficits. Bowel and/or bladder dysfunction may result from autonomic or cauda equina involvement. The neurological presentation depends on the nature and extent, transverse and longitudinal, of involvement of the spinal cord. Bacterial infections causing spinal/epidural abscesses can often present in a similar fashion to an acute cord syndrome with pain as an important feature. Whilst this could be due to cord compression, complications of bacterial meningitis such as spinal cord ischemia as a result of either hypotensive shock, vasculitis or arachnoiditis are well described and important to consider.

Certain viruses have a predilection for anterior horn cells and therefore will present with a flaccid lower motor neurone paralysis—these include enteroviruses such

as polio virus. Although wild-type infections have been eradicated from the world except in Pakistan and Afghanistan, vaccine-related cases still occur worldwide [7]. Flaviviruses such as West Nile virus, Japanese B and Zika virus also result in a flaccid lower motor neurone paralysis. These diagnoses need to be considered in the differential of patients with GBS.

Varicella zoster virus (VZV) (shingles) can also present with a myeloradiculopathy in both immunocompetent and immunocompromised individuals; a typical herpetic rash is not always present—'herpes varicella zoster sine herpete'.

Animal bites can result in the transmission of rabies, which can either present with the more typical encephalomyelitis associated with hydrophobia and autonomic dysfunction or as the paralytic form with localised weakness near the site of the bite, progressing rapidly to global weakness and death typically in 5–10 days [8, 9].

A rare presentation of bacterial infection is a centromedullary longitudinally extensive myelitis which has been reported in bacterial meningitis due to Neisseria meningitidis and Streptococcus pneumoniae [8]. Syphilitic myelitis can also present in a similar fashion, and important clues to this could be the presence of associated findings such as osteitis and gumma [8]. Neuro-brucellosis, caused by gram-negative coccobacilli, is due to the consumption of unpasteurised dairy products and which is common in the Middle East, Mediterranean and Latin America. It presents in a myriad of ways. These include a myeloradiculopathy, usually with systemic symptoms (fever, anorexia), but also sacroiliitis, lymphadenopathy and hepatosplenomegaly. Lyme myeloradiculopathy (Bannwarth's syndrome) due to *B. burgdorferi* can present with a combination of radicular and myelopathic features due to involvement of the cord and the cauda equina.

In certain areas of the world, the diagnosis of schistosomiasis is the most common cause of a lower spinal cord and cauda equina syndrome. It should be noted that presentations can be delayed years after exposure to a causative agent [2]. The pathological mechanism can be either a rapidly progressive necrotic myelopathy, which has a poor prognosis, or a granulomatous form which if treated early has a better outcome.

Dorsal Root Ganglion, Nerve Roots and Plexus

Herpes varicella zoster, or shingles, is one of the most common acute infections of the peripheral nervous system. It is caused by the reactivation of VZV which lies latent in the sensory and autonomic ganglia. Any condition that affects cell-mediated immunity can theoretically cause this reactivation to occur. Typically, neuropathic pain and the vesicular rash limited to a dermatome, not crossing the midline, is seen. Acute infection can result in an acute progressive weakness due to involvement of the spinal cord and/or nerve root.

Post-infectious GBS, which is synonymous with acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the most common infection-associated peripheral nerve disorder (see also Chaps. 3 and 6).

The typical presentation is that of an ascending, progressive, sensorimotor weakness with a flaccid paralysis with areflexia noted clinically. By definition, the nadir is reached within 4 weeks. *C. jejuni* infection is the predominant infection found in 2–50% of

adult patients and seems to occur more commonly in Asian countries. Other infections associated with GBS include cytomegalovirus (CMV), Epstein-Barr Virus (EBV), influenza A, mycoplasma pneumoniae, haemophilus influenzae and HIV at seroconversion. More recently, hepatitis E, Zika, Japanese encephalitis virus, Chikungunya and Sars-CoV-2 infections have been added to the list of associated infections [10, 11].

Emergencies seen in this context include involvement of cranial nerves presenting with bulbar dysfunction, respiratory muscle weakness and autonomic involvement with cardiac arrhythmias and labile hemodynamic stability. A typically difficult to manage associated condition is post-infectious acute pure autonomic failure which is one of the rarer variants encountered in clinical practice.

Acute brachial neuritis (Parsonage-Turner syndrome) and lumbosacral plexopathies may be described as post-infectious inflammatory disorders affecting mainly motor nerve roots and plexus. In the former syndrome, respiration may be affected due to diaphragmatic paralysis as a result of phrenic nerve involvement which is well recognised.

Peripheral Nerve

Peripheral nerve disorders can be classified anatomically into either a length-dependant neuropathy, a mononeuritis multiplex or a radiculoneuropathy. The history and neurological examination will confirm the diagnosis, but neurophysiological investigations, which are important to distinguish between demyelinating and axonal neuropathy, may provide clues to the underlying aetiologies.

The most common infectious cause of a length-dependant neuropathy worldwide is HIV infection. This mainly sensory small fibre neuropathy is not an emergency but HIV can occasionally be associated with a vasculitic neuropathy which can rapidly progress to severe widespread weakness rendering the patient bed-bound with all its inherent complications. The mechanism is immune complex-mediated disease.

Hepatitis B is a well-characterised infection which may cause vasculitis with features on biopsy of a medium-sized artery vasculopathy due to immune complex deposition. Hepatitis C vasculitis is more common and is related to a mixed cryoglobulinaemia. Up to 50% of patients infected with hepatitis C have a mixed cryoglobulinaemia but only 15% will go on to develop symptomatic disease usually years after the initial infection. The clinical presentation is with either a mononeuritis multiplex, a symmetrical or asymmetrical sensory-motor axonal polyneuropathy. Systemic features include glomerulonephritis, leg ulcers, arthritis and purpura [12, 13].

Mycobacterium leprae infection is a chronic granulomatous disorder that principally affects skin and peripheral nerves (leprosy or Hansen's disease). The presentation may be a mononeuritis multiplex (tuberculoid leprosy) or a distal symmetrical neuropathy (lepromatous) with considerable overlap. Although not usually classified as emergencies, leprosy reactions should be treated as such. These sudden episodes of acute inflammation occur in 30% of patients usually in the first 6 months of starting leprosy treatment. The clinical manifestations of type 1 reaction are acute neuritis and erythema as well as oedema of skin lesions causing further damage. Type 2 reaction (erythyma nodosum leprosum, ENL) is a systemic illness with

patients rapidly becoming very ill with high temperatures, painful subcutaneous nodules, oedema, inflammation of peripheral nerves, eyes, joints and testes. This requires in-patient treatment with high-dose prednisolone [14].

Subgroups that Warrant Special Attention

Children, Pregnant Women and Elderly Populations

Special populations such as children and pregnant women are thought to be more susceptible or more severely affected by various infectious diseases [15]. It is also important to be aware of the physiological changes in pregnancy and puerperium while interpreting clinical presentations and investigations [16].

The elderly population is increasingly susceptible to infection. Immune senescence [17, 18] leads to impaired immune defences, increased risk of infection and sensitivity to pathogens. There is a decreased inflammatory and antibody response and the clinical presentation may be obtunded with minimal or non-specific symptoms and signs at presentation. Furthermore, the immune response to vaccinations may be weak and inadequate (Case Vignette 1). As an example, VZV reactivation leading to shingles is a common cause of morbidity in the elderly population. Tetanus and diphtheria may present in elderly individuals whose immunity has waned with time after initial immunisation programmes in their youth. Serological surveys among adults in industrialised countries indicate that 20–60% have diphtheria antibody levels below the minimal protective levels [19].

Other complicating issues include co-morbid conditions such as diabetes, autoimmune disease, cancer and effects of ongoing treatment such as corticosteroids. The source of other infections such as pneumonia, urinary or skin infections can also lead to disseminated infection by hematogenous spread (See Table 8.3).

Case Vignette 1: Reproduced with Permission [20]
A 74-year-old Caucasian man, who had a fall with head injury, and sustained a wound on the right side of his forehead, presented a week later to the hospital, with progressive bilateral facial muscles weakness, with difficulty speaking and swallowing. He had no diplopia/sensory symptoms/bowel/bladder problems. A day later he developed lower jaw muscle spasms, and subsequent difficulty opening his jaw. There was no history of systemic symptoms such as fever, night sweats, change in appetite, shortness of breath or chest pain. He was well prior to the current illness, but he was not sure about his prior immunisation history. He had retired from work, lived with his wife and was independent in basic activities of daily living. There was no recent travel history. He did not smoke or consume alcohol. There was no family history of neurological problems.

On examination, a 3–4 cm healing superficial wound was noted on the right side of his forehead. Pupils and eye movements were normal. There was bilateral facial weakness and ptosis. Intermittent spasm of his jaw muscles was noted on the second day of admission. Jaw jerk was normal, but corneal reflexes were absent. Limb examination showed normal tone, power and deep tendon reflexes. There was no sensory loss. Systemic examination was unremarkable.

Investigations were normal/negative for Hb, WBC, Platelet count, serum calcium, magnesium, renal profile, serum ACE, ANA, ANCA, creatine kinase and blood glucose, HIV, Treponema pallidum serology, Lyme serology. Mild hypophosphatemia was noted, ESR was 38 mm/1st h (1–30) and CRP was 28 mg/L (0–5). There was no growth in the blood culture. Wound debridement specimen culture showed Clostridium tetani; tetanus antibodies titre: 0.060 IU/L (>0.1 IU/L) suggesting his immunisation cover was inadequate. Plasma immunoglobulins profile showed normal IgG, IgM and mildly elevated IgA.

He was given tetanus toxoid and a dose of tetanus anti-toxin. Wound debridement was performed and antibiotics to cover C. tetani were commenced intravenously immediately after wound debridement. He was transferred to the intensive therapy unit to protect his airway. He had a tracheostomy and was commenced on ventilatory support. He was treated with intravenous benzyl penicillin and metronidazole in the intensive care unit and made a partial recovery.

Learning Points
Tetanus still occurs in the elderly in whom the immune system has waned.

Table 8.3 Infections associated with specific host defence defect

Drug/infection	Effect on immune system	Associated pathogens
Treatment related		
Corticosteroids	Inhibition of phagocytes, T-cell function	Bacterial, herpes virus, *Candida* species infections
Cytotoxic drugs, i.e., metho-trexate, DMP, 5-fluorouracil	Bone marrow suppression	Gram-positive and Gram-negative bacteria, *Candida* species, invasive mould infections
Purine analogues, i.e., cladribine	Neutropenia, lymphopenia, hypogamma-globulinemia	Encapsulated organisms, Gram-positive and Gram-negative organisms, herpes viruses (HSV, VZV, CMV), mycobacteria, *Candida* species, *Aspergillus* species, cryptococcus
Azathioprine	Inhibition of B- and T-cell proliferation, decreased antibody production, myelosuppression	Bacterial infections, VZV, CMV, PML, worsening of hepatitis B and C
Ciclosporin, tacrolimus	Inhibited production of interleukin-2 and cytokines by CD4 cells	CMV, EBV, PTLD, PML, hepatitis C activation

(continued)

Drug/infection	Effect on immune system	Associated pathogens
Mycophenolate	Inhibition of B- and T-cell proliferation, decreased antibody production	Herpes viruses, hepatitis B and C activation, *Candida* species, cryptococcus, *Aspergillus* species
Phenytoin	Immunoglobulin A deficiency/ hypogammaglobulinemia	Bacteria including encapsulated organisms, respiratory viruses, enteroviruses, *Giardia*
Monoclonal antibodies		
• Rituximab	B-cell depletion	Hepatitis B reactivation, PML, possibly increased/severe complications of mycobacterial disease
• Alemtuzumab	Rapid but protracted peripheral lymphopenia (B and T cells)	Infections caused BY HSV, VZV and mycetes, *Listeria monocytogenes*
• Infliximab	TNF inhibitors	Reactivation of latent TB; hepatitis B, VZV, CMV infection
Related to co-morbidities, co-infections		
HIV		
• Seroconversion		Aseptic meningo-encephalitis, acute disseminated encephalomyelitis, transverse myelitis or involvement of the peripheral nervous system with polymyositis, brachial neuritis or cauda equina syndrome
• Early symptomatic phase		VZV and peripheral neuropathy presenting during the early symptomatic phase
• With progressive CD4 decline		AIDS-defining conditions including HAD, opportunistic infections (CMV, *Toxoplasma*, *Mycobacterium*, *Cryptococcus*), PML, cerebral lymphoma
Diabetes mellitus	Defects in humoral and cellular innate immunity	Rhino-orbital-cerebral mucormycosis, non-tropical pyomyositis, pyogenic spinal infections, *Listeria* meningitis, blastomycosis; infection with West Nile virus, VZV
Specific groups		
Neonates		Bacterial meningitis is often caused by group B *Streptococcus*, *Listeria monocytogenes*, *Escherichia coli* (<3 months old) and >3 months – pneumococcus, meningococcus, *Haemophilus influenza* type B
Elderly individuals		Streptococcus pneumoniae, Neisseria meningitidis, Listeria monocytogenes, aerobic Gram-negative organisms
Pregnant women		Bacterial meningitis caused by *Listeria monocytogenes*

CMV cytomegalovirus, *DMP* 1,4-dimethyl pyridine, *EBV* Epstein–Barr virus, *HAD* HIV-associated dementia, *HSV* herpes simplex virus, *PML* progressive multifocal leukoencephalopathy, *PTLD* post-transplant lymphoproliferative disease, *TB* tuberculosis, *TNF* tumour necrosis factor, *VZV* varicella–zoster virus

Source: Adapted from (Clarke et al. 2016; Dropulic and Lederman 2016; Jay and Solbrig 2014; Sethi and Davies 2020)

Immunosuppression Due to Treatment

Various medications alter the predisposition of a host to infection (Table 8.3). Rituximab, a humanised chimeric monoclonal antibody which binds to the surface receptor CD20, is widely expressed on CD20 lymphocyte cells. The drug is now used in haematological malignancies but also in a number of antibody-mediated neurological disorders such as myasthenia gravis, inflammatory myopathies, neuromyelitis optica and NMDA antibody encephalitis. A depletion in B cells, as well as depletion of immunoglobulin levels, can lead to reactivation of latent hepatitis B infection, complications of mycobacterial disease and also to reactivation of latent JCV infection leading to progressive multifocal leukoencephalopathy (PML). Alemtuzumab, which suppresses both T and B cells, has been associated with an increased risk of HSV and VZV infections, and a resurgence of Listeria infection, which usually causes meningitis and rhombencephalitis. Anti-TNF agents such as infliximab can cause reactivation of latent TB and hepatitis B and are associated with increased VZV and CMV infections. In addition to reactivation of latent infections, primary infection with herpes zoster and CMV must be considered in the immunocompromised host. CMV causes a devastating polyradiculopathy, often lumbosacral in distribution, especially in HIV-infected individuals with a low CD4 count. Although now rare in the HIV-treated population, it is still seen in resource-poor settings or where HIV remains untreated or undiagnosed.

Neuromuscular Emergencies in Low-Income Societies

Whilst the advent of newer diagnostic modalities and access to healthcare is considered the norm in much of the developed world, diagnosis and treatment in settings of low-income societies (see also Chap. 15) requires a keen appreciation of the factors such as no vaccination programmes or incomplete immunisation schedules with delayed or missed booster doses, influencing the increased likelihood of seeing emergencies such as diphtheria and tetanus. A good example is access to HIV antiretroviral therapy which varies considerably worldwide. Where widely available, the rate of opportunistic infections, tumours and HIV-related neurological complications have declined dramatically.

The reliance on astute clinical assessment and ability to diagnose in resource-poor settings is clearly essential in these conditions. Access to imaging such as computed tomography/magnetic resonance imaging (CT/MRI), and in the context of the peripheral nervous system, access to neurophysiology or special MR neurography/MRI muscles is usually not available. Serological and CSF tests for the myriad of infection and post-infectious aetiologies might also be sparse. The natural history of diseases as we are familiar with might also differ given the lack of appropriate and timely treatment.

As detailed above, the role of a good history of presentation cannot be overemphasised in these settings. A good knowledge of local disease prevalence, common aetiologies and knowledge of cultural and social lifestyle factors can be relevant in helping to limit the morbidity due to neurological emergencies.

The Returning Traveller

A detailed travel history including places visited in transit is crucial when trying to diagnose an infection in a returning traveller. Dates of travel and consideration of the incubation periods are important variables [2]. Lower motor syndromes that must be considered in the returning traveller include bacterial infections (botulism, tetanus, *Brucella*, *Borrelia*, *T. pallidum*), viral infections (Japanese B, polio and other enteroviruses, West Nile, dengue, rabies, Zika, and hepatitis E). In patients presenting with a post-infectious GBS-like syndrome, a history of infection with *C. Jejuni*, malaria, HIV (seroconversion), Zika and EBV must be sought in detail. Syndromes associated with HIV seroconversion include myelitis, GBS, brachial neuritis, polymyositis and a cauda equina syndrome.

Other relevant history includes previous known co-morbidities, ongoing treatment, details of which vaccines have been taken and when (as part of primary immunisation, boosters, travel vaccinations), any exposure to undercooked food, exposure to areas endemic to mosquitoes, ticks, flies and adventure sports resulting in exposure to forest/freshwater/soil, sexual contacts and if any contact with relatives or friends with TB [2].

Incubation periods can be considered by dividing them as short, intermediate and long. Influenza, dengue, African tick bite fever and Rocky Mountain spotted fever have a short (<10 day) incubation period. Malaria, hepatitis (A, B, C, E), schistosomiasis, TB and Brucellosis can be long (> 21 days) and an intermediate incubation period is seen in Q-fever, viral haemorrhagic fevers, malaria and African trypanosomiasis (10–21 days).

The Non-immunised/Partially Immunised Host

Polio, diphtheria and tetanus are the vaccine preventable disorders. In individuals who have not been vaccinated, the elderly or those individuals who have not had required booster doses, or in those where perhaps the requirement of the booster is accelerated (on immunosuppressive or immunomodulatory treatment), these aetiologies must be considered in the relevant presentations. It is important to note that protection from vaccines and chemoprophylaxis for malaria is not absolute.

With the use of treatments such as stem cell transplants, specific vaccination guidelines should be followed in the months post-transplant, to ensure adequate immunity against infection. If recommended guidelines have not been met or if there are concerns that the host status would interfere with the generation of an

appropriate immune response, then the differentials being considered must take this into account.

Migration of populations needs to be kept in mind, especially when they move to/from endemic areas in the absence of appropriate vaccination. For example, adults moving from a non-endemic to an endemic region for TB may not have been vaccinated as children with BCG as this may not be part of the local guidelines.

Specific Infections

Viruses

HIV

HIV is a retrovirus which targets and infects CD4+ lymphocytes. HIV can involve different parts of the neuroaxis causing meningitis, encephalitis, myelopathy, cauda equina syndrome and radiculopathy, brachial or lumbosacral plexopathy, neuropathy and myopathy [1]. Some of the presentations occur at seroconversion [21].

HIV-related direct effects on the peripheral nervous system include a painful distal sensory peripheral neuropathy, GBS and chronic inflammatory demyelinating neuropathy (CIDP) and a vasculitic neuropathy. A vacuolar myelopathy resembling subacute combined degeneration of the spinal cord, similar to that encountered in vitamin B12 deficiency, and HIV polymyositis are also described. A diffuse inflammatory lymphocytic syndrome (DILS) which mimics Sjögren's syndrome presents with inflammatory neuropathy. Myelitis in the context of HIV can be a direct result of HIV usually at seroconversion. A myelopathy should also alert physicians to the possibility of opportunistic infections with VZV, CMV and toxoplasmosis. Every patient with HIV must be screened for TB and syphilis. CMV lumbosacral radiculopathy and a rapidly progressive cauda equina syndrome occur in very immunosuppressed patients with CD4 counts below 100 cells/$mm^{3.}$

Drug-related peripheral neuropathy is commonly seen with ddC, ddI and d4T. These anti-retroviral drugs, especially d4T, are still used in resource-poor settings. Thalidomide, Isoniazid and Dapsone are other drugs that might be implicated in appropriate clinical settings.

When managing patients with HIV, it is important to recognise that presentations can be atypical:

- In the treatment-naïve individual, the CD4 count can be helpful in formulating a differential diagnosis:
  - CD4 < 350—Mycobacterium tuberculosis related complications
  - CD4 < 200—Toxoplasma, cryptococcal meningitis, HSV and M. tuberculosis related opportunistic infections, PML (note JCV can cause a neuronopathy), vacuolar myopathy
  - CD4 < 50—CMV polyradiculopathy more likely

- Multiple organisms, multiple causes and multiple sites can be affected simultaneously
- Unlike the immunocompetent hosts, serological tests may not be diagnostic

About 10–25% patients develop a paradoxical worsening or develop new symptoms, days to months (up to 8 weeks) after starting antiretroviral therapy (ART). This is due to the immune reconstitution inflammatory syndrome (IRIS). Neuro-IRIS has been described in the context of infection with Mycobacterium [22], Cryptococcus, CMV, JCV (PML) [23] and HIV itself. There have also been reports of neuro-IRIS due to Toxoplasma [24–26], strongyloidiasis [27] and a late onset of herpes zoster [25].

Corona Virus: Sars-CoV-2 (COVID-19)

Since the onset of the COVID-19 pandemic in December 2019, there are increasing reports of neurological complications [28, 29]. These have included an association with GBS [30] (case 2). Since GBS is a post-infectious syndrome usually after infections such as *C. jejuni*, mycoplasma, EBV and HIV, this complication was not unexpected. The underlying mechanism is postulated to be due to molecular mimicry although unlike Acute motor axonal neuropathy (AMAN) and *C. jejuni*, the specific gangliosides have to date, not been isolated. The presentation and response to standard treatment with intravenous immunoglobulin is similar to non-COVID-19 cases.

There is also an association described with acute disseminated encephalomyelitis (ADEM) with spinal cord involvement [29] (case 2). ADEM is also classified as a post-infectious neurological syndrome usually occurring in children after viral infections such as influenza and mycoplasma. Some of the other peripheral nerve complications described in this group of patients result from the prolonged stay in the intensive care units (ICU) and include critical care neuro-myopathy and brachial plexus damage as a result of stretching when patients are nursed in the prone position for prolonged periods in order to alleviate the respiratory compromise that occurs frequently.

A recent publication describes mononeuritis multiplex in a cohort of COVID-19 patients in the ICU. The underlying mechanism is to date undetermined but possibilities include inflammation and/or micro-thrombosis in combination [31].

Case Vignette 2: Reproduced with Permission [28]

A previously healthy 52-year-old Caucasian man presented with a 3-day history of occipital headache, back pain and vomiting (without diarrhoea). The day before admission, he developed bilateral proximal weakness in all limbs without sensory disturbance.

On admission, his temperature was 36.3 °C, pulse 69 beats per minute, blood pressure 220/110 mmHg, respiratory rate of 15 breaths per minute and an oxygen saturation of 99% while breathing ambient air. Cardiovascular,

respiratory and abdominal examinations were unremarkable. Neurological examination: Glasgow Coma Scale (GCS) 15/15, no meningism and mild bilateral facial weakness. Muscle tone was reduced throughout. He had bilateral symmetrical upper and lower limb weakness of 2/5 proximally and 4-/5 distally. Neck flexion and extension were weak (4-/5). He was areflexic throughout. Plantar responses were extensor. Sensation was normal. His forced vital capacity (FVC) was 2.8 L and electrocardiogram showed normal sinus rhythm.

*Admission laboratory investigations were unremarkable, except for a mildly elevated ALT 86 IU/L (<42) and ESR 22 mm/h (<15). MRI of neuraxis was normal except for subtle post-contrast enhancement of the brachial and lumbar nerve roots (*Fig. 8.2*). Cerebrospinal fluid (CSF) was acellular, with a raised protein (1.01 g/L) and normal glucose level. Nerve conduction studies and electromyography confirmed an acquired primary demyelinating polyradiculoneuropathy. A five-day course of intravenous immunoglobulin (0.4 g/kg/day) was commenced after a diagnosis of GBS had been established. His blood pressure was controlled with amlodipine 5 mg/day.*

Three days later, he deteriorated with increasing weakness, dysphagia, new ophthalmoplegia, FVC reduction to 1.2 L, C-reactive protein level of 127 mg/L and lymphopenia (800 per microliter). He was transferred to intensive care and underwent a percutaneous tracheostomy for mechanical ventilation. The next day he became febrile (38.9 °C), with increasing oxygen requirements. CRP climbed to 253 mg/L (0–4) and d-dimer was raised at 1988 ugFEU/L (270–500). Piperacillin/tazobactam and erythromycin were commenced for suspected pneumonia. CT of the chest showed bilateral pulmonary infiltrates with no evidence of pulmonary embolism. SARS-CoV-2 RNA PCR testing was positive on throat swab but negative in CSF.

Subsequently, he became completely unresponsive despite sedation being withheld and repeat MRI brain showed an unusual pattern of T2 hyperintensities (without corresponding diffusion-weighted imaging changes) in the white matter, affecting the pontine tegmentum, the posterior limb of the internal capsule and sparing the U-fibres, associated with microhaemorrhages (See Fig. 8.2*). A second diagnosis of acute demyelinating encephalomyelitis (ADEM) secondary to COVID-19 was made. Serial MRI brain showed marked radiological progression Electroencephalography showed diffuse irregular delta waves with no epileptiform activity. Intravenous methylprednisolone (IVMP) 1 g/day was given over the next 5 days. He made a partial recovery with normal cognition and upper limb strength but still has leg weakness.*

Learning Points
COVID-19 is now in the differential diagnosis of most neurological syndromes.

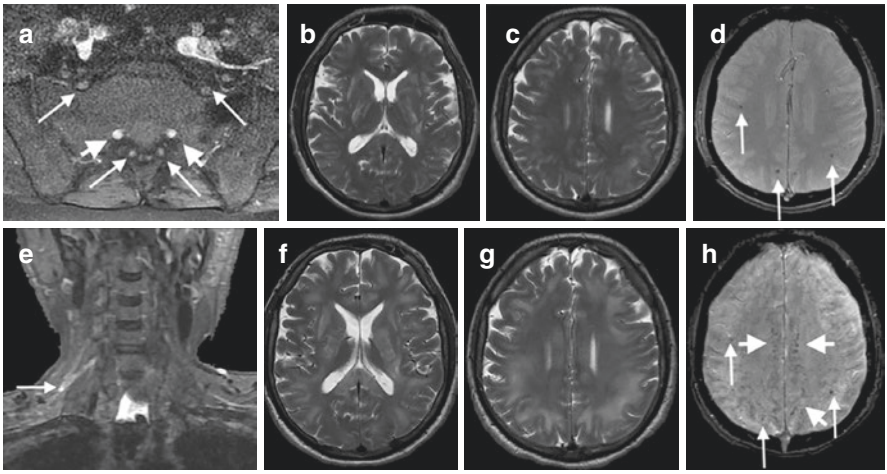


Fig. 8.2 MRI appearances in a case of post COVID ADEM—reproduced with permission from Paterson et al. [29]. (**a**–**h**) Patient 16: axial post-gadolinium fat-suppressed T1-weighted images (**a**) demonstrating pathologically enhancing extradural lumbosacral nerve roots (arrows). Note physiological enhancement of nerve root ganglia (short arrows). Coronal short tau inversion recovery (STIR) image (**b**) shows hyperintense signal abnormality of the upper trunk of the right brachial plexus (arrow). Initial axial T2 (**b** and **c**) and T2-weighted images (**d**) show multifocal confluent T2 hyperintense lesions involving internal and external capsules, splenium of corpus callosum (**b**), and the juxtacortical and deep white matter (**c**), associated with microhaemorrhages (**d**, arrows). Follow-up T2-weighted images (**f** and **g**) show marked progression of the confluent T2 hyperintense lesions, which involve a large proportion of the juxtacortical and deep white matter, corpus callosum and internal and external capsules. The follow-up SWI (Susceptibility-weighted image) (**h**) demonstrates not only the previously seen microhaemorrhages (arrows) but also prominent medullary veins (short arrows)

Rabies

Rabies is a disease caused by viruses of the Lyssavirus genus, the prototype virus being the rabies virus (RABV). This is most commonly transmitted by the bite of an infected mammal. More than 99% cases of human rabies are due to dog bites. Organ transplantation from undiagnosed donors and infection via aerosol has also been reported. A specific enquiry about the endemicity of the virus must be ascertained if patients and travellers present with a syndrome suggestive of the disease especially if they give a history of the bite of a stray/rabid dog.

A conservative estimate of annual mortality in Asia and Africa is 55,000 persons. India, Pakistan and Bangladesh are countries with a high incidence of the disease and returning travellers to these countries (often immigrants) need to be carefully questioned about dog bites in the appropriate clinical setting. In the US the majority of indigenous infections were due to bat rabies viruses.

The incubation period can vary from about 20 days to as long as 90 days [9]. The viral replication in the dorsal root ganglia can cause the initial symptoms such as pain and pruritis. This is followed by a short prodromal phase leading to the acute neurological phase. The clinical presentation can be either (i) furious/encephalitic

or (ii) paralytic (dumb). Furious rabies is characterised by agitation, hydrophobia and increased salivation. In the context of emergencies affecting the peripheral nervous system, the paralytic presentation is with prodromal symptoms of fever, headache and local paraesthesia. A flaccid paralysis, usually in the bitten limb, then spreads to eventually involve the respiratory and bulbar muscles. This can mimic the acute motor axonal neuropathy (AMAN) form of GBS [32].

When rabies is suspected, investigative samples that should be collected include saliva, CSF, serum and a biopsy of the skin containing hair follicles with peripheral nerve endings, usually from the nape of the neck, and tests repeated daily as initial tests have been noted to be negative. Rabies has been considered universally fatal although most patients will be given the Milwaukee protocol in the ICU setting. This includes therapeutic coma with a combination of ketamine, ribavirin and amantadine.

Prevention of rabies through dog vaccination campaigns is an important strategy, especially in endemic regions. Rabies pre-exposure immunisation is also stressed when travelling to endemic regions. In addition to these approaches to primary prevention, secondary prevention with post-exposure prophylaxis is also advised. For pre-exposure prophylaxis, WHO issued recommendations are to be followed. Commonly used regimes advocate the administration of the vaccine in 4 doses on days 0, 7, 14, 21 and 21 or 28, especially for high-risk groups including vets, scientists and workers exposed to bats [33, 34]. Following infection, secondary infection includes care of the wound, vaccination (or booster if pre-exposure immunisation was given) and administration of immunoglobulins.

Bacteria

Borrelia Burgdorferi (Lyme Disease)

This zoonotic disease caused by the spirochaete *B. burgdorferi* is transmitted to humans by the Ixodes tick. Neurological manifestations are varied and include facial palsy, a painful myeloradiculitis (Bannwarth's syndrome), meningitis and vasculitis affecting both the central (stroke) and peripheral nervous system.

In the UK, the disease is endemic in the South West of England (particularly around the New Forest), but also in the Lake District and the Highlands of Scotland. Internationally, it is seen in environmentally similar areas such as Scandinavia, Austria, Germany and also the North East and Upper Midwest USA [1, 35, 36]. Therefore, as emphasised, a detailed travel and work history outdoors (forests) is necessary, and also enquiries about hobbies such as shooting and fishing or playing golf should be made.

The commonest manifestation of Lyme disease is the skin rash of erythema migrans (EM) which appears 7–10 days after exposure. Approximately 5% of patients with EM go on to develop neuroborreliosis. However, only 25% of patients with neuroborreliosis recall a tick bite and 50% will report a skin lesion [37].

Bannwarth's syndrome is typically a triad of painful radiculitis, with motor and sensory deficits and a CSF lymphocytic pleocytosis. MRI may reveal enhancing nerve roots and/or myelopathic changes.

Lyme disease is a systemic disorder with manifestations of carditis, arthritis and uveitis. In the US, where the subspecies *B. burgdorferi sensu stricto* is the pathogenic organism, arthritis and carditis are more frequently reported. Emergencies can also involve conduction abnormalities leading to complete heart block requiring temporary pacing in 5–10% patients. In the UK and Europe, the prevalent organisms are *Borrelia afzelii* and *Borrelia garnii*, which seem to be more frequently associated with neuroborreliosis.

The testing recommended for diagnosis is a two-tier test for antibodies to *B. burgdorferi*—an ELISA/immunoassay initially and if this is positive an immunoblot at a reference laboratory. The enzyme immunoassay is highly sensitive but not specific with false positives due to other spirochaete infections and also autoimmune disorders such as SLE. The sensitivity of such a two-tier approach is up to 80–100% in patients with early disseminated cardiac or neurologic disease.

The treatment guidelines from the European Federation of Neurological Societies recommend doxycycline 200 mg daily for 21 days for cranial nerve, peripheral nervous system or meningeal limited disease. In non-responsive patients, intravenous ceftriaxone 2 g daily can be considered. In patients with CNS parenchymal complications (encephalitis, myelitis, vasculitis and stroke), intravenous ceftriaxone 2 g twice daily for 21 days is recommended [38, 39].

Clostridium Botulinum (Botulism)

The eight known strains of *C. botulinum*, which is an aerobic, gram-positive bacillus, produce a single potent neurotoxin which causes a paralytic illness. Food-borne botulism is caused by consumption of food contaminated with preformed botulinum toxin. Prior to effective sterilisation procedures, canned foods were a common source of infection. However, home canning continues to be a problem in Eastern Europe and Southern USA. Wound botulism occurs as a result of absorption of toxin by contamination of the wound site. Nowadays in developed countries, this complication is seen in drug users as a result of 'skin or muscle popping' of contaminated heroin. Following absorption and haematogenous spread, the toxin blocks acetylcholine release at the presynaptic terminals of motor and autonomic nerves. The clinical presentation is usually with cranial nerve palsies with bilateral facial weakness, ophthalmoplegia and ptosis. As the disease progresses, bulbar, respiratory and limb weakness ensues—'dysphonia, dysphagia, dysarthria and descending paralysis' [40]. The differential diagnosis includes GBS, Miller-Fisher Syndrome (MFS) and myasthenia gravis (see Table 8.4).

In view of the potential respiratory and bulbar complications, patients must be managed in the ICU setting—up to 50% of botulism patients will require ventilatory support.

Table 8.4 Differential diagnosis of Botulism, Guillain-Barré syndrome, Miller-Fisher syndrome and myasthenia gravis

	Botulism	GBS	MFS	MG
Weakness	Descending	Ascending	Ascending	Variable, fatiguability
Reflexes	Depressed in 50%	Depressed or absent	Absent	Normal
Ataxia	No	Sensory ataxia	Yes	No
Ophthalmoplegia	Yes	No	Yes	Yes
Pupils	Fixed mid-position, sluggish response	Normal	Normal	Normal
Sensory symptoms	No	Yes	No	No
Autonomic dysfunction	Yes	Yes	No	No
CSF protein	Normal	Elevated	Elevated	Normal
Neurophysiology	Normal CV, small MAP, repetitive stimulation at high frequencies or after exercise shows facilitation similar to Lambert-Eaton syndrome	Slowing CV, variable MAP, temporal dispersion, conduction block		On repetitive stimulation, decrement of MAP.
Toxin/Antibodies	Botulinum toxin in serum, food sample	Ganglioside antibodies (Variable)	GQ1b antibodies	Acetylcholine or MuSK anti bodies.

The diagnosis is primarily clinical since the laboratory confirmation takes time in specialised laboratories. The toxin can be detected in serum, gastric secretions, stool and in cases of food-borne botulism, the food sample. In patients suspected of suffering from botulism, treatment with antitoxin, which contains equine-derived antibodies, should be initiated promptly. In wound botulism, to prevent relapses due to ongoing toxin production, all wounds need surgical debridement and antibiotics until completely healed.

Corynebacterium Diphtheriae (Diphtheria)

Corynebacterium diphtheriae is another toxin-producing gram-positive rod which usually infects the pharynx and upper respiratory tract with the formation of a typical dirty-grey pseudomembrane. Complications arise with the absorption of the toxin causing a myocarditis. Around two-thirds of patients will also go on to develop the neurological complications of bulbar weakness, ophthalmoplegia and a demyelinating neuropathy [41].

The diagnosis should be suspected in any patient with a sore throat, a grey tonsillar pseudomembrane, hoarseness, dysphagia and signs of systemic toxicity. The diagnosis is confirmed by culturing toxicogenic *C. diphtheriae* from throat swabs. The differential diagnosis includes streptococcal or viral tonsillitis, Vincent's angina, oral candidiasis and acute epiglottitis. Patients with swallowing problems must be treated in the ICU for close monitoring. Severe diaphragmatic and respiratory muscle weakness can lead to the need to protect the airway with intubation and often prolonged intubation [1, 42].

Prompt treatment with an equine antiserum antitoxin is critical in the management of patients and is effective in reducing morbidity and mortality. Antibiotic therapy will eliminate the organism—IM procaine penicillin G (600,000 units for adults) every 12 h until the patient can swallow after which penicillin V 250 mg, four times a day for 14 days is administered. In penicillin-allergic patients, erythromycin can be used.

Clostridium Tetani (Tetanus)

Tetanus is caused by a neurotoxin, that is produced by the spore-forming bacteria *C. tetani*. Though preventable by vaccination with tetanus toxoid, the disease is still prevalent in low- and middle-income countries with 100,000 individuals dying annually [43]. In high-income countries, the disease is more common in subgroups such as intravenous drug users, and in those older than 60 years of age in whom immunity has waned with age. Boosters should be administered every 10 years.

Unlike botulinum toxin which remains at the neuromuscular junction, tetanus toxin is transported within the motor nerves to the central system. The toxin targets the inhibitory gamma aminobutyric (GABA-ergic) interneurons leading to the typical muscle spasms, rigidity and autonomic dysfunction. Lockjaw or trismus is the pathognomonic feature of tetanus ('risus sardonicus') which in the right context provides a clue to the potential diagnosis. This is followed by more axial symptoms, respiratory and autonomic storms in more severe cases. Respiratory muscle contraction leads to asphyxia, hypersalivation and autonomic involvement, which lead to arrythmias and circulatory failure requiring emergency ITU management [43].

It is essential that patients are nursed in the ICU setting—laryngeal muscle spasm can make endotracheal intubation difficult in severe cases. Tetanus antitoxin should be given as early as possible in an attempt to neutralise and prevent uptake of any circulating toxin. Human tetanus immunoglobulin is preferred to equine antitoxin since an anaphylactic reaction is less likely. Symptomatic therapies for the spasms include magnesium sulphate, dantrolene and intrathecal baclofen which have some evidence of efficacy in tetanus but are best offered in the ICU. With intensive care treatment and tracheostomy, the mortality rate of tetanus has reduced from about 45% in the 1950s to 15% in the 1980s to 7% in recent years.

Treponema Pallidum (Syphilis)

The incidence of primary and secondary syphilis in the US has increased every year since 2000, with 9.5 cases/100,000 persons in 2017 [44]. In the UK, in 2019, 8000 cases were reported—an increase of 10% since 2018 [45]. This was especially noted amongst men who have sex with men (MSM), and those with HIV infection.

The treponeme invades the nervous system in up to 50% of cases after early infection even in the absence of clinical features. The tertiary or late manifestations are due to meningovascular or parenchymatous complications. Meningovascular syphilis can occur 1–10 years after infection. The underlying pathology is meningitis causing a vasculitis of small- and medium-sized vessels (endarteritis obliterans) in the brain and spinal cord as well as a spinal arachnoiditis. The clinical presentation is with strokes including spinal artery syndrome and myelopathies [46]. The parenchymal syphilitic syndromes are the well-described tabes dorsalis and general paresis of the insane (GPI).

Although relatively rare, neurosyphilis still needs to be considered in any patients with a neurological disorder since the manifestations are protean. Cerebrospinal fluid examination typically shows a lymphocytic pleocytosis with cell count ranging from five to 100 cells /mm3. Whilst the protein is elevated, it is usually <1 g/dL; the range of these abnormalities depends on the stage of disease, being more dramatic in symptomatic meningitis.

Diagnostic serological laboratory investigations include a combination of non-specific tests such as the VDRL (Venereal disease research laboratory) and RPR (Rapid plasm reagin). Specific treponemal tests include the FTA-Abs (Fluorescent treponemal antibody absorption test) and TPPA (*T. pallidum* particle agglutination assay). Serum non-treponemal tests are reactive in almost all cases of neurosyphilis during and after the secondary stages. In late neurosyphilis, titres may wane with time and become negative. The CSF VDRL, if positive, confirms the diagnosis of neurosyphilis but a negative test does not exclude it as the test is only 30–70% sensitive. The serum and CSF FTA and TPPA serology may be negative in the primary stages of syphilis but are usually positive in cases of neurosyphilis [46].

Mycobacterium Tuberculosis (Tuberculosis)

In 2019, ten million people developed TB worldwide; 1.4 million patients died (including 208,000 with HIV co-infection) [47]. In the UK, 5132 cases of TB were reported to Public Health England. Although central nervous system TB accounts for 5–10% of extrapulmonary cases and only 1% of all cases of TB, the morbidity and mortality of these cases are disproportionately high [48, 49].

The usual presentations are with meningitis or intracranial mass lesions (granulomatous tuberculomas or tuberculous abscesses). Ten percent of patients with TB meningitis have some form of spinal involvement [50]. The spinal cord may be involved with or without these complications with an arachnoiditis, myelitis or

spinal tuberculoma. Involvement may also occur with vertebral bodies collapse (Pott's disease) or involvement of paraspinal tissue in the form of a paravertebral tuberculous abscess resulting in cord compression. An associated vasculitic response to TB infection can rarely result in involvement of the anterior spinal artery leading to ischemic injury of the spinal cord.

Depending on the site of involvement, the presentation will be with an acute or progressive paraparesis, back and radicular pain, as well as bladder dysfunction. Constitutional symptoms such as loss of weight, low-grade fever, history of primary TB, travel or residence to an endemic area should alert to the possibility of the diagnosis. BCG vaccination, though common in many endemic countries, does not prevent against TB.

In a study of 71 patients with tuberculous meningitis from Lucknow, India, 33 (46%) had symptoms and signs of spinal cord and/or nerve root involvement. It was also noted that 15% of cases were a paradoxical presentation, i.e. developed spinal cord problems after starting anti-tuberculous therapy [51]. Paraparesis was present in 22 (33%) of patients—upper motor neurone in 6 (8%), lower motor neurone in 10 (14%) and mixed in 6 (8%). Quadriparesis was present in 3 (4%). The most frequent MRI finding was meningeal enhancement in 40 (56%). In the rest, myelitis 16 (22%), tuberculoma 4 (6%), CSF loculations 4 (6%), cord atrophy 3 (4%) and syrinx 2 (3%).

A markedly elevated CSF protein was associated with spinal cord and radicular involvement probably due to spinal block resulting from the tenacious exudate. This study also found that patients with myeloradiculopathy have a worse prognosis in terms of residual neurological deficits [51].

A CSF examination, when not contraindicated, is essential—typically revealing a leucocytosis (10–1000 cells × 10^3/mL), mostly lymphocytes; an elevated protein (0.5-3 g/L) and a CSF:plasma glucose <50%. Atypical findings are not uncommon with, for example, a predominance of neutrophils or even an acellular CSF in immunocompromised patients [50]. The sensitivity of acid-fast staining for a diagnosis of TB meningitis is 30–60%. The diagnostic yield is increased with a larger volume of CSF (10-15 mL) and repeated lumbar punctures (up to 4) [52].

A recent systemic review and meta-analysis on the diagnostic accuracy of nucleic acid amplification tests (NAAT) for the diagnosis of TBM concluded that 'NAA tests may be used in conjunction with culture due to the advantages of time to result and in scenarios where culture is not feasible'. The pooled estimates compared to culture were sensitivity 82% (95%CI: 75–87) and specificity 99% (95%CI: 98–99). A negative result does not definitely exclude a diagnosis of TBM [53]. In suspected cases, it is also important to look for TB outside the nervous system such as the lungs or lymph nodes which may facilitate diagnosis since these sites are more amenable to biopsy.

The NICE guidelines suggest that the initial treatment phase of 2 months consists of four drugs—rifampicin, isoniazid (+ pyridoxine), ethambutol and pyrazinamide. High-dose dexamethasone or prednisolone is started with initial therapy and tailed

off over 4–8 weeks. This may need to be modified according to organism sensitivities and local prevalence. For CNS TB, it is recommended to continue with isoniazid and rifampicin for a further 10 months [50].

Treatment of TB can be more optimally monitored by checking for drug levels to ensure adequate dosing, and if there are concerns of multidrug-resistant (MDR) TB then checking for resistance mutations can allow early modification of drug regime. Determining the susceptibility requires either a nucleic acid assay that can detect TB as well as gene mutations associated with resistance (i.e. rpoB gene mutations related to rifampin) or culture of the organism. Ongoing challenges include the management of MDR TB (resistance to isoniazid and rifampin) and extensively drug-resistant TB (XDR, resistance to isoniazid, rifampin, any fluoroquinolone and at least one injectable drug of amikacin, capreomycin or kanamycin) [54].

For patients who are co-infected with HIV, WHO recommended regime must be adhered to, starting treatment irrespective of the CD4 count, to be followed by ART within 8 weeks of treatment, unless the CD4 <50 cells/cu mm in which case ART should be started within 2 weeks of starting TB treatment [22, 55, 56]. In patients with vertebral collapse and cord compression, neurosurgical input is mandatory.

Helminths

Schistosomiasis

Infection with the helminthic blood fluke schistoma is second only to malaria in terms of socioeconomic and public health importance in tropical and subtropical areas. Worldwide, almost 200 million people are infected. *Schistosoma japonicum* is mainly found in China, the Philippines and South-East Asia; *Schistosoma mansoni* is found in Africa, South-East Asia, the Caribbean, the Middle East and parts of South America; and *Schistosoma haematobium* occurs mainly in Africa.

Humans, the definitive hosts, excrete the parasite eggs through faeces and urine into freshwater. The released miracidia then penetrate the intermediate host—the freshwater snail—where asexual multiplication occurs. The released cercariae penetrate human skin exposed to freshwater. The mature schistosomulae worms form mating pairs that inhabit the venous plexus around the bladder (*S. haematobium*), rectum (*S. mansoni*) and portal vein and liver (*S. japonicum*).

Neuroschistosomiasis occurs when eggs pass into the central nervous system by retrograde venous flow from the iliac veins and inferior vena cava through the valveless Batson venous plexus. The mature larvae elicit a variable inflammatory reaction depending on the host immune status. In naïve patients, such as travellers to endemic areas, the response is often more intense with a severe granulomatous reaction or occasionally a vasculitis.

A myeloradiculopathy is usually caused by *S. mansoni* or *S. haematobium*. The presentation may be acute or subacute with a lower spinal cord and cauda equina syndrome. Occasionally, as in the case below, the onset may be delayed (Case 3). The underlying pathological mechanism of damage can be either myelitic (with a rapidly progressive necrotic myelopathy and a relatively poor prognosis) or a granulomatous form that, if treated early, has a better outcome.

Blood tests are usually normal, although eosinophilia may be an indicator. The CSF may show a lymphocytosis with or without eosinophils with an elevated protein concentration. Serological tests in blood with ELISA are positive in >90% of patients but cannot distinguish between exposure and acute infection. A positive CSF ELISA may help more in confirming the diagnosis. Antischistosomal antibodies occur in 80%–90% of neuroschistosomiasis cases. Schistoma eggs may be detected in faeces (*S. mansoni* and *S. japonicum*) or urine (*S. haematobium*). Repeat sampling and centrifugation of urine and examination of the sediment increase the diagnostic rate. The treatment is with praziquantel 60 mg/kg/day for 3 days with prednisolone cover.

Case Vignette 3: Reproduced with Permission [2]

A 44-year-old woman presented with a one-week history of progressive symptoms of paraparesis, altered sensation and micturition difficulties. Five years prior to presentation, she had spent a 4-year period in Zimbabwe, during which time she recalled having swum in Lake Malawi.

On examination, she had a flaccid paraparesis with a T11 sensory level. MR imaging (See Fig. 8.3*) showed conus medullaris expansion with high T2 signal extending rostrally up to the T10 level, with irregular gadolinium enhancement of the conus and cauda equina. With an impression of a neoplastic lesion, she was started on corticosteroid treatment, with improvement in symptoms. However, surgical resection and subsequent histology identified Schistosoma eggs within necrotising granulomas. Examination of urine and stool found no Schistosoma eggs. Specific Schistosoma ELISA antibody test was positive.*

She was treated with praziquantel and gradually made a full motor recovery, although with a mild sensory deficit. This case of schistosomiasis myelopathy illustrates that patients with schistosomiasis can present years after exposure, emphasising the importance of a detailed travel history.

Learning Points

Schistosomiasis may occur years after exposure.

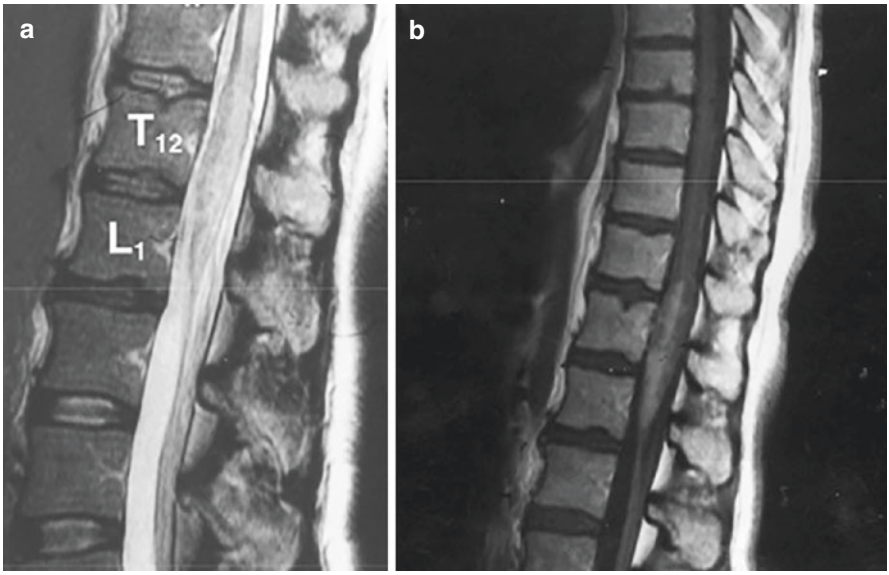


Fig. 8.3 MRI Spine in a case of Schistosomiasis. Image (**a**) shows sagittal T2w sequences of the spine showing swelling and hyperintense signal change of the caudal spinal cord and conus medullaris. Image (**b**) shows postcontrast sagittal T1w sequences of the spine showing patchy avid enhancement of the caudal spinal cord and conus medullaris. There is also some caudal nerve root thickening and enhancement

Self Assessment Questions

1. Which microbial organism has a direct neurotropic effect on the anterior horn cell.

   (a) Borrelia Burgdorferi.
   (b) Clostridium tetani.
   (c) Rabies virus.
   (d) West Nile virus. (*)

Micro-organisms may reside in the human body and cause new problems in the long term.

2. Where do these micro-organisms preferentially reside?

   (a) In the CSF-plexus.
   (b) In the lymph nodes.
   (c) In the dorsal root ganglia. (*)
   (d) In the spinal grey matter.

3. What is a para-infectious syndrome?

   (a) A syndrome occurring at the same time as the infection and is immune mediated.(*)
   (b) A syndrome frequently seen as a direct co-morbidity with an infection.
   (c) A syndrome caused by secondary tissue damage by an infection.
   (d) A syndrome caused by overgrowth of another infectious agent.

4. Which of the following is recognized as a post-infectious inflammatory disorder?

   (a) Acute brachial neuritis. (*)
   (b) Herpes Zoster.
   (c) Presynaptic myasthenia.
   (d) Trigeminal neuralgia.

5. Which of the following is a granulomatous disorder?

   (a) Leprosy. (*)
   (b) Lyme disease.
   (c) Neurosyphilis.
   (d) Toxoplasmosis.

6. When do leprosy reactions, to be considered as neurological emergencies, usually occur?

   (a) Before any other leprosy manifestation.
   (b) Together with the first skin presentations.
   (c) During the first months of starting leprosy treatment. (*)
   (d) After a silent period of several years since the first clinical manifestations. (*)

7. Which neurological syndrome occurs in the context of a leprosy reaction?

   (a) Encephalitis.
   (b) Meningitis.
   (c) Myelitis.
   (d) Neuritis. (*)

8. How should a leprosy reaction be treated? With a high dose of …

   (a) Chloroquine.
   (b) Erythomycin.
   (c) Prednisolone. (*)
   (d) Rifampicin.

9. Which populations are more susceptible to and more severely affected by various infectious diseases?

   (a) Agriculture workers.
   (b) Aviation personnel.
   (c) Military soldiers.
   (d) Pregnant women (*).

10. What is the main reason that many older individuals are more susceptible to infections? Because of …

    (a) immune senescence. (*)
    (b) impaired hygiene.
    (c) malnutrition.
    (d) vascular insufficiency.

11. Which of the following infections should be considered in a returning traveller who develops a GBS-like syndrome?

    (a) Brucellosis. (*)
    (b) Dengue.
    (c) Leprosy.
    (d) Malaria.

12. Which of the following measures should be taken when Rabies infection is suspected?

    (a) Administration of immunoglobulins
    (b) (Booster) Vaccination.
    (c) Wound care.
    (d) All of the above. (*)

13. What is the recommended first policy in case of a neuroborreliosis presenting by bilateral affection of the facial nerve?

    (a) Wait and see.
    (b) Ceftriaxone.
    (c) Doxycycline. (*)
    (d) Erythromycin.

14. Any patient suspected from botulism should be managed in the ICU setting.

    (a) True. (*)
    (b) False.

15. Which of the following neuromuscular symptoms is most likely to be caused by Diphteria in a patient with a sore throat and hoarseness?

    (a) Demyelinating neuropathy. (*)
    (b) Mononeuritis multiplex.
    (c) Myositis.
    (d) Presynaptic myasthenia.

16. Which of the following cranial nerve symptoms is most likely to be encountered in a patient with Diphtheria?

    (a) Double vision.
    (b) Lower facial weakness. (*)
    (c) Sensorineural deafness.
    (d) Trigeminal neuropathy.

17. Which of the following infections is likely to cause laryngospasm?

    (a) Botulism.
    (b) Diphtheria.
    (c) Tetanus. (*)

18. Schistosomiasis in tropical and subtropical countries commonly involves the spinal cord.

    (a) True. (*)
    (b) False.

19. A negative result of a nucleic acid amplification test (NAAT) in CSF practically excludes the diagnosis of tuberculoid meningitis.

    (a) True.
    (b) False. (*)

References

1. Howard R, Curtis C, Manji H. Neurology – a queen square textbook. Wiley; 2016. p. 337–89.
2. Bharucha T, Manji H. 'Montezuma's revenge': neurological disorders in the returning traveller. Pract Neurology. 2018;18(5):359.
3. Thakur K, Zunt J. Neurologic parasitic infections in immigrants and travelers. Semin Neurol. 2011;31(3):231–44.
4. Brizzi KT, Lyons JL. Peripheral nervous system manifestations of infectious diseases. Neurohospitalist. 2014;4(4):230–40.
5. Scalfaro C, Auricchio B, Medici DD, Anniballi F. Foodborne botulism: an evolving public health challenge. Infect Dis. 2019;51(2):97–101.
6. Wakerley BR, Yuki N. Mimics and chameleons in Guillain-Barré and Miller Fisher syndromes. Pract Neurol. 2015;15(2):90–9.
7. Chard AN. Progress toward polio eradication — worldwide, January 2018–March 2020. CDC Morbidity and Mortality Weekly Report; 26 Jun 2020.
8. Grill MF. Infectious myelopathies. Continuum (Minneap Minn). 2018;24(2, Spinal Cord Disorders):441–73.
9. Jackson AC. Human rabies: a 2016 update. Curr Infect Dis Rep. 2016;18(11):38.
10. Wang G, Li H, Yang X, Guo T, Wang L, Zhao Z, et al. Guillain–Barré syndrome associated with JEV infection. New Engl J Med. 2020;383(12):1188–90.
11. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. Lancet. 2016;388(10045):717–27.
12. Beachy N, Satkowiak K, Gwathmey K. Vasculitic neuropathies. Semin Neurol. 2019;39(05):608–19.
13. Gwathmey KG, Burns TM, Collins MP, Dyck PJB. Vasculitic neuropathies. Lancet Neurol. 2014;13(1):67–82.
14. Lockwood D, Lambert S. In: Magill A, Hill D, Solomon T, Ryan E, editors. Hunters Tropical Medicine and Emerging Infectious Diseases. 9th ed. Elsevier; 2012.
15. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. Am J Reprod Immunol. 2010;63(6):425–33.
16. Edlow JA, Caplan LR, O'Brien K, Tibbles CD. Diagnosis of acute neurological emergencies in pregnant and post-partum women. Lancet Neurol. 2013;12(2):175–85.

17. Heppner HJ, Cornel S, Peter W, Philipp B, Katrin S. Infections in the elderly. Crit Care Clin. 2013;29(3):757–74.
18. Htwe TH, Mushtaq A, Robinson SB, Rosher RB, Khardori N. Infection in the elderly. Infect Dis Clin N Am. 2007;21(3):711–43.
19. Galazka A, Dittmann S. The changing epidemiology of diphtheria in the vaccine era supplement 1. J Infect Dis. 2000;181(Supplement_1):S2–9.
20. Tahir A, Pokorny P, Malek N. Cephalic tetanus presenting with bilateral facial palsy. Scot Med J. 2019;64(3):108–11.
21. Centner CM, Bateman KJ, Heckmann JM. Manifestations of HIV infection in the peripheral nervous system. Lancet Neurol. 2013;12(3):295–309.
22. Kumarasamy N, Venkatesh KK, Vignesh R, Devaleenal B, Poongulali S, Yepthomi T, et al. Clinical outcomes among HIV/tuberculosis-coinfected patients developing immune reconstitution inflammatory syndrome after HAART initiation in South India. J Int Assoc Provid AIDS Care. 2012;12(1):28–31.
23. Jelcic I, Jelcic I, Kempf C, Largey F, Planas R, Schippling S, et al. Mechanisms of immune escape in central nervous system infection with neurotropic JC virus variant. Ann Neurol. 2016;79(3):404–18.
24. Brahim HB, Hchicha T, Zrig A, Kooli I, Aouam A, Toumi A, et al. Toxoplasma gondii: a rare pathogen causing a neurological immune inflammatory reconstitution syndrome in HIV infected patient. HIV AIDS Rev. 2015;14(2):46–8.
25. Espinosa E, Peña-Jiménez A, Ormsby CE, Vega-Barrientos R, Reyes-Terán G. Later onset of herpes zoster-associated immune reconstitution inflammatory syndrome. HIV Med. 2009;10(7):454–7.
26. Wattjes MP, Wijburg MT, Vennegoor A, Witte BI, de Vos M, Richert ND, et al. MRI characteristics of early PML-IRIS after natalizumab treatment in patients with MS. J Neurol Neurosurg Psychiatry. 2016;87(8):879–84.
27. Bar-Yoseph H, Zohar Y, Lorber M. Strongyloidiasis-related IRIS: a case report and literature review. J Int Assoc Provid AIDS Care. 2016;16(1):8–10.
28. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol. 2020;19(9):767–83.
29. Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, Bharucha T, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain. 2020;143(10):3104–20.
30. Toscano G, Palmerini F, Ravaglia S. Guillain–Barré syndrome associated with SARS-CoV-2. New Engl J Med. 2020;382(26):2574–6.
31. Needham E, Newcombe V, Michell A, Thornton R, Grainger A, Anwar F, et al. Mononeuritis multiplex: an unexpectedly frequent feature of severe COVID-19. J Neurol. 2021;268(8):2685–9.
32. Solomon T, Michael BD, Miller A, Kneen R, editors. Case studies in neurological infections of adults and children. Cambridge University Press; 2019.
33. Fooks A. Rabies. Nat Rev Dis Primers. 2017;3(1):17092.
34. Müller T, Freuling CM. Rabies vaccines for wildlife. In: Hildegund CJ, editor. Rabies and rabies vaccines. Springer Nature Switzerland AG; 2020. p. 45–70.
35. Burgdorfer W. How the discovery of Borrelia burgdorferi came about. Clin Dermatol. 1993;11(3):335–8.
36. Tardieu M, Deiva K. Rare inflammatory diseases of the white matter and mimics of multiple sclerosis and related disorders. Neuropediatrics. 2013;44(6):302–8.
37. Russell ALR, Dryden MS, Pinto AA, Lovett JK. Lyme disease: diagnosis and management. Pract Neurol. 2018;18(6):455.
38. Halperin JJ. Nervous system Lyme disease: diagnosis and treatment. Curr Treat Options Neurol. 2013;15(4):454–64.
39. Mygland A, Ljøstad U, Fingerle V, Rupprecht T, Schmutzhard E, Steiner I, et al. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. Eur J Neurol. 2010;17(1):8–e4.

40. Aston S, Beeching N. Botulism. In: Ryan ET, Hill DR, Solomon T, Aronson NE, Endy TP, editors. Hunter's tropical medicine and emerging infectious diseases. Elsevier; 2020. p. 551–4.
41. Logina I, Donaghy M. Diphtheritic polyneuropathy: a clinical study and comparison with Guillain-Barré syndrome. J Neurol Neurosurg Psychiatry. 1999;67(4):433.
42. Racca F, Vianello A, Mongini T, Ruggeri P, Versaci A, Vita GL, et al. Practical approach to respiratory emergencies in neurological diseases. Neurol Sci. 2020;41(3):497–508.
43. Yen LM, Thwaites CL. Tetanus. Lancet. 2019;393(10181):1657–68.
44. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance 2017. Atlanta: U.S. Department of Health and Human Services; 2018.
45. Public Health England. Sexually transmitted infections and screening for chlamydia in England, 2019. PHE; 2020.
46. Ropper AH. Neurosyphilis. New Engl J Med. 2019;381(14):1358–63.
47. WHO. Global TB progress at risk. 2020.
48. Logan C, Mullender C, Mirfenderesky M, Feasey N, Cosgrove C, Riley P, et al. Presentations and outcomes of central nervous system TB in a UK cohort: the high burden of neurological morbidity. J Infect. 2021;82(1):90–7.
49. Thakur K, Das M, Dooley K, Gupta A. The global neurological burden of tuberculosis. Semin Neurol. 2018;38(02):226–37.
50. Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. J Infect. 2009;59(3):167–87.
51. Gupta R, Garg RK, Jain A, Malhotra HS, Verma R, Sharma PK. Spinal cord and spinal nerve root involvement (Myeloradiculopathy) in tuberculous meningitis. Medicine. 2015;94(3):e404.
52. Thwaites GE, Chau TTH, Farrar JJ. Improving the bacteriological diagnosis of tuberculous meningitis. J Clin Microbiol. 2004;42(1):378–9.
53. Pormohammad A, Nasiri MJ, McHugh TD, Riahi SM, Bahr NC. A systematic review and meta-analysis of the diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis. J Clin Microbiol. 2019;57(6):e01113-18.
54. Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, et al. Treatment of highly drug-resistant pulmonary tuberculosis. New Engl J Med. 2020;382(10):893–902.
55. Migliori GB, Tiberi S, Zumla A, Petersen E, Chakaya JM, Wejse C, et al. MDR/XDR-TB management of patients and contacts: challenges facing the new decade. The 2020 clinical update by the Global Tuberculosis Network. Int J Infect Dis. 2020;92:S15–25.
56. Zunt JR. Tuberculosis of the central nervous system. Continuum (Minneap Minn). 2018;24(5):1422–38.

Chapter 9
The Acute and Emergency Management of Neuromuscular Junction Disorders

Maxwell Damian, Jennifer Spillane, and Pinki Munot

Introduction: The Physiology of Neuromuscular Junction Transmission

In order to understand the pathophysiology of myasthenia gravis (MG) and other disorders of the neuromuscular junction, it is important to understand the mechanism of neuromuscular transmission (Fig. 9.1).

Voltage-gated calcium channels open at the presynaptic endplate in response to the nerve action potential. The subsequent influx of calcium ions triggers the release of acetylcholine (ACh) from presynaptic vesicles in a mechanism that is dependent on SNARE proteins (soluble NSF attachment receptor proteins). Binding of ACh to the post-synaptic membrane receptor leads to muscle depolarisation which can be measured as the end plate potential (EPP), and this in turn leads to muscle contraction via a process involving release of calcium from the sarcoplasmic reticulum. The ACh receptors are kept clustered at the post-synaptic membrane by a group of proteins that include muscle-specific tyrosine kinase (MuSK) and low-density lipoprotein receptor protein 4 (LRP4).

M. Damian (✉)
Cambridge University Hospitals, Cambridge, UK

Essex Cardiothoracic Centre, Basildon, UK
e-mail: msdd2@cam.ac.uk

J. Spillane (✉)
The National Hospital for Neurology and Neurosurgery, University College Hospital, London, UK
e-mail: Jennifer.Spillane@uclh.nhs.uk

P. Munot (✉)
Great Ormond Street Hospital, London, UK
e-mail: Pinki.munot@gosh.nhs.uk

M. Damian, M. de Visser (eds.), *Emergencies in Neuromuscular Disorders*,
https://doi.org/10.1007/978-3-030-91932-0_9

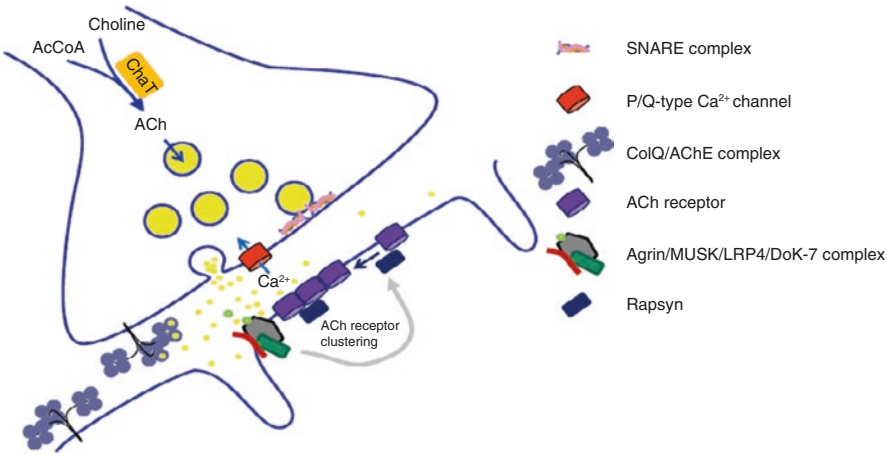


Fig. 9.1 Physiology of neuromuscular transmission. Key steps in acetylcholine (ACh) synthesis and release at the neuromuscular junction and the core pathway responsible for ACh receptor clustering. *AChE* acetylcholinesterase, *AcCoA* acetyl coenzyme A, *ChAT* choline acetyltransferase, *ColQ* AChE collagen-like tail subunit, *Dok-7* downstream of tyrosine kinase 7, *LRP4* low-density lipoprotein receptor-related protein 4, *MuSK* muscle-specific kinase, *SNARE* soluble NSF attachment protein receptor (from: Spillane J, Beeson DJ, Kullmann DM. Myasthenia and related disorders of the neuromuscular junction. J Neurol Neurosurg Psychiatry. 2010 Aug;81(8):850–7. doi: 10.1136/jnnp.2008.169367. Epub 2010 Jun 14. PMID: 20547629)

Under normal conditions, the EPP is more than sufficient to trigger a muscle action potential. However, if any of the steps of neuromuscular transmission are impaired, the EPP can become subthreshold which leads to neuromuscular weakness.

This may occur because of a problem with the presynaptic release of ACh as occurs in the Lambert-Eaton myasthenic syndrome (LEMS) and in Botulism or because of a failure of ACh to bind to post-synaptic AChR as occurs in autoimmune MG. Congenital Myasthenic Syndromes (CMS) can affect any of the different proteins involved in neuromuscular transmission.

Autoimmune Myasthenia Gravis

Epidemiology and Clinical Presentation

MG is the most common neuromuscular junction disorder, caused by an immune attack against nicotinic acetylcholine receptors (AChR) and related proteins leading to a defect of transmission at the neuromuscular junction. It is clinically characterised by muscle fatigability on exertion, and fluctuating weakness [1], which can present at any age but tends to be earlier in females (mean 28 years) than in males (mean 42 years). With an overall incidence of 0.5–5 cases per 100,000, its prevalence varies from 1 to 40/100000, and seems to be increasing, most likely due to

increased recognition of cases especially in older patients [2]. In 80% of cases myasthenic symptoms will begin with ocular symptoms manifesting as ptosis and diplopia, the majority of whom will go on to develop generalised symptoms [3]. Generalised symptoms may affect the limbs, causing fatigable weakness; the bulbar muscles, causing speech and swallowing problems; or most seriously respiratory muscles, causing dyspnoea or respiratory failure, and this is a neurological emergency. The prognosis of MG is variable; if symptoms remain purely ocular for 2 years it is less likely to generalise and up to 35% of cases may go into spontaneous remission [3]. Late-onset MG can have a more benign course but may be misdiagnosed; moreover, patients can present in crisis, though interestingly despite quite severe presentations patients with late-onset MG can often do quite well in the long term [4]. However, exacerbations and myasthenic crises in the elderly carry a higher mortality than in younger patients. Ultimate quality of life is largely determined by development of fixed or refractory diplopia and weakness, but also by the secondary effects of immunosuppressive therapy, which may include recurrent infections, osteoporosis, cataract or malignancy [5–7].

It is useful when characterising MG to subdivide it into

- Early vs late onset
- AChR vs MuSK vs seronegative (see below)
- Ocular vs generalised
- Thymoma vs non-thymomatous

Refractory MG is the term commonly used for patients who require repeated rescue treatments despite adequate trials of more than one standard immunosuppressant regimen, or who have intolerance of the commonly used immunosuppressant drugs, and affects some 10% of patients [8, 9].

Myasthenic crisis has been estimated to occur in 10–60% of MG patients [10], and is broadly understood as MG complicated by respiratory failure or oropharyngeal weakness requiring intubation and/or mechanical ventilation for more than 24 h. Large series have reported that a third of the patients may have recurrent myasthenic crisis, pointing towards some individual predisposition, but recurrent myasthenic crises may also point towards compliance problems or flaws in the individual treatment strategy.

Eighty-five to ninety percent of patients with generalised MG harbor antibodies to AChR, which originate from the thymus [11]. These antibodies have been demonstrated to be pathogenic in passive transfer experiments [12]. Up to 2/3 of patients who do not have antibodies detectable using conventional mechanisms have antibodies to AChR that are detectable only on cell-based assay using clustered AChR receptors [13].

A variable proportion of patients who do not have antibodies to AChR will have antibodies to MuSK, a post-synaptic protein that is critical for the clustering of AChR at the neuromuscular junction [14]. MuSK antibody-positive MG is a clinically as well as immunologically distinct variant of autoimmune MG: 80% of patients are female with a peak incidence of 40 years, older than anti-AChR antibody-positive females, but younger than anti-AChR antibody-positive males,

and with a predilection for certain ethnic groups [15]. The course is often acute or subacute and rapidly progressive, affecting the facial, oropharyngeal and respiratory more than limb muscles at onset. Neurophysiological testing results and response to treatment differs from AChR-antibody-related MG [15]. MuSK MG may be more difficult to diagnose on neurophysiology, pyridostigmine can make the symptoms of MusK MG worse and MuSK MG is often more refractory to immunosuppressive treatment [16]. Antibodies against other neuromuscular junction proteins such as LRP-4 and agrin have been described in small numbers of patients but their significance is less certain [17, 18]. The LRP4 antibody has been associated with a more severe course, but this is not consistently the case [19].

About 10% of patients with MG have a lymphoepithelial thymoma [20], and patients with malignant thymoma may be the most difficult to manage, particularly where the tumour has spread beyond the capsule.

Pathophysiology

The antibodies in MG exert their effect in different ways. AChR ab are IgG3 antibodies and are divalent; one of the main mechanisms of action is the cross-linking and internalisation of AChR receptors, reducing the number of available AchR. IgG 3 antibodies also activate the complement cascade leading to the creation of the membrane attack complex which can destroy the post-synaptic nerve terminal membrane and finally the antibodies can directly block the binding of ACh to the receptor [21]. AChR antibodies reduce the number of functional post-synaptic receptors at the muscle cell membrane, resulting in impaired responsiveness of the neuromuscular junction and requiring a higher percentage to be occupied by ACh. If all receptors are blocked by antibodies or occupied by ACh, the transmission will be blocked, and a decrement in action potential amplitude results, as fewer muscle cells contract. In the course of the disease, if the immunological attack remains unchecked, secondary degeneration of the post-synaptic membrane follows [22].

MuSK antibodies are IgG4 and do not activate complement, so do not activate the membrane attack complex or cause dimerisation of receptors. However, they do block the assembly of the agrin-LRP-4-MuSK complex which in turn leads to the disassembly of post-synaptic AChR clusters [23, 24]. Ten to fifteen percent of cases of MG are associated with a tumour of the thymus gland. They are usually benign and slow growing but can occasionally become invasive [20]. Even in the absence of a thymoma, the thymus can play an important role in the pathogenesis of MG; approximately 70% of AChR antibody-positive patients have lymphoid follicular hyperplasia. Possible immunologic mechanisms initiating MG in the thymus include the fact that thymic myoid cells share epitopes with the AChR and are located close to mature lymphocytes and dendritic cells; persistence of the embryonic gamma subunit within the thymus may diminish self-tolerance and dendritic cells expressing HLA-DR may play a role in AChR antigen presentation. The myoid

and dendritic cells could provide both an antigen and a mechanism for autosensitisation to the AChR [22].

Diagnosis of MG

The diagnosis of MG rests heavily on the history which of course is difficult in an emergency situation or if the patient presents in crisis. The history should aim at looking for evidence of fatigable weakness, for example slurring speech at the end of a long phone conversation, ptosis at the end of the day, upper and lower limb weakness and in particular, a diurnal variation in symptoms. Pain is characteristically not a symptom of MG but many patients do complain of neck pain because of strain related to neck muscle weakness. Diagnostic testing in MG starts with the clinical examination looking for fatigability, for instance with 90 seconds upgaze and horizontal gaze; 60 s head raise from the flat; 90 s arm abduction; 90 s leg flexion and knee extension. The Tensilon test (2 mg then 8 mg intravenous edrophonium under ECG control demonstrating resolution of weakness) is no longer easily available. Neostigmine 0.5 mg iv. can similarly demonstrate a similar improvement of myasthenic symptoms, but this is not a routine diagnostic test. The "Ice-pack test" demonstrates transient improvement of neuromuscular transmission through external cold application to a ptotic eyelid, and can improve diagnostic accuracy used together with other tests such as sfEMG, although the phenomenon itself may be observed in other neuromuscular disorders [25]. Proof of fatiguing is essential to avoid confounding other neuromuscular disorders featuring external ophthalmoplegia, such as mitochondrial disease, oculopharyngeal muscular dystrophy or some congenital myopathies. Cogan's lid twitch is considered a characteristic sign of MG and is demonstrated by asking the patient to look straight, then down and then back to the neutral position; the affected ptotic lid will overshoot [26].

Stimulated EMG (3/s repetitive stimulation trains of 6) shows more than 10% decrement of the compound muscle action potential, sometimes followed by post-exercise facilitation (Fig. 9.2). Single-fibre EMG reveals increased variability of the time interval for transmission through intermittent transmission blocking, so-called

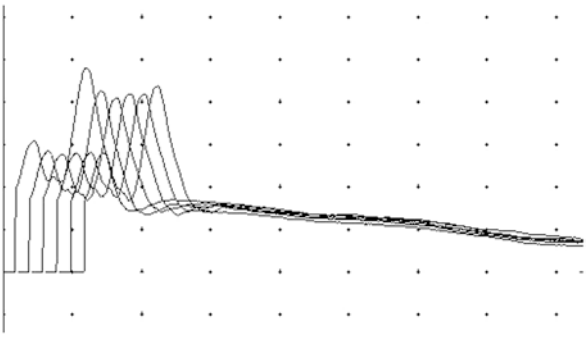


Fig. 9.2 3 Hz Repetitive nerve stimulation of the right nasalis muscle in a 74-year-old man with facial and oropharyngeal weakness showing >30% maximum amplitude decrement (Courtesy Dr. L. Wijesekera, Department of Clinical Neurophysiology, Ipswich Hospital)

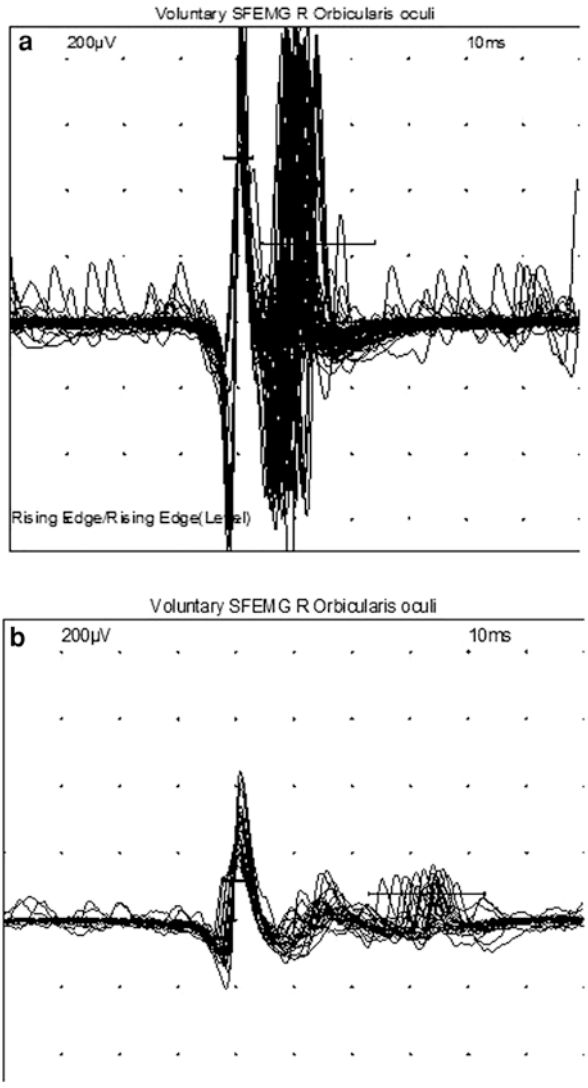


Fig. 9.3 (**a**, **b**) Voluntary "single fibre" jitter studies of the same patient: right orbicularis oculi performed with concentric needle electrode showing increased jitter and impulse blocking in most muscle fibre pairs recorded

"jitter" (Fig. 9.3a, b). Although a full neurophysiological assessment may be difficult in the ICU situation, we find it exceedingly useful as patients in myasthenic crisis are likely to have clearly abnormal results, and alternative diagnoses can be reliably excluded by an experienced examiner. In milder cases, however, electrophysiological tests may be normal in up to 50%. The diagnostic yield from the neurophysiological examination very much depends on the quality of clinical information available to the neurophysiologists and of their interaction with the clinicians.

Antibody tests are highly specific: a positive antibody test confirms the diagnosis and "clustered" antibody tests may be AChR antibody positive in cases seemingly seronegative in the standard assay [13]. All patients with AChR antibodies should

have a CT scan of the chest to exclude thymoma. Anti-striational antibodies, which include anti-Titin, anti-Ryanodine receptor and anti-Kv1.4 antibodies, are associated with thymoma; anti-Kv1.4 may indicate a risk of complicating myocarditis [27, 28]. Immunological tests results, unfortunately, tend to be delayed, and treatment needs to be started before they are available.

General Principles of Treatment of MG

The treatment of MG can be thought of as symptomatic, immunosuppressive and immunomodulatory; thymectomy, in addition, potentially removes the source of antibody production surgically. Each treatment has its own advantages and drawbacks: symptomatic treatment alone may ultimately lose effect if antibodies persist; thymectomy will work best early in the course, presumably before germinating centres spread antibody production outside the thymus; immunomodulatory treatments (plasma exchange and IVIG) have only a short-term effect and access to either may be limited. Immunosuppression with steroids carries multiple long-term side effects; and steroid-sparing drugs have a delayed onset of benefit, often high cost and increased risk of opportunistic infection and malignancy with long-term use.

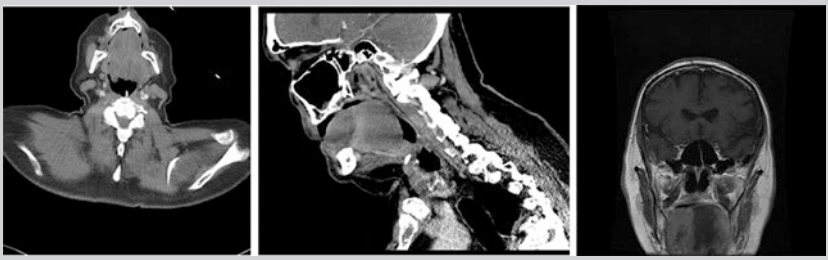
Case Vignette 1

*A 64-year-old man with Parkinson's disease since 2009 developed head drop and was admitted to the ICU in 2012 with a chest infection. There he was noted to have fatiguing ptosis on the left side, and was diagnosed with ACh receptor antibody-positive myasthenia. He rapidly improved with pyridostigmine and was extubated, but in further course required high doses of prednisolone and developed diabetes before stabilising with azathioprine (175 mg/d for a body weight of 90 kg). From 2013 he was stable except for 2x episodes of mild head extensor weakness during steroid taper. In 2015, he was found to have blood counts with low lymphocytes (0.2–0.8 10 * 9/L), and was seen by haematologists, who advised "no change if benefits outweigh risks".*

He developed swallowing problems from late December 2016 and was diagnosed with candida in the oropharynx; he was given fluconazole, but swallowing did not improve. He lost weight and was admitted to hospital in January 2017 for a chest infection. The otorhinolaryngology review was unremarkable, and no fatiguing was found when seen by the neurologist, who observed: "He now describes burning back of throat and regurgitation when swallowing; he has lost weight significantly. These symptoms are not described in a fashion typical for MG and he has no obvious fatiguing. Myasthenia seems stable and does not account for the symptoms. Suggest GI investigations in the first line". His endoscopic investigations were however normal; a liver lesion of uncertain significance was found in the CT scan for abdominal

pain; no primary tumour was found. The medical team concluded the speech disorder was due to myasthenia, and he had a "therapeutic trial" of pyridostigmine, and a course of IVIG, which had no effect.

The patient was transferred to the neurological unit where scans were repeated and showed a necrotic lesion in the left side of his tongue, which was recognised to be an Epstein-Barr virus-related lymphoma.



Learning Points

EBV-associated primary central nervous system lymphomas are seen in long-term (>5 years) immunosuppression in neurological and rheumatological disorders especially in older patients [Kleinschmidt-DeMasters BK. J Neuropathol Exp Neurol. 2008 Nov;67(11):1103–11]. Post-transplant lymphoproliferative disorders were observed less frequently with calcineurin inhibitors than with mycophenolate mofetil [Crane G. Oncotarget 6(32) 2015].

Symptomatic treatment increases ACh at the endplate with cholinesterase inhibitors such as pyridostigmine (Mestinon^{R}). Prednisolone is generally the first-line immunosuppressive agent and is effective in the majority of MG patients. There are two schools of thought about when to start a steroid-sparing agent. If steroids are required, some would commence a steroid-sparing agent immediately. Unless the patient has had a very severe first relapse, others would argue against starting steroid-sparing agents straight away as a proportion of patients will go into remission or have minimal manifestations after their first relapse. A number of different steroid-sparing agents are used, the most common ones are azathioprine, mycophenolate and methotrexate.

Azathioprine has traditionally been considered first line due to a longstanding familiarity with the side effect profile and its favourable safety profile in pregnancy, bearing in mind a large proportion of patients will be women of childbearing age. It has been shown to allow a reduction in steroid dose; the target dose is 2–3 mg/kg/d [29]. Thiopurine methyltransferase (TPMT) activity must be checked before commencement as patients with reduced activity of this enzyme may develop severe, potentially life-threatening bone marrow toxicity at normal doses.

Mycophenolate is probably the most frequently used second-line agent in the UK. There were two randomised trials looking at the effect in mycophenolate in MG that failed to meet their endpoints but the duration of follow-up was probably too short to show a robust effect. Case series and personal experience suggest its efficacy [30]. Methotrexate is also used though of course is contraindicated in women of childbearing age. All steroid-sparing drugs have a delayed onset of benefit—between 6 and 18 months and require assiduous monitoring of blood tests. Cyclophosphamide has been described as a rapidly effective option for refractory cases [31], but is associated with more concerns about tolerability and long-term side effects and is not frequently used. Ciclospirin 2–3 mg/kg or tacrolimus 50mcg/kg also take effect relatively quickly; tacrolimus is more frequently used in Japan, but there is less experience in Europe. There is an increasing body of evidence supporting the efficacy of Rituximab, an anti-CD 20 monoclonal antibody, in severe and refractory cases [32–34]. Rituximab has been used sporadically for many years, and systematic trials are currently underway. Case series and retrospective reviews support its use, particularly in MuSK MG where it seems to be particularly efficacious [35, 36].

Case Vignette 2

A 40-year-old woman had a 10 years history of MuSK positive MG that was refractory to treatment. She had been on two different steroid-sparing agents, prednisolone and three-monthly plasmapheresis (PLEX), but had ongoing bulbar and respiratory weakness. She had four episodes of myasthenic crisis necessitating intubation and ventilation. Once Rituximab was approved for use by NHS England in 2018, she received two infusions 1 g, 14 days apart. Since then she has not required PLEX and has been able to reduce her prednisolone dose and has not had any further admissions for MG.

Learning Points

Rituximab can be very effective in MusK MG, even in long-term refractory cases.

The complement inhibitor Eculizumab has recently achieved EMA approval as an immunosuppressant drug in severe myasthenia; it would not be expected to be effective in MuSK MG as IgG4 antibodies do not activate complement [37]. A novel treatment approach, currently under investigation involves targeting of neonatal Fc receptors, which may result in the reduction of IgG antibody tires [38].

Thymectomy is indicated in generalised MG with AChR antibodies, within the first years of illness. All patients need a CT chest looking for thymoma, which occurs in 10% and may be infiltrative. Thymectomy was introduced in clinical practice in the 1930s [39], but the effect was controversial for decades; the debate was finally resolved in 2016 through a long-running multicentre trial [40] which compared 3-year outcomes showing a clinically relevant benefit of transsternal extended

Table 9.1 Drugs to be used with caution in myasthenia gravis: "the 14 A's"

ACTH and corticosteroids	Prednisone
Analgesics	Narcotics
Anesthetics, local	Cocaine, procaine, lidocaine, bupivacaine, prilocaine
Antacids or laxatives containing magnesium	Maalox, Mylanta
Antiarrhythmics	Quinidine, lidocaine, procainamide
Antibiotics	Aminoglycosides, quinolones, telithromycin, azithromycin, erythromycin, clindamycin, ampicillin, imipenem, vancomycin, metronidazole
Anticonvulsants	Phenytoin
Antihypertensives	Beta-blockers, calcium channel blockers
Antimanics	Lithium salts
Antipsychotics	Chlorpromazine
Antirheumatic	Chloroquine
Arthritis agents	Penicillamine-induced myasthenia gravis
All neuromuscular blocking agents	
Antimalarials	Chloroquine, hydroxychloroquine

thymectomy in patients between 18 and 65 years of age with generalised, AChR antibody positive, non-thymomatous MG and a disease duration of <5 years. Its effect outside these parameters is less certain. Video-assisted "keyhole" procedures (VATS) or robitic access procedures are less invasive, but it remains unclear whether they remove thymic tissue as thoroughly [41].

Apart from managing the immune process, great attention should be given to avoiding medications that affect function of the neuromuscular junction. Many drugs can have a negative effect on MG. Table 9.1 gives a list of some of the commonest known, but it is not exhaustive, and it is prudent to check every newly prescribed drug. The variant of myasthenia caused by immunomodulatory drugs such as immune checkpoint inhibitors is discussed below.

In most clinical practice, *early management* starts with pyridostigmine starting at 30 mg three times a day (tds) for immediate symptomatic effect, titrating up to 60 mg 6× daily. Pyridostigmine is an oral cholinesterase inhibitor effective in the neuromuscular junction used as the initial treatment for MG at a dose of 30 mg tds; each dose is effective for roughly 4–5 h, so often 4–6 doses are needed. More than 360 mg daily is seldom helpful and very high doses may cause "cholinergic crisis". Gastrointestinal side effects such as cramps, commonly occur and are controlled with additional propantheline 15 mg qds. Hypersecretion may be a problem with respiratory weakness and can improve with glycopyrrolate. Patients unable to swallow may need IV preparations such as pyridostigmine IV (1 mg IV is equivalent to 15–30 mg oral) or neostigmine im (1 mg equivalent to 60 mg pyridostigmine p.o.). Pyridostigmine will lose effect if continued without immune treatment. Patients with MuSK antibody-positive MG may deteriorate when given pyridostigmine, and for them, early escalation of immunosuppressive treatment is preferred.

Early immunosuppression typically starts with prednisolone, beginning at 10 mg, daily or every other day, increasing by 10 mg every fourth dose, stopping at

significant clinical improvement or at 50 mg daily or 100 mg every other day. The full dose is maintained for ca. 6 months, then tapered by 5 mg per month, and the rate is slowed when down to 20 mg per day. Concomitant medication should be calcium/Vit D3 substitution and bisphosphonate plus a proton pump inhibitor. Steroid treatment is typically incremental: There is well-documented deterioration with high doses of steroids, especially in the elderly, and with bulbar or severe symptoms [42]. There is also experimental evidence that higher doses of steroids abolish anticholinesterase support of the neuromuscular junction, and halving the dose re-institutes the anticholinesterase effect [43].

Steroid-sparing agents are discussed in the previous paragraph, but all the options require a significant amount of time to take effect, and if steroids and pyridostigmine do not provide enough symptom control in the acute exacerbation, the clinician well needs to consider a course of so-called *rescue treatment.*

Rescue treatments for severe generalised myasthenia include plasma exchanges (PLEX) or intravenous immunoglobulins (IVIG) when other treatments are unsuccessful, or when deterioration is too quick to await the effect of conventional drugs (Fig. 9.4). IVIG is a blood product created by the separation of plasma containing IgG from about 10,000 blood donors and is used in MG as well as other immune disorders. It has multiple different immunomodulatory effects including interference

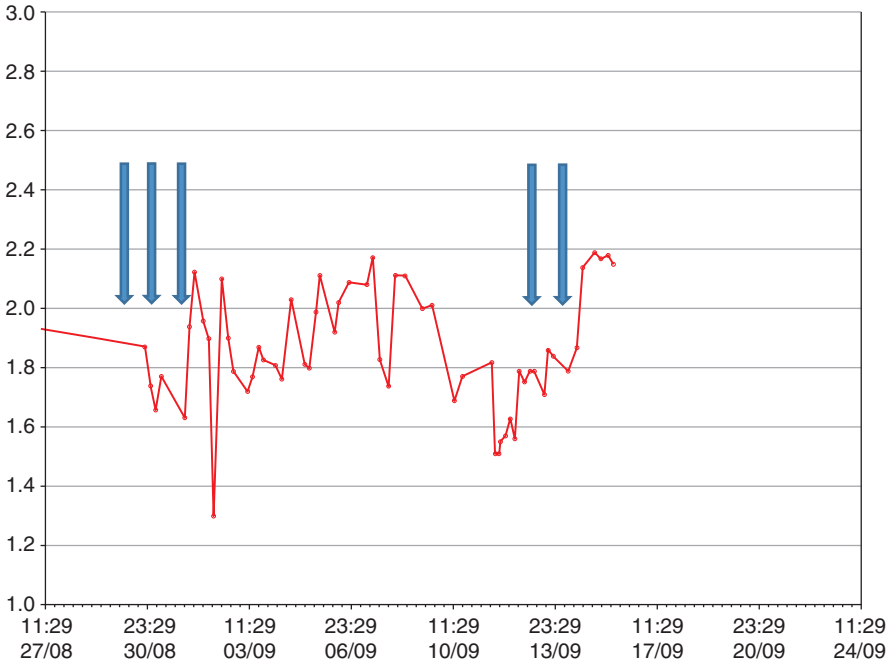


Fig. 9.4 Regular respiratory monitoring may establish a need for plasma exchanges: Deterioration of respiratory function in a 23-year-old patient despite high-dose steroid treatment, pyridostigmine 360 mg/d. The first three exchanges achieved an unstable improvement; the second course of two exchanges achieved stable remission. Rituximab had been started but had not yet taken effect

with cytokine production, and effects on complement activation, phagocytosis and T-cell function, whereas PLEX is an extra-corporeal process by which plasma, containing antibodies is removed and replaced with fluid such as human albumin [44]. Their overall effect is comparable [45], but PLEX generally needs inpatient admission and a central venous access and carries risks of infection, coagulopathy and air embolism; IVIG seems less invasive than PLEX, but its effect may be slower, it may cause migraine headaches and can have severe side-effects in the elderly or debilitated patient.

A number of excellent evidence-based guidelines for general management of MG provide the clinician with detailed recommendations, although there is a paucity of randomised trials [46–48].

Assessment of the Acutely Unstable MG Patient

MG always has the potential to deteriorate acutely. This is particularly important when speech or swallowing muscles are affected and even more so if respiratory muscles are affected—this is a neurological emergency.

In the unstable patient, reliable documentation of the patient's trajectory and early recognition of the need for ICU monitoring are key. A pragmatic score such as the Myasthenia Composite Score [48] for assessment of fatiguing may help improve reliability, but staff need to be trained and familiar with its use [49]. Patients with oropharyngeal and neck weakness often also have failure of respiratory muscles, and both neck flexion and extension need to be tested. Bedside respiratory assessment is crucial for recognising impending danger. Commonly, too much reliance is placed on blood gas analyses, or even worse, oxygen saturation monitoring, which only become abnormal in advanced neuromuscular failure. Transcutaneous capnography is not yet widely available, and its reliability for monitoring acutely deteriorating patients has not been fully assessed. Bedside respiratory testing (see online video Chap. 3) requires considerable training, as it may be technically difficult and time-consuming. Medical and nursing staff dealing with neuromuscular patients need to be instructed on how to perform the bedside lung function tests reliably, and need to know the pitfalls in testing, for instance from unsatisfactory posture, failure to cooperate or inadequate mouth and nasopharyngeal seal. Importantly, the salient feature in MG is fatiguing, and this is not easily captured by typical respiratory tests; repeated assessment will give a better picture, so retesting may be needed at short intervals. A range of parameters should be tested, as this allows equivocal results to be judged better, and because focal muscle involvement may not affect all parameters equally. Diaphragmatic failure will affect vital capacity and reduce FVC when lying flat in particular, as the diaphragm is the strongest inspiratory muscle. Intercostal muscles are important particularly for expiration, cough and airway clearance. Apart from formal testing, staff need to be aware of the clinical features of developing respiratory failure and regularly document clinical indicators such as inability to lie flat, failure to complete a sentence without taking a breath, visible use of auxiliary respiratory muscles, decreasing ability to count aloud in one breath or

paradoxical abdominal movement [indrawing of the abdomen and partially of the chest when the patient breathes in, and protrusion when she or he breathes out] (see online video link in Wijdicks (2013) [50]).

If bedside respiratory monitoring cannot be guaranteed in the neurological ward, patients need to be transferred to a High Dependency Unit or the ICU [51]. When respiratory competency is deteriorating, the "20/30/40" rule is a simple way to assess the potential need for monitoring in an ICU (see Chap. 2). This was originally developed for Guillain-Barré syndrome patients, but can also be applied to MG (Table 9.2) [52]. Emergency admission of a patient in extremis mostly signifies a failure in preceding monitoring. If in doubt as to whether ICU admission is needed, it is prudent to admit the patient for monitoring, even if only for 24 h.

Myasthenic Crisis: Management in the ICU

Myasthenic crisis is defined as respiratory failure requiring mechanical ventilation in a myasthenic patient, and can be broadened to include patients who are slow to wean from ventilation following a general anaesthetic. Historically crisis was said to occur in 15–30% of patients with MG but the feeling is that is much less now [53]. Crisis can occur any time in the disease course but is more common in the first 2–3 years. Myasthenic crisis may be a patient's first presentation of MG, in such cases occasionally symptoms have been present for many years but overlooked and in other cases, the diagnosis comes to light during intercurrent illness or post-operatively. Patients with MuSK MG may be more prone to develop myasthenic crisis [54]. Myasthenic crisis may develop when diagnosis and treatment are delayed, or in a patient who already started treatment, it can often be explained by a specific precipitating cause. Infection has been shown to be associated with >30% of cases of myasthenic crisis, particularly respiratory tract infections [55]. Other causes are medication errors such as pyridostigmine dosing mistakes or incautious initiation of drugs with neuromuscular blocking action such as aminoglycosides, other antibiotics and occasionally, botulinum toxin [56]. Sometimes deterioration is triggered by incautiously initiating high-dose IV corticosteroids. Other precipitating factors are surgical procedures (particularly extensive thoracic or abdominal surgeries affecting respiratory mechanics), pregnancy or even emotional stress [10].

Table 9.2 Monitoring of respiratory function in determining admission to the Intensive Care Unit (ICU)

Parameter	Normal value	Critical value for ICU and/or intubation
Vital capacity	40–70 mL/kg	15–20 mL/kg
Peak inspiratory Pressure	Male: > −90 cm H^2O Female: > −70 cm H^2O	−30 to −40 cm H^2O
Peak expiratory Pressure	Male: >100 cm H^2O Female: >90 cm H^2O	40 cm H^2O
Cough	Male: > 330 L/min Female: > 280 L/min	Peak cough flow >160 L/min at mouth or PEF >60 L/min at tube needed for safe extubation

Patients with overdose of cholinergic drugs may present with massive secretions and diarrhoea. Warning signs of impending myasthenic crisis include rapidly progressive weakness, difficulty with speech and swallow and head drop. An attentive clinician can often recognise impending myasthenic crisis early enough to ward off full crisis through rescue treatment with IVIG or PLEX.

In the ICU, priority is given to securing airways; and the patient should be intubated if in doubt. Usually, the need for ventilatory support in MG follows weakness of diaphragmatic or accessory respiratory muscles, but mechanical ventilation also may become necessary because of airway collapse from oropharyngeal muscle weakness, stridor from vocal cord weakness [57] or the inability to clear secretions. Apart from treating infection and rehydration, medications with the potential to impair neuromuscular transmission should be avoided as far as possible, such as betablockers given for tachycardia, or numerous commonly used antibiotics such as vancomycin. Patients may have been overdosed with cholinesterase inhibitors and may have excessive salivation and sweating, abdominal cramps and urinary urgency. Pyridostigmine can be discontinued initially during ventilation and reintroduced gradually for weaning. In a ventilated patient it is feasible to start steroids in high doses such as 1 g IV methylprednisolone, then 100 mg oral prednisolone. Thymectomy is of proven benefit but as this only becomes significant after months, it is not commonly performed while the patient is unstable. The situation may be different if there is an occult thymoma, and that must be considered with refractory crises.

Case Vignette 3

*A 42-year-old woman was admitted to hospital in July 2016 with shortness of breath and difficulty swallowing. She had lost weight. She was admitted to the ICU, intubated and there diagnosed with antibody-positive MG. She was found to have malignant thymoma with local spreading (*Fig. 9.5*); thymectomy and chemotherapy were planned to take place once she had stabilised. She required tracheostomy, but after 2 weeks she was liberated from the ventilator and discharged. Her course was characterised by "brittle" myasthenia and she was readmitted in November and intubated again. This time she failed to wean despite IVIG and she required PLEX. After 9 weeks she could be discharged from the ICU, and in hospital started chemotherapy for thymoma (cisplatin/cyclophosphamide/doxorubicin). For several months she also continued monthly IVIG (1 g/kg). Thymoma and pleural metastases regressed on further imaging. She is now stable on 10 mg/d prednisolone only.*

Learning Points

Patients with thymoma may fail to stabilise until after treatment of the tumour, and suboptimal clinical conditions for surgery or chemotherapy may need to be accepted.

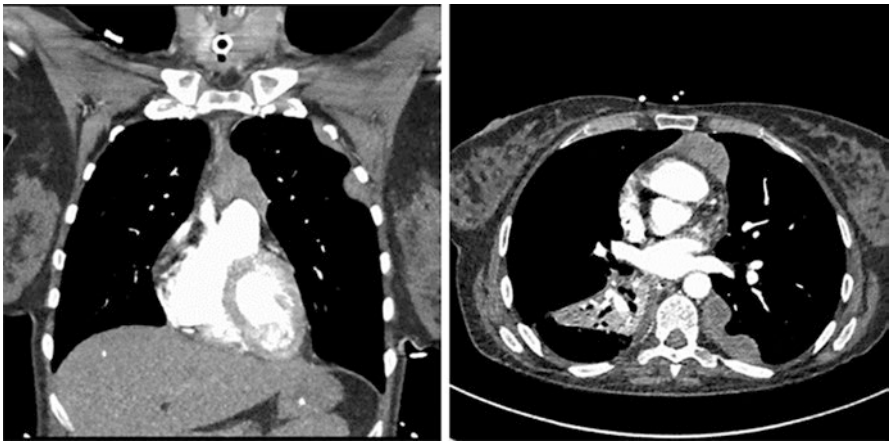


Fig. 9.5 Mediastinal mass and left pleural metastases

Initial non-invasive BiPAP via mask may avoid intubation if oropharyngeal function is preserved, and may help reduce ventilator days [58]. Tracheostomy should not be performed early, as a rapid recovery is possible. It is important to reintroduce cholinesterase inhibitors before extubation trials are initiated. Before attempting to wean from the ventilator, in addition to the satisfactory treatment of the myasthenic symptoms, there should be no major pulmonary problem or difficulty handling secretions, which compromise alveolar recruitment and increase work of breathing. Weaning can be initiated once VC reaches 25 mL/kg and the patient achieves spontaneous tidal volumes of 10–12 mL/kg. Secretion volume, whether the patient is comfortable with a T-piece trial, and a completely normal chest x-ray, have some predictive value for successful extubation. PI max exceeding −50 cm H_2O and VC improvement by 4 mL/kg from pre-intubation to pre-extubation are also associated with successful extubation, but nevertheless, repeated extubation failure is common [59]. Weaning methods can include BiPaP with daily small decreases in positive pressure support, or intermittent mandatory ventilation with gradual reduction in the mandatory frequency. Further research is needed to evaluate novel weaning techniques such as Neutrally Adjusted Ventilatory Assist (NAVA) [60] in MG as in other neuromuscular diseases, which theoretically allows an assessment of work of breathing, and there is no information whether this can be used to monitor for fatiguing.

The mortality rate for myasthenic crisis has declined from a nearly always fatal outcome in the 1920s to <5% in the twenty-first century as a result of timely treatment [61]. However, the statistics from selected centres may not reflect real life: mortality in UK ICUs was found to be 8.7% overall, sometimes considerably higher and acute hospital mortality after an ICU stay from myasthenic crisis reaches 22% [62]. Deaths can be attributed to delayed treatment and unrecognised complications, belated admission to the ICU (suggesting shortcomings of ward-based monitoring); inappropriate transfer from ITU to the general ward, where monitoring may not be

taken into account that fatiguability can develop rapidly in a patient who hours before seemed safe [63].

Case Vignette 4

A 50-year-old female was diagnosed with MG 10 years earlier, and previously intolerant to treatment with mycophenolate, methotrexate and azathioprine. She had been stable on prednisolone only for several years, but reduced her dose and was admitted in October 2014 with worsening limb weakness, requiring two courses of IVIG, the second taking place in the ICU, as she had required respiratory monitoring for 4 days. She had refused several doses of pyridostigmine and was considered a "difficult patient". After her second course of IVIG she was considered stable and transferred to the HDU ward during Sunday night, where she was given a side room. On Monday morning she was discovered cyanosed and struggling for breath. She underwent an emergency intubation, and in her ECG after resuscitation she had changes which were considered compatible with a NSTEMI, leaving persistent ECG changes. Myasthenia now stabilised on prednisolone and mycophenolate and she was discharged, appearing satisfactory on follow-up. Further cardiological follow-up was planned. However, she was readmitted after 4 weeks having suffered a cardiac arrest and died.

Learning Points

Cardiac damage is well recognised in MG crisis, from which chronic problems may result. In this case, it is unclear whether the patient suffered true myocardial infarction related to the stress of respiratory decompensation, or whether this was a case of so-called "neurogenic stunned myocardium".

Regrettably, patients with recurrent crises or repeated failure of extubation may be refused readmission; however, recurrent crises are not predictive of ultimate outcome and "futility" can never be an argument to deny re-intubation. There must a strategy for adequate long-term immunosuppression as repeated rescue treatment with IVIG and PLEX will seldom achieve lasting stability. Intermittent scheduled IVIG or repeated PLEX can be a strategy to bridge until an adequate effect is achieved through second-line immunomodulators.

Elective ICU Admission in Myasthenia Gravis

Perioperative management must be well planned; patients should be stabilised as well as possible prior to surgery, for which preoperative IVIG or PLEX are useful. The specialist clinic should provide a comprehensive preoperative neurological

status. Customary medications should be taken with as little interruption as possible, by giving pyridostigmine via nasogastric tube or intravenously (adapting the dose to IV use). Prednisolone should remain unchanged, but for major surgery, hydrocortisone should be given for 48 h as perioperative stress cover in patients on long-term steroids, for example, 50 mg hydrocortisone at induction, and post-operatively 25 mg three times daily. Sugammadex can reverse vecuronium-induced neuromuscular blockade. Post-operative VCs should be monitored 8-hourly, or more often if clinically indicated, and any weakness or reduced mobility needs to be precisely documented. We typically schedule an admission to ICU overnight for all MG patients who undergo major surgery.

The effect of pregnancy on myasthenia is unpredictable, and myasthenia worsens in about one-third of pregnant patients. Respiratory function may deteriorate when thoracic expansion is impaired in advanced pregnancy. Prolonged labour may worsen fatigability, and postpartum exacerbations are not uncommon. IVIG may help stabilise MG during pregnancy [64]. Pyridostigmine, steroids, azathioprine and PLEX are probably also safe in pregnancy. Perinatal management requires joint management between the neuromuscular clinic to monitor for deterioration of MG and the high-risk obstetrics clinic. Early regional anaesthesia has been advised [65]. Antibodies are transferred through the placenta in the second half of pregnancy, and transient neonatal myasthenia can be expected in 20 to 50% of children. Weakness of swallow, suck, breathing and limbs may develop hours after birth and last for days, in some cases requiring treatment with pyridostigmine and/or respiratory support, but almost always with complete resolution.

Myasthenia Related to Immune Checkpoint Inhibitors

A relatively recent issue is the development of acute severe myasthenia after treatment of cancer with immune checkpoint inhibitors. Checkpoint inhibitors are immunomodulatory antibodies designed to enhance the immune system's response to malignancy. They have dramatically altered the landscape of treatment of advanced cancer, in particular that of melanoma and renal cancer. Targets of these agents include the programmed cell death receptor (agents such as pembrolizumab and nivolumab) and the cytotoxic T-lymphocyte associated antigen (agents such as ipilimumab).

However, these agents have been associated with a wide range of immune-related adverse events affecting multiple systems. Neurological adverse events reported in association with immune checkpoint inhibitors include GBS, encephalitis and MG. Patients with pre-existing autoimmune disease may be more at risk of developing immune-mediated adverse events [66].

Myasthenia associated with ICI can be severe and have an explosive onset with up to 45% of patients requiring invasive ventilation and up to one-third of patients have an associated myositis and/or myocarditis [67]. Treatment rests on stopping the ICI and commencement of immunomodulatory agents. Patients are generally treated with high-dose steroid and PLEX and/or IVIG. Myasthenia related to ICI can have a high fatality with up to 20% mortality reported. As the use of these

agents becomes more widespread in oncology, it is likely that we will observe more ICI-related neurological emergencies.

Case Vignette 5

A 77-year-old man was treated with Pembrolizumab for metastatic melanoma. Two weeks after his first infusion, he developed generalised weakness and difficulty with speech and swallowing.

On admission he was found to be in complete heart block with a raised Troponin (1000 ng/L) and CK (8000 iU/L). He had bilateral fatigable ptosis, ophthalmoplegia, dysphonia, dysphagia and fatigable limb weakness. He required intubation for Type 2 Respiratory failure and a permanent pacemaker was inserted.

AChR antibodies were positive. Neurophysiology showed small-amplitude polyphasic potentials and fibrillations consistent with a myositis and single-fibre EMG showed jitter and block suggesting myasthenia. A muscle biopsy was consistent with a necrotising myositis. A diagnosis of checkpoint inhibitor-induced myositis, myasthenia and myocarditis was made. He was immediately commenced on high-dose steroids—1 g IV methylprednisolone for 3 days followed by a very slow oral tail. Once the pacemaker was inserted, he was treated with PLEX. He required a tracheostomy and had a slow respiratory wean but made a slow but steady recovery and was discharged after 3 months in hospital.

Learning Points

Immune checkpoint inhibitors used to treat malignancy can be associated with an explosive onset of myasthenia that may present along with a necrotising myositis and myocarditis.

Other Neuromuscular Junction Syndromes

Lambert-Eaton Syndrome

LEMS is a presynaptic disorder of the neuromuscular junction. It is generally caused by antibodies against the voltage-gated calcium channel in the presynaptic nerve terminal [68]. The antibodies interfere with the calcium influx triggered by the nerve terminal action potential, which in turn reduces presynaptic ACh release. Approximately 60% of cases are paraneoplastic, most often associated with a small cell lung cancer. The neurological syndrome may present before the tumour is detected and so, a diagnosis of LEMS much spark a search for an underlying malignancy with CT and FDG PET scans. If initial screening is negative, investigations should be repeated. Most malignancies are detected within 12 months and diagnosis of a cancer more than 2 years after a diagnosis of LEMS is very unusual [69]. Antibodies against SOX 1 proteins (Sry-like high-mobility group box 1) have been found to be associated with

small cell lung cancer in LEMS with a high specificity [70]. LEMS usually presents with proximal muscle weakness, affecting the legs initially in 80% of cases but upper limb weakness usually develops soon after. The fluctuations of symptoms and fatigability so typical of MG are not as prominent in patients with LEMS, and facial and extraocular weakness are less commonly seen in LEMS compared to MG [71]. Respiratory failure in LEMS is uncommon but is recognised and may be a presenting symptom, it is more commonly seen in patients with a malignancy [72]. Autonomic dysfunction is found in 80–90% of patients with LEMS and can precede the onset of neuromuscular weakness [73]. Dry mouth is the most common symptom followed by erectile dysfunction—orthostatic hypotension and micturition difficulties are seen less frequently. Neurophysiology is the cornerstone of LEMS diagnosis before antibody confirmation. Compound muscle action potentials are typically low at rest but show a short-lived incremental response after maximal exercise or high-frequency stimulation [74]. This facilitatory response to high-frequency stimulation has been postulated to be due to the build-up of calcium in the nerve terminal [75].

The treatment of LEMS depends on the presence of an underlying malignancy, and if a tumour is detected, treatment must be directed towards this. If the tumour that is "driving" the immune process is removed, the neurological symptoms may improve [76]. 3,4 diaminopyridine (3,4-DAP) is a potassium channel blocker that prolongs the duration of the action potential and improves the symptoms of LEMS [77]. Immunomodulatory treatment may be needed if the symptoms of LEMS; prednisolone and azathioprine are the most common immunosuppressive agents used and IVIG and PLEX can be used as "rescue" treatments [78].

Botulism

This is by contrast a toxic presynaptic disorder caused by toxins of *Clostridium botulinum*, most often occurring after ingestion of anaerobic foods or home-made canned products (food-borne botulism) [79]; by wounds infected by *C. botulinum* (wound botulism), including the practice of skin popping, subcutaneous injection of illicit drugs [80, 81]; or in infants mainly by ingestion of soil containing spores of *Clostridium* (infantile botulism). The toxins inhibit ACh exocytosis by proteolyzing SNARE proteins such as VAMP, SNAP-25 or Syntaxin, depending on the type of botulinum toxin (A, B, E). Stool samples are the preferred tissue to detect botulinum toxin, as it is demonstrable in stool much longer than it will be in blood. Annually, approximately 1000 cases are recorded worldwide, presenting with weakness and dysphagia associated with prominent autonomic features. Botulism typically causes a descending paralytic illness with autonomic features including fixed dilated pupils, ileus and diarrhoea [82]. The diagnosis rests on having a high degree of clinical suspicion, bearing in mind that fixed pupils are not ubiquitous in the condition. The neurophysiology is similar to that seen in LEMS—both are presynaptic disorders. Botulism can be rapidly fatal due to respiratory failure, and transfer to a critical care environment and ventilation are often required. Treatment comprises early antitoxin, clearance of the gut or wound, and supportive critical care management for a prolonged period; mortality is 5%. Anti-toxin is most

effective very early in the disease course before the toxin binds to nerve terminals; there is often controversy on how long after ingestion antitoxin treatment has value, but this may be for longer than expected as passage of the gut may be delayed as a feature of autonomic dysfunction.

Case Vignette 6
A 7-month-old healthy boy spent a day by the seaside with his parents where he played in the sand. The next day he developed swallowing difficulty, and presented in the early hours of the morning in respiratory distress. He was admitted to the PICU where he was intubated and diagnosed with a severe chest infection. On sedation hold, he appeared unresponsive and showed minimal movements, flaccid tone and areflexia. Hypoxic brain injury was suspected but brain imaging was normal. His cerebrospinal fluid was normal. On the fourth day, his pupils were reported as fixed and dilated. His EEG was normal. His EMG indicated "findings in keeping with acute motor neuropathy with a differential diagnosis of a neuromuscular junction disorder". Stool samples were taken, which after 5 days in culture returned positive for C. botulinum. With a diagnosis of infantile botulism, he was given Botulism Immune Globulin (BIG) intravenously. He required ventilatory support for a further 3 months before being discharged from the PICU. Nutrition remained via a gastric tube, and he has suffered long-term difficulties with wound healing and laryngeal strictures.

Learning Points
Botulism should be suspected where there is rapid onset of neuromuscular weakness with pupillary dysfunction, and the history should be interrogated for potential ingestion of C. botulinum spores.

Nerve Agents

Thankfully, neuromuscular junction dysfunction due to nerve agents has so far been rarely encountered, but as was witnessed, in Salisbury in England in 2018, it is important to be aware of effects of these deadly substances. Nerve agents such as Sarin and Novichok are related to organophosphate insecticides and exert their effect by inhibiting acetycholinesterase, thus precipitating a cholinergic crisis. The use of Sarin has been documented in Iraq in the 1980s and Japan in the 1990s with more recent use alleged in Syria [83]. One person died and six people were investigated for exposure to Novichok in England in 2018. More often than deliberate attacks, however, neuromuscular failure due to organophosphates has mainly been described in people self-poisoning by drinking pesticides, killing up to 200,000 people a year [84]. These agents can cause dysfunction of the central, autonomic and peripheral nervous systems. Central affects include agitation, seizures and lack of respiratory drive. Autonomic features include sweating, tachycardia,

hypertension, diarrhoea and bronchospasm. At the neuromuscular junction the lack of breakdown of ACh causes depolarising neuromuscular blockade. Management centres on admission to critical care, resuscitation with fluids and administration of atropine. The benefit of oximes, agents that reactivate ACh is less certain [85].

Congenital Myasthenic Syndromes (CMS)

Epidemiology and Classification

CMS are a rare heterogeneous group of neuromuscular disorders caused by genetic defects (more than 30 known genes) impacting the structure and function of the neuromuscular junction, with an overall incidence estimated to be 9.2 cases per million children below the age of 18 [86]. Unlike autoimmune MG, the immune system is not involved and antibody tests are negative. They are commonly classified based on the location of the encoded protein i.e. presynaptic, synaptic and post-synaptic. Inheritance is usually autosomal recessive, although slow channel syndromes and some pre-synaptic disorders are dominant. Post-synaptic disorders are the most frequent, εAChR subunit (*CHRNE*) mutations being the commonest. *COLQ, DOK7, RAPSN, CHAT and GFPT1*-related CMS are more common than others. In a review by Rodriguez, a full list of genes associated with CMS are reported (86).

Clinical Presentation and Diagnosis

CMS usually present in childhood often at birth or in the first year of life with hypotonia, fatigable weakness and ptosis, early respiratory and feeding difficulties but can present at any age. These features may be similar to the congenital muscular dystrophies and myopathies, but disordered NMJ transmission may be demonstrated in neurophysiology, with genetic confirmation in a specialist laboratory. Recurrent, life-threatening episodic apnoea in early infancy and childhood particularly during intercurrent infections or excitement is one of the more severe respiratory problems associated with CMS and has been described in approximately 3% of all CMS cases, with the most common genes responsible being CHAT, COLQ and RAPSN [87]. There may be a history of unexplained sudden infant death in previous siblings. Diagnosis in older infants may be more straightforward, with ongoing hypotonia and motor delay, more obvious fluctuating weakness and ptosis, feeding difficulty and frequent chest infections, often requiring ventilation. CMS manifestations in older children and adults include more overt diurnal, day-to-day or even week-to-week fluctuation in weakness and fatigue. A limb girdle pattern of involvement often without ocular or facial weakness occurs in *DOK7*, *GFPTI* and *DPAGT1* CMS. Ophthalmoplegia is a notable feature of mutations in *CHRNE* and directs genetic diagnosis. Diagnosis is often suspected after abnormal neuromuscular junction transmission studies showing an increased jitter on stimulated single-fibre EMG or decrement on repetitive nerve stimulation. Final diagnosis is established by

genetic analysis. Diagnosis may be delayed, as symptoms resemble congenital myopathies or mitochondrial disorders. Muscle biopsy and muscle MRI may help delineate: in a very weak child CMS should be considered when muscle biopsy shows only mild, non-specific myopathic features (notably type 2 fibre atrophy) and muscle MRI is normal or fails to show the selective involvement usually seen in congenital myopathies [88–90].

General Principles of Treatment of CMS

Respiratory problems are a major cause of morbidity and mortality in patients with CMS. Infants with episodic apnoeas and respiratory difficulties need immediate assessment in a specialist respiratory centre and parents must be taught emergency resuscitation measures, including use of non-invasive mask ventilation. These patients may require home apnoea monitors, basic life support training and access to suction and non-invasive ventilation for emergency use. All CMS with respiratory manifestations should have fast track access to hospital in the event of illness and early antibiotic treatment for chest infections, as increasing weakness may cause respiratory failure. Those with significant bulbar difficulties require feeding via nasogastric tube or percutaneous gastrostomy. In addition, even those with normal or mildly abnormal bulbar function may require pacing and texture modifications or artificial feeding during intercurrent illnesses.

Respiratory arrest becomes less frequent in adolescence and disappears before adulthood. Neonatal stridor and bilateral vocal cord palsy have been described in CMS associated with DOK7 and these can often be helped with tracheostomy to maintain their airway.

Hypoventilation and progressive respiratory failure are seen with certain genetic sub-type such as DOK7, slow channel syndromes and COLQ and these patients should have regular Respiratory surveillance in the form of spirometry and polysomnography for early detection and intervention with initiation of non-invasive ventilation.

In the absence of a genetic diagnosis, any empirical treatment should be started in hospital. Timed functional measures are useful to monitor treatment response. Some genotypes e.g. *CHRNE* remain stable, some improve e.g. *RAPSN*, but others (*DOK7, COLQ*) may develop increased weakness, scoliosis and nocturnal hypoventilation necessitating NIV. All CMS require multidisciplinary follow-up.

Pharmacological Treatment of CMS

At the outset, it is important to note that treatment is life-long and not curative but supportive and symptomatic. Currently, there are no licensed drugs for treatment of congenital myasthenia. The drugs used are off-label, the doses and formulations in CMS can be different from the licensed doses, and hence, these should be initiated

and monitored under the supervision of a specialist neurologist with neuromuscular expertise. Molecular genetic diagnosis facilitates appropriate treatment, as some medications are detrimental in certain genotypes.

Acetylcholinesterase inhibitors (e.g. pyridostigmine), are effective almost immediately in many genotypes, including CHAT, AChR deficiency (notably CHRNE), fast channel syndromes, RAPSN and glycosylation disorders but are ineffective or may worsen *COLQ, DOK7, MUSK, AGRN* and slow channel CMS. Typical dose required is usually 4–7 mg/kg/day in four to six divided doses (88). Careful titration of dose and timing depending on levels of activity during awake periods is often required to achieve maximum benefit. Long-acting slow-release preparation may be useful in some children who experience significant weakness in the mornings. These can be combined if necessary with 3,4 diaminopyridine. Typical dose used is up to 1 mg/kg/day in four divided doses, but lower doses can be efficacious with less side effects. This enhances ACh release from the presynaptic nerve terminal, B-adrenergic agonists, ephedrine and salbutamol improve strength in COLQ, DOK7, MUSK and AGRN CMS. The exact mechanism of action of these at the neuromuscular junction (NMJ) is not fully understood. It is thought they stabilise the structure of the NMJ and reduce the dispersion of AChR (89) and hence unlike pyridostigmine, the treatment effect builds up gradually over several months to show effect and patient should be supported with supportive respiratory management until the treatments shows effect. Slow channel CMS is treated with open channel blockers, quinidine or fluoxetine (88,89,90). It reduces reduce the duration of opening of the AChR ion channel and as a result, they prevent the depolarisation block and desensitisation of AChR at physiologic rates of stimulation and mitigate the cationic overloading of the post-synaptic region and its sequelae. ICU admission is rarely required in adult life but is common in infants and children.

Case Vignette 7

An infant (birth weight >2 kg) was born to consanguineous healthy parents at 33 weeks of gestation in poor condition following an emergency LSCS for pathological CTG with maternal history of polyhydramnios. He required resuscitation and ventilation after birth. He failed several attempts at extubation in the first 6 weeks of life and each time after extubation he demonstrated increasing oxygen requirement within a few hours due to respiratory fatigue requiring re-intubation. In between these episodes, he was awake and intermittently active with good tone and antigravity movements in arms and legs but there was suspicion of weakness in the shoulders more than hips in addition to the main problem of ventilator dependence. He had good eye opening and normal eye movements with a good suck. He was nasogastric tube fed since birth. Stimulated single-fibre EMG of Orbicularis oculi showed blocking and increased jitter and repetitive nerve stimulation performed at 3 Hz showed clear and consistent decrement suggesting a diagnosis of CMS which was genetically confirmed by demonstrating a homozygous mutation in the CHAT gene with both parents detected as carriers. He was started on

treatment with acetylcholinesterase inhibitor pyridostigmine (7 mg/kg/day in 6 divided doses) which allowed him to be extubated on to NIV. When the dose was increased to 8 mg/kg/day he developed increased secretions and the dose needed to be reduced back to 7 mg/kg/day. He remains on 24/7 NIV and has started to develop episodic apnoea with triggers such as bathing.

Learning Points
CMS should be suspected in infants presenting with fatigable neuromuscular weakness with episodic apnoea or ventilator-dependence and neuromuscular junction transmission studies (SFEMG and/or repetitive nerve stimulation should be considered in these infants who can benefit from pharmacological treatments outlined above).

Self Assessment Questions

1. What is the pathophysiologic mechanism in most patients with autoimmune myasthenia gravis?
   (a) A shortage of acetylcholine in the synaptic cleft.
   (b) A problem with binding acetylcholine with the post-synaptic receptor.
   (c) A shortage of functioning post-synaptic receptors on the muscle membrane. (*)
   (d) Failure of generating a muscle action potential after transmitter-receptor binding.
2. What is the pathophysiological mechanism of presynaptic myasthenia, e.g. in the Lambert Eaton Myasthenic syndrome?
   (a) A problem with the synthesis of acetylcholine in the nerve endings.
   (b) A problem with the release of acetylcholine in the nerve endings. (*)
   (c) Breakdown of transmitter in the synaptic cleft before post-synaptic receptor binding.
3. What is the pathophysiological mechanism in MuSK myasthenia?
   (a) Increased turn-over of functional acetylcholine receptors.
   (b) Intrasynaptic breakdown of transmitter by MuSK antibodies.
   (c) Surface spreading of receptors, that are not kept clustered together anymore. (*)
   (d) Antagonism between antibodies and transmitter on the post-synaptic receptors.

4. When do myasthenic crises mostly occur?

   (a) In the first ½ year of the disease.
   (b) In the first 5 years of the disease. (*)
   (c) In the second 5 years of the disease.
   (d) In the long run of the disease, i.e. after >10 years.

5. What is the definition of a myasthenic crisis?

   (a) Need for hospital admission and worse.
   (b) Need for help regarding ADL and worse.
   (c) Need for parenteral medication and worse.
   (d) Need for artificial ventilation for >24 h. (*)

6. It is generally accepted that MG patients should not be intubated for artificial ventilation anymore after more than 3 crises.

   (a) True.
   (b) False. (*)

7. How do patients with MuSK myasthenia differ from patients with AchR myasthenia? MuSK patients do have more pronounced and more often …

   (a) ocular weakness.
   (b) bulbar weakness. (*)
   (c) limb weakness.
   (d) myasthenic crises.

8. What can be said about anticholinesterases as a first-line therapy in MG?

   (a) This holds for patients with AchR MG, not for MuSK MG. (*)
   (b) This holds for patients with MuSK MG, not for AchR MG.
   (c) This holds both for patients with AchR MG and for patients with MuSK MG.
   (d) They are nowadays other effective therapies available that are not first line anymore.

9. A positive AchR test in a patient with clinical features of MG should be confirmed by complementary EMG examination before making the diagnosis MG for sure.

   (a) True.
   (b) False. (*)

10. Which patients with NMJ problem should have a CT scan of the chest to exclude thymoma?

    (a) All patients with NMJ problem.
    (b) All patients with a post-synaptic NMJ problem.
    (c) All patients with AchR antibodies. (*)
    (d) Only patients with more than ocular symptoms.

11. What is the best way to treat a patient with MG in a crisis not benefitting sufficiently from steroid therapy?

    (a) Adding azathioprine to the medication.
    (b) Adding rituximab to the medication.
    (c) IVIG or PLEX in addition to the current regime. (*)
    (d) An emergency thymectomy in addition to the current regimen.

12. Which of the following "new" therapies in oncology may induce MG as side effect? Agents that target….

    (a) CD20-B-cells.
    (b) Complement.
    (c) Immune checkpoint inhibitors (*)
    (d) Tumor necrosis factor.

13. In how many percent of the LEMS patients this disease is paraneoplastic?

    (a) In >70%
    (b) In about 50% (*)
    (c) In <30%

14. Respiratory failure in LEMS is less frequent than in MG.

    (a) True. (*)
    (b) False.

15. Which of the following is the most common in LEMS?

    (a) Erectile dysfunction. (*)
    (b) Micturition problems.
    (c) Orthostatic hypotension.

16. Which of the following infectious diseases resembles LEMS as far as pathophysiology is concerned?

    (a) Botulism. (*)
    (b) Diphtheria.
    (c) Rabies.
    (d) Tetanus.

17. MuSK antibody-positive myasthenia gravis is predominantly found in middle-aged females.

    (a) True. (*)
    (b) False.

18. Repetitive nerve stimulation is a very sensitive (>80%) test even in mild generalised MG.

    (a) True.
    (b) False. (*)

19. Pregnancy may change the clinical symptoms. In which direction?

    (a) Myasthenia usually gets better during pregnancy.
    (b) Myasthenia usually gets worse during pregnancy.
    (c) Both may occur. The course during pregnancy is unpredictable. (*)

20. Congenital Myasthenic Syndrome may present in adulthood.

    (a) True. (*)
    (b) False.

21. Which type of medication may be effective in congenital myasthenia?

    (a) Parasympathicolytics.
    (b) Parasympathicomimetics.
    (c) Orthosympathicolytics.
    (d) Orthosympathicomimetics. (*)

22. Hypoventilation is uncommon in congenital myasthenia.

    (a) True.
    (b) False. (*)

23. Anticholinesterases may work beneficially in congenital myasthenia.

    (a) True. (*)
    (b) False.

Acknowledgments Dr. Lokesh Wijesekera, Ipswich and Cambridge University Hospitals, provided electrophysiological images (Figs. 9.1 and 9.2).

References

1. Luchanok U, Kaminski HJ. Natural history of myasthenia gravis. In: Engel HG, editor. Myasthenia gravis and myasthenic disorders. New York: Oxford University Press; 2012. p. 90–107.
2. Vincent A, Clover L, Buckley C, Grimley Evans J, Rothwell PM. UK myasthenia gravis survey. Evidence of underdiagnosis of myasthenia gravis in older people. J Neurol Neurosurg Psychiatry. 2003;74(8):1105–8.
3. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. Muscle Nerve. 2008;37(2):141–9.
4. Cortés-Vicente E, Álvarez-Velasco R, Segovia S, et al. Clinical and therapeutic features of myasthenia gravis in adults based on age at onset. Neurology. 2020;94(11):e1171–80.
5. Ertz-Archambault M, Kosiorek H, Taylor GE, et al. Association of therapy for autoimmune disease with myelodysplastic syndromes and acute myeloid leukemia. JAMA Oncol. 2017;3(7):936–43.
6. Confavreux C, Saddier P, Grimaud J, Moreau T, Adeleine P, Aimard G. Risk of cancer from azathioprine therapy in multiple sclerosis: a case-control study. Neurology. 1996;46(6):1607–12.

7. Khan N, Abbas AM, Lichtenstein GR, Loftus EV, Bazzano LA. Risk of lymphoma in patients with ulcerative colitis treated with thiopurines: a nationwide retrospective cohort study. Gastroenterology. 2013 Nov;145(5):1007–15.
8. Mantegazza R, Antozzi C. When myasthenia gravis is deemed refractory: clinical signposts and treatment strategies. Ther Adv Neurol Disord. 2018;11:1756285617749134.
9. Schneider-Gold C, Hagenacker T, Melzer N, Ruck T. Understanding the burden of refractory myasthenia gravis. Ther Adv Neurol Disord. 2019;12:1756286419832242.
10. Alshekhlee A, Miles JD, Katirji B, Preston DC, Kaminski HJ. Incidence and mortality rates of myasthenia gravis and myasthenic crisis in US hospitals. Neurology. 2009;72(18):1548–54.
11. Almon RR, Andrew CG, Appel SH. Serum globulin in myasthenia gravis: inhibition of a-bungarotoxin binding to acetylcholine receptors. Science. 1974;186:55–7.
12. Toyka KV, Drachman DB, Griffin DE, et al. Myasthenia gravis. Study of humoral immune mechanisms by passive transfer to mice. N Engl J Med. 1977;296(3):125–31.
13. Leite MI, Jacob S, Viegas S, et al. IgG1 antibodies to acetylcholine receptors in 'seronegative' myasthenia gravis. Brain. 2008;131(Pt 7):1940–52.
14. Hoch W, McConville J, Helms S, Newsom-Davis J, Melms A, Vincent A. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. Nat Med. 2001;7(3):365–8.
15. Evoli A, Tonali PA, Padua L, et al. Clinical correlates with anti-MuSK antibodies in generalized seronegative myasthenia gravis. Brain. 2003;126(Pt 10):2304–11.
16. Wolfe GI, Oh SJ. Clinical phenotype of muscle-specific tyrosine kinase-antibody-positive myasthenia gravis. Ann N Y Acad Sci. 2008;1132:71–5.
17. Higuchi O, Hamuro J, Motomura M, Yamanashi Y. Autoantibodies to low-density lipoprotein receptor-related protein 4 in myasthenia gravis. Ann Neurol. 2011;69(2):418–22.
18. Gasperi C, Melms A, Schoser B, et al. Anti-agrin autoantibodies in myasthenia gravis. Neurology. 2014;82(22):1976–83.
19. Zisimopoulou P, Evangelakou P, Tzartos J, et al. A comprehensive analysis of the epidemiology and clinical characteristics of anti-LRP4 in myasthenia gravis. J Autoimmun. 2014;52:139–45.
20. Aarli JA. Myasthenia gravis and thymoma. In: Lisak RP, editor. Handbook of myasthenia gravis and myasthenic syndromes. New York: Marcel Dekker; 1994. p. 207–49.
21. Engel AG, Lindstrom JM, Lambert EH, Lennon VA. Ultrastructural localization of the acetylcholine receptor in myasthenia gravis and in its experimental autoimmune model. Neurology. 1977;27:307–15.
22. DeBaets MH, Kuks JJ. Immunopathology of myasthenia gravis. In: DeBaets MH, Oosterhuis HJ, editors. Myasthenia gravis. Boca Raton: CRC Press; 1993. p. 160.
23. Burden SJ, Yumoto N, Zhang W. The role of MuSK in synapse formation and neuromuscular disease. Cold Spring Harb Perspect Biol. 2013;5(5):a009167.
24. Shigemoto K. Myasthenia gravis induced by autoantibodies against MuSK. Acta Myol. 2007;26(3):185–91.
25. Giannoccaro MP, Paolucci M, Zenesini C, Di Stasi V, Donadio V, Avoni P, Liguori R. Comparison of ice pack test and single-fiber EMG diagnostic accuracy in patients referred for myasthenic ptosis. Neurology. 2020;95(13):e1800–e6.
26. Singman EL, Matta NS, Silbert DI. Use of the Cogan lid twitch to identify myasthenia gravis. J Neuroophthalmol. 2011;31(3):239–40.
27. Gilhus NE, Skeie GO, Romi F, Lazaridis K, Zisimopoulou P, Tzartos S. Myasthenia gravis - autoantibody characteristics and their implications for therapy. Nat Rev Neurol. 2016;12(5):259–68.
28. Gilhus NE, Aarli JA, Christenson B, Matre R. Rabbit antisera to a citric extract of human skeletal muscle cross-reacts with thymomas from myasthenia gravis patients. J Neuroimmunol. 1984;7:55–64.
29. Palace J, Newsom-Davis J, Lecky B. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. Neurology. 1998;50(6):1778–83.

30. Sanders DB, Siddiqi ZA. Lessons from two trials of mycophenolate mofetil in myasthenia gravis. Ann N Y Acad Sci. 2008;1132:249–53.
31. Buzzard KA, Meyer NJ, Hardy TA, Riminton DS, Reddel SW. Induction intravenous cyclophosphamide followed by maintenance oral immunosuppression in refractory myasthenia gravis. Muscle Nerve. 2015;52(2):204–10.
32. Banerjee S, Adcock L. Rituximab for the treatment of myasthenia gravis: a review of clinical effectiveness, cost-effectiveness, and guidelines. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018.
33. Topakian R, Zimprich F, Iglseder S, et al. High efficacy of rituximab for myasthenia gravis: a comprehensive nationwide study in Austria. J Neurol. 2019;266(3):699–706.
34. Singh N, Goyal V. Rituximab as induction therapy in refractory myasthenia gravis: 18 month follow-up study. J Neurol. 2019;66(7):1596–600.
35. Hehir MK, Hobson-Webb LD, Benatar M, et al. Rituximab as treatment for anti-MuSK myasthenia gravis: multicenter blinded prospective review. Neurology. 2017;89(10):1069–77.
36. Díaz-Manera J, Martínez-Hernández E, Querol L, et al. Long-lasting treatment effect of rituximab in MuSK myasthenia. Neurology. 2012;78(3):189–93.
37. Howard JF Jr, Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. Lancet Neurol. 2017;16(12):976–86.
38. Gable KL, Guptill JT. Antagonism of the neonatal fc receptor as an emerging treatment for myasthenia gravis. Front Immunol. 2020;10:3052.
39. Blalock A. Thymectomy in the treatment of myasthenia gravis: report of 20 cases. J Thorac Surg. 1944;13:316–39.
40. Wolfe GI, Kaminski HJ, Aban IB, et al. Randomized trial of Thymectomy in myasthenia gravis. N Engl J Med. 2016;375(6):511–22.
41. O'Sullivan KE, Kreaden US, Hebert AE, Eaton D, Redmond KC. A systematic review of robotic versus open and video assisted thoracoscopic surgery (VATS) approaches for thymectomy. Ann Cardiothorac Surg. 2019;8(2):174–93.
42. Seybold ME, Drachman DB. Gradually increasing doses of prednisone in myasthenia gravis: reducing the hazards of treatment. N Engl J Med. 1974;290(2):81–4.
43. Dengler R, Rüdel R, Warelas J, Birnberger KL. Corticosteroids and neuromuscular transmission: electrophysiological investigation of the effects of prednisolone on normal and anticholinesterase-treated neuromuscular junction. Pflugers Arch. 1979;380(2):145–51.
44. Burakgazi AZ. Immunoglobulin Treatment in Neuromuscular Medicine. J Clin Neuromuscul Dis. 2019;20(4):182–93.
45. Barth D, Nabavi Nouri M, Ng E, Nwe P, Bril V. Comparison of IVIg and PLEX in patients with myasthenia gravis. Neurology. 2011;76(23):2017–23.
46. Munot P, Robb SA, Niks EH, Palace J. ENMC workshop study group 242nd ENMC international workshop: diagnosis and management of Juvenile Myasthenia Gravis Hoofddorp, the Netherlands, 1-3 March 2019. ENMC workshop with guidelines for juvenile myasthenia gravis. Neuromuscul Disord. 2020;30(3):254–64. Epub 2020 Feb 7
47. Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. Myasthenia gravis: Association of British Neurologists' management guidelines. Pract Neurol. 2015;15(3):199–206.
48. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, Kuntz N, Massey JM, Melms A, Murai H, Nicolle M, Palace J, Richman DP, Verschuuren J, Narayanaswami P. International consensus guidelines for management of myasthenia gravis: executive summary. Neurology. 2016;87(4):419–25.
49. Burns TM, Conaway MR, Cutter GR, Sanders DB. Muscle study group. Construction of an efficient evaluative instrument for myasthenia gravis: the MG composite. Muscle Nerve. 2008;38(6):1553–62.

50. Wijdicks EF. Neurogenic paradoxical breathing. J Neurol Neurosurg Psychiatry. 2013;84(11):1296.
51. Wijdicks EFM. The neurology of acutely failing respiratory mechanics. Ann Neurol. 2017;81:489–98.
52. Lawn ND, Fletcher DD, Henderson RD, Wolter TD, Wijdicks EF. Anticipating mechanical ventilation in Guillain-Barré syndrome. Arch Neurol. 2001 Jun;58(6):893–8.
53. Oosterhuis HJ. Observations of the natural history of myasthenia gravis and the effect of thymectomy. Ann N Y Acad Sci. 1981;377:678–90.
54. Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neurol. 2009;8:475–90.
55. Thomas CE, Mayer SA, Gungor Y, et al. Myasthenic crisis: clinical features, mortality, complications, and risk factors for prolonged intubation. Neurology. 1997;48:1253–60.
56. Karcic AA. Drugs that can worsen myasthenia gravis. Postgrad Med. 2000;108(2):25.
57. Teramoto K, Kuwabara M, Matsubara Y. Respiratory failure due to vocal cord paresis in myasthenia gravis. Respiration. 2002;69(3):280–2.
58. Seneviratne J, Mandrekar J, Wijdicks EF, Rabinstein AA. Noninvasive ventilation in myasthenic crisis. Arch Neurol. 2008;65(1):54–8.
59. Damian MS, Wijdicks EFM. The clinical management of neuromuscular disorders in intensive care. Neuromuscul Disord. 2019 Feb;29(2):85–96.
60. Dugernier J, Bialais E, Reychler G, Vinetti M, Hantson P. Neurally adjusted ventilatory assist during weaning from respiratory support in a case of Guillain-Barré syndrome. Respir Care. 2015;60(4):e68–72.
61. Oosterhuis HJ. The natural course of myasthenia gravis: a long-term follow-up study. J Neurol Neurosurg Psychiatry. 1989;52(10):1121–7.
62. Damian MS, Ben-Shlomo Y, Howard R, Bellotti T, Harrison D, Griggs K, Rowan K. The effect of secular trends and specialist neurocritical care on mortality for patients with intracerebral haemorrhage, myasthenia gravis and Guillain-Barré syndrome admitted to critical care: an analysis of the Intensive Care National Audit & Research Centre (ICNARC) national United Kingdom database. Intensive Care Med. 2013;39(8):1405–12.
63. Seneviratne J, Mandrekar J, Wijdicks EF, Rabinstein AA. Predictors of extubation failure in myasthenic crisis. Arch Neurol. 2008;65:929–33.
64. Gamez J, Salvado M, Casellas M, Manrique S, Castillo F. Intravenous immunoglobulin as monotherapy for myasthenia gravis during pregnancy. J Neurol Sci. 2017;383:118–22.
65. Almeida C, Coutinho E, Moreira D, Santos E, Aguiar J. Myasthenia gravis and pregnancy: anaesthetic management--a series of cases. Eur J Anaesthesiol. 2010;27(11):985–90.
66. Abdel-Wahab N, Shah M, Lopez-Olivo MA, Suarez-Almazor ME. Use of immune checkpoint inhibitors in the treatment of patients with cancer and preexisting autoimmune disease: a systematic review. Ann Intern Med. 2018;168(2):121–30.
67. Safa H, Johnson DH, Trinh VA, et al. Immune checkpoint inhibitor related myasthenia gravis: single center experience and systematic review of the literature. J Immunother Cancer. 2019;7(1):319.
68. O'Neill JH, Murray NM, Newson-Davis J. The Lambert-Eaton myasthenic syndrome. A review of 50 cases. Brain. 1988;111(Pt 3):577–93.
69. Titulaer MJ, Wirtz PW, Willems LN, van Kralingen KW, Smitt PA, Verschuuren JJ. Screening for small-cell lung cancer: a follow-up study of patients with Lambert-Eaton myasthenic syndrome. J Clin Oncol. 2008;26(26):4276–81.
70. Sabater L, Titulaer M, Saiz A, Verschuuren J, Güre AO, Graus F. SOX1 antibodies are markers of paraneoplastic Lambert-Eaton myasthenic syndrome. Neurology. 2008;70(12):924–8.
71. Titulaer MJ, Lang B, Verschuuren JJ. Lambert-Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. Lancet Neurol. 2011;10(12):1098–107.
72. Smith AG, Wald J. Acute ventilatory failure in Lambert-Eaton myasthenic syndrome and its response to 3,4-diaminopyridine. Neurology. 1996;46(4):1143–5.
73. Waterman SA. Autonomic dysfunction in Lambert-Eaton myasthenic syndrome. Clin Auton Res. 2001;11(3):145–54.

74. AAEM Quality Assurance Committee. American Association of Electrodiagnostic Medicine. Literature review of the usefulness of repetitive nerve stimulation and single fiber EMG in the electrodiagnostic evaluation of patients with suspected myasthenia gravis or Lambert-Eaton myasthenic syndrome. Muscle Nerve. 2001;24(9):1239–47.
75. Flink MT, Atchison WD. Ca2+ channels as targets of neurological disease: Lambert-Eaton syndrome and other Ca2+ channelopathies. J Bioenerg Biomembr. 2003;35(6):697–718.
76. Chalk CH, Murray NM, Newsom-Davis J, O'Neill JH, Spiro SG. Response of the Lambert-Eaton myasthenic syndrome to treatment of associated small-cell lung carcinoma. Neurology. 1990;40(10):1552–6.
77. Keogh M, Sedehizadeh S, Maddison P. Treatment for Lambert-Eaton myasthenic syndrome. Cochrane Database Syst Rev. 2011;2011(2):CD003279.
78. Newsom-Davis J, Murray NM. Plasma exchange and immunosuppressive drug treatment in the Lambert-Eaton myasthenic syndrome. Neurology. 1984;34(4):480–5.
79. Keezer M, Benini R, Chalk C. Botulism. In: Katirji B, Kaminski H, Ruff RL, editors. Neuromuscular disorders in clinical practice. 2nd ed. New York: Springer; 2014. p. 1101–9.
80. Anniballi F, Auricchio B, Fiore A, et al. Botulism in Italy, 1986 to 2015. Euro Surveill. 2017;22(24)
81. Sam AH, Beynon HL. Images in clinical medicine: wound botulism. N Engl J Med. 2010;363(25):2444.
82. Guidon AC. Lambert-Eaton myasthenic syndrome, botulism, and immune checkpoint inhibitor-related myasthenia gravis. Continuum (Minneapolis, Minn). 2019;25(6):1785–806.
83. Hulse EJ, Haslam JD, Emmett SR, Woolley T. Organophosphorus nerve agent poisoning: managing the poisoned patient. Br J Anaesth. 2019;123(4):457–63.
84. Gunnell D, Eddleston M, Phillips MR, Konradsen F. The global distribution of fatal pesticide self-poisoning: systematic review. BMC Public Health. 2007;7:357.
85. Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. Lancet. 2008;371(9612):597–607.
86. Rodríguez Cruz PM, Palace J, Beeson D. Inherited disorders of the neuromuscular junction: an update. J Neurol. 2014;261(11):2234–43.
87. McMacken G, Whittaker RG, Evangelista T, et al. Congenital myasthenic syndrome with episodic apnoea: clinical, neurophysiological and genetic features in the long-term follow-up of 19 patients. J Neurol. 2018;265:194–203.
88. Engel AG. The therapy of congenital myasthenic syndromes. Neurotherapeutics. 2007;4:252–7.
89. Beeson D. Congenital myasthenic syndromes: recent advances. Curr Opin Neurol. 2016;29:565–71.
90. Harper CM, Fukodome T, Engel AG. Treatment of slow-channel congenital myasthenic syndrome with fluoxetine. Neurology. 2003;60:1710–3.

Chapter 10
Emergencies in Acute Myopathies: Acute Toxic Myopathies, Rhabdomyolysis, and Malignant Hyperthermia

Benedikt Schoser and Heinz Jungbluth

Rhabdomyolysis and Acute Toxic Myopathies

Introduction and Definition

The term rhabdomyolysis (RML) describes an acute massive necrosis and subsequent destruction of skeletal muscle tissue. Depending on dynamics and amount of tissue destruction, ICU care is required. Multiple triggers and causes have been reported in the literature, including a spectrum of physical, chemical, and pharmacological hazards, and inherited metabolic, membrane, or channel-associated skeletal muscle protein alterations. After recovery from the acute ICU treatment period, the long-term prognosis and recovery is good, if a causative factor for the RML is recognizable.

Summarizing the current literature, RML is defined as a clinical syndrome of acute muscle weakness, myalgia, and muscle swelling combined with a serum creatine kinase activity (CK) cut-off value of >1000 U/l/ or CK >5× the upper limit of normal (ULN). Additional unequivocally documented myoglobinuria and unequivocal evidence of acute kidney injury (AKI) indicate a severe type of RML. Exclusion criteria, such as heart CK-MB/CK elevation with cardiac etiology/myocardial infarction, kidney disease/renal end-stage disease/chronic renal failure, cerebral vascular accident/stroke/status epilepticus, and specific neuromuscular disease as well as the chronological sequence, need to be considered for a conclusive RML definition [1].

B. Schoser (✉)
Department of Neurology, Friedrich-Baur-Institute, Ludwig-Maximilians-University Munich, Munich, Germany
e-mail: benedikt.schoser@med.uni-muenchen.de

H. Jungbluth (✉)
Department of Paediatric Neurology—Neuromuscular Service, Evelina Children's Hospital, Guy's and St Thomas' NHS Foundation Trust and King's College London, London, UK
e-mail: Heinz.Jungbluth@gstt.nhs.uk

M. Damian, M. de Visser (eds.), *Emergencies in Neuromuscular Disorders*,
https://doi.org/10.1007/978-3-030-91932-0_10

Epidemiology and Clinical Presentation

The incidence and prevalence of RML is unknown mainly because of the lack of a universally agreed clinical definition. Therefore, a systematic review based on the definition suggested above was performed and published in 2019 [1], indicating that up to 40% of patients with RML develop an AKI, and concluding that up to 20% of all cases of AKI can be ascribed to acute RML.

Case Vignette 1

A 36-year-old man was admitted with rapidly developing proximal muscle weakness. He had abused alcohol for a period of 8 years, with a mean ethanol consumption of about 120 g/day. One month before admission, he got divorced followed by a depressive episode. Over this period, his ethanol consumption increased to about 300 g/day. Two days before admission he developed an acute illness with diarrhoea, nausea, and vomiting. He experienced increasing exercise intolerance and fatigue. He was unable to get up from a chair unassisted and became unable to climb a staircase.

On examination, he was pale and dehydrated. There were multiple cutaneous stigmata of chronic liver disease with hepatomegaly. Cognitive functions were preserved, and examination of the cranial nerves was normal. He was unable to get up from a chair or to stand. Examination of the limb muscles showed marked symmetrical hip flexion weakness (MRC 3), with moderate weakness (MRC 4) in elbow flexion, knee extension, and ankle dorsiflexion. Muscle tone was increased, and vastus lateralis and gluteal muscles were slightly swollen. Deep tendon reflexes were generally depressed. Plantar responses were normal. Perception of pain and light touch was reduced in a glove and stocking distribution. Laboratory investigations revealed hypokalaemia of 1.8 mmol/l serum potassium. Serum CK activity was elevated to 2987 IU/l (normal < 190 IU/l). There was no myoglobinuria. Electrophysiological studies showed reduced amplitude of sensory nerve action potentials in the sural nerves, with normal sensory conduction velocity (CV). In the median nerve, the distal motor latency, the compound muscle action potential (CMAP) amplitude, and the motor CV were normal. Electromyography (EMG) of the right vastus lateralis muscle showed motor unit potentials of decreased amplitude and duration with a reduced recruitment pattern. Multiple fibrillation potentials and positive sharp waves were identified. A muscle biopsy was obtained from the left vastus lateralis muscle. The histopathology revealed a microvacuolar myopathy in some fibres. Additionally, moderate type-2 fibre atrophy was found (Fig. 10.1). *Intravenous potassium chloride equilibrium therapy led to an improvement in muscle strength with almost complete recovery by the end of the third week of admission. His serum potassium had increased to 4.6 mmol/l and CK had declined to 160 U/l (see also* [2]*).*

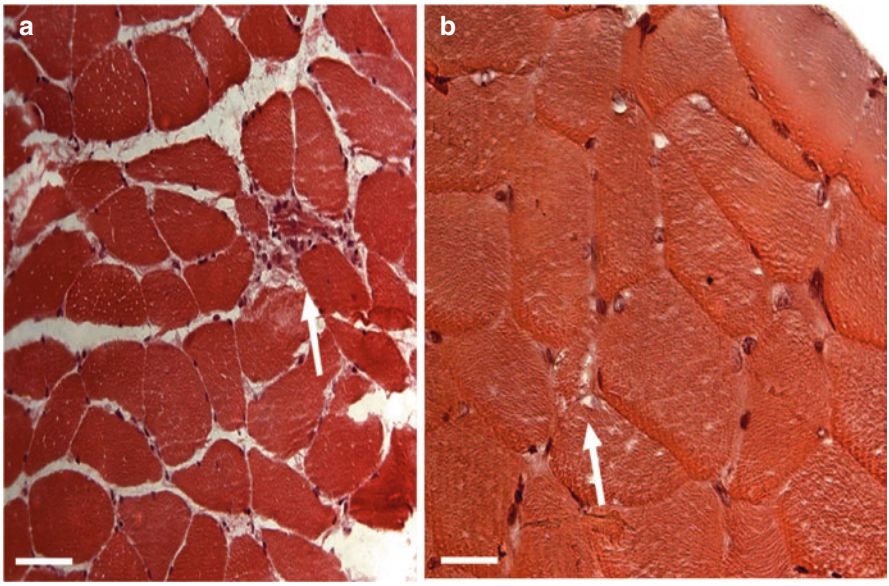


Fig. 10.1 Toxic hypokalaemia alcohol myopathy (Haematoxylin & eosin stain): Muscle biopsy of vastus lateralis. (**a**) Scattered myofiber necrosis (arrow) and fibre size variation. (**b**) There is limited subsarcolemmal vacuolization of some fibres (arrow). Bars in **a** & **b** adjusted to 50 μm

Learning Points
Alcohol consumption is one of the most common reasons for developing a severe RML. Especially under the development of a severe hypokalaemia, a microvacuolar myopathy can occur.

Clinical Presentation

The core presentation of RML includes a clinical triad of acute-onset proximal muscle weakness, myalgia, and dark urine; however, it is present in 10–20% of the cases only. Visible myoglobinuria occurs if the level of myoglobin in the urine exceeds 100 mg/dl so it often escapes attention. Swelling of the myalgic muscles is common. Within 24 h of presentation, this clinical syndrome is followed by a massive increase in serum CK activity, typically at least 5 to 100 times of the normal value *[case vignette 1]*. The level of CK is dependent on the CK assay used, ethnicity, gender, daily exercise level, and can be very high at the time of the acute event but may decline quickly to normal. The most severe critical complication is an AKI with increased serum creatinine, myoglobinuria, and low urine outflow syndrome. Possible pathophysiological mechanisms implicated in RML-related AKI include tubular obstruction by myoglobin and ischemic tubular injury. Moreover, RML can

lead to cardiac arrhythmia due to hyperkalaemia and is frequently accompanied by coagulopathy. If massive muscle necrosis occurs, swelling and edema may compress vessels and nerves, resulting in an overt compartment syndrome necessitating immediate surgical fasciotomy. An early indicator for such a neuromuscular emergency is the decline of cutaneous sensation in distal legs and arms, followed by foot or toe elevator paresis. Later stages will present with an ischemic cold and pale distal leg and foot, and complete loss of sensation [1, 3–8].

Pathophysiology

RML may start with a mismatch between muscle workload and individual muscle performance ability, for example in the scenario of a relatively untrained person running a marathon. In some neuromuscular conditions like metabolic myopathies, even slight increases in muscle workload may trigger an episode of RML. Depletion of potassium or phosphate can trigger such episodes, e.g. induced by alcohol consumption, abuse of other substances, drugs, or malnutrition. Other triggers are substrate reduction or elimination, sepsis, autoimmune or neoplastic disorders *[case vignette 2]*. Furthermore, inherited, in particular, pre- or paucisymptomatic neuromuscular disorders are major contributors to RML (Tables 10.1, 10.2, 10.3, and 10.4). Frequently, exercise-induced cramps, myalgia, and features such as dark urine are suggestive for RML [1, 3–8].

Table 10.1 Inherited causes of acute nontoxic rhabdomyolysis

Localization of the defect	Example
Glycogen pathway	Myophosphorylase (McArdle disease/GSD5) Phosphorylase-b kinase deficiency Phosphofructokinase deficiency (Tarui disease/GSD7)
Beta-oxidation	Carnitine-palmityl-transferase deficiency/CPT2 Acetyl-CoA-dehydrogenase deficiency
Mitochondrial respiratory chain complexes	Complex-III- deficiency Succinate-dehydrogenase/complex-II deficiency Cytochrome-C-oxidase deficiency
Muscle membrane/ channelopathies/various	Limb girdle dystrophies Myotonic dystrophies and myotonia congenita Central core disease Malignant hyperthermia

Table 10.2 Acute mechanical and environmental causes of rhabdomyolysis

Injury	Immobilization/ischemia	Overload
Direct muscle trauma, compartment syndrome („crush syndrome“) Prolonged reanimation Hypothermia Heat-/electric shock	Intoxication, coma, stillage Arterial vessel occlusion, sickle cell crisis, thrombosis Intraoperative positioning (e.g. bariatric surgery)	Grand mal seizure Extreme exercise, raving, psychosis, hyperthermia Status asthmaticus Catatonia

Table 10.3 Acute toxic causes of rhabdomyolysis

Drugs	Medication (examples)	Toxins
Alcohol excess Benzodiazepines Amphetamines (LSD, ecstasy) and cocaine Opiates (esp. heroin) Barbiturates	Lipid-lowering drugs (statins, fibrate) Hypnotics, muscle relaxants Erythromycin, psychopharmaca Analgetics, antiepileptics Immunosuppressive drugs: Azathioprine, cyclosporin A, interferon, rapamycin Hypokalaemia inducing drugs: e.g. diuretics, laxatives, theophylline	Strychnins, arsen Hornisses, wasp toxine Tetanus, botulinum Snakes, spiders, tropical sea animals

Table 10.4 Preexisting diseases as causes of rhabdomyolysis

Metabolic: Potassium-, calcium-, & phosphate deficiency, endocrine crisis, e.g. hypo- or hyperthyrosis, Addison crisis, diabetic crisis
Muscle disorders: Myopathies (manifest or latent)
Inflammation: Bacteriaemia, viraemia, malaria, autoimmune diseases, e.g. legionella sepsis, streptococcus, salmonellosis, clostridum difficile, influenza A, coxsackie, Epstein-Barr, lupus erythematodes, immune-mediated necrotizing myopathy
Deficiency: Substance withdrawal (alcohol, dopaminergic drugs, baclofen)

Case Vignette 2

A 53-year-old female was diagnosed with a small lung cell carcinoma with local hepatic and bone metastases and started first-line treatment with combined Nivolumab (an anti-PD-1 immune checkpoint inhibitor antibody) and Ipilimumab (an anti-CTLA-4 immune checkpoint inhibitor antibody). Eight weeks later, after completion of 4 cycles of treatment, she started complaining of binocular diplopia, dysphagia, and moderate exercise-related dyspnea. Neurological examination revealed limited abduction of both eyes, mild bilateral ptosis, and repetitive exercise-induced muscle proximal weakness. Blood laboratory tests revealed increased levels of CK at 1660 IU/l (normal < 180 IU/l). Anti-acetylcholinesterase receptor (AChR), anti-muscle-specific kinase (MuSK), and myositis-associated autoantibodies were negative. The EMG was consistent with a myopathic pattern and demonstrated some spontaneous activities in both biceps and deltoid muscles. Repetitive nerve stimulation was negative, and motor and sensory nerve conduction studies were normal. A biopsy from the right biceps muscle revealed numerous necrotic myofibers with focal atrophy. No inflammation was detected. Immunostaining demonstrated sarcolemmal MHC-class-I positive fibres. Cardiac studies including ECG, echocardiogram, and cardiac MRI revealed atrial fibrillation only. The diagnosis of immune-checkpoint-inhibitor-related myasthenic syndrome with RML was made. Checkpoint inhibitor immunotherapy was stopped and intravenous high-dose steroid treatment (prednisolone 2 mg/kg/day) was initiated. During the following week, marked clinical improvement and CK normalization was observed. Steroids could be gradually tapered over 2 more weeks. No additional immunomodulating therapy was needed. Six months later the patient died from the consequences of lung carcinoma progression.

Learning Points
Any type of novel drugs or novel drug mechanism may be a potent initiator of a toxic myopathy. In most cases, a stop of the therapy should prevent further decline.

Diagnosis

Diagnosis can be made based on clinical features of acute-onset painful peripheral muscle weakness and muscle swelling, and suddenly highly elevated serum CK, which quickly normalizes after recovery. EMG may reveal some minor spontaneous activity and rarely early myopathic alterations. Muscle biopsy or any other procedures are usually required, if obvious triggers are excluded, to prove the cause of RML. Muscle MRI may be helpful in selected cases, showing increased signal intensity on T2-weighted and STIR sequences, and decreased signal intensity on T1-weighted sequences. Additional characteristic MRI findings may include intramuscular hemorrhage, stippled enhancement, a well-defined rectangular shape with a ragged margin in the longitudinal plane [9, 10]. Finally, serum and urine myoglobin measurements are warranted. As a quick initial bedside test, urine tests for hemoglobulin may also be used.

Consider a diagnostic muscle biopsy after the first episode of RML in all cases. The biopsy should be performed with a delay of 4 to 8 weeks. Otherwise, you might find necrotic myofibers only. Particularly consider a muscle biopsy after repeated episodes of RML. An early biopsy whin days after the acute RML might be considered if one suspects an inflammatory or ongoing process (e.g. if CK does not decline timely).

Prognosis

The key prognostic factor in RML is the development of AKI, with very rapid and high CK (more than 20× of normal, or above 15.000 U/l) and myoglobin increases are good predictive factors for the development of AKI. Other prognostic parameters are summarized in Table 10.5 [4, 7, 11]. A timely decline of CK indicates that the toxic impact on the tissue is being eliminated, with CK levels usually reducing by half within 2–3 days provided kidney function is normal.

Table 10.5 Complications of rhabdomyolysis

Acute kidney injury (AKI)
Hyperkalaemia with cardiac conduction alteration
Compartment syndrome with nerve and vessel compression
Metabolic coma
Acute diaphragmatic respiratory insufficiency

General Principles of Rhabdomyolysis Treatment

Clinical warning signs to consider an immediate transfer of a RML patient to the ICU include (1) severe paresis and aggravated by potassium deficiency or massive elevation; (2) cardiac arrhythmias, high potassium levels, preexisting heart disease; (3) renal failure as indicated by reduced diuresis and increased retention parameters; and (4) progressive metabolic deterioration and pending coma, or any additional factor (e.g. hyperthermia, drugs) that might lead to further complications [3–7, 11].

RML treatment follows three major aims: (1) elimination of the toxic agent; (2) avoiding any cardiac or renal complication; (3) rehabilitation and recovery. During the course of RML monitoring of CK (e.g. showing a reduction by half within 3 days after presentation is indicative of RML remission). Standard RML neuromonitoring encompasses muscle tone testing, MRC grading, and sensory examination of all extremities and the back muscles (including the gluteal compartment), in particular to detect early signs of compartment syndrome. Most important is the elimination of any toxic agent, in particular iatrogenic factors (polymedication) that are major contributors; myotoxic side-effects are frequent, for example with lipid-lowering drugs. Here inductors of the cytochrome-P450 isoenzyme CYP3A4 may elevate drug levels of cholesterol-synthase-inhibitors. Other known triggers of RML are sedative drugs like midazolam, analgesics like lidocaine and fentanyl, antiarrhythmics such as amiodarone, antihypertensives such as verapamil, or antibiotics and antimycotics. Furthermore, short or long-term treatment with propofol may trigger RML and lead to lactate acidosis, hyperlipidemia, and ECG alterations. The Propofol-related infusion syndrome (PRIS) is a feared well-known trigger of RML and may already be caused by short-term infusion rates of 5 mg/kg/h propofol over more than 48 h. Risk factors for PRIS are: young age, high catecholamine demand, brain trauma, and the cumulative propofol dose. Clinical signs include lactate acidosis, cardiac arrhythmias, and heart failure combined with typical ECG changes of the Brugada type (ST elevations) [12, 13]. Finally, opioids, non-depolarizing relaxants, and glucocorticoids, all frequently used in an ICU setting, are recognized triggers. It is also of utmost importance not to overlook RML in sedated ICU patients, thus sequential monitoring of CK and potassium levels is crucial.

Pharmacological therapy of RML is based on volume replacement therapy in combination with diuretics. Diuresis should be kept at up to 300 ml/h under regular control of potassium, calcium, and phosphate levels. The use of NaCl 0.9% is recommended. Considering the frequent occurrence of cardiac arrhythmias in RML, ECG monitoring is advisable. For prophylaxis of renal insufficiency, urine pH levels should be kept over pH 6.50, using bicarbonate infusions as indicated (e.g. by adding 50 mmol to 2 l infusion solution) [3, 4, 14–17]. Renal replacement therapy needs to be commenced without delay if prolonged hyperkalaemia occurs. Infusions of calcium gluconate or correction of hyperphosphatemia ought to be avoided, as this may further trigger myonecrosis [7].

After recovery from the acute RML phase and once CK levels have started to decrease, initially passive and then active physiotherapy should be commenced to

address muscle weakness and atrophy. Similarly, early training of the respiratory and swallowing muscles by respiratory and speech and language therapists ought to be considered. Further diagnostic workup is needed in those patients who have no obvious lifestyle trigger, who have had repeated RML episodes, and/or clinical evidence of neuromuscular disorder. Here you may consider a genetic workup including exome analysis.

Malignant Hyperthermia

Introduction and Definition

Malignant Hyperthermia (MH) is a potentially life-threatening pharmacogenetic reaction to volatile anaesthetics and muscle relaxants (for review, see [18]). MH was initially recognized as an autosomal-dominantly inherited trait by Denborough and colleagues in a large Australian pedigree in the 1960s [19], and subsequently attributed to mainly dominant mutations in the skeletal muscle ryanodine receptor *(RYR1)* gene. MH susceptibility (MHS) has been identified in individuals of different ethnicities from all over the world.

Epidemiology

There is a difference between the incidence of clinically overt MH episodes, depending on definition and samples surveyed currently estimated at between 1 in 10,000–25,000 anaesthetics, and the incidence of the MHS trait due to an underlying predisposing genetic background, currently estimated between 1 in 3000–8500 individuals but possibly higher [18]. The discrepancy between the incidence of MH and MHS remains currently unaccounted for and cannot be explained by the lack of exposure to triggering agents alone. MH reactions are more common in males and in the young, and it has been suggested that more than half of all MH reactions occur in children less than 15 years of age [20].

Clinical Description

MH may occur at any time during the anaesthesia but not more than 1 h after triggering agents have been discontinued. The typical MH reaction (for review, [18]) is a hypermetabolic syndrome characterized by early signs of tachycardia and increase in end-tidal carbon dioxide (ETCO2), followed by marked hyperpyrexia often well in excess of 40C. Masseter spasm may be the earliest neuromuscular sign, followed by generalized muscle rigidity (in particular if succinylcholine was

the trigger) and, eventually, extensive RML. Downstream complications are a reflection of progressive metabolic decompensation and generalized muscle breakdown, and may include disseminated intravascular coagulation (DIC), metabolic acidosis and hyperkalaemia, myoglobinuria, and AKI. Other complications include heart failure, bowel ischaemia, compartment syndrome, cerebellar swelling, and even death [21].

Etiology and Pathophysiology

MHS is predominantly due to dominant mutations in *RYR1*, and, much less frequently, dominant mutations in *CACNA1S* encoding the main subunit of the dihydropyridine (DHPR) receptor, and recessive mutations in *STAC3* [22], encoding another component of the excitation-contraction (EC) coupling machinery. Several other loci have been implicated in MHS by linkage but not mutational analysis, and a proportion of cases remains genetically unresolved (for review, [18]).

RYR1 encodes the principal sarcoplasmic reticulum (SR) calcium release channel with, in conjunction with the DHPR, a crucial role in EC coupling (for review, [23]). Both dominant and recessive mutations in *RYR1* have been associated with a wide range of early-onset neuromuscular disorders, the congenital myopathies, whereas mainly dominant mutations in *RYR1* have not only been implicated in MHS but, for example, also in (exertional) myalgia and rhabdomyolysis (RML) [24]. A continuum between certain myopathies—in particular central core disease (CCD) and the King-Denborough Syndrome (KDS) [25]—was already recognized by Denborough and colleagues and ought to be considered when managing such patients.

Simplistically speaking, *RYR1* mutations associated with muscle weakness are due to impaired calcium release, whereas those associated with MHS and/or ERM cause disproportionate and massive calcium release prompted by triggering agents and/or other stimuli. Although not every single detail is as yet fully understood, the initial disproportionate calcium release in MH triggers a vicious hypermetabolic cycle involving hyperpyrexia, increased oxygen and ATP consumption, secondary modifications further increasing the sensitivity of the mutated RYR1 receptor, and ultimately, loss of muscle membrane integrity with release of CK and potassium. Some of the underlying metabolic mechanisms have also been replicated in mouse models of MH [26].

Diagnosis

The diagnostic process with regards to MH and MHS involves two steps, the correct classification of a suspicious anaesthesia event as MH, and the subsequent confirmation of MHS by specific functional and genetic testing (for review, see [18]).

Larach and colleagues have devised a specific Clinical Grading Scale (CGS) [27] based on the presence of certain clinical and laboratory features, to determine if or if not a suspicious anaesthesia event is likely to have reflected a genuine MH episode. In those where a genuine MH episode was likely, MHS can then be further determined by an in vitro contracture test, currently considered the gold standard for MH diagnosis. Taking aside some differences between North American and European protocols, this test is essentially based on assessing the response of the patient muscle biopsy to two potentially triggering agents, halothane and caffeine. In individuals where MHS has been confirmed on in vitro contracture testing (or in those where this is not feasible), the underlying genetic defect can then be further investigated by specific genetic testing, increasingly through next-generation sequencing (NGS) approaches. The website of the European Malignant Hyperthermia Group (www.emhg.org) currently lists 48 *RYR1* and 2 *CACNA1S* mutations that are considered unequivocally diagnostic based on stringent assessment criteria, but there is likely to be a larger number of, in particular, *RYR1* variants implicated in MHS which have just not been assessed as rigorously yet. Considering the challenges of *RYR1* variant interpretation even in a suggestive clinical context, MHS diagnosis should always be conducted at a specialist MH expertise center. Counseling of the patient, but equally important, of potentially affected family members may be challenging and should involve a geneticist with experience in MH genetics.

Principles of Malignant Hyperthermia (MH) Treatment

MH is a severe and potentially life-threatening event, and treatment should be instituted immediately and aggressively as soon as an MH episode is suspected, ideally in close liaison with an MH expertise center.

The principles of managing an acute MH episode (for review, see [18]) involve immediate discontinuation of the suspected triggering agent, administration of the RYR1 antagonist Dantrolene, aggressive cooling, and anticipation and management of downstream complications. In an emergency, anaesthesia may have to be switched to non-triggering agents. Dantrolene is available in two preparations, Dantrium® and Ryanodex®, with differences in solubility and concentration. Initial doses of Dantrolene are usually 2.5 mg/kg in an emergency and are then titrated against clinical response. Signs and symptoms of DIC, blood gas and electrolyte abnormalities, RML and myoglobinuria, and renal and cardiac failure should be closely monitored for and proactively treated.

Prognosis and Prevention

When MH was initially recognized mortality was as high as 70–80%, but due to proactive management and, in particular, introduction of Dantrolene, this has now reduced to less than 5% [27]. However, as illustrated in Case Vignette 3 below, MH remains a potentially life-threatening and potentially lethal event even with appropriate treatment.

Prevention of future MH episodes in MHS patients and their relatives is beyond the remit of this chapter and should be discussed with an MH expertise center.

Case Vignette 3

A 14-year-old boy (reported in [21]*) was admitted to the hospital with symptoms suggestive of acute appendicitis. He was prepared for emergency surgery, and following anaesthesia induction with a volatile anaesthetic, he almost immediately developed hyperpyrexia up to 42.3C and an elevated end-tidal CO2. CK levels increased to 38,805 IU/l with associated myoglobinuria. Despite immediate institution of Dantrolene treatment and aggressive cooling, he developed pulmonary oedema requiring extracorporal membrane oxygenation for 7 h.*

Because of progressive neurological deterioration, CT and MRI scans were performed at 7 and 12 h, respectively, after onset of the MH episode, showing marked cerebellar swelling with supratentorial hydrocephalus and incipient herniation. Despite neurosurgical craniectomy and decompression, he deteriorated further, with evidence of supratentorial herniation and herniation of the swollen cerebellum through the foramen magnum, subsequently leading to brainstem death.

Postmortem examination revealed marked swelling in particular of cerebellar Purkinje cells, signs of widespread DIC and pulmonary oedema. Despite clinical signs of ongoing RML and myoglobinuria, there were only a few regenerative changes but no other abnormalities on postmortem muscle biopsy. Kidneys were intact.

On postmortem genetic testing, a RYR1 mutation previously associated with MH was identified in the index case but also his father. There had been no previous family history of MH, however, both his father and a paternal uncle had a personal history of (exertional) myalgia and muscle cramps.

Learning Points

One of the most important causes for developing a MH is a mutation in the RYR1 gene. In unclear hyperCKemia cases with perisurgical complications, performing a RYR1 gene analysis is highly recommended.

Self Assessment Questions

1. More than half of the patients with rhabdomyolysis (RML) develop an acute kidney injury.

   (a) True
   (b) False (*)

2. Alcohol consumption is one of the most common reasons for developing a severe rhabdomyolysis.

   (a) True (*)
   (b) False

3. Which of the following is more than the others a frequent complication of rhabdomyolysis?

   (a) Cardiac arrhythmia (*)
   (b) Diabetes insipidus
   (c) Liver failure with hyperammonemia
   (d) Profuse diarrhea

4. What is the direct reason for decline of cutaneous sensation in distal legs and arms in the context of RML?

   (a) Break-down of peripheral neural conduction by hypokalemia
   (b) Compartment syndrome due to swelling and edema (*)
   (c) Instability of nerve membranes by hypermyoglobulinaemia
   (d) Massive microvascular thrombosis

5. RML may be caused by a mismatch between muscle workload and individual muscle performance.

   (a) True (*)
   (b) False

6. Which of the following electrolyte conditions enhances RML more than the others do?

   (a) Hypocalcemia
   (b) Hypokalemia (*)
   (c) Hypomagnesemia
   (d) Hyponatremia

7. Which of the following biochemical conditions enhances RML more than the others do?

   (a) Hypoglycemia
   (b) Hypolipidemia
   (c) Hypophosatemia (*)
   (d) Hypoproteinemia

8. When should a muscle biopsy be performed after the first episode of RML?

   (a) As soon as possible
   (b) Within 1–2 weeks
   (c) Within 2–4 weeks
   (d) After at least 4 weeks (*)

9. Which of the following is the most urgent indication for a muscle biopsy after RML without a causal diagnosis? A suspicion of …..

   (a) dystrophinopathy
   (b) glycogenosis
   (c) mitochondrial cytopathy
   (d) myositis (*)

10. Which of the following electrolytes should be monitored most carefully once an RLM is treated?

    (a) Calcium
    (b) Magnesium
    (c) Potassium (*)
    (d) Sodium

11. Mutations in which gene are associated with malignant hyperthermia susceptibility?

    (a) CACNA1S (*)
    (b) NOTCH1
    (c) SMN1
    (d) SOD1

12. How long after discontinuation of a triggering agent malignant hyperthermia should be feared as a possibility? This risk may last ….

    (a) 1 h at most (*)
    (b) 2 h at most
    (c) 4 h at most
    (d) 8 h at most

13. Which of the following blood gas parameters is most indicative for development of malignant hypothermia?

    (a) Increase of pCO_2 (*)
    (b) Decrease of pCO_2
    (c) Increase of pO_2
    (d) Decrease of pO_2

14. Which of the following methods is most adequate to monitor a change in blood gas parameters necessary for the early diagnosis of MH immediately and continuously?

    (a) ^{13}C-Breath test
    (b) Continuous blood gas analysis (*)
    (c) Muscle spectrometry
    (d) Spirometry
    (e) Transdermal measurement

15. Which of the following structures of a muscle fibre is primarily involved in malignant hyperthermia?

    (a) Contractile proteins
    (b) Mitochondrion
    (c) Sarcolemma
    (d) Sarcoplasmatic reticulum (*)

16. Which of the following types of myopathy is most closely associated with malignant hyperthermia syndrome?

    (a) Central core myopathy (*)
    (b) Centronuclear myopathy
    (c) Myotubular myopathy
    (d) Nemaline myopathy

17. Which of the following processes during muscle contraction is primarily disturbed in the MHS?

    (a) Actin-Myosin interaction
    (b) Calcium release (*)
    (c) Propagation of the muscle action potential
    (d) Troponin-regulation

18. Which of the following drugs has a central position in the treatment of MHS?

    (a) Baclofen
    (b) Dantrolene (*)
    (c) Sulpiride
    (d) Tetrabenazine

19. Even despite extensive genetic testing, many cases of MH remain unexplained.

    (a) True (*)
    (b) False

References

1. Stahl K, Rastelli E, Schoser B. A systematic review on the definition of rhabdomyolysis. J Neurol. 2019;267:877–82.
2. Urbano-Marquez A, Estruch R, Navarro-Lopez F, Grau JM, Mont L, Rubin E. The effects of alcoholism on skeletal and cardiac muscles. N Engl J Med. 1989;320:409–15.

3. Zutt R, van der Kooi AJ, Linthorst GE, Wanders RJ, de Visser M. Rhabdomyolysis: review of the literature. Neuromuscul Disord. 2014;24:651–9.
4. Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. N Engl J Med. 2009;361:62–72.
5. Bagley WH, Yang H, Shah KH. Rhabdomyolysis. Intern Emerg Med. 2007;2(3):210–8.
6. Kellum JA, Lameire N, Group KAGW. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (part 1). Crit Care. 2013;17:204.
7. Chavez LO, Leon M, Einav S, Varon J. Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. Crit Care. 2016;20:135.
8. Scalco RS, Gardiner AR, Pitceathly RD, Zanoteli E, Becker J, Holton JL, Houlden H, Jungbluth H, Quinlivan R. Rhabdomyolysis: a genetic perspective. Orphanet J Rare Dis. 2015;10:51.
9. Moratalla MB, Braun P, Fornas GM. Importance of MRI in the diagnosis and treatment of rhabdomyolysis. Eur J Radiol. 2008;65:311–5.
10. Kim JH, Kim YJ, Koh SH, Kim BS, Choi SY, Cho SE, Song JH, Kim CH, Lee KH, Cho SG. Rhabdomyolysis revisited: detailed analysis of magnetic resonance imaging findings and their correlation with peripheral neuropathy. Medicine. 2018;97(33):e11848.
11. Shapiro ML, Baldea A, Luchette FA. Rhabdomyolysis in the intensive care unit. J Intensive Care Med. 2012;27:335–42.
12. Mijzen EJ, Jacobs B, Aslan A, Rodgers MG. Propofol infusion syndrome heralded by ECG changes. Neurocrit Care. 2012;17:260–4.
13. Otterspoor LC, Klakman CJ, Cremer OL. Update on the propofol infusion syndrome in ICU management of patients with head injury. Curr Opin Anaesthesiol. 2008;21:544–51.
14. Scharman EJ, Troutman WG. Prevention of kidney injury following rhabdomyolysis: a systematic review. Ann Pharmacother. 2013;47:90–105.
15. Huerta-Alardin AL, Varon J, Marik PE. Bench-to-bedside review: rhabdomyolysis—an overview for clinicians. Crit Care. 2005;9:158–69.
16. Zimmerman JL, Shen MC. Rhabdomyolysis. Chest. 2013;144:1058–65.
17. Nielsen JS, Sally M, Mullins R, Slater M, Groat T, Gao X, de la Cruz JS, Ellis MKM, Schreiber M, Malinoski D. Bicarbonate and mannitol treatment for traumatic rhabdomyolysis revisited. Am J Surg. 2017;213:73–7.
18. Rosenberg H, Pollock N, Schiemann A, Bulger T, Stowell K. Malignant hyperthermia: a review. Orphanet J Rare Dis. 2015;10:93.
19. Denborough MA, Forster JF, Lovell RR, Maplestone PA, Villiers JD. Anaesthetic deaths in a family. Br J Anaesth. 1962;34:395–6.
20. Strazis KP, Fox AW. Malignant hyperthermia: a review of published cases. Anesth Analg. 1993;77:297–304.
21. Forrest KM, Foulds N, Millar JS, Sutherland PD, Pappachan VJ, Holden S, Mein R, Hopkins PM, Jungbluth H. RYR1-related malignant hyperthermia with marked cerebellar involvement—a paradigm of heat-induced CNS injury? Neuromuscul Disord. 2015;25:138–40.
22. Zaharieva IT, Sarkozy A, Munot P, Manzur A, O'Grady G, Rendu J, Malfatti E, Amthor H, Servais L, Urtizberea JA, Neto OA, Zanoteli E, Donkervoort S, Taylor J, Dixon J, Poke G, Foley AR, Holmes C, Williams G, Holder M, Yum S, Medne L, Quijano-Roy S, Romero NB, Fauré J, Feng L, Bastaki L, Davis MR, Phadke R, Sewry CA, Bönnemann CG, Jungbluth H, Bachmann C, Treves S, Muntoni F. STAC3 variants cause a congenital myopathy with distinctive dysmorphic features and malignant hyperthermia susceptibility. Hum Mutat. 2018;39:1980–94.
23. Jungbluth H, Treves S, Zorzato F, Sarkozy A, Ochala J, Sewry C, Phadke R, Gautel M, Muntoni F. Congenital myopathies: disorders of excitation-contraction coupling and muscle contraction. Nat Rev Neurol. 2018;14:151–67.
24. Dlamini N, Voermans NC, Lillis S, Stewart K, Kamsteeg EJ, Drost G, Quinlivan R, Snoeck M, Norwood F, Radunovic A, Straub V, Roberts M, Vrancken AF, van der Pol WL, de Coo RI, Manzur AY, Yau S, Abbs S, King A, Lammens M, Hopkins PM, Mohammed S, Treves S, Muntoni F, Wraige E, Davis MR, van Engelen B, Jungbluth H. Mutations in RYR1 are a common cause of exertional myalgia and rhabdomyolysis. Neuromuscul Disord. 2013;23:540–8.

25. Dowling JJ, Lillis S, Amburgey K, Zhou H, Al-Sarraj S, Buk SJ, Wraige E, Chow G, Abbs S, Leber S, Lachlan K, Baralle D, Taylor A, Sewry C, Muntoni F, Jungbluth H. King-Denborough syndrome with and without mutations in the skeletal muscle ryanodine receptor (RYR1) gene. Neuromuscul Disord. 2011;21:420–7.
26. Durham WJ, Aracena-Parks P, Long C, Rossi AE, Goonasekera SA, Boncompagni S, Galvan DL, Gilman CP, Baker MR, Shirokova N, Protasi F, Dirksen R, Hamilton SL. RyR1 S-nitrosylation underlies environmental heat stroke and sudden death in Y522S RyR1 knockin mice. Cell. 2008;133:53–65.
27. Larach MG, Localio AR, Allen GC, Denborough MA, Ellis FR, Gronert GA, Kaplan RF, Muldoon SM, Nelson TE, Ording H, et al. A clinical grading scale to predict malignant hyperthermia susceptibility. Anesthesiology. 1994;80:771–9.

Chapter 11
Emergencies in Idiopathic Inflammatory Myopathies

Hannah A. W. Walter, Stefanie Glaubitz, Jens Schmidt, and Anneke J. van der Kooi

Introduction

Case Vignette 1

A 47-year-old, previously healthy woman presented with progressive weakness, myalgia and fatigue which developed over a period of 3 weeks. Because of a hyperCKaemia of 4000 IU/L, the patient was admitted to the hospital. On admission, physical examination showed skin involvement with thoracic rash, other skin changes were not observed. On neurologic examination, she had no signs of weakness. Six days later, generalized muscular weakness with a muscle strength of MRC 3/5 of the upper limbs and MRC 2/5 of the lower limbs was present. Especially the neck flexors and the pharyngeal muscles showed very rapid, progressive weakness, which resulted in dysphagia and required insertion of a gastric feeding tube 10 days after hospital admission. She also developed dyspnea, possibly due to respiratory failure, and received mechanical ventilation. Because of slow recovery and complications like anemia and pneumonia, the patient received a tracheostomy and PEG tube insertion. Because of impaired mobility, she received heparin to prevent thrombosis.

Diagnostic tests included an EMG, which showed myopathic changes, while neurography was normal. CK was elevated to 15,000 IU/L. The myositis-specific antibody NXP2 and the myositis-associated antibody Ro52

H. A. W. Walter · A. J. van der Kooi (✉)
Amsterdam University Medical Centres, location Academic Medical Centre, Amsterdam, the Netherlands
e-mail: a.w.walter@amsterdamumc.nl; a.j.kooi@amsterdamumc.nl

S. Glaubitz · J. Schmidt
University Medical Center Göttingen, Göttingen, Germany
e-mail: stefanie.glaubitz@med.uni-goettingen.de; j.schmidt@med.uni-goettingen.de

M. Damian, M. de Visser (eds.), *Emergencies in Neuromuscular Disorders*,
https://doi.org/10.1007/978-3-030-91932-0_11

were positive. Muscle biopsy displayed necrotic fibers and inflammatory infiltrates. ILD or cardiomyopathy were not present. No infectious or malignant causes could be identified.

Based upon proximal weakness with atypical skin involvement, inflammation in the skeletal muscle biopsy and NXP2 antibodies, she was diagnosed with dermatomyositis.

The patient received intravenous methylprednisone 1000 mg/day for 3 days, followed by a maintenance dose of 80 mg prednisone per day for 4 months. Due to a severe progression despite treatment, an add-on treatment with intravenous immunoglobulin at a total dose of 2 g/kg, divided over the course of 5 days was initiated, 1 week after the intravenous methylprednisone therapy.

After stabilization and treatment of pneumonia and heparin-induced thrombocytopenia, the patient received rehabilitation treatment. At the end of the rehabilitation program which lasted three-and-a-half months, gastric tube and tracheostomy could be removed. Therapy with azathioprine was started and prednisolone was slowly reduced. Three years later, she was still stable with azathioprine, low-dose prednisone and intermittent IVIG at a dose of 30 g every 6 weeks. However, mild weakness of hip flexion and arm abduction remained. No tumor was found on repeated assessment including whole body scans.

Learning Points

- **Muscle weakness in myositis can progress very fast and may involve the diaphragm muscles as well, causing respiratory distress and necessitating mechanical ventilation.**
- **Dysphagia can cause risk of choking and extensive weight loss. To prevent an aspiration pneumonia or malnutrition, a naso-gastric feeding tube or PEG tube may be required.**

Idiopathic Inflammatory Myopathies

Idiopathic inflammatory myopathies (IIMs), in short, myositis, are a group of acquired myopathies with an autoimmune origin. Multiple organs, such as lung, heart, and skin can be involved. The standard treatment includes immunosuppression, except for inclusion body myositis (IBM), which is mostly treatment refractory. IIMs are typically characterized by subacute onset of muscle inflammation, resulting in symmetrical muscle weakness of the proximal muscles of arms and legs. Weakness of neck flexors and dysphagia due to involvement of the

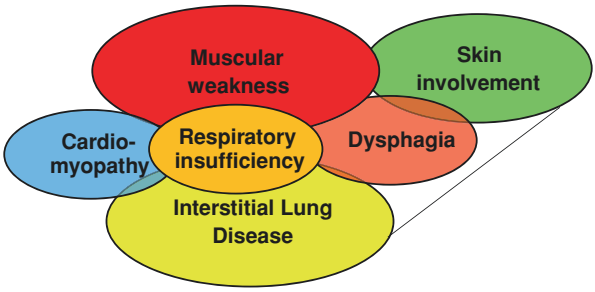


Fig. 11.1 Organ manifestations in myositis: Symptoms in myositis may vary between minor complaints and emergency requiring illness, including muscle weakness with impaired ambulation and diaphragm involvement resulting in respiratory failure. Interstitial lung disease and cardiomyopathy can cause life-threatening conditions. Dysphagia may result in severe weight loss and choking, with the risk of aspiration pneumonia. Skin involvement can result in severe ulcers

pharyngeo-oesophageal muscles is often present. An exception is IBM, which is characterized by a slow onset and slow progression, as well as cases without muscle weakness (i.e. amyopathic dermatomyositis). Emergencies in myositis may be related to rapid progression of weakness, severe skin involvement, cardiomyopathy, dysphagia, interstitial lung disease (ILD), or concomitant cancer (Fig. 11.1). Symptoms and disease progression of IIMs are very variable, which may cause difficulties in diagnosis and treatment.

Over 25 different myositis-specific (MSA) and myositis-associated antibodies (MAA) have been identified during the last decades.

This chapter provides an overview of the diagnosis and pathogenesis of myositis and its associated emergencies. The appropriate management of emergencies will be presented.

The classification of IIMs remains a subject of debate. In this chapter, we chose to use a comprehensive classification of IIM with the following distinct subgroups [2–4]:

- Dermatomyositis (DM) and juvenile dermatomyositis (JDM)
- Anti-synthetase syndrome (ASS)
- Overlap myositis (OM)
- Immune-mediated necrotizing myopathy (IMNM)
- Polymyositis (PM)
- Inclusion body myositis (IBM)

Polymyositis (PM) is a contested entity within the group of IIMs [5, 6]. It is the rarest form of myositis and currently considered a diagnosis of exclusion of all subsequent forms of myositis. In addition, immune checkpoint inhibitors-related myositis and cancer-associated myositis (CAM) will be discussed.

Epidemiology and Clinical Presentation of Idiopathic Inflammatory Myopathies

Epidemiology

IIMs are a group of rare diseases, although they account for the most common cause of acquired muscle diseases in adults [7]. The overall estimated prevalence is 14 cases per 100.000 inhabitants (range 2.4–33.8) [8]. The incidence is estimated at 7.98 cases per million per year (range 1.16–19).

For adults, the peak age of onset is between 30 and 50 years of age. IIMs occur more commonly in women than in men (ratio F/M 2:1), with the exception of IBM. The estimated annual incidence for children is 2.5 to 4.1 cases per million per year [7]. The peak incidence for JDM is at the age of 7 [7]. The prevalence of IBM is estimated at 1.85 cases per million per year, and the incidence at 2.01 cases per 100.000 per year [8]. IBM occurs more commonly in men than in women (ratio M/F 3:2) and predominantly Caucasian males are affected [7, 9]. Disease onset in IBM is mainly above 50 years of age.

Clinical Presentation and Ancillary Investigations

Muscle Involvement

Clinically, IIMs are characterized by proximal, symmetrical muscle weakness in limb-girdle pattern, which develops sub-acutely (weeks to months) in DM and ASS and frequently faster (within a week) in IMNM. Mostly, proximal leg muscles show more weakness compared to the proximal arm muscles. There are some exceptions, since DM is associated with anti-MDA5 antibodies and ASS may be amyopathic. Due to muscle weakness, patients will increasingly experience problems in climbing stairs, rising from a (deep) chair, walking and lifting objects, and performing overhead activities such as combing their hair [10, 11]. Myalgia and muscle tenderness are common. Neck flexor muscles can be involved in all subtypes, resulting in problems holding up the head (head drop). The involvement of oral, pharyngeal, and proximal and distal oesophageal muscles may result in dysphagia, with sometimes excessive weight loss and the risk of choking and concomitant risk of aspiration pneumonia [12]. The vocal cords may be affected, resulting in a soft voice or hoarseness.

IBM develops in a different manner: this subtype has a gradual onset and is slowly progressive over years, and characterized by asymmetric weakness of predominantly quadriceps and deep finger flexor muscles. However, IBM patients can also present with solitary dysphagia or asymmetrical weakness of distal leg muscles. In daily life, patients with IBM often have difficulties in buttoning or holding objects due to deep finger flexor involvement [10]. Muscular atrophy is commonly observed in finger flexors and quadriceps muscles.

As a result of muscle damage, the serum creatine kinase (CK) activity is typically highly elevated during acute phases of all IIMs, especially in IMNM. In IBM and in a proportion of cases of DM, the CK elevation is usually <10–15 times the upper limit of normal. Furthermore, serum levels of ASAT, ALAT, LDH, creatine, and aldolase can be elevated. Additionally, muscle imaging such as muscle magnetic resonance imaging (MRI) can detect oedema, or replacement of muscle tissue by fat in the affected muscles, and may identify a suitable location for muscle biopsy. Further details about diagnostic tests are displayed under section 'Diagnosis and Classification of Idiopathic Inflammatory Myopathies'.

Skin Abnormalities

In DM, skin changes can either precede or accompany muscle weakness. In some patients, abnormalities remain restricted to the skin, the so-called amyopathic DM. Three abnormalities form the main characteristics for DM, and include heliotrope (purple) periorbital oedema, 'Gottron's papules' and 'Gottron sign', which are firm papules with a silvery superficial layer, which can be mistaken for psoriasis, or red rashes at the extensor side of the metacarpophalangeal and interphalangeal joints (Figs. 11.2, 11.3, and 11.4). Other typical abnormalities include erythema on the chest ('V-sign'), shoulders, arms, and upper back ('shawl-sign') or over the outside of the hip ('holster sign'). The skin of the fingertips may be cracked, and cuticles swollen, irregular, overgrowing the nails and in black people they are often darkened. Patients, especially children, with anti-NXP2 antibodies often display subcutaneous calcifications (see below), which may extrude and cause infections or ulcera [11]. Atypical skin abnormalities may be present in anti-MDA5 DM, including palmar papules, ulceration of the fingers and around the elbow and mechanic's hands (claimed to be characteristic for ASS, but also found in TIF1 gamma positive DM patients) may occur. Skin changes in DM may overlap with skin changes caused by connective tissue diseases such as systemic sclerosis or rheumatoid arthritis. In ASS, typical skin abnormalities include mechanic's hands, cracked skin, or fissures at the lateral side of the index finger at thumb side. Of note, Gottron's sign and papules are found in 27% of the ASS patients, heliotrope rash in 14%, and both in 6% [13]. Furthermore, Raynaud's phenomenon may be present in patients with ASS or OM.

Calcinosis may be a skin manifestation of DM. Calcinosis is defined as a dystrophic calcification in injured tissue with normal serum calcium and serum phosphate levels [14]. It can occur in multiple forms, including circumscribed calcinosis (a superficial plaque or nodule), and tumoral calcinosis which are bigger and occur in deeper tissues. Calcinosis can also occur in tendons and lead to contractures, pain, and immobility [15].

Calcinosis is more common in JDM than in adult DM, occurring in about 50% of patients with JDM and 6% of the adult patients [16]. Risk factors are NXP2 and Pm-Scl antibodies, inadequate and delayed therapy as well as chronic and severe disease progression.

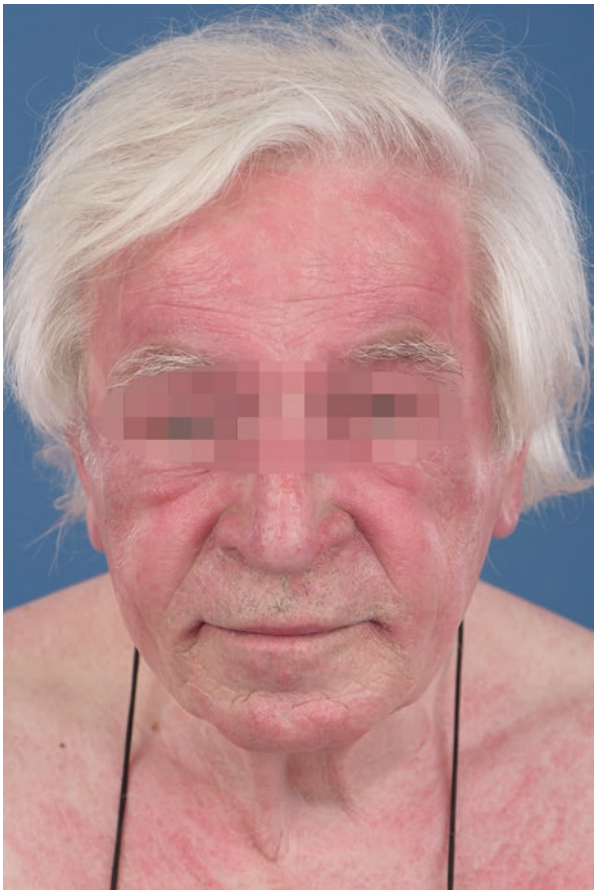


Fig. 11.2 Heliotrope erythema in a dermatomyositis patient

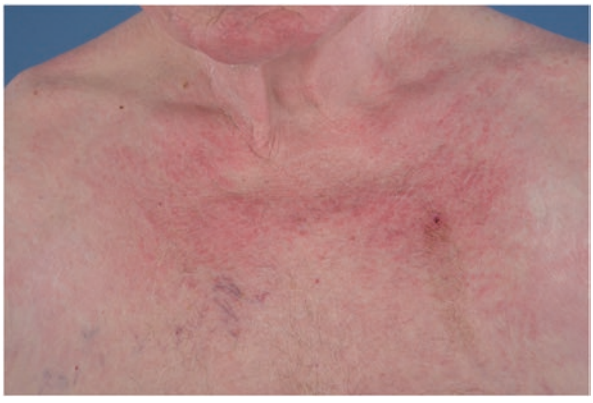


Fig. 11.3 Erythema on the chest of a dermatomyositis patient, so-called 'V-sign'

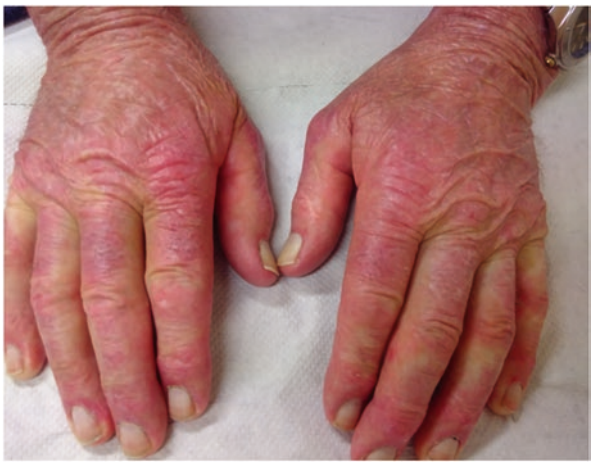


Fig. 11.4 Gottron's papules on the metacarpophalangeal and interphalangeal joints of a dermatomyositis patient

Respiratory Failure

In ASS, MDA5-associated DM, and OM, patients often experience dyspnoea. Respiratory failure has also been described in IMNM and immune checkpoint inhibitor associated myositis [17]. This may be caused by ILD, myocarditis or respiratory muscle involvement. Acute respiratory distress (ARD) that needs ventilatory support on ICU can be the initial presentation of ASS or anti-MDA5 DM [18]. The diagnosis can be very challenging, especially when muscle weakness and cutaneous manifestations are lacking. In this specific patient group with ARD, the majority (96%) shows bilateral, predominantly lower condensation on chest X-ray. On pulmonary CT, around 75% shows ground glass attenuation and alveolar condensation, and almost 40% shows lung fibrosis and mediastinal lymphadenopathies [18].

Dysphagia

Dysphagia is a clinical sign that is often present in IIM [19] and affects on average 40% of the patients with DM, ASS, OM and IMNM [16]. Dysphagia in IBM is more frequent (60%) and it may be the initial symptom [20]. The pharynx and upper oesophageal sphincter are affected as these consist of skeletal muscle [21]. Motility disturbances of the distal oesophagus (which contains predominantly smooth muscle rather than skeletal muscle) causes dysphagia in two-third of the myositis patients [12]. Recent studies in IBM indicate a reduced upper oesophageal sphincter opening, possibly caused by fibrosis of crico-pharyngeal muscle and weakness of suprahyoid muscles. Early symptoms include problems with clearing one's throat with solids and later liquids, coughing during eating and a prolonged duration of food intake, whereas choking or unwanted weight loss are later symptoms [3].

Other symptoms include hoarseness. Dysphagia increases the risk of aspiration pneumonia and death and, therefore, swallowing function should be tested and one should specifically ask for symptoms of dysphagia (there are excellent scales, like EAT-10). Two questions reliably predict impaired swallowing: 'Does food get stuck in your throat' and 'Do you have to swallow repeatedly in order to get rid of food'. [22] Diagnostic tests such as video fluoroscopic swallow studies (VFSS) and fibre-optic endoscopic evaluation of swallowing (FEES) can confirm the diagnosis [23]. Real time MRI or manometry may have future potential [17], but—so far—are mostly considered beyond clinical practice. The presence of Mi-2, TIF1-γ, NXP2, U1RNP, and PM-Scl antibodies is strongly associated with the presence of dysphagia, but it may also develop in absence of antibodies [24].

Systemic Symptoms

Fever, fatigue, arthralgia, or arthritis may occur in all subtypes, but are more common in ASS and OM [16]. Arthralgia or arthritis is the presenting symptom in 21–35% of ASS patients [25]. Within the ASS spectrum, arthritis is most common in anti-Jo1 positive patients; 61% show arthritis or arthralgia at onset, and this is mostly poly-articular and symmetrical [26]. Subluxation arthropathy has been described in about one-fifth of anti-Jo1 ASS patients. Radiographic damage, such as bone erosion and joint narrowing, may be present in wrist, metacarpophalangeal joints, proximal interphalangeal joints and distal interphalangeal joints, and are more common in patients with an overlapping syndrome of rheumatoid arthritis and ASS [25].

Cardiac Involvement

Cardiac manifestations of IIM develop in the coronary arteries, epicardium, myocardium as well as the endocardium. The myocardium is mostly affected. Myocarditis may subsequently evolve into cardiomyopathy, cardiac conduction system and automatism disorders and supra- and ventricular arrhythmias [27].

According to the Euromyositis registry, 9% of the IIM patients suffer from cardiac involvement, including pericarditis, myocarditis, arrhythmia, or sinus tachycardia [16]. However, this may be an underestimation since inflammation of cardiac muscle was detected in 25–30% of patients with IIM in post-mortem studies [27].

Elevated cardiac enzymes (troponin T and troponin I) indicate myocardial damage, but have divergent specificity and sensitivity. A cohort of 123 IIM patients (no IBM) was screened on cardiac involvement via troponin testing and compared to the IMACS' cardiac domain of the Myositis Disease Activity Assessment Tool (MDAAT) [28]. Troponin T showed a sensitivity of 83% and specificity of 46%, whereas troponin I had a sensitivity of 44% and a specificity of 95%. Prospective predictive values were 21% and 62%, respectively. Troponins may originate from regenerating skeletal muscle, and therefore serum elevation can erroneously point to myocardial involvement. Cardiac troponin-I appears to be more specific for

myocardial damage than troponin T [29]. Troponin T assessment may offer guidance for myocarditis screening.

Elevated NT-pro-BNP is correlated with reduced cardiac function in IIM [30]. The presence of anti-Ro and anti-SRP antibodies is suggested to be associated with cardiac complications [27].

Presentation in Children

Clinical features of juvenile IIMs (JIIMs) generally correspond to the clinical presentation in adults, however there are several important differences [31]. In young children, muscle weakness is noticed by changes in physical function (i.e. difficulties in climbing stairs and getting up from the floor), as children are less likely to complain about weakness. As in adults, Gottron papules and heliotrope erythema are pathognomic features for juvenile DM. Furthermore, erythema on the extensor surfaces of the hands, forearms, thighs or feet is common. V-sign and shawl sign are less common than in adults. Other possible skin lesions are skin ulceration, associated with more severe disease, and abnormalities of the nail folds. Calcinosis is found in approximately 40% of children, often presenting with superficial ulceration and drainage of white material.

Extra-muscular, non-cutaneous manifestations are arthritis, dysphagia or dysphonia, and pulmonary involvement. Although less common than in adults, ILD (affecting 3–8% of patients), can cause progressive pulmonary fibrosis. A rare feature, but of great clinical significance is gastrointestinal involvement. It may be caused by vasculitis in the bowel, can be associated with skin ulcers, and may cause massive bleeding or perforation and is therefore important.

Immune-mediated necrotizing myopathy can also occur in children. Anti-SRP-associated necrotizing myopathy presents at later age (median 15 years) than the other JDM subtypes (median 7 years), and mostly in black children (83%). Other than in adult patients the onset speed can be insidious (33%) or slow in 3–6 months (17%) [32]. It may therefore be difficult to distinguish it from a muscular dystrophy. ASS can also occur in children, albeit rarely [33].

Anti TIF-1-γ and anti-NXP2 antibodies can be found in children, but are not associated with malignancy. Presence of TIF-gamma antibodies in children is associated with chronic disease course and lipodystrophy [34].

Pathophysiology

IIMs are known to be autoimmune-mediated diseases. The exact pathogenic cause and factors triggering the immune response in myositis remain unknown. Many studies have unravelled individual aspects of the pathophysiology such as antigen presentation and the myogenic concert of dendritic cells (DCs), T-cells, B cells and muscle fibres.

Dermatomyositis

From histological studies, it appears that CD4+ T-cells and B-cells play a main role in DM [35]. One of the main components of the pathophysiology is as yet unidentified antibodies against endothelial cells with subsequent activation of the complement membrane attack complex C5b-9 [36]. This leads to cell damage and reduced density of endomysial capillaries, ischemia, and muscle fibre destruction resembling micro-infarcts [37]. The resulting perifascicular atrophy is most prominent at the periphery of muscle fascicles. Activation of membrane attack complex is associated with release of pro-inflammatory cytokines which contribute towards migration of B-cells, CD4+ T-cells, and plasmacytoid dendritic cells to the perimysial and endomysial space. The perifasicular muscle fibres are in a state of remodelling, regeneration and immune activation—by expressing major compatibility complex (MHC) class I and releasing pro-inflammatory chemokines [38]. However, there is evidence, that the perifascicular atrophy is not caused by the impaired blood supply [39]. An alternate explanatory approach for the pathogenesis is based on the role of type 1 interferons. In comparison to all other types of IIM, DM shows an overexpression of type 1 interferon–inducible transcripts and proteins in muscle, like MxA and ISG15. The inappropriate intracellular production of type 1 interferon–inducible molecules leads to cell injury and atrophy in DM [40]. Furthermore, DM can be caused by cancer-induced autoimmunity. In particular, NPX-2 and anti-TIF1-γ show the strongest association with cancer in DM [41]. T-cell response and antibodies against new tumour antigens cross-react with antigens in muscle and lead to the autoimmune phenotype. It is shown, that regenerating myoblasts in affected muscles in myositis express higher levels of these antigens than healthy controls [42]. Presence of anti-TIF1-γ or anti-NXP2 is associated with an increased risk for cancer in DM [43].

Other Subtypes

In contrast, CD8+ T-cells play a predominant role in PM and IBM. MHC-I is upregulated at the cell surface of healthy appearing muscle fibres, probably in reaction to cytokine release from activated T-cells. Antigen-presenting dendritic cells contribute to endomysial activation of CD8+ T-cells, which form immunological synapses with muscle fibres via CD8 and MHC-I. As a result, CD8+ T-cells release cytotoxic molecules—perforin and granzyme B—into the muscle fibres. The subsequent muscle fibre necrosis adds to the inflammation by recruiting more lymphocytes and dendritic cells, thus, functioning as a vicious cycle that can maintain myoinflammation [35]. In addition, a crucial role of B-cells in the pathogenesis of IIM is evidenced by endomysial production of B-cell activating factor, B-cells and plasma cells in muscle tissue, antibody production, and endomysial B-cell-maturation in part within muscle itself [44, 45].

Antibodies. Antibodies such as histidyl t-RNA synthetases (Jo-1, PL-7, PL-12, EJ) which are associated with anti-synthetase syndrome, can be expressed in different tissues, including muscles and lungs [46]. These antibodies induce the activation of innate immune cells and act as chemo-attractants, inducing the migration of immune cells into the lung.

In immune-mediated necrotizing myopathies, SRP and HMGCR antibodies lead to a different disease activity and are directly linked to the myositis phenotype [47]. Muscle biopsies of anti-SRP and anti-HMGCR positive patients contain necrotic fibres, with numerous macrophages and sparse lymphocytes. Additionally, it was shown that the classical complement pathway was activated and sarcolemmal C5b-9 deposits correlated with necrosis of the muscle cells [48].

Among the inflammatory findings, a degenerative mechanism plays an important role in IBM. In the muscle biopsy, β-amyloid deposits and rimmed vacuoles can be found. The etiology of inflammation and degeneration is so far unresolved. It is currently assumed that an initial inflammatory trigger can cause production of β-amyloid. In this context of inflammatory/degenerative cross-talk, muscle fibres develop intracellular cell stress and may become irreversibly damaged [49–51].

Diagnosis and Classification of Idiopathic Inflammatory Myopathies

The diagnosis of IIMs is based on a combination of clinical signs and symptoms, laboratory findings, MSA and MAA, results of imaging (MRI or ultrasound), and histological findings [2, 3, 52–54].

Dermatomyositis is characterized by muscle weakness in proximal more than in distal muscles and in neck flexors more than in neck extensors, in combination with a typical skin rash, in particular Gottron papules/sign or heliotrope erythema. CK is often elevated, but may be normal. Various MSA are typical for DM (e.g. MDA5 and NXP2-antibodies, see below in section Diagnostic Tests). Muscle biopsy changes include perivascular inflammation and perifascicular atrophy [52]. Sarcoplasmic MxA (myxovirus resistant A) expression in the cytoplasm of myofibres is a new immunohistochemical marker for the diagnosis of DM, indicating interferon type 1 pathology. Sarcoplasmic MxA expression has a sensitivity and specificity of 71% and 98%, respectively, as compared to 47% sensitivity and 98% specificity for perifascicular atrophy [55].

Anti-synthetase syndrome is defined by clinical features that include a combination of myositis, ILD, and non-erosive arthritis (considered the ‘triad’, and Raynaud’s phenomenon, fever, and/or mechanic’s hands, in the presence of one or more AS-related antibody). Arthritis or ILD are often the presenting symptoms [56]. Within the IIM spectrum, patients with anti-MDA5 or ASS antibodies are significantly at higher risk to develop ILD [24]. The presence of an antibody may favour early detection of ILD, although antibody-negative patients can also develop ILD. A

diagnosis of ILD in patients with IMM is associated with higher morbidity and mortality compared to patients without ILD, and patients positive for anti-MDA5 have an even worse prognosis compared to ASS [18, 57].

Overlap myositis is nowadays considered a distinct subtype, defined as patients fulfilling criteria for IIM plus criteria for another CTD, such as systemic sclerosis, systemic lupus erythematosus, mixed connective tissue disease, rheumatoid arthritis, and primary Sjögren's syndrome [3, 58]. The presence of autoantibodies such as anti-SSa, anti-SSb, anti-Ro52, anti-U1-nRNP, anti-PM-Scl, and anti-Ku suggests an overlap syndrome and these patients may develop a CTD during the disease course [59].

Immune-mediated necrotizing myopathy is characterized by severe muscle weakness, very high serum CK, activity, and muscle biopsy showing necrotic muscle fibres with a diffuse pattern in different stages of necrosis with regenerating fibres and without a specific, primary immune cell infiltration. When anti-HMGCR antibodies are present, previous statin use is found in about half of the patients, but the antibody also frequently occurs in statin-naïve patients [60].

Inclusion body myositis is a slowly progressive disease with involvement of the knee extensors more than hip flexors and finger flexors more than shoulder abduction, and muscle biopsy showing endomysial inflammatory infiltrates and, at the same time, rimmed vacuoles and protein accumulations [53]. It was shown that the combination of finger flexor or quadriceps weakness, endomysial inflammation, and either invasion of non-necrotic muscle fibres or rimmed vacuoles, has a 90% sensitivity and 96% specificity for IBM [61]. The diagnosis may be supported by the presence of anti-cN1A (anti-cytosolic 5′-nucleotidase 1A) antibody IBM, but a large study demonstrated a sensitivity of 30–50% and a low predictive value [62]. Subsequent studies showed that anti-cNA1 antibody is present in systemic autoimmune diseases as well, even in absence of any muscle impairment [63].

Juvenile myositis affects children and adolescents. The diagnosis can (mostly) be based on clinico-pathological features and antibodies, and the same diagnostic criteria as adults can be used [54]. MSA's and MAA's in children represent the same subgroups compared to adults, but the prevalence is different.

The most common form is JDM, representing approximately 80% of juvenile myositis cases [64, 65]. In 70% of the patients with JDM, antibodies are present. Juvenile OM represents the second largest group, occurring in 6–11% of the juvenile myositis patients. The smallest group is juvenile PM (IMNM (SRP, HMGCR) and ASS), which is seen in 4–8% of the juvenile myositis cases. As juvenile myositis is often misdiagnosed in patients who actually have non-inflammatory myopathies, particularly muscular dystrophies, a muscle biopsy is often required for diagnosis [66].

Polymyositis (PM) is a contested entity within the group of IIMs. It is the rarest form of myositis and currently considered a diagnosis of exclusion of all subsequent forms of myositis [3].

One should be aware that IIMs are a spectrum of diseases, hence one patient may present with extensive muscle weakness, while another manifests with predominant dyspnoea due to ILD.

Diagnostic Tests

Unfortunately, no gold standard exists to establish the diagnosis of IIMs. To establish a valid diagnosis, a patient suspected of an IIM should undergo extensive muscle strength testing, laboratory testing, including at least CK, ASAT, ALAT, LDH, aldolase, and troponin T.

Muscle imaging can be performed either by muscle ultrasound or by muscle MRI. Muscle ultrasound can detect structural muscle changes, such as oedema, atrophy, and fibrosis and has proven to be useful in juvenile inflammatory myopathies but its value in the diagnosis of adult IIMs remains unclear [67, 68]. A whole body MRI of the muscles can detect muscle oedema (inflammation) and fatty replacement of muscle [69].

Whole body muscle MRI should be preferably performed to guide the biopsy by detecting localized muscle inflammation in order to decrease the chance of a false negative biopsy [70]. Since the specificity of individual MSA's is unknown, a muscle biopsy should remain the gold standard in order to achieve a correct diagnosis. Muscle biopsy is of great importance, not only because the classification criteria [52] rely on histological features, but also because some congenital, dystrophic, toxic, or metabolic myopathies can be mistaken for IIM. There are some exceptions: when DM is suspected and classical skin abnormalities are present, and when anti-Jo1 or other tRNA-synthetases antibodies are present [54].

In addition, EMG usually shows myopathic changes and is useful to differentiate between myopathies and neuropathies [71]. However, EMG changes are non-specific and do not help to differentiate between the different myopathies.

Autoantibody testing can be performed with a myositis line blot with additional testing of anti-HMGCR and/or anti-cN-1A antibodies. In 70% of the IIM patients, an autoantibody, either MSA or MAA, can be detected in the serum; in 50% of the cases this is a MSA [72]. MSA's are associated with rather well defined subtypes (DM, ASS, IMNM) and include MDA5, NXP-2, Mi-2, TIF1γ, SAE1, Jo-1, PL-7, PL-12, OJ, KS, ZO, EJ, SRP, HMGCR and cN1A. MAA's include PM-Scl, Ku, U1RNP, U1/U2RNP, U3RNP, Ro52 and Ro60, and are not specific for myositis and may occur within all IIM subtypes, and in particular in OM. Existence of an antibody simplifies the differentiation of myositis subtypes, in particular when typical clinical and histological findings are present (Table 11.1).

If ILD is suspected, either because clinical symptoms are present or antibodies are associated with a risk of ILD, pulmonary function tests including diffusion capacity should be performed and, in most cases, also a pulmonary high-resolution computer tomography (CT) should be conducted.

When cardiomyopathy is suspected, cardiac imaging can confirm the diagnosis. Cardiac MRI (cMRI) is recommended as the primary non-invasive method [73]. An echocardiography can provide useful information, but the findings lack specificity. More information can be found in the chapter 'Management of cardiac involvement'.

Table 11.1 Classical clinical features of idiopathic inflammatory myopathies, adapted from Rietveld et al. [1]

Disease	Demographic features	Clinical key features	Autoantibodies	Possible clinical features
Dermatomyositis	All ages. Peak incidence adults 30–50 years. 7 years in children. Female preponderance.	Symmetrical weakness. Proximal > distal weakness. Neck flexor > neck extensor weakness. Dysphagia. Subacute onset. Classic dermatomyositis rash.	MDA5	• Amyopathic/pauci-myopathic. • Rapidly progressive severe interstitial lung disease. • Classic and atypical dermatomyositis rash, mechanic's hands, palmar papules, digital ulcers, panniculitis. • Polyarthritis. • High prevalence in East-Asia
			NXP2	• Cancer (adults). • Severe weakness. • Calcinosis and ulceration • Children: vascular involvement.
			MI2	• Severe weakness and high serum creatine kinase. • Classic dermatomyositis rash in light-exposed areas.
			TIF1-γ	• Cancer (adults). • Pauci-myopathic. • Dysphagia. • Classic dermatomyositis rash. • Mechanic's hands • Children: Skin involvement, lipodystrophy, chronic disease course.
			SAE1	• Cancer (Asia). • Amyopathic at onset—Skin symptoms precede weakness. • Dysphagia. • Interstitial lung disease (Asia).
Anti-synthetase and related syndromes	Adolescents/adults.	Symmetric weakness. Proximal > distal weakness. Neck flexor > neck extensor weakness. Dysphagia. Anti-synthetase syndrome triad: • inflammatory myositis • interstitial lung disease (ILD) • arthritis • subacute onset • Mechanic's hands/skin lesions • Fever • Raynaud's phenomenon • Cardiac involvement	Jo1	• Cancer (Asia). • Severe weakness. • Arthritis. • Early treatment with rituximab.
			PL7	• Mild weakness. • Severe interstitial lung disease. • Arthritis.
			PL12	• Cancer (Asia). • Mild weakness • Severe interstitial lung disease
			OJ	• Severe weakness. • Severe interstitial lung disease
			KS	Severe interstitial lung disease
			ZO	Anti-synthetase syndrome
			EJ	Anti-synthetase syndrome
			Tyrosyl	Anti-synthetase syndrome

Table 11.1 (continued)

Disease	Demographic features	Clinical key features	Autoantibodies	Possible clinical features
Overlap myositis	Adolescents/ adults.	Symmetric weakness. Proximal > distal weakness. Neck flexor > neck extensor weakness. Dysphagia. Subacute onset. Association with connective tissue disorder.	PM-Scl (75/100)	• Associated with scleroderma and systemic lupus erythematosus • Remission rare • Cardiac involvement • Interstitial lung disease.
			RNP	• Associated with mixed connective tissue disease.
			Ku	• Associated with systemic sclerosis, systemic lupus erythematosus, Sjögren's syndrome. • Therapy-resistant interstitial lung disease.
			SSA (Ro52, Ro60) and SSB (La)	• Associated with systemic sclerosis, systemic lupus erythematosus, Sjögren's syndrome, anti-synthetase syndrome, rheumatoid arthritis.
Immune-mediated necrotizing myopathy	All ages. Female preponderance	Severe symmetric limb weakness. Axial weakness. Muscle atrophy. Dysphagia. Very high serum creatine kinase (>10× upper limit of normal). Subacute onset.	HMGCR	• Cancer (adults). • Statin exposure. • Intravenous immunoglobulins are preferred over rituximab.
			SRP	• Severe weakness. • Treatment resistance. • Children: Cardiac disease, arthritis; early treatment sometimes favourable outcome. • Early treatment with rituximab or eventually intravenous immunoglobulins.
			Seronegative	• Interstitial lung disease. • Cancer (adults). • Cardiac involvement. • Connective tissue disease
Inclusion body myositis	>60 years. Male predominance. Co-occurrence with autoimmune disease in one-third, e.g. Sjögren syndrome.	(A)symmetric weakness. Selective involvement of quadriceps and deep finger flexors. Dysphagia. Facial/axial/distal leg muscle weakness. Insidious onset.	cN1A	• Involvement of quadriceps, finger flexors, and dysphagia. • Increased mortality • Proximal arm weakness in later stages.

Cancer-Related IIM

Cancer-related myositis (CAM) is defined as the diagnosis of cancer within 3 years of the diagnosis of IIM. Risk factors for CAM are older age, male gender, severe cutaneous lesions like skin necrosis and vasculitis, rapid onset and progression of the symptoms, and laboratory findings like the elevation of erythrocyte sedimentation rate, C-reactive protein, and serum CK [74]. The most common cancers in CAM are tumours of the lung, breast, adenocarcinomas of the cervix, ovaries, pancreas, bladder, colorectal, as well as lymphomas and leukemia [75, 76]. The presence of particular subtypes and antibodies is associated with a high risk on CAM. DM can occur as a paraneoplastic syndrome. In presence of TIF1-γ antibodies, the chance of CAM is 60–80%, and in case of anti-NXP2 24–38%. Although these antibodies may also be present in JDM, there is no relation between JDM and cancer.

Furthermore, patients with IMNM have an increased risk of CAM with an occurrence of malignancy in 29%, either when anti-HMGCR antibodies are present or in seronegative patients, but rarely in patients with anti-SRP antibodies [77, 78].

Myositis with highly elevated serum CK levels and subacute proximal muscle weakness can also be induced by modern cancer therapy, specifically in response to immune checkpoint inhibitors, which aim to enhance the killing of tumour cells by cytotoxic T cells via blocking the PD-L1 interaction with PD-1 or the B7-1/B7-2 interaction with CTLA-4. As immune checkpoint inhibitors are being approved to treat an increasing number of cancers, the number of immune-related serious adverse events such as myositis is expected to increase gradually. The limited data available thus far demonstrate rheumatic serious adverse events at a rate of 4.5–6% [1, 79], and, amongst these, myositis as the second common disease occurring in 0.4–6% [80, 81]. IIM related to ICI can start as early as after the first infusion. Apart from IBM, all entities of IIMs may develop after ICI [80, 81], and myocarditis and myasthenia gravis are frequently reported to be concomitantly induced along with myositis and can be life threatening.

General Principles of Treatment for Inflammatory Myopathies

Corticosteroids are the first-line treatment in all IIMs except for IBM. In IBM, there is no evidence of sustained treatment effects, although a few treatment studies and case reports have shown positive effects on dysphagia in selected patients. Usually, the therapy starts with oral prednisolone (1 mg/kg/day) for 4 weeks with tapering over weeks until a stable disease is achieved. The dosage of prednisolone in maintenance therapy should be as low as possible to avoid any side effects. Oral dexamethasone pulse therapy (six cycles of 40 mg/day for four consecutive days with 28-day intervals) could replace prednisone, and showed less side effects in a randomized controlled trial compared to prednisone [82]. Long-term corticosteroid

therapy should be avoided because of the significant side effects. Timely start of corticosteroid-sparing therapy is advocated. Typical side effects of long-term corticosteroid therapy are diabetes, hypertension, steroid-induced muscle weakness, osteoporosis, adrenal insufficiency, and ophthalmological complications (i.e. cataract and glaucoma) [83].

In a rapidly progressive myositis, methylprednisolone pulse therapy (0.5-1 g/day for 3–5 days) instead of oral corticosteroids is advocated.

If weakness is severe or life-threatening comorbidities such as ILD are present, treatment needs to be intensified by other immunosuppressive or immunomodulating agents (e.g. azathioprin, mycophenolate mofitil, methotrexate, rituximab, intravenous immunoglobulins) (Fig. 11.5). Especially IMNM often responds insufficiently to corticosteroid monotherapy and requires additional immunosuppressants or intravenous immunoglobulins. Most existing therapies are based on expert opinions and case series. The benefit of early treatment of rituximab in refractory DM in comparison to a later initiation of rituximab therapy was tested in a randomized controlled trial and showed no significant differences, albeit further controlled studies are needed [85].

If the clinical condition of the patient allows, one should always try to postpone the start of immunosuppressive therapy until the diagnosis has been confirmed by a muscle biopsy.

Emergencies and their Management

As IIMs are a spectrum of diseases, emergencies can present in many different ways. During the course of IIMs, ILD, malignancy, and cardiac involvement are the three most common causes of death and, thus, these need to be considered during emergency treatment in IIM [27].

Management of Severe Muscle Weakness

The disease course of IIM is often subacute, but particularly IMNM may lead to rapid, severe weakness. Delayed treatment may cause irreversible muscle damage and atrophy, and contractures and disability may ensue. To prevent this, severe muscle weakness needs to be treated quickly and according to an adequate, rigorous treatment escalation scheme. Initial oral corticosteroids are usually complemented early with immunosuppressants such as azathioprine or methotrexate. Add-on treatment with IVIG and escalation treatment with rituximab and other drugs is often required (Fig. 11.5). For anti-SRP as well as anti-HMGCR-associated necrotizing myopathies, the addition of a second agent (such as methotrexate) is required within 1 month if there is no significant improvement [60]. For anti-SRP myopathy rituximab should always be added within 6 months if initial corticosteroids and

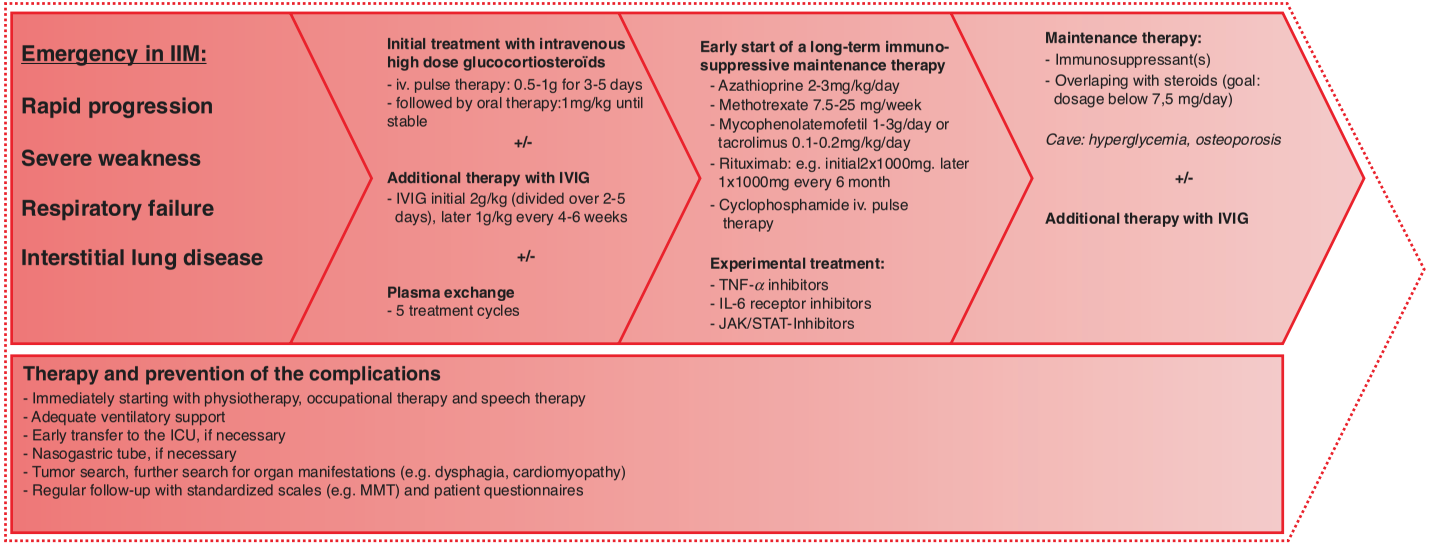


Fig. 11.5 Treatment of emergencies in idiopathic inflammatory myopathy, some elements modified from Glaubitz et al. [84]

immunosuppressants are insufficient. For anti-HMGCR IVIG should be added if other therapeutics are not effective.

The intensive care unit (ICU) team must be reassured that chances for good recovery are high, even with severe prolonged weakness [86]. Timely physiotherapy and suitable splints are very important to avoid disabling contractures.

Management of Severe Dysphagia

Dysphagia is associated with a high risk for choking, concomitant aspiration, pneumonia, and severe weight loss. Immunosuppressive treatment of dysphagia is similar to that of the other manifestations of IIM, albeit in severe dysphagia intravenous methylprednisolone instead of oral corticosteroids should be administered. In addition, nutritional advices and counselling for speech therapy are necessary. When the risk of choking is high, one needs to consider a nasogastric feeding tube until the swallowing function has improved. A PEG tube should be considered if swallowing does not improve.

Dysphagia is a serious symptom because of its high risk for aspiration with subsequent pneumonia, choking hazard and malnutrition. Patients with relevant dysphagia should receive nutritional counseling and, if necessary, a feeding tube.

Management of Interstitial Lung Disease

Case Vignette 2

A 42-year-old Afro-American woman started experiencing malaise, arthralgia and dyspnea 1 month before her visit to the outpatient clinic. Laboratory tests showed anti-SSA, anti-SM and anti-RNP antibodies. A pulmonary CT showed infiltrative abnormalities consistent with an organizing pneumonia and the patient was diagnosed with Sjögren/Mixed Connective Tissue Disease. Prednisone 15 mg/day was started, without improvement of dyspnea and arthralgia. Although a new CT showed a decrease of the pulmonary abnormalities, her dyspnea became incapacitating, with a vital capacity (VC) of 1.2L (42%). She was then referred to the pulmonology outpatient clinic of an academic hospital.

Additional pulmonary diffusion tests showed a diffusing capacity for carbon monoxide of 25% with a total lung capacity of 1.99 l/44%. Ultrasonography of diaphragm showed decreased excursions. Pulmonary CT showed interstitial abnormalities and NSIP (Nonspecific Interstitial Pneumonitis). Laboratory investigations showed a CK of 1800 U/L. A myositis immunoblot

*was performed and showed strongly positive anti-EJ and anti-Ro52 antibodies. Examination at the Neurology outpatient clinic revealed symmetrical proximal muscle weakness of deltoid, biceps brachii, iliopsoas, gluteus medius and maximus muscles (MRC grade 4), and dyspnea. She could only get up from a chair with the support of her arms. Her cuticles were darkened and showed small lesions. A whole-body MRI was performed and showed oedema in the musculus obturatorius, gluteal musculature, hamstrings and gastrocnemius muscles, without atrophy or fatty replacement (*Fig. 11.6*). Because of the combination of proximal muscle weakness, elevated CK, muscle oedema on MRI, positive anti-EJ antibodies and reduced pulmonary function, she was diagnosed with anti-synthetase syndrome.*

Troponine-T was elevated (0.384 μg/L), but cardiac MRI appeared normal. Because of incapacitating ILD and concomitant myositis, she was treated with intravenous methylprednisolone pulse therapy, and continued at home with 20 mg prednisone per day. Tacrolimus was added after three cycles of methylprednisolone, 5 months after disease onset. Clinically she markedly improved and was able to resume normal daily activities. Repeat pulmonary function tests 4 months later also showed improvement.

Learning Points

- **Dyspnea can be the initial symptom of myositis.**
- **Pulmonary function tests and pulmonary CT are needed to establish the diagnosis of interstitial ling disease (ILD).**
- **When ILD is present in addition to myositis, escalation treatment with rituximab or cyclophosphamide is often required in addition to high-dose corticosteroid and other immunosuppressants.**

Early recognition of ILD in IIM patients is the key to prevent irreversible lung damage. Once a patient with IIM is admitted to the (outpatient) clinic and ILD is suspected, the patient should undergo pulmonary function tests including (sitting and supine) vital capacity and diffusion/restriction and/or a HRCT of the lungs to detect interstitial pneumonia.

In case of unknown cause of ARD, broncho-alveolar lavage is not very useful to diagnose ASS or anti-MDA5 IIM, but can be performed to rule out other diagnoses. The presence of increased C-reactive protein, in the absence of increased serum procalcitonine could indicate a non-infectious inflammatory process. Demonstration of MSA using myositis immunoblot may support the existence of a myositis-related respiratory distress.

The poor prognosis of ILD calls for quick and rigorous treatment. Unfortunately, knowledge about immunosuppressant treatment is mostly based on retrospective

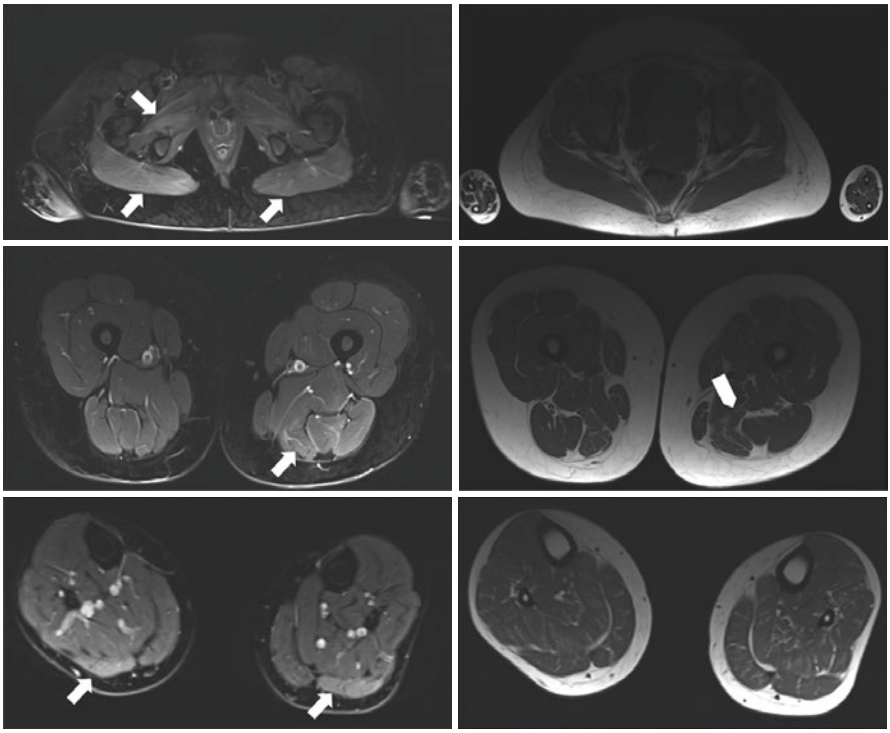


Fig. 11.6 Axial images of lower limbs by T2 Dixon muscle MRI, left images display water-sensitive sequences, and right images fat-sensitive sequences. *Upper level*: white arrows show oedema in gluteus musculature bilaterally (left image). No fatty infiltration was shown (right image). *Middle level*: Oedema in hamstring musculature (left). Starting of fatty infiltration (right). *Lower level*: Oedema in gastrocnemius muscles bilaterally (left image). No fatty infiltration was found (right image)

studies due to the absence of randomized clinical trials. High doses (intravenous) steroids are the cornerstone of the treatment. There is consensus to start a steroid-saving immunosuppressant drug early on. As such, mycophenolate mofetil, tacrolimus, rituximab, or cyclophosphamide can be given [18, 46]. Since methotrexate can occasionally be associated with lung injury (i.e. pneumonitis), this drug should be used with caution in ILD [87]. In addition, plasmapheresis and IVIG can be used. Escalation to rituximab is often required. One should be aware that ILD in anti-MDA5 positive patients can progress very fast and is often refractory to standard immunosuppressive treatment [88]. ILD in ASS often responds to immunosuppressive therapy, but tends to show a recurrent clinical course. Besides drug treatment, referral to a lung transplant specialist is advocated to inform and counsel the patient in a non-urgent setting. If the pulmonary status is severe, a lung transplant specialist should be consulted directly.

Lung transplantation may be an option when, despite immunosuppressive therapies, patients suffer from progressive decline in pulmonary function [89].

Importantly, inflammation of respiratory muscles can cause weakness, and subsequently, dyspnoea and respiratory failure may develop. This needs to be considered during diagnosis of patients with IIM and respiratory failure.

Patients with ASS or presence of MDA5-antibodies are at high risk of developing an ILD, which can be the presenting sign. These patients should undergo regular pulmonary function tests, including sitting and supine VC measurement and diffusion analysis. If abnormalities are found or if clinical symptoms suggest ILD, a HRCT should be performed to confirm the diagnosis. Both, pulmonary fibrosis and ARDS can be the result of ILD with the need of ventilatory support.

Therapy consists of high dose steroids and additional immunosuppressants like mycophenolate mofetil, tacrolimus or rituximab, IVIG or plasmapheresis.

An important differential diagnosis is dyspnea due to diaphragm muscle weakness.

Management of Cardiac Involvement

Electrocardiogram, ultrasonography, and cMRI can show abnormalities in IIM patients. cMRI is suggested to be a useful and non-invasive modality to diagnose and monitor myocardial inflammation in IIM. cMRI detects subclinical involvement of the myocardium in patients with myositis more precisely than cardiac muscle scintigraphy or ultrasonography [90, 91], and contrast-enhanced MRI with gadolinium can differentiate between myocardial infarction and inflammatory tissue from myocarditis [89].

Treatment of myocarditis relates to the underlying pathophysiology [92], i.e., the systemic standard treatment consisting of corticosteroids and other immunosuppressive therapy is applied to treat cardiac involvement. Cyclophosphamide, cyclosporine, methotrexate, and azathioprine have been used as treatment of cardiac involvement, but their efficacy remains unsure since reliable study data are not available. IVIG may be considered, but interdisciplinary care including the cardiologist is necessary to prevent volume overload [91].

Research about the effects of corticosteroid treatment or other treatment options on cardiac complications is limited. No guidelines or randomized trials exist.

Studies show conflicting results: one study showed normalization of heart failure and cMRI abnormalities, but another study reported poor response of ECG abnormalities on corticosteroid treatment [93, 94]. When congestive heart failure is present, traditional cardiac medication including β-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin-II receptor blockers (ARBs) can be used [92].

Cardiac management should consist of immunosuppressive therapies focusing on the underlying cause. Traditional cardiac medication can be used in case of congestive heart failure.

Management of Cancer-Associated Myositis (CAM)

The association between IIMs and cancer is well known and extensively reported. The muscular and skin involvement can be severe and often rapidly progressive. Therefore, early diagnosis of the tumour is important. The standard treatment of myositis is not sufficient in CAM, while treatment of the tumour usually improves the myositis symptoms. Relapse of cancer typically leads to a relapse of CAM [95].

The malignancy should be treated according to specific therapeutic standards (surgery, chemotherapy, radiotherapy, hormone therapy). It was shown that, after tumour surgery, the serum CK activity was reduced significantly and the symptoms had improved [96]. In addition, immunosuppressive treatment is part of the standard care. Glucocorticoids and/or IVIG do not pose a risk of tumour development as side effect. In addition, positive data are available for cyclosporine [97].

Research about malignancy treatment with immune checkpoint inhibitors in patients with concomitant paraneoplastic syndromes is scarce, and should therefore the discussed within a multidisciplinary team.

The overall prognosis of CAM is poor and depends on the nature of the tumour and its progression.

Cancer screening is advocated in all IIM patients except ASS and IBM. In particular, an annual cancer screening for 3 years after diagnosis is recommended in myositis patients with presence of TIF1-γ or NXP-2 antibodies, IMNM with HMGCR antibodies, or without myositis antibodies [98].

Conventional tumour screening is performed by clinical history and physical examination, CT of chest, abdomen and pelvis, urine cytology, faecal occult blood testing, and mammography and gynaecological examination for females [99]. Additional test such as gastroscopy or colonoscopy should be considered, depending on the age, sex, and medical history of the patient. Particularly in patients with TIF1-γ and NXP-2-antibodies or b-symptoms (fever, weight loss, night sweats), a PET/computed tomography should be considered.

In CAM oncological treatment and immunosuppressive treatment should be combined.

Cancer screening is important in patients with high risk of cancer and should consist of clinical history, physical examination, CT of chest, abdomen and pelvis, urine cytology, faecal occult blood testing and mammography and gynaecological examination for females. Additional tests including gastroscopy or colonoscopy need to be decided case-by-case.

Management of Immune Checkpoint Inhibitor-Related Myositis

Treatment should be carefully discussed with the oncologist and rheumatologist or neurologist, balancing quality of life against the priority to control malignancy [78]. If the patient suffers from mild weakness, ICI can be continued and myalgia can be treated with NSAID. Moderate weakness that limits normal activity of daily living (ADL) requires at least a temporary stop of ICI and start of steroids (prednisone 1–1.5 mg/kg). ICI treatment should be stopped permanently if myositis with myocarditis or respiratory impairment occurs. Consider to start steroids intravenously, together with plasmapheresis, IVIG or immunosuppressant therapy (azathioprine, or mycophenolate mofetil, rituximab) [100].

Therapy with immune checkpoint inhibitors can cause all IIM subtypes, except IBM. If the patient suffers from moderate or severe weakness, the ICI therapy has to be temporarily withheld or stopped. The myositis should be treated according to standards of care (Fig. 11.5) including steroids. In patients with organ manifestation (ILD, myocarditis), the ICI therapy should be permanently stopped.

Management of Severe Cutaneous Lesions

To characterize the disease's severity and the activity of the cutaneous lesions, the 'Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI)' can be used. It rates the existence of erythema, scale, erosion, and ulceration in 15

anatomical locations, as well as problems of calcinosis, poikiloderma and rates the severity of alopecia and Gottron papules [101].

The initial therapy of IIM consisting of corticosteroids and immunosuppressants should improve the skin changes and the muscle symptoms [102]. Furthermore, topical calcineurin inhibitors like tacrolimus ointment (0,1%) may lead to improvement of the skin lesions [101]. Antihistamines can help patients with pruritus [103]. In addition to the systemic therapy, topical substances like mild-potency steroids, menthol or pramoxine can ameliorate generalized pruritus [104].

Patients have to use sun protection (sun protection factor (SPF) 50 minimum) and should always avoid direct sunlight [105]. When this therapy fails, a combination of antimalarial medication like hydroxychloroquine and quinacrine can further improve clinical manifestations [103, 106]. However, cutaneous drug eruption is a common adverse event in patients with DM taking antimalarial medication [107]. In case of non-responders, the use of low-dose MTX [108], or mycophenolate mofetil was shown to be effective [109].

In patients with a rapid progression and refractory cutaneous lesions, IVIG can be effective [110]. IVIG has shown beneficial effects on the cutaneous lesions in up to 83% of the patients with DM [111]. Rituximab also displayed beneficial effects regarding refractory skin rashes [112].

Some patients with severe cutaneous lesions do not respond to the standard treatment with corticosteroids, antimalarial medication, various immunosuppressants, and IVIG. For these cases, JAK-inhibitors can be an experimental treatment alternative. JAK inhibitors like tofacitinib affect the 'JAK-STAT pathway' ('Janus kinase' [JAK], 'signal transducer and activator of transcription' [STAT]), which controls the pathways of different cytokines [113]. Several case series suggest a benefit from JAK inhibitors in non-responders with DM and severe cutaneous lesion [114, 115].

Therapy recommendation for calcinosis consists of immunosuppressive therapy in addition to calcium channel blockers and bisphosphonates [116]. Mechanical therapies like surgery in addition to diltiazem [117, 118] or electric shock wave lithotripsy can alleviate the pain and immobility [117].

Skin lesions are typical for dermatomyositis (and a proportion of patients with anti-synthetase syndrome) and usually improve on standard treatment with steroids and other immunosuppressants like azathioprine or methotrexate. Topical therapy and sun protection are of additional value. Antimalarial medication like hydroxychoroquine or a combination with immunosuppressants can be used additionally. Non-responders can be treated with IVIG and JAK-inhibitors can be considered in selected cases.

Conclusion

- Idiopathic inflammatory myopathies should be considered when patients suffer from subacute-onset symmetrical proximal muscle weakness.
- Interstitial lung disease can be the first presenting symptom in anti-synthetase syndrome.
- Dysphagia can be the sole presenting symptom in inclusion body myositis.
- Diagnostic workup of myositis usually relies on a muscle biopsy. Additional tests include MRI, EMG, and autoantibody testing.
- Thorough, efficient workup and detection of organ involvement including heart, oesophagus, and lung are crucial for the therapeutic outcome.
- The most common emergencies in idiopathic inflammatory myopathies are severe muscle weakness, dysphagia, respiratory failure (due to ILD or respiratory muscle weakness), cardiac involvement, and severe cutaneous lesions.
- Idiopathic inflammatory myopathies can be a paraneoplastic syndrome. In case of anti-TIF1γ, anti-NXP, anti-HMGCR antibodies, or seronegative IMNM patients, a malignancy screening is required.
- Standard treatment consists of corticosteroids. Corticosteroid-sparing agents should be added early, depending on the subtype and severity of the symptoms.
- Treatment escalation for a relapse or insufficient response to standard care includes intravenous immunoglobulin (IVIG) and rituximab.

Self Assessment Questions

1. Which out of the following muscles are most frequently involved in an immune-mediated inflammatory myopathy?

   (a) Distal limb muscles.
   (b) Lumbar spine muscles.
   (c) Ocular muscles.
   (d) Pharyngeo-oesophageal muscles. (*)

2. Which of the following extra-muscular manifestations is most frequently associated with an inflammatory myopathy?

   (a) Glomerulonephritis.
   (b) Interstitial lung disease. (*)
   (c) Splenomegaly.
   (d) Thyroid dysregulation.

3. Dysphagia as a presenting symptom is rare in myositis.

   (a) True.
   (b) False. (*)

4. CK remains within the normal range in a considerable part of patients with idiopathic inflammatory myositis.

   (a) True.
   (b) False. (*)

5. Elevation of ASAT, ALAT of LDH indicates liver involvement in immune-medicated inflammatory myopathy (IIM).

   (a) True.
   (b) False. (*)

6. The risk of respiratory failure in inflammatory myopathies is directly related to the degree of muscle weakness.

   (a) True.
   (b) False. (*)

7. Smooth muscle involvement is a common feature of inflammatory myopathy.

   (a) True. (*)
   (b) False.

8. Cardiac muscle involvement is a common feature of inflammatory myopathy.

   (a) True. (*)
   (b) False.

9. Immune-mediated necrotizing myopathy is associated with the use of medications from which group?

   (a) Colchicine derivatives.
   (b) Quinine preparations.
   (c) Statins. (*)
   (d) Steroids.

10. What is currently the gold standard for the diagnosis of inflammatory myopathy?

    (a) Immunoserology.
    (b) MR-imaging.
    (c) Muscle biopsy. (*)
    (d) PET-scanning.

11. Which of the following tumours is the most frequent in cancer-associated myositis?

    (a) Melanoma.
    (b) Ovarial carcinoma. (*)
    (c) Prostate carcinoma.
    (d) Renal carcinoma.

12. Which of the following is currently the first-line treatment in immune-mediated inflammatory myopathy?

    (a) Corticosteroids. (*)
    (b) Immune checkpoint inhibitors.
    (c) Intravenous immunoglobulin.
    (d) Rituximab.

13. Which of the following is more than the others a cause of death in IIMs?

    (a) Generalized vasculitis.
    (b) Interstitial lung disease. (*)
    (c) Side effects of treatment.
    (d) Respiratory insufficiency by muscle weakness.

14. Which of the following specialists should be involved as soon as the diagnosis anti-synthetase syndrome is made in order to improve the outcome?

    (a) A dermatologist.
    (b) An oncologist.
    (c) A pulmonologist. (*)
    (d) A rheumatologist.

15. Interstitional lung disease in association with IIM may lead to lung transplantation.

    (a) True. (*)
    (b) False.

16. Which of the following may be a complication of IIM?

    (a) Endocarditis.
    (b) Pericarditis.
    (c) Myocardial infarction.
    (d) All of them. (*)

17. Cancer-related myositis is defined as the diagnosis of cancer which is timely related with the manifestation of IIM. How should this relation be? The diagnosis is only made if the cancer ……

    (a) was already diagnosed at the time of the first manifestation of IIM.
    (b) is found at the work-up of IIM.
    (c) is found within 1 year after the first manifestation of IIM.
    (d) is found within 3 years after the first manifestation of IIM. (*)

18. Acute respiratory distress that needs ventilatory support in ICU can be the initial presentation of anti-synthetase syndrome.

    (a) True. (*)
    (b) False.

19. Dermatomyositis is the only myositis subtype that can be found in children.

    (a) True.
    (b) False. (*)

20. Cancer-associated myositis is only found in the subgroup dermatomyositis.

    (a) True.
    (b) False. (*)

21. A muscle biopsy is obligatory for a diagnosis of myositis.

    (a) True.
    (b) False. (*)

22. Inclusion body myositis may develop after immune checkpoint inhibitors.

    (a) True.
    (b) False. (*)

References

1. Kostine M, Rouxel L, Barnetche T, et al. Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer-clinical aspects and relationship with tumour response: a single-centre prospective cohort study. Ann Rheumat Dis. 2018;77(3):393–8.
2. Mariampillai K, Granger B, Amelin D, et al. Development of a new classification system for idiopathic inflammatory myopathies based on clinical manifestations and myositis-specific autoantibodies. JAMA Neurol. 2018;5(12):1528–37.

3. Schmidt J. Current classification and management of inflammatory myopathies. J Neuromusc Dis. 2018;5(2):109–29.
4. Lundberg IE, de Visser M, Werth VP. Classification of myositis. Nat Rev Rheumatol. 2018;14(5):269–78.
5. Loarce-Martos J, Lilleker JB, Parker M, et al. Polymyositis: is there anything left? A retrospective diagnostic review from a tertiary myositis Centre. Rheumatology. 2020;60(7):3398–403.
6. Tanboon J, Uruha A, Stenzel W, et al. Where are we moving in the classification of idiopathic inflammatory myopathies? Curr Opin Neurol. 2020;33(5):590–603.
7. Rider LG, Miller FW. Deciphering the clinical presentations, pathogenesis, and treatment of the idiopathic inflammatory myopathies. JAMA. 2011;305(2):183–90.
8. Meyer A, Meyer N, Schaeffer M, et al. Incidence and prevalence of inflammatory myopathies: a systematic review. Rheumatology. 2015;54(1):50–63.
9. Mastaglia FL. Sporadic inclusion body myositis: variability in prevalence and phenotype and influence of the MHC. Acta Myol. 2009;28(2):66–71.
10. Dalakas MC. Review: An update on inflammatory and autoimmune myopathies. Neuropathol Appl Neurobiol. 2011;37(3):226–42.
11. Ernste FC, Reed AM. Idiopathic inflammatory myopathies: current trends in pathogenesis, clinical features, and up-to-date treatment recommendations. Mayo Clin Proc. 2013;88(1):83–105.
12. de Merieux P, Verity MA, Clements PJ, et al. Esophageal abnormalities and dysphagia in polymyositis and dermatomyositis. Arthritis Rheum. 1983;26(8):961–8.
13. Noguchi E, Uruha A, Suzuki S, et al. Skeletal muscle involvement in antisynthetase syndrome. JAMA Neurol. 2017;74(8):992–9.
14. Walsh JS, Fairley JA. Calcifying disorders of the skin. J Am Acad Dermatol. 1995;33:693–706.
15. Blane CE, White SJ, Braunstein EM, et al. Patterns of calcification in childhood dermatomyositis. AJR Am J Roentgenol. 1984;142(2):397–400.
16. Lilleker JB, Vencovsky J, Wang G, et al. The EuroMyositis registry: an international collaborative tool to facilitate myositis research. Ann Rheum Dis. 2018;77(1):30–9.
17. Shelly S, Triplett JD, Pinto MV, et al. Immune checkpoint inhibitor-associated myopathy: a clinicoseropathologically distinct myopathy. Brain Comm. 2020;2(2):fcaa181.
18. Vuillard C, Pineton de Chambrun M, de Prost N, et al. Clinical features and outcome of patients with acute respiratory failure revealing anti-synthetase or anti-MDA-5 dermato-pulmonary syndrome: a French multicenter retrospective study. Ann Intens Care. 2018;8(1):87.
19. Zeng R, Schmidt J. Impact and management of dysphagia in inflammatory myopathies. Curr Rheum Rep. 2020;22(10):74.
20. Price MA, Barghout V, Benveniste O, et al. Mortality and causes of death in patients with sporadic inclusion body myositis: survey study based on the clinical experience of specialists in Australia, Europe and the USA. J Neuromusc Dis. 2016;3(1):67–75.
21. Ebert EC. Review article: the gastrointestinal complications of myositis. Aliment Pharmacol Ther. 2010;31(3):359–65.
22. Cox FM, Verschuuren JJ, Verbist BM, et al. Detecting dysphagia in inclusion body myositis. J Neurol. 2009;256(12):2009–13.
23. Mohannak N, Pattison G, Hird K, et al. Dysphagia in patients with sporadic inclusion body myositis: management challenges. Int J Gen Med. 2019;12:465–74.
24. Betteridge Z, Tansley S, Shaddick G, et al. Frequency, mutual exclusivity and clinical associations of myositis autoantibodies in a combined European cohort of idiopathic inflammatory myopathy patients. J Autoimmun. 2019;
25. Meyer A, Lefevre G, Bierry G, et al. In antisynthetase syndrome, ACPA are associated with severe and erosive arthritis: an overlapping rheumatoid arthritis and antisynthetase syndrome. Medicine. 2015;94(20):e523.

26. Cavagna L, Trallero-Araguas E, Meloni F, et al. Influence of antisynthetase antibodies specificities on antisynthetase syndrome clinical spectrum time course. J Clin Med. 2019;8(11)
27. Opinc AH, Makowski MA, Łukasik ZM, et al. Cardiovascular complications in patients with idiopathic inflammatory myopathies: does heart matter in idiopathic inflammatory myopathies? Heart Fail Rev. 2019.
28. Lilleker JB, Diederichsen ACP, Jacobsen S, et al. Using serum troponins to screen for cardiac involvement and assess disease activity in the idiopathic inflammatory myopathies. Rheumatology. 2018.
29. Hughes M, Lilleker JB, Herrick AL, et al. Cardiac troponin testing in idiopathic inflammatory myopathies and systemic sclerosis-spectrum disorders: biomarkers to distinguish between primary cardiac involvement and low-grade skeletal muscle disease activity. Ann Rheum Dis. 2015;74(5):795–8.
30. Chen F, Peng Y, Chen M. Diagnostic approach to cardiac involvement in idiopathic inflammatory myopathies. Internat Heart J. 2018.
31. Huber AM. Clinical features of myositis: juvenile dermatomyositis. In: Aggarwal R, Oddis C, editors. Managing myositis. Springer Nature Switzerland AG; 2020. p. 81–9.
32. Rider LG, Shah M, Mamyrova G, et al. The myositis autoantibody phenotypes of the juvenile idiopathic inflammatory myopathies. Medicine. 2013;92(4):223–43.
33. Pachman LM, Khojah AM. Advances in juvenile dermatomyositis: myositis specific antibodies aid in understanding disease heterogeneity. J Pediatr. 2018;195:16–27.
34. Bingham A, Mamyrova G, Rother KI, et al. Predictors of acquired lipodystrophy in juvenile-onset dermatomyositis and a gradient of severity. Medicine. 2008;87(2):70–86.
35. Haq SA, Tournadre A. Idiopathic inflammatory myopathies: from immunopathogenesis to new therapeutic targets. Internat J Rheum Diseases. 2015;18(8):818–25.
36. Dalakas MC. Inflammatory muscle diseases. New Engl J Med. 2015;372(18):1734–47.
37. Mammen AL. Dermatomyositis and polymyositis: clinical presentation, autoantibodies, and pathogenesis. Ann N Y Acad Sci. 2010;1184:134–53.
38. Harris-Love MO, Shrader JA, Davenport TE, et al. Are repeated single-limb heel raises and manual muscle testing associated with peak plantar-flexor force in people with inclusion body myositis? Phys Ther. 2014;94(4):543–52.
39. Kissel JT, Halterman RK, Rammohan KW, et al. The relationship of complement-mediated microvasculopathy to the histologic features and clinical duration of disease in dermatomyositis. Arch Neurol. 1991;48(1):26–30.
40. Greenberg SA. Type 1 interferons and myositis. Arthritis Res Ther. 2010;12(Suppl 1):S4.
41. Shah AA, Casciola-Rosen L, Rosen A. Review: cancer-induced autoimmunity in the rheumatic diseases. Arthritis Rheumatol. 2015;67(2):317–26.
42. Casciola-Rosen L, Nagaraju K, Plotz P, et al. Enhanced autoantigen expression in regenerating muscle cells in idiopathic inflammatory myopathy. J Exp Med. 2005;201(4):591–601.
43. Fiorentino DF, Chung LS, Christopher-Stine L, et al. Most patients with cancer-associated dermatomyositis have antibodies to nuclear matrix protein NXP-2 or transcription intermediary factor 1gamma. Arthritis Rheum. 2013;65(11):2954–62.
44. Matsushita T, Kobayashi T, Kano M, et al. Elevated serum B-cell activating factor levels in patients with dermatomyositis: association with interstitial lung disease. J Dermatol. 2019.
45. Bradshaw EM, Orihuela A, McArdel SL, et al. A local antigen-driven humoral response is present in the inflammatory myopathies. J Immunol. 2007;178(1):547–56.
46. Hervier B, Uzunhan Y. Inflammatory myopathy-related interstitial lung disease: from pathophysiology to treatment. Front Med. 2019;6:326.
47. Allenbach Y, Benveniste O. Peculiar clinicopathological features of immune-mediated necrotizing myopathies. Curr Opin Rheumatol. 2018;30(6):655–63.
48. Allenbach Y, Arouche-Delaperche L, Preusse C, et al. Necrosis in anti-SRP(+) and anti-HMGCR(+)myopathies: role of autoantibodies and complement. Neurology. 2018.

49. Schmidt J, Barthel K, Wrede A, et al. Interrelation of inflammation and APP in sIBM: IL-1 beta induces accumulation of beta-amyloid in skeletal muscle. Brain. 2008;131:1228–40.
50. Keller CW, Schmidt J, Lunemann JD. Immune and myodegenerative pathomechanisms in inclusion body myositis. Ann Clin Transl Neurol. 2017;4(6):422–45.
51. Benveniste O, Stenzel W, Hilton-Jones D, et al. Amyloid deposits and inflammatory infiltrates in sporadic inclusion body myositis: the inflammatory egg comes before the degenerative chicken. Acta Neuropathol. 2015;129(5):611–24.
52. Hoogendijk JE, Amato AA, Lecky BR, et al. 119th ENMC international workshop: trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10-12 October 2003, Naarden, the Netherlands. Neuromuscul Disord. 2004;14(5):337–45.
53. Rose MR. 188th ENMC international workshop: inclusion body myositis, 2-4 December 2011, Naarden, the Netherlands. Neuromuscul Disord. 2013;23(12):1044–55.
54. Lundberg IE, Tjarnlund A, Bottai M, et al. 2017 European league against rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. Arthritis Rheumatol. 2017;69(12):2271–82.
55. Uruha A, Nishikawa A, Tsuburaya RS, et al. Sarcoplasmic MxA expression: a valuable marker of dermatomyositis. Neurology. 2017;88(5):493–500.
56. Connors GR, Christopher-Stine L, Oddis CV, et al. Interstitial lung disease associated with the idiopathic inflammatory myopathies: what progress has been made in the past 35 years? Chest. 2010;138(6):1464–74.
57. Cottin V, Thivolet-Bejui F, Reynaud-Gaubert M, et al. Interstitial lung disease in amyopathic dermatomyositis, dermatomyositis and polymyositis. Eur Resp J. 2003;22(2):245–50.
58. Nuño-Nuño L, Joven BE, Carreira PE, et al. Overlap myositis, a distinct entity beyond primary inflammatory myositis: a retrospective analysis of a large cohort from the REMICAM registry. Internat J Rheum Dis. 2019.
59. van der Meulen MF, Bronner IM, Hoogendijk JE, et al. Polymyositis: an overdiagnosed entity. Neurology. 2003;61(3):316–21.
60. Allenbach Y, Mammen AL, Benveniste O, et al. 224th ENMC International Workshop: clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14–16 October 2016. Neuromuscul Disord. 2018;28(1):87–99.
61. Lloyd TE, Mammen AL, Amato AA, et al. Evaluation and construction of diagnostic criteria for inclusion body myositis. Neurology. 2014;83(5):426–33.
62. Felice KJ, Whitaker CH, Wu Q, et al. Sensitivity and clinical utility of the anti-cytosolic 5′-nucleotidase 1A (cN1A) antibody test in sporadic inclusion body myositis: report of 40 patients from a single neuromuscular center. Neuromuscul Disord. 2018.
63. Ikenaga C, Findlay AR, Goyal NA, et al. Myositis associated anti-NT5C1A autoantibody in clinical practice. Ann Clin Transl Neurol. 2021;8(3):571–8.
64. Rider LG, Nistala K. The juvenile idiopathic inflammatory myopathies: pathogenesis, clinical and autoantibody phenotypes, and outcomes. J Intern Med. 2016;280(1):24–38.
65. Shah M, Mamyrova G, Targoff IN, et al. The clinical phenotypes of the juvenile idiopathic inflammatory myopathies. Medicine. 2013;92(1):25–41.
66. Mamyrova G, Katz JD, Jones RV, et al. Clinical and laboratory features distinguishing juvenile polymyositis and muscular dystrophy. Arthritis Care Res. 2013;65(12):1969–75.
67. Habers GE, Van Brussel M, Bhansing KJ, et al. Quantitative muscle ultrasonography in the follow-up of juvenile dermatomyositis. Muscle Nerve. 2015;52(4):540–6.
68. Albayda J, van Alfen N. Diagnostic value of muscle ultrasound for myopathies and myositis. Curr Rheumat Rep. 2020;22(11):82.
69. Ten Dam L, van der Kooi AJ, Verhamme C, et al. Muscle imaging in inherited and acquired muscle diseases. Eur J Neurol. 2016;23(4):688–703.
70. Van De Vlekkert J, Maas M, Hoogendijk JE, et al. Combining MRI and muscle biopsy improves diagnostic accuracy in subacute-onset idiopathic inflammatory myopathy. Muscle Nerve. 2015;51(2):253–8.

71. Gutiérrez GG, López CB, Navacerrada F, et al. Use of electromyography in the diagnosis of inflammatory myopathies. Reumatol Clín. 2012;8(4):195–200.
72. McHugh NJ, Tansley SL. Autoantibodies in myositis. Nat Rev Rheumat. 2018;14(5):290–302.
73. Myhr KA, Pecini R. Management of myocarditis in myositis: diagnosis and treatment. Curr Rheumatol Rep. 2020;22(9):49.
74. Jakubaszek M, Kwiatkowska B, Maslinska M. Polymyositis and dermatomyositis as a risk of developing cancer. Reumatologia. 2015;53(2):101–5.
75. Hill CL, Zhang Y, Sigurgeirsson B, et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. Lancet. 2001;357(9250):96–100.
76. Chen YJ, Wu CY, Huang YL, et al. Cancer risks of dermatomyositis and polymyositis: a nationwide cohort study in Taiwan. Arthritis Res Ther. 2010;12(2):R70.
77. Allenbach Y, Keraen J, Bouvier AM, et al. High risk of cancer in autoimmune necrotizing myopathies: usefulness of myositis specific antibody. Brain. 2016;139:2131–5.
78. Yang H, Peng Q, Yin L, et al. Identification of multiple cancer-associated myositis-specific autoantibodies in idiopathic inflammatory myopathies: a large longitudinal cohort study. Arthritis Res Ther. 2017;19(1):259.
79. Narvaez J, Juarez-Lopez P, LLuch J, et al. Rheumatic immune-related adverse events in patients on anti-PD-1 inhibitors: fasciitis with myositis syndrome as a new complication of immunotherapy. Autoimmun Rev. 2018;17(10):1040–5.
80. Abdel-Wahab N, Suarez-Almazor ME. Frequency and distribution of various rheumatic disorders associated with checkpoint inhibitor therapy. Rheumatology. 2019;58(Supplement_7) :vii40–8.
81. Steven NM, Fisher BA. Management of rheumatic complications of immune checkpoint inhibitor therapy - an oncological perspective. Rheumatology. 2019;58(Supplement_7): vii29–39.
82. van de Vlekkert J, Hoogendijk JE, de Haan RJ, et al. Oral dexamethasone pulse therapy versus daily prednisolone in sub-acute onset myositis, a randomised clinical trial. Neuromuscul Disord. 2010;20(6):382–9.
83. Buchman AL. Side effects of corticosteroid therapy. J Clin Gastroenterol. 2001;33(4):289–94.
84. Rietveld A, Lim J, de Visser M, et al. Autoantibody testing in idiopathic inflammatory myopathies. Pract Neurol. 2019.
85. Oddis CV, Reed AM, Aggarwal R, et al. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. Arthritis Rheum. 2013;65(2):314–24.
86. Damian MS, Srinivasan R. Neuromuscular problems in the ICU. Curr Opin Neurol. 2017;30(5):538–44.
87. Fragoulis GE, Conway R, Nikiphorou E. Methotrexate and interstitial lung disease: controversies and questions. A narrative review of the literature. Rheumatology. 2019;58(11):1900–6.
88. Yoshifuji H. Biomarkers and autoantibodies of interstitial lung disease with idiopathic inflammatory myopathies. Clin Med Insights Circ Respir Pulm Med. 2015;9(Suppl 1):141–6.
89. Ameye H, Ruttens D, Benveniste O, et al. Is lung transplantation a valuable therapeutic option for patients with pulmonary polymyositis? Experiences from the Leuven transplant cohort. Transplant Proc. 2014;46(9):3147–53.
90. Pipitone N. Value of MRI in diagnostics and evaluation of myositis. Curr Opin Rheumatol. 2016;28(6):625–30.
91. Bae S, Charles-Schoeman C. Clinical features of myositis: cardiac manifestations. In: Aggarwal R, Oddis C, editors. Managing myositis. Springer Nature Switzerland AG; 2020. p. 63–74.
92. Kindermann I, Barth C, Mahfoud F, et al. Update on myocarditis. J Am Coll Cardiol. 2012;59(9):779–92.
93. Stern R, Godbold JH, Chess Q, et al. ECG abnormalities in polymyositis. Arch Internal Med. 1984;144(11):2185–9.

94. Allanore Y, Vignaux O, Arnaud L, et al. Effects of corticosteroids and immunosuppressors on idiopathic inflammatory myopathy related myocarditis evaluated by magnetic resonance imaging. Ann Rheumat Dis. 2006;65(2):249–52.
95. Kang EH, Lee SJ, Ascherman DP, et al. Temporal relationship between cancer and myositis identifies two distinctive subgroups of cancers: impact on cancer risk and survival in patients with myositis. Rheumatology. 2016;55(9):1631–41.
96. Andras C, Ponyi A, Constantin T, et al. Dermatomyositis and polymyositis associated with malignancy: a 21-year retrospective study. J Rheumatol. 2008;35(3):438–44.
97. Selva-O'Callaghan A, Trallero-Araguás, Pinal-Fernandez I. Cancer-associated myositis. In: Aggarwal R, Oddis C, editors. Managing myositis. Springer Nature Switzerland AG; 2020. p. 237–45.
98. Fayyaz B, Rehman HJ, Uqdah H. Cancer-associated myositis: an elusive entity. J Community Hosp Intern Med Perspect. 2019;9(1):45–9.
99. Selva-O'Callaghan A, Martinez-Gómez X, Trallero-Araguás E, et al. The diagnostic work-up of cancer-associated myositis. Curr Opin Rheum. 2018.
100. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2018;36(17):1714–68.
101. Anyanwu CO, Fiorentino DF, Chung L, et al. Validation of the cutaneous dermatomyositis disease area and severity index: characterizing disease severity and assessing responsiveness to clinical change. Br J Dermatol. 2015;173(4):969–74.
102. Hollar CB, Jorizzo JL. Topical tacrolimus 0.1% ointment for refractory skin disease in dermatomyositis: a pilot study. J Dermatolog Treat. 2004;15(1):35–9.
103. Mainetti C, Terziroli Beretta-Piccoli B, Selmi C. Cutaneous manifestations of dermatomyositis: a comprehensive review. Clin Rev Allergy Immunol. 2017;53(3):337–56.
104. Sontheimer RD. Skin manifestations of systemic autoimmune connective tissue disease: diagnostics and therapeutics. Best Pract Res Clin Rheumatol. 2004;18(3):429–62.
105. Dourmishev LA, Draganov PV. Paraneoplastic dermatological manifestation of gastrointestinal malignancies. World J Gastroenterol. 2009;15(35):4372–9.
106. Ang GC, Werth VP. Combination antimalarials in the treatment of cutaneous dermatomyositis: a retrospective study. Arch Dermatol. 2005;141(7):855–9.
107. Anyanwu CO, Chansky PB, Feng R, et al. The systemic management of cutaneous dermatomyositis: results of a stepwise strategy. Internat J Women's Dermatol. 2017;3(4):189–94.
108. Hornung T, Ko A, Tuting T, et al. Efficacy of low-dose methotrexate in the treatment of dermatomyositis skin lesions. Clin Exp Dermatol. 2012;37(2):139–42.
109. Wolstencroft PW, Casciola-Rosen L, Fiorentino DF. Association between autoantibody phenotype and cutaneous adverse reactions to hydroxychloroquine in dermatomyositis. JAMA Dermatol. 2018.
110. Wang DX, Shu XM, Tian XL, et al. Intravenous immunoglobulin therapy in adult patients with polymyositis/dermatomyositis: a systematic literature review. Clin Rheumatol. 2012;31(5):801–6.
111. Galimberti F, Kooistra L, Li Y, et al. Intravenous immunoglobulin is an effective treatment for refractory cutaneous dermatomyositis. Clin Exp Dermatol. 2018.
112. Aggarwal R, Loganathan P, Koontz D, et al. Cutaneous improvement in refractory adult and juvenile dermatomyositis after treatment with rituximab. Rheumatology. 2017;56(2):247–54.
113. Jamilloux Y, El Jammal T, Vuitton L, et al. JAK inhibitors for the treatment of autoimmune and inflammatory diseases. Autoimmun Rev. 2019;18(11):102390.
114. Moghadam-Kia S, Charlton D, Aggarwal R, et al. Management of refractory cutaneous dermatomyositis: potential role of Janus kinase inhibition with tofacitinib. Rheumatology. 2019;58(6):1011–5.

115. Paik JJ, Christopher-Stine L. A case of refractory dermatomyositis responsive to tofacitinib. Semin Arthritis Rheum. 2017;46(4):e19.
116. Hoeltzel MF, Oberle EJ, Robinson AB, et al. The presentation, assessment, pathogenesis, and treatment of calcinosis in juvenile dermatomyositis. Curr Rheumatol Rep. 2014;16(12):467.
117. Balin SJ, Wetter DA, Andersen LK, et al. Calcinosis cutis occurring in association with autoimmune connective tissue disease: the Mayo Clinic experience with 78 patients, 1996-2009. Arch Dermat. 2012;148(4):455–62.
118. Chan AY, Li E. Electric shock wave lithotripsy (ESWL) as a pain control measure in dermatomyositis with calcinosis cutis-old method, new discovery. Clin Rheumatol. 2005;24(2):172–3.

Chapter 12
The Emergency and Intensive Care Management of Metabolic Myopathies

Annika Saak and Jochen Schaefer

Introduction Epidemiology, Pathophysiology, and Clinical Presentation

Epidemiology and Classification

Metabolic myopathies are hereditary disorders of muscle carbohydrate (glycogen degradation, glycolysis), lipid (fatty acid oxidation) and purine metabolism, and of the mitochondrial respiratory chain.

Disorders of Glycogen and Glucose Metabolism

Glycogen storage diseases (GSD) can be subclassified into disorders of glycogen synthesis, glycogen degradation, and anaerobic glucose degradation. Based on the enzyme defect and the clinical pattern, 14 types of glycogenoses have been identified, so far. Here we will only discuss the clinically relevant disorders of glycogen degradation: these may be caused by defects of lysosomal glycogen breakdown leading to lysosomal glycogen storage, or defects of anaerobic glycogenolysis and glycolysis leading to cytosolic glycogen storage. The best-known representative of lysosomal glycogen storage is Pompe disease (type II glycogenosis) due to a deficiency of lysosomal alpha-1,4 -glucosidase (acid maltase). Cytosolic glycogen accumulation is a hallmark of McArdle's disease (type V glycogenosis), caused by a deficiency of myophosphorylase, or may occur with some rare defects of anaerobic glycolysis such as Tarui disease (type VII glycogenosis) due to a deficiency of phosphofructokinase.

A. Saak (✉) · J. Schaefer
Universitätsklinikum Carl Gustav Carus Dresden, Dresden, Germany
e-mail: Annika.Saak@ukdd.de; Jochen.Schaefer@ukdd.de

M. Damian, M. de Visser (eds.), *Emergencies in Neuromuscular Disorders*,
https://doi.org/10.1007/978-3-030-91932-0_12

Pompe disease may manifest before the 6th month of life (infantile form) with a reported incidence of 1:100,000, or as an adult or late-onset variant with an incidence of 1:60,000 in individuals of European descent [1]. Children with infantile-onset usually have a severe deficiency of alpha-1,4-glucosidase and progress rapidly, whilst those affected by late-onset Pompe disease might even live into their 70s, mainly depending on their respiratory function.

McArdle disease is the most common glycogenosis with a prevalence of 1:100,000 [2]. The majority of patients are diagnosed between ages 10 and 30 years, but some individuals with only mild symptoms may only be identified after the age of 50, or the diagnosis may be missed entirely.

Type VII glycogenosis (Tarui) shows a symptom onset usually in the second or third decade and is the rarest of the GSD described here, with around 100 cases worldwide, to date.

Disorders of Fatty Acid Metabolism

Lipid storage myopathies are a genetically heterogenous group of muscular lipid metabolism disorders giving rise to myocellular lipid storage in the majority, but not all, cases. The affected pathways may involve endocellular triglyceride degradation, cellular carnitine uptake, mitochondrial fatty acid uptake and fatty acid beta-oxidation, coenzyme Q10 biosynthesis, and phosphatidic acid degradation. The individual disorders are rare; as a group, however, lipid storage myopathies have a prevalence of 1:6000. By far the most relevant are the disturbances of mitochondrial fatty acid uptake and mitochondrial fatty acid beta-oxidation. Infantile cases usually have a severe clinical course with profound metabolic crises and early death, whilst patients manifesting in early adulthood show a much more benign course with isolated muscle symptoms.

All of the above glycogenoses and lipid storage myopathies show an autosomal-recessive inheritance pattern.

Pathophysiology

Disorders of Glycogen and Glucose Metabolism

In conditions of short-term strenuous exercise, glycogen can be utilized as an energy source for muscle contraction. Muscle glycogen breakdown (glycogenolysis) is localized in the lysosomal compartment and in the cytosol.

Dysfunction of *alpha-1,4-glucosidase (GAA)*, the lysosomal enzyme, is caused by recessive mutations in the GAA-gene and results in the accumulation of glycogen in lysosomes of skeletal and smooth muscle cells, cardiomyocytes, hepatocytes, endothelial cells, and central nervous system neurons. Pompe disease is therefore a multiorgan disorder. The clinical phenotype and age of onset correlate with the amount of residual enzyme activity.

Recessive mutations in the *myophosphorylase gene (PYGM)* impair anaerobic glycogenolysis, which releases glucose-1-phosphate from the glycogen chain. Patients with McArdle disease usually have no detectable myophosphorylase activity, and consequently glycogen accumulates in the cytosol. A common mutation (p.R50X) is found in Caucasians, but there is also a plethora of private mutations.

In Pompe disease, destruction of the lysosomes releases aggressive lysosomal enzymes into the cytoplasm eventually leading to cell death. In contrast, McArdle's disease causes solely cytosolic glycogen accumulation which is less deleterious for cellular metabolism.

In Tarui disease anaerobic glycolysis is disturbed by mutations in the *PFKM* gene which encodes the muscle isoenzyme *phosphofructokinase*.

All other glycolytic defects are exceedingly rare and will not be discussed separately.

Disorders of Fatty Acid Metabolism

Long-chain fatty acids (LCFA) are the predominant fuels used by muscle during rest, fasting or prolonged exercise. They are predominantly taken up by the muscle from the bloodstream, and to a lesser extent, they are also derived from endogenous muscle triglycerides that are hydrolyzed by triglyceride lipases. LCFA have to be actively transported into the mitochondria via a transmembrane shuttle consisting of two carnitine palmitoyltransferases (CPT-1 and CPT-2) and a translocase. Carnitine is an essential carrier for the shuttle and is imported into the cell by means of a plasma-cellular transporter (OCTN2) (Fig. 12.1). Inside the mitochondria, LCFA

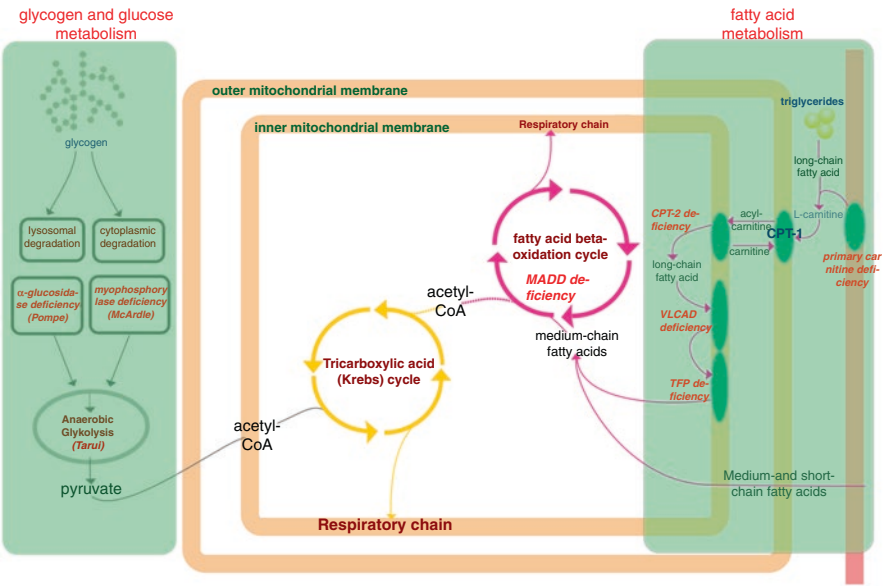


Fig. 12.1 Basic pathways of muscle energy metabolism

undergo a cycle of repetitive enzymatic reactions, the mitochondrial fatty acid beta-oxidation, in which the acyl-CoA derivative of the fatty acid is shortened by two carbon units (acetyl-CoA) at the end of each cycle. The acetyl-CoA generated is subsequently oxidized by the Krebs cycle and the mitochondrial respiratory chain to produce ATP. Short- and medium-chain fatty acids, however, can diffuse freely into the mitochondria, thus being able to bypass the CPT-shuttle system.

All told, there are at least 21 genes encoding the enzymatic machinery required for uptake and complete breakdown of fatty acids, and for most of these genes, hereditary defects have been described. Summed up, fatty acid oxidation (FAO) disorders are amongst the most common inborn errors of metabolism.

Contrary to previous beliefs, a number of other organs besides liver, skeletal, and cardiac muscle conduct high rates of FAO, i.e. type II pneumocytes (which produce surfactant), proximal renal tubule cells, and even the immune system. Not surprisingly, many FAO patients in need of intensive care treatment may therefore be at a high risk of developing respiratory distress [3] and renal fibrosis.

Depending on the site of the metabolic block within the FAO pathway, a characteristic pattern of intermediary metabolites (acylcarnitines, free fatty acids, lack of free carnitine) will accumulate in the affected tissues. These intermediates appear to be particularly toxic to mitochondria and are—besides the reduced production of ATP—mainly responsible for the pathophysiology of these disorders.

Clinical Presentation

Disorders of Glycogen and Glucose Metabolism

In the infantile form of **Pompe disease**, residual GAA-activities below 1% give rise to a severe clinical course and glycogen deposition in multiple organs; affected patients will present in the first few months of life with rapidly progressive limb-girdle myopathy, hypotonia (floppy infant), feeding difficulties, failure to thrive, hepatomegaly, macroglossia, respiratory distress, hypertrophic cardiomyopathy, and cardiac arrhythmias. Without treatment, these symptoms will rapidly progress and eventually lead to death from cardiorespiratory failure in infancy or early childhood [4].

Patients with will usually have a residual enzyme activity of >5% and a much milder clinical course; they can present at any age, although an earlier presentation goes along with more severe symptoms. Clinical features include slowly progressive, proximal limb weakness with fatigue [5], poor exercise tolerance, and axial weakness. Sometimes selective muscle hypertrophy, winging scapulae and spinal deformities are present. Involvement of the respiratory muscles and diaphragmatic weakness may occur even in patients who are still ambulatory (**Case Vignette 1**). Respiratory insufficiency often manifests itself initially as sleep apnoea [6] and should therefore be carefully monitored. Without treatment, death will occur from the third decade onwards mainly as a result of respiratory failure. Unlike infants

with Pompe disease, LOPD patients do not develop a hypertrophic cardiomyopathy, although some adults have been reported to have aneurysms in the aorta and basilar artery caused by glycogen deposition in the vascular endothelium.

Case Vignette 1

A 49-year-old female was admitted with rapidly developing respiratory insufficiency. She had no fever, was a non-smoker, and had no history of asthma, allergies, or any other medical symptoms. In retrospect, she had, however, complained about mildly increasing exercise intolerance and fatigue in the past 5 years. Family history was unremarkable. On examination she was pale, gasping for breath, and needed to sit in an upright position. Cognitive functions were preserved, and examination of the cranial nerves was normal. She was able to get up from a chair and stand. There was symmetrical weakness (MRC 4) of hip extensors and the medial gluteal muscles, without any further weakness or muscular atrophy. However, her walking revealed a waddling gait (bilateral Trendelenburg's sign). Deep tendon reflexes were depressed. The plantar responses were flexor. Perception of pain and light touch was normal. Laboratory investigations revealed a creatine kinase (CK) elevation of 1588 U/l (normal < 180 U/l), and lactate dehydrogenase (LDH) was 3xULN. There was no myoglobinuria. Electrophysiological examination showed normal nerve conduction. EMG of the right vastus lateralis showed motor unit potentials of decreased amplitude and duration with a reduced recruitment pattern. No fibrillation potentials or positive sharp waves were identified. Forced vital lung capacity sitting was 62% (normal > 80%) and further decreased in supine position to 41%. There was CO_2 retention with metabolic compensation (Table 12.1).

These findings implied weakness of the respiratory muscles, in particular diaphragmatic weakness, as shown by the marked reduction of FVC in a supine position. Because of the rapid development of respiratory insufficiency in conjunction with daytime hypercapnia non-invasive ventilation (NIV) was immediately commenced, which promptly improved the respiratory situation.

After stabilization of the patient, further diagnostic workup was initiated. Based on the clinical presentation with pronounced respiratory failure despite preserved ambulation, the reduced FVC, and the elevations of CK and LDH, our differential diagnosis mainly covered FKRP-deficiency, hereditary myopathy with early respiratory failure (HMERF, Titin deficiency), late-onset rod myopathy, ALS and LOPD. Myasthenia gravis, another important and treatable cause of respiratory failure with retained ambulation, appeared less

likely in view of the CK elevation. Because of its simple feasibility, analysis of glucosidase alpha (GAA) enzyme activity was performed in a dried blood spot. It was reduced to 15% (normal > 50%) and further molecular genetic workup identified the common IVS1 splice site mutation in combination with a large deletion of the GAA gene, thus confirming LOPD. Enzyme replacement therapy was then promptly started with subsequent gradual stabilization of the motor and pulmonary function. Eventually, NIV could be reduced to overnight ventilation only.

Learning Points

- **LOPD may manifest with acute respiratory failure even in patients who are still ambulant.**
- **LOPD can be successfully treated with enzyme replacement therapy and therefore has to be considered early in the diagnostic workup of myopathies with early respiratory failure.**
- **Dried blood spot analysis for GAA activity is an easy and fast screening tool for the diagnosis of LOPD, but molecular genetic testing is always required, since adult-onset forms may present with significant residual enzyme activity.**

Glycogen is of particular importance during short-term, high-intensity exercise; hence in **McArdle disease** exercise-induced fatigue, myalgia, muscle cramps and swelling of mainly proximal muscles start early during exercise. In contrast, moderate low-activity exercise is much better tolerated, because fatty acids are then the predominant energy suppliers. Many patients experience a "second-wind" phenomenon, which is characterized by improved exercise tolerance if motor activity is continued at a moderate level. Rhabdomyolysis and myoglobinuria occur in 50% of cases and may lead to acute renal failure in 25% [7] (see also Chap. 10). About 30%

Table 12.1 Blood gas analysis

	Ref. value	Unit	Pat. result
Oxymetry			
pH(T)	7.35–7.45		7.385
pCO2(T)	4.27–6.40	kPa	8.20+
pO2(T)	11.1–14.4	kPa	6.31-
sO2	95.0–99.0	%	82.1-
Acid base status			
ABE	<3.0–3.0	mmol/L	9.9+
HCO3	20.0–27.0	mmol/L	33.2+
Lac	0.5–1.6	mmol/L	0.5-

of patients develop muscle wasting and persisting weakness, which is confined to proximal muscle groups, and is rare below age 40 [8]. Involvement of respiratory muscles is not a feature of McArdle disease except in patients with manifestation in early childhood.

Case Vignette 2

A 57-year-old patient complaining of chest pain, palpitations, and cold sweats was admitted as an emergency. Significant ST-elevations were demonstrated in leads II, III, and avF by ECG, creatine kinase was increased at 3000 U/l (norm < 180) and troponin T at 240 µg/l (norm < 14). An acute STEMI was diagnosed and confirmed by coronary angiography, and coronary artery bypass grafting was successfully performed. During convalescence, repeated CK elevations higher than 6000 IU/l were noted despite complete resolution of all cardiac symptoms.

In the further course of the disease, the patient presented to the emergency department with swelling and severe pain in his forearm muscles after strenuous exercise during gardening. He reported a dark discoloration of his urine, so acute rhabdomyolysis was assumed. This was confirmed by massively elevated plasma levels of CK (31,200 U/l) and myoglobin (6840 µg/l; norm < 70). The patient was admitted and intravenous fluids were administered. Renal function remained stable, and the patient was transferred to the rheumatology ward with a provisional diagnosis of myositis.

On further questioning, the patient reported intermittent, exercise-induced muscle weakness associated with proximally accentuated limb pain. He had noticed similar episodes, also with recurrent dark discoloration of his urine, since childhood. On examination, there was no muscle weakness and the muscles were not tender to palpation. An EMG and a muscle MRI were normal. A muscle biopsy showed a regional, mild, myopathic pattern. There was no evidence of myositis, and myositis-associated antibodies (Ku, PM-Scl, Scl70, Scl100, Jo-1, Mi-2, PL12, PL7, U1-RNP) were negative.

Therefore, the patient was referred to our neuromuscular clinic. He mentioned that his muscle weakness and cramp-like muscle pains were always exercise-induced and that he had noticed an improvement in his exercise capacity if he took a short break and then continued the exercise. This is the classical "second wind phenomenon", which supported the suspected diagnosis of McArdle disease. A follow-up assessment of the muscle biopsy showed a complete loss of myophosphorylase staining. The forearm exercise test demonstrated an excessive rise of plasma ammonia levels without a concurrent increase in lactate concentrations (Fig. 12.2). Molecular genetic testing confirmed the diagnosis of McArdle disease by demonstrating the presence of the most common pathogenic mutation, p.R50X, in the PYGM gene. With physiotherapy and regular aerobic training, the patient could eventually accomplish all activities of daily living without relevant problems.

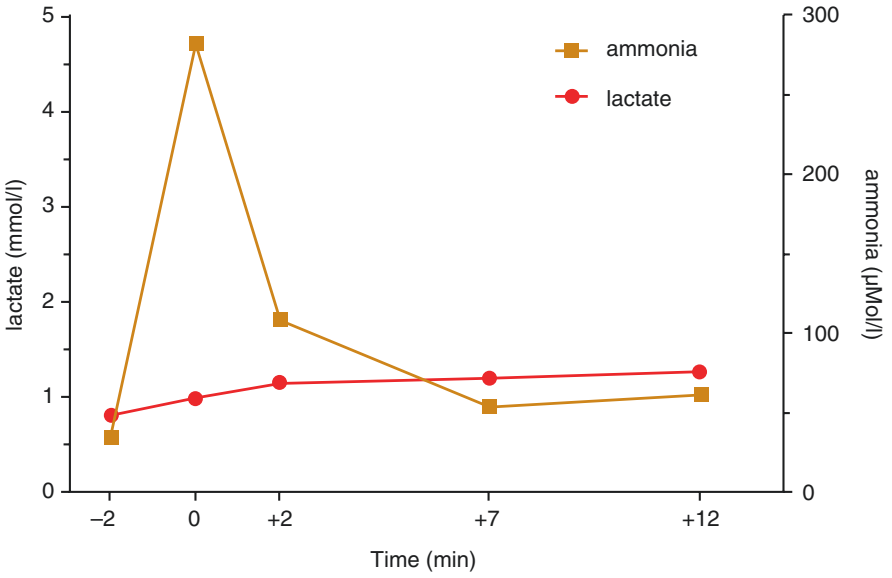


Fig. 12.2 Forearm exercise test in McArdle disease

Learning Points

- **In rare cases, the initial manifestation of McArdle disease is rhabdomyolysis.**
- **Even in the context of established McArdle disease, other causes of increased CK activities, as in our case due to myocardial infarction, must be carefully investigated.**

Tarui disease is clinically similar to McArdle disease, but patients lack the "second-wind" phenomenon and complain of exercise intolerance, myalgia, and cramps, often associated with nausea and vomiting, and already starting in childhood. Different to McArdle disease, high-carbohydrate meals decrease stress tolerance ("out-of-wind"), because glucose lowers the blood concentrations of fatty acids. Myoglobinuria attacks are less frequent than in McArdle disease.

Disorders of Fatty Acid Metabolism

Fatty acids are the major metabolic fuel in prolonged low-intensity exercise; therefore myalgia, muscular fatigue, and stiffness occur later than in glycogen storage disorders, usually many hours after completion of the work. Recurrent rhabdomyolysis and myoglobinuria following prolonged exercise are common, particularly

if associated with fasting. Other precipitating factors include cold exposure, fasting, infections, lack of sleep, pregnancy, and emotional stress. Between attacks, the patients are mostly symptom-free with normal neurological examination results.

Case Vignette 3

A 32-year-old woman presented to the A&E department with a one-day history of severe pain, stiffness, tenderness, and swelling of her limb-girdle muscles, more pronounced in the legs. Prior to this, she had been suffering from a viral upper airway infection. The patient further mentioned that she had been passing dark-coloured urine. Her past medical history was unremarkable apart from hyperlipidaemia, for which she took simvastatin. She had not had any similar attacks in the past, and there was no family history of neuromuscular disease.

On examination, muscle strength was reduced in the legs, but this was thought to be secondary to the severe myalgias and muscle tenderness. Otherwise, general medical and neurological examination were normal with no signs of cardiac involvement.

Serum ALT was raised at 564 U/l (norm < 35), AST was 594 U/l (norm < 35), and GGT was normal. CK was massively elevated at 19500 U/l (norm < 180) and myoglobin at 3637 µg/l (norm < 72). Urinary myoglobin was 650 µg/l (norm < 21). Nerve conduction studies disclosed no abnormality; EMG of the thigh muscles revealed florid denervation with a dense interference pattern.

A provisional diagnosis of acute rhabdomyolysis with myoglobinuria was made and treatment in the ICU was initiated. The viral infection was regarded to either be the sole cause of the rhabdomyolysis or to act as a trigger for an underlying inflammatory, toxic (simvastatin), or metabolic myopathy.

To further elucidate the etiology of the rhabdomyolytic episode, a muscle biopsy was performed, but this only showed necrotic fibres with invasion of macrophages, i.e. a necrotizing myopathy. Myositis-associated antibodies including HMGCR-antibodies were all negative, thus making a statin-induced necrotizing myopathy unlikely.

To exclude metabolic myopathies, a dried blood spot (Fig. 12.3) was analyzed for alpha-glucosidase and acylcarnitines, but did not give any pathological results. Additional acylcarnitine profiling using plasma rather than dried whole blood eventually revealed an abnormal ratio of long-chain to short-chain acylcarnitines, implying CPT-2 deficiency. Subsequent molecular genetic workup confirmed CPT-2 deficiency.

The patient was asymptomatic when discharged home and she was advised to avoid prolonged fasting and long-term exercise, particularly in combination with concomitant infections.

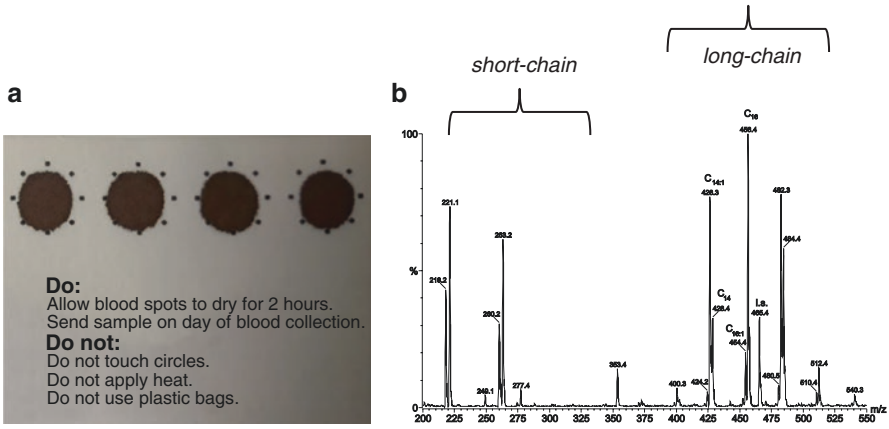


Fig. 12.3 (**a**) Dried blood-spot card for acylcarnitine analysis. (**b**) Acylcarnitine pattern in VLCAD deficiency demonstrating elevated long-chain acylcarnitines (C16, C14, C14:1)

Learning Points

- **The initial presentation of patients with fatty-acid oxidation defects is not infrequently with a first rhabdomyolytic episode without past history of exercise intolerance.**
- **Concomitant viral infections may either be directly myotoxic or act as a trigger for underlying metabolic myopathies.**
- **Acylcarnitine analysis should be the primary investigation for FAO defects, but the choice of the matrix (dried blood or plasma) may be relevant for the detection of some defects (CPT-2 rather in plasma than in dried blood)**
- **Use of statins should be avoided in FAO disorders, as they might contribute to the development of a myopathy.**

The majority of FAO defects, including **primary carnitine deficiency**, **CPT-2 deficiency,** and the **Acyl-CoA-dehydrogenase deficiencies**, can present with a severe and often lethal neonatal or infantile phenotype or a much milder juvenile/adult-onset, myopathic phenotype: (1) Severe infantile forms are characterized by multiorgan involvement with hypotension, liver failure (Reye-syndrome), organ malformations, hypoketotic hypoglycaemia, encephalopathy, coma, seizures and frequently cardiomyopathy. (2) In the much more common juvenile/adult forms, exercise-induced muscular symptoms predominate, consisting of episodic myalgia, muscle tenderness, cramps, and possibly rhabdomyolysis. Fixed weakness may rarely occur. Children who survive the infantile form will develop an adult phenotype. There have been some reports of adult patients presenting with a systemic infantile phenotype and cardiomyopathy [9].

Clinical differentiation of the various FAO defects is difficult and requires additional biochemical and molecular genetic testing. Only few defects have additional clinical features pointing towards a specific defect, e.g. lactic acidosis, polyneuropathy, and cardiomyopathy in trifunctional enzyme deficiency.

Diagnosis and General Principles of Management

Diagnostic Testing in Glycogenoses

Detailed *clinical examination* might already point towards a specific diagnosis. In this respect, respiratory failure early during the course of the disease is an important diagnostic feature (Table 12.2). Fixed proximal and axial weakness, myalgia, and muscle atrophy in conjunction with early respiratory failure, particularly in a patient who is still ambulatory, would suggest late-onset Pompe disease. Conversely, muscle cramps, muscle swelling, and myoglobinuria, if brought on shortly after initiation of high-intensity exercise and featuring a "second-wind-phenomenon", are indicative of McArdle disease. Reduced stress tolerance after a carbohydrate-rich meal implies Tarui disease.

CK is constantly elevated (up to 20-fold) in patients with complete enzyme block, as observed in McArdle disease and Tarui disease; Pompe patients show various levels of hyperCKemia depending on the severity of the myopathy (1.5—15× ULN). A useful distinctive feature for Tarui disease are increased bilirubin and LDH, reticulocytosis, and reduced haptoglobin (reflecting compensated hemolytic anemia) [10].

Forearm exercise testing (not to be performed under ischemic conditions according to current guidelines), is highly indicative of McArdle disease if the lactate

Table 12.2 Metabolic myopathies with early respiratory distress

A. *Glycogen metabolism*
• Infantile Pompe (GSD-II)
• Juvenile/adult Pompe (GSD-II)
• Debrancher (Cori) (GSD-III)
B. *Lipid storage myopathies:*
• Primary carnitine deficiency
• Infantile CPT-2 deficiency
• Infantile VLCAD deficiency
• Multiple acyl-CoA dehydrogenase deficiency
C. *Mitochondrial myopathies (respiratory chain)*
• Leigh disease (complex I)
• Coenzyme Q10 deficiency
• Complex IV-deficiency
• mtDNA deletion (e.g. POLG)
• mtDNA depletion (e.g. Thymidin kinase 2)
D. *Iron-sulfur cluster myopathy*

increase is absent and the ammonia increase overshoots; a similar result can be expected with Tarui disease (Fig. 12.2). Pompe disease will exhibit a normal lactate and ammonia response, because lysosomal glycogen does not contribute significantly to the supply of muscular energy demands.

Muscle MRI might suggest Pompe disease because of its typical pattern of muscular atrophy and fatty degeneration involving paravertebral muscles and adductors with sparing of sartorius and gracilis muscles.

EMG only shows non-specific myopathic changes, prolonged insertion, and pathological spontaneous activity in Pompe disease, but can be normal in McArdle and Tarui disease.

Muscle biopsy is nowadays no longer required to establish the diagnosis of a GSD. If performed, it will demonstrate PAS-positive vacuoles, which in Pompe disease are membrane-bound and show increased activity of acid phosphatase (Fig. 12.4). Late-onset forms may, however, not reveal these characteristic features. In McArdle disease, complete or almost complete absence of myophosphorylase activity can be established, and there may be some subsarcolemmal, non-membrane-bound, glycogen accumulation (Fig. 12.5). A compensatory abundance of mitochondria is often also present. Similar findings are observed with Tarui disease (reduced phosphofructokinase activity). It is important to remember that a biopsy taken too soon after a rhabdomyolytic event will show non-specific inflammatory changes, which could be mistaken for idiopathic inflammatory myopathy. Moreover, the presence of immature myophosphorylase enzyme in regenerating fibres might further impede the diagnosis of McArdle disease.

Enzyme activities of alpha-glucosidase can rapidly be analyzed from a dried blood spot and should be the initial diagnostic procedure if Pompe disease is suspected. The measurement of enzyme activities in leukocytes or fibroblast cultures is more laborious and therefore less commonly performed.

Ultimately, *molecular genetic* confirmation of the underlying disorder should be sought. Both for Pompe disease and for McArdle disease common mutations have been described, but there is also a growing number of private mutations. With the

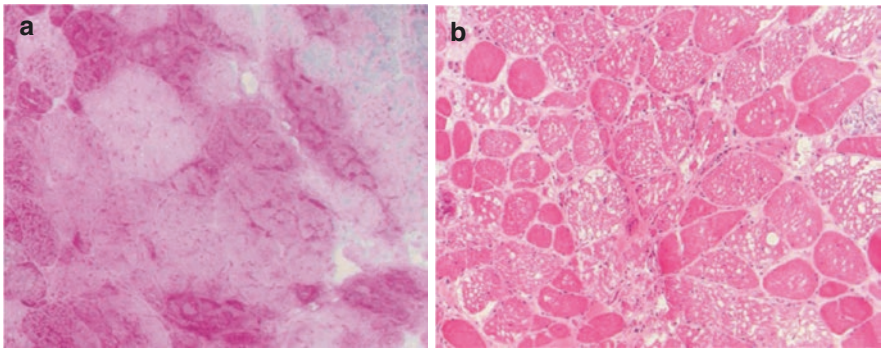


Fig. 12.4 Muscle biopsy in a patient with Pompe disease. (**a**) PAS stain showing glycogen accumulation. (**b**) HE stain showing increased variation in muscle fibre size with intracellular vacuoles

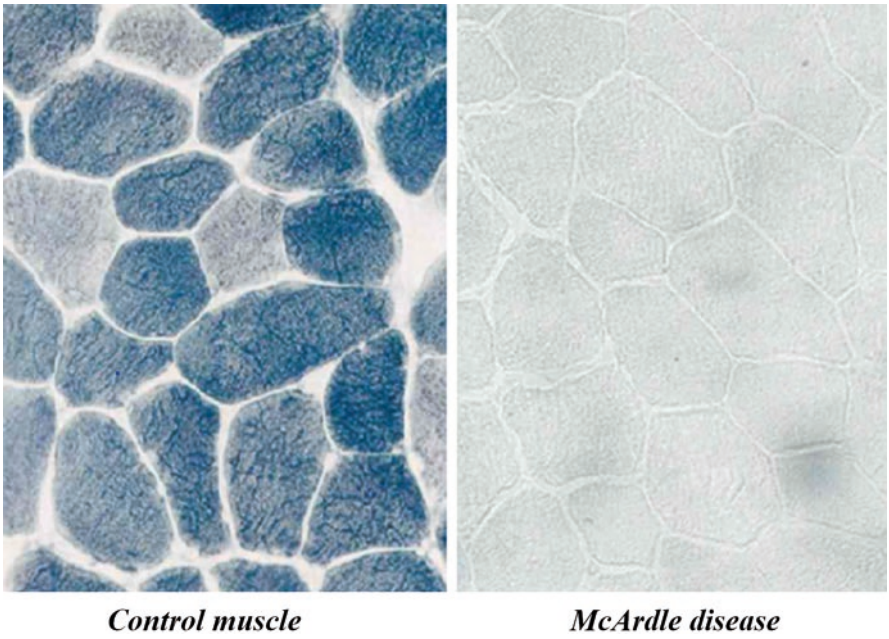


Fig. 12.5 Muscle biopsy in McArdle disease (myophosphorylase stain)

advent of sophisticated molecular genetic techniques (next-generation sequencing) an increasing number of patients with limb-girdle weakness and hyperCKemia will be diagnosed with possible Pompe disease. In many cases, however, sequence variants of unknown significance will require additional investigations (MRI, biopsy, enzyme activity analysis) to confirm the diagnosis.

Diagnostic Testing in Disorders of Fatty Acid Metabolism

In *clinical practice*, the neurointensivist will only very rarely be required to treat patients with multiorgan manifestations of FAO disorders, unless for neonatal cases. Hence, exercise-induced episodes of rhabdomyolysis and myoglobinuria, especially if recurrent and preceded by fasting, should always raise suspicion towards a hereditary disorder of FAO. Due to their phenotypical similarity, classification of the individual disorders always requires laboratory support.

Routine *biochemistry panels* including CK, myoglobin, glucose, liver function tests (LFT), lactate and even ketone bodies tend to be normal in the free interval between episodes. Nevertheless, they are obviously important for the emergency management of rhabdomyolytic episodes.

Plasma acylcarnitine profiles in dried blood spots are the mainstay for establishing the diagnosis of a FAO defect. In the stable phase, a normal acylcarnitine profile may be observed, whereas during episodes of rhabdomyolysis the acylcarnitine

profile is almost always abnormal and, depending on the pattern of acylcarnitines, also indicative of the underlying biochemical defect (Fig. 12.3). *Organic acids* in blood and urine might also show specific changes, but with the advent of acylcarnitine analysis, they are nowadays rarely performed.

EMG will show normal or only non-specific findings and is therefore not helpful to secure the diagnosis of a FAO defect.

Muscle biopsies may show mild myopathic changes and increased amounts of lipid in type-1 fibres, but may also be normal. Massive lipid storage is characteristic, but not definitive, for primary carnitine deficiency or multiple acyl-CoA dehydrogenase deficiency (MADD).

Molecular genetic analysis is therefore mandatory for final confirmation of the diagnosis.

General Principles of Management

Metabolic myopathies may manifest with fixed muscle weakness (Pompe, MADD), exercise intolerance (McArdle, CPT-2), or a combination of both (Table 12.3). The management of metabolic myopathies is therefore guided by which of these features is prominent.

With **Pompe disease**, assessments of cardiac (ECG, Echo) and respiratory function (vital capacity, maximum inspiratory pressure, early morning blood gases, bodyplethysmography) must be performed in regular intervals; if VC falls below 60% also sleep and nocturnal ventilation have to be evaluated. Polysomnography is then recommended to investigate for sleep apnoea or alveolar hypoventilation. Cough peak flow values <160 L/min can identify patients at risk for impaired clearance of airway secretions. Appropriate measures (cardiac pacemaker, home ventilation non-invasive or via tracheostomy, mechanical cough assistance) have to be

Table 12.3 Key clinical syndromes in metabolic myopathies

Fixed weakness	
Glycogen storage disorders	Pompe, debrancher, Brancher, glycogenin
Lipid storage myopathies	Multiple acyl-CoA-dehydrogenase, short-chain acyl-CoA-dehydrogenase, primary carnitine deficiency, neutral lipid storage disease
Exercise intolerance, myoglobinuria	
Glycogen storage disorders	McArdle, Tarui, phosphorylase kinase, other glycolytic enzymes (very rare)
Lipid storage myopathies	CPT-2, VLCAD, trifunctional protein, Lipin-1 (children)
Respiratory chain disorders	mtDNA-encoded enzymes, nDNA-encoded enzymes, iron-sulfur cluster, CoQ10-deficiency

initiated following the existing guidelines for neuromuscular disorders [11]. Due to endothelial glycogen deposition, Pompe patients are at risk of arterial hypertension and formation of aortic and basilar aneurysms. Regular check-ups should therefore also include ultrasound investigation of aorta and cerebral circulation.

As patients with Pompe disease are prone to malnutrition, which might further deteriorate respiratory function, a high-protein diet is recommended [12].

Enzyme replacement therapy (ERT) with alglucosidase is the only established drug therapy for Pompe disease and results in temporary stabilization or improvement of muscular and cardiorespiratory function in over 50% of both infantile and adult patients [13]. ERT should be administered to all children and to those symptomatic adults in whom the predicted effects of ERT on muscle outcome would improve the functional status of the patient. It is given intravenously every 2 weeks at 20 mg/kg body weight.

Although no specific treatment is available, **McArdle disease** patients benefit from several interventions to improve exercise tolerance and protect against rhabdomyolysis [14, 15]: (1) Ingestion of carbohydrates (glucose or cane sugar) prior to exercise; (2) Adaptation of exercise habits (avoidance of short-term high-intensity exercise, utilization of the "second-wind" phenomenon by gradual increase of muscular strain); (3) moderate aerobic training (see above); (4) in rare cases trials with creatine monohydrate [16], vitamin B6 or ACE-inhibitors might be warranted, depending on the pathogenic mutation.

The primary goal in the management of **FAO defects** is avoidance of precipitating factors, such as strenuous prolonged exercise, extended fasting (>12 h), exposure to cold or emotional stress. Intercurrent infections should be treated early and aggressively with administration of i.v. glucose as an alternative metabolic fuel, and dehydration must strictly be avoided. A normocaloric, low-fat (<15% of total calories), high-carbohydrate diet can improve muscular capacity; moreover, glucose supplements before, during, and after extensive aerobic activities are recommended.

Defects of long-chain FAO (CPT-2, very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD), trifunctional protein (TFP)) respond well to a diet, which is low in LCFA, with dietary supplements of medium-chain triglycerides (1 g/kg body weight, 30% of calories), because the latter bypass the carnitine shuttle and enter the FAO cycle downstream of the biochemical defect [17]. Recently, another medium-chain fatty acid, triheptanoin, has proven some efficacy [18].

Primary carnitine deficiency is a treatable cause of a metabolic cardiomyopathy, if started early enough with high doses of L-carnitine (2–4 g/days).

In patients with multiple acyl-CoA-dehydrogenase deficiency, riboflavin (200–400 mg/day) in combination with coenzyme Q10 (600 mg/day) may dramatically improve muscle symptoms within a few days [19].

For all metabolic myopathies, moderate aerobic endurance training at 60–70% of the maximum heart rate has been reported to be beneficial in counteracting disuse atrophy and muscle weakness [20].

Management of Emergencies in Metabolic Myopathies

Glycogen Storage Disorders

Rhabdomyolytic episodes and consecutive renal failure are the main complications associated with McArdle disease and FAO defects; respiratory failure and cardiac morbidity (in infants) are the most important aspects to consider in Pompe disease.

Baseline intensive care management, such as correction of electrolyte imbalances, adequate caloric intake, and administration of i.v. glucose and nutrients, treatment of infections, and maintenance of adequate oxygenation and tissue perfusion will in many cases already suffice to prevent an impending metabolic crisis. Furthermore, care must be taken to avoid myotoxic substances, in particular statins, alcohol and muscle relaxants. Steroids should be discontinued or at least only be administered in the lowest possible dose.

In the majority of patients with **Pompe** disease, the diagnosis will have been established previously or can be clinically suspected based on limb-girdle and axial weakness. Not infrequently, however, patients might develop acute respiratory failure as the presenting symptom, usually associated with a respiratory tract infection or following an operation. In some instances, acute respiratory failure may simply reflect an insidious decompensation of progressive respiratory impairment. Alpha-glucosidase enzyme analysis in a dried blood spot should then be aimed for, which will in most, but not all, cases confirm the diagnosis.

Bedside respiratory assessment **(see online Video 1, Chap. 3)** is crucial for further management planning: Since diaphragmatic weakness is particularly common in Pompe disease, it should be specifically looked for. Clinically, patients report that lying flat increases dyspnea, as the auxiliary respiratory muscles cannot fully compensate for the impaired diaphragmatic function. Paradoxical breathing (**see online video link** https://doi.org/10.1136/jnnp-2013-305485) and failure to count aloud beyond 10 in one breath further indicate significant diaphragmatic dysfunction. This can be confirmed by measuring VC, which in supine position will be >20% reduced compared to upright position. Furthermore, function of the intercostal muscles, which are essential for exspiration, coughing, and clearance of airway secretions, should be tested with a peak-flow meter: a peak flow <160 L/min reflects inadequate airway clearance. Finally, diaphragmatic ultrasound can give accurate information on structure (diameter) and function (mobility) of the diaphragm, but this is hardly necessary in the acute situation. The indication for admission to ICU follows general guidelines, which have been set up for other neuromuscular disorders, such as Guillain-Barré syndrome [21] or myasthenia gravis. One has to keep in mind, however, that Pompe disease patients often do not regain lost motor functions, even if the respiratory crisis can be treated successfully. We therefore prefer early admission to the ICU for monitoring, safeguarding of airway clearance, and treatment of any underlying infection or other exacerbating factors, such as concomitant COPD.

Cardiac function is generally well preserved in late-onset patients, but echocardiography and continuous ECG monitoring are still recommended to exclude arrhythmias and hypertrophic cardiomyopathy.

Unlike in Pompe disease, **McArdle disease** patients not infrequently manifest with acute rhabdomyolysis as the presenting symptom. More commonly, however, alternative causes, such as physical exertion, fasting, or dehydration, are first suspected to be causative for the rhabdomyolytic episode; but it has to be kept in mind that some of these suspected etiologies may indeed only be exacerbating triggers for an underlying metabolic myopathy rather than themselves constitute the underlying problem. Particular emphasis should therefore be attributed to the patient's history: recurrent, strictly exercise-induced cramps, muscle swelling, and previous episodes of dark-coloured urine should focus the attention to an underlying hereditary metabolic myopathy, in particular if persistently elevated CK-values are reported. Masticatory and bulbar muscles may be affected in up to 60% of patients [22], though not usually severe enough to provoke aspiration. Nevertheless, swallowing should be assessed by a speech therapist or by indirect fibre laryngoscopy.

A seemingly simple, but potentially dangerous, trap is the use of intermittent pneumatic compression devices for venous thromboprophylaxis in ICU [23]. Because of the risk of developing ischemic limb necrosis and compartment syndrome, we strongly recommend the use of heparin prophylaxis instead.

The prognosis of McArdle disease largely depends on the appropriate management of rhabdomyolysis and renal failure, which is described in Chap. 8. If further episodes can be avoided, the prognosis is generally favourable, because the cardiac musculature is spared.

Fatty Acid Oxidation Disorders

The majority of patients with FAO defects are asymptomatic in everyday life. They come to the attention of the intensive care physician either in childhood with acute metabolic decompensation, hypoketotic hypoglycaemia, encephalopathy, and sometimes cardiomyopathy, or in adulthood with episodic rhabdomyolysis. Whilst the infantile cases tend to show a fulminant and often lethal course, adult patients usually make a full recovery. In adults, the symptoms may be very subtle with only myalgia, malaise, and moderate hyperCKemia—these patients only require hospital admission with close monitoring and i.v. fluids, but not necessarily in an ICU.

Intensive care treatment in these patients is primarily geared towards handling the rhabdomyolysis and its complications (see Chap. 8). Potential causative factors (prolonged fasting, exposure to cold, excessive alcohol consumption, excessive physical activity, vomiting, diarrhoea, infections, recent surgery, aspirin intake) should be sought and treated.

The key to the acute management of symptomatic patients entails prevention and treatment of catabolism and hypoglycaemia, which would further mobilize fatty

acids that cannot be metabolized. This is achieved by the provision of copious amounts of carbohydrates, preferentially intravenously: i.v. fluids should contain at least 10% dextrose and be applied at 2 ml/kg/h (=14 g/h for a 70 kg patient), with adjustments based on glucose levels [24]. The additional use of L-carnitine is controversial and cannot be generally recommended, unless for primary carnitine deficiency where it is essential for treatment [25].

Cardiac dysfunction, which is very rare in adult patients, is usually reversible with early, intensive therapy, correction of electrolyte imbalances, and diet modification. Restriction of LCFA and supplementary MCT oil (0.5 g/kg) and, more recently, triheptanoin [26], have been shown to improve heart function and promote metabolic stability.

However, for patients with multiple-acyl-CoA dehydrogenase deficiency, MCT are contra-indicated, because oxidation of all chain length fats is impaired with this particular beta-oxidation defect.

Certain medications should be used with caution: valproate inhibits FAO and is relatively contra-indicated; adrenaline stimulates lipolysis and may further worsen a FAO defect; propofol is a mixture of long-chain unsaturated and medium-chain fatty acids and may in higher doses supply large quantities of non-metabolizable LCFA.

Once discharged from hospital, all patients should be issued with an "emergency letter" stating the management of acute metabolic decompensations and emphasizing the importance of glucose infusions.

An algorithm for the management of patients with metabolic myopathies is shown in Table 12.4.

Planned Anaesthesia and Ventilation in ICU

As with all metabolic myopathies, potential malignant hyperthermia triggering substances, i.e. depolarizing muscle relaxants and volatile anaesthetics, must be avoided, even though there is only weak support in the literature [27] for a connection between glycogenoses or FAO disorders with malignant hyperthermia.

In **Pompe disease**, a decrease in blood pressure and cardiac output is the most likely reason for the occurrence of arrhythmias during induction of anaesthesia; therefore agents such as ketamine or midazolam, which maintain blood pressure, should be aimed for rather than, for example, propofol, sevoflurane or thiopental, which lower blood pressure. Short-acting opiates such as remifentanil are preferred when respiratory insufficiency is prevalent.

Generally, Pompe patients benefit from rapid initiation of ventilatory support, where non-invasive BIPAP via mask could avoid intubation, if oropharyngeal functions are intact (Table 12.5). Weaning attempts should only be undertaken if the precipitating factors (infection) have been dealt with and the patient is able to clear his airway secretions sufficiently. In many cases, however, patients will not reach their pre-morbid state again and will have to continue with NIV.

Table 12.4 Management algorithm for patients with metabolic myopathies

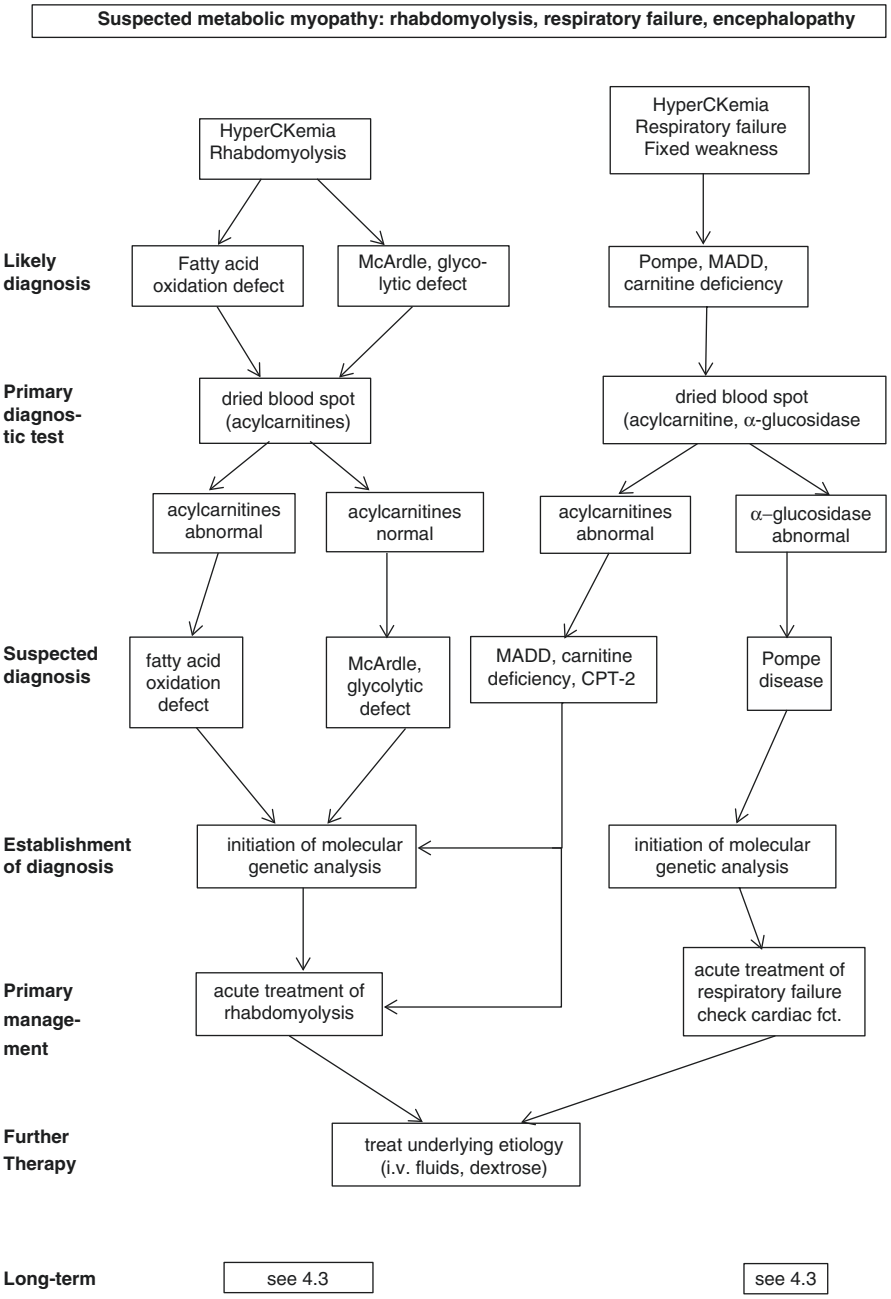


Table 12.5 Management of acute respiratory failure in metabolic myopathies (adapted from [28])

• Admission to ICU, insert arterial line
• Stop or reduce myotoxic drugs (statins, steroids, muscle relaxants, opiates)
• Treat infections and concomitant pulmonary diseases (COPD) aggressively
• Prefer non-invasive to invasive ventilation, if possible (airway clearance?)
• Improve mucociliary clearance (thoracic percussion, insufflation/exsufflation devices, high-frequency chest wall oscillations, bronchoscopy)
• Safeguard adequate nutrition for cachectic patients (nasogastric tube, gastrostomy)
• Evaluate pulmonary and neurological status of patients prior to acute respiratory failure, to decide upon indication for NIV after recovery from the acute episode
• Initiate long-term prophylactic measures (cough assist, pneumococcal and influenza vaccination) unless already implemented
• Continue enzyme replacement therapy during ICU treatment
• Consider palliative care, if sustained improvement does not seem achievable despite intensive treatment

Depending on the procedure, preference should be given to regional anaesthesia, as no complications related to local anaesthetics have been reported, so far.

Anaesthesia and care of the ventilated **McArdle and FAO** patient has to pay particular attention to maintenance of blood glucose, which should be monitored closely (initially 1–2 hourly). CK, liver enzymes, and lactate should be evaluated daily.

Propofol should be avoided (see above) in FAO patients. The use of tourniquets can cause muscle damage in McArdle patients and must therefore be limited to a minimum [27].

In contrast to muscular dystrophies, metabolic myopathies often do not cause permanent structural muscle damage and may therefore respond well to supportive treatment. Hence, the need for mechanical ventilation is mostly only temporary and tracheostomy should therefore not be performed too early.

Self Assessment Questions

1. When does the adult type of Pompe disease become manifest at the latest?

   (a) Ultimately at the age of 30
   (b) Ultimately at the age of 50
   (c) Ultimately at the age of 70
   (d) Probably no age limit (*)

2. By what age are most McArdle patients symptomatic?

   (a) Before the age of 10 years
   (b) Between 10–30 years (*)
   (c) Between 30–50 years
   (d) Over the age of 50

3. Which inheritance pattern is shown in most metabolic myopathies?

   (a) Autosomal recessive (*)
   (b) X-linked recessive
   (c) Mitochondrial

4. How can muscle weakness in Pompe disease be explained?

   (a) By structural changes in muscle (*)
   (b) By shortage of glycogen
   (c) By shortage of pyruvate
   (d) By shortage of glucose

5. How can muscle weakness after exercise in fatty acid metabolism disorder be explained?

   (a) By structural changes in muscle due to metabolic products
   (b) By lack of energy supply after depletion of glucose (*)
   (c) By acidosis after anaerobic metabolism

6. What is the role of carnitine in disorders of fatty acid metabolism?

   (a) Carnitine enhances the intracellular production of lipids
   (b) Carnitine carries lipids from the bloodstream into the cell
   (c) Carnitine carries lipids form the cytosol into the mitochondrion (*)
   (d) Carnitine plays a role in the mitochondrial lipid metabolism

7. Patients with a fatty acid oxidation disorder may develop respiratory distress. This is because of …

   (a) Muscle weakness
   (b) Disturbance of intrinsic pulmonary physiology
   (c) Both a and b (*)

8. Muscle weakness in fatty acid disorders occurs because of……

   (a) Shortage of ATP in certain situations
   (b) Direct toxic effect of intermediates on mitochondria
   (c) Both a and b (*)

9. Which of the following complications most likely occurs first in late-onset Pompe disease?

   (a) Arteriosclerosis
   (b) Cardiomyopathy
   (c) Hepatic insufficiency
   (d) Respiratory insufficiency (*)

A 40-year-old man has a lifelong history of exertion intolerance. He seeks help because of painful cramps and stiffness in his legs while climbing stairs. These symptoms are relieved by rest. He noted that these symptoms are less pronounced

after a meal and worse when he is hungry. Moderate exercise is tolerated pretty well but stiffness is still a problem; if he continues motor activity at a low level, symptoms improve.

10. Which diagnosis is most likely?

    (a) Fatty acid oxidation disorder
    (b) McArdle disease (*)
    (c) Mitochondrial myopathy
    (d) Pompe disease

11. Which diagnosis is most likely in an ambulant patient with axial weakness and shortness of breath at exercise or in supine position?

    (a) Fatty acid oxidation disorder
    (b) McArdle disease
    (c) Mitochondrial myopathy
    (d) Pompe disease (*)

12. Which symptom is most suspect for metabolic myopathy?

    (a) Dark urine after exercise
    (b) Fluctuating muscle weakness within minutes
    (c) Muscle cramps during exercise
    (d) Muscle symptoms in relation to fasting and eating (*)

13. What may most likely be found at EMG in patients with myopathy in fatty acid metabolism?

    (a) Paraspinal pseudomyotonic discharges
    (b) Increased insertion activity
    (c) Typical cramp features
    (d) No abnormalities (*)

14. Which of the following is most important for confirmation of myopathy due to fatty acid metabolism disturbance?

    (a) Molecular genetic analysis (*)
    (b) MR-spectroscopy of muscles
    (c) Muscle biopsy
    (d) Plasma acylcarnitine profile

15. Metabolic myopathies may manifest with fixed muscle weakness.

    (a) True (*)
    (b) False

16. Metabolic myopathies may manifest with exercise intolerance.

    (a) True (*)
    (b) False

17. Patients with Pompe disease are especially at risk of which of the following problems?

    (a) Aortic stenosis
    (b) Cerebral aneuryms (*)
    (c) Mitral insufficiency
    (d) Varicosis

18. Which diet is recommended in Pompe disease?

    (a) High-glycogen
    (b) High-lipid
    (c) High-protein (*)

19. Which of the following diseases can nowadays be treated with enzyme replacement therapies?

    (a) CPT-2 deficiency
    (b) McArdle
    (c) Pompe disease (*)
    (d) Mitochondrial myopathy

20. Which rescue diet is helpful in fatty acid oxidation defects?

    (a) High-glucose (*)
    (b) High-lipid
    (c) High-protein

21. Which diet is recommended in CPT-2 deficiency?

    (a) Low glucose
    (b) Low long-chain fatty acids (*)
    (c) Low medium-chain fatty acids
    (d) Low protein

22. Which is the main complication associated with McArdle disease?

    (a) Dehydration
    (b) High susceptibility to infections
    (c) Respiratory insufficiency
    (d) Rhabdomyolysis (*)

23. Which of the following substances should be avoided especially in patients with glycogen storage disease?

    (a) Alcohol (*)
    (b) Caffein
    (c) Soft drink
    (d) Tonic

24. Which of the following drugs should be avoided in patients with glycogen storage disease?

    (a) ACE-inhibitors
    (b) Morphinomimetic agents
    (c) Sodium channel inhibitors
    (d) Statins (*)

25. Which symptom is indicative of McArdle disease?

    (a) Brittle nails
    (b) Laceration of tendons
    (c) Muscle swelling (*)
    (d) Skin discoloration

26. Which of the following devices should be avoided in patients with McArdle disease?

    (a) Egg-crate mattress
    (b) Humidifiers
    (c) Pneumatic compression devices (*)
    (d) Soft pillows

27. Which drug may precipitate rhabdomyolysis in fatty oxidation disease?

    (a) Aspirin (*)
    (b) Carbamazepine
    (c) Melatonin
    (d) Thyroxyine

28. Which muscle relaxants are preferred to prevent rhabdomyolysis?

    (a) Depolarizing muscle relaxants
    (b) Non-depolarizing muscle relaxants (*)

29. Decrease in blood pressure should be avoided in anaesthesia in Pompe disease, to prevent……

    (a) Cardiac arrhythmias (*)
    (b) Rhabdomyolysis
    (c) Renal failure
    (d) Respiratory distress

30. Intubation may result in long term or definitive dependence on invasive ventilation in patients with metabolic myopathy.

    (a) True
    (b) False (*)

31. Which is the most likely presentation of so far undiagnosed Pompe disease?

    (a) Cardiac arrhythmia
    (b) Circulatory shock
    (c) Respiratory failure (*)
    (d) Rhabdomyolysis

References

1. Martiniuk F, Chen A, Mack A, Arvanitopoulos E, Chen Y, Rom WN, et al. Carrier frequency for glycogen storage disease type II in New York and estimates of affected individuals born with the disease. Am J Med Genet. 1998;79(1):69–72.
2. Santalla A, Nogales-Gadea G, Encinar AB, Vieitez I, González-Quintana A, Serrano-Lorenzo P, et al. Genotypic and phenotypic features of all Spanish patients with McArdle disease: a 2016 update. BMC Genomics. 2017;18(Suppl 8):819.
3. Goetzman ES, Alcorn JF, Bharathi SS, Uppala R, McHugh KJ, Kosmider B, et al. Long-chain Acyl-CoA dehydrogenase deficiency as a cause of pulmonary surfactant dysfunction. J Biol Chem. 2014;289(15):10668–79.
4. Giuliani L, Di Toro A, Urtis M, Smirnova A, Concardi M, Favalli V, et al. Hereditary muscle diseases and the heart: the cardiologist's perspective. Eur Hear J Suppl. 2020;22(Supplement_E):E13–9.
5. Kanungo S, Wells K, Tribett T, El-Gharbawy A. Glycogen metabolism and glycogen storage disorders. Ann Transl Med. 2018;6(24):474.
6. Menzella F, Codeluppi L, Lusuardi M, Galeone C, Valzania F, Facciolongo N. Acute respiratory failure as presentation of late-onset Pompe disease complicating the diagnostic process as a labyrinth: a case report. Multidiscip Respir Med. 2018;13(1):40248.
7. Tsujino S, Nonaka I, DiMauro S. Glycogen storage myopathies. Neurol Clin. 2000;18(1):125–50.
8. Quinlivan R, Jungbluth H. Myopathic causes of exercise intolerance with rhabdomyolysis. Dev Med Child Neurol. 2012;54(10):886–91.
9. Kluge S, Kühnelt P, Block A, Merkel M, Gocht A, Lukacs Z, et al. A young woman with persistent hypoglycemia, rhabdomyolysis, and coma: recognizing fatty acid oxidation defects in adults. Crit Care Med. 2003;31(4):1273–6.
10. Tarnopolsky MA. Metabolic myopathies. Contin Lifelong Learn Neurol. 2016;22(6):1829–51.
11. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002;166(4):518–624.
12. Slonim AE, Coleman RA, McElligot MA, Najjar J, Hirschhorn K, Labadie GU, Mrak R, Evans OB, Shipp E, Presson R. Improvement of muscle function in acid maltase deficiency by high-protein therapy. Neurology. 1983;33(1):34–8.
13. Harlaar L, Hogrel JY, Perniconi B, Kruijshaar ME, Rizopoulos D, Taouagh N, et al. Large variation in effects during 10 years of enzyme therapy in adults with Pompe disease. Neurology. 2019;93(19):e1756–67.
14. Preisler N, Haller R, Vissing J. Exercise in muscle glycogen storage diseases. J Inherit Metab Dis. 2015;38(3):551–63.
15. Vissing J, Haller R. The effect of oral sucrose on exercise tolerance in patients with McArdle's disease. N Engl J Med. 2003;349(26):2503–9.

16. Vorgerd M, Grehl T, Jager M, et al. Creatine therapy in myophosphorylase deficiency (McArdle's disease): a placebo-controlled crossover trial. Arch Neurol. 2000;57:956–63.
17. Behrend A, Harding C, Shoemaker J, Matern D, Sahn D, Elliot D, et al. Substrate oxidation and cardiac performance during exercise in disorders of long-chain fatty acid oxidation. Mol Genet Metab. 2012;105(1):110–5.
18. Vockley J, Charrow J, Ganesh J, Eswara M, Diaz GA, McCracken E, et al. Triheptanoin treatment in patients with pediatric cardiomyopathy associated with long chain-fatty acid oxidation disorders. Mol Genet Metab. 2016;119(3):223–31.
19. Horvath R. Update on clinical aspects and treatment of selected vitamin-responsive disorders II (riboflavin and CoQ10). J Inherit Metab Dis. 2012;35(4):679–87.
20. Haller RG, Wyrick P, Taivassalo T, Vissing J. Aerobic conditioning: an effective therapy in McArdle's disease. Ann Neurol. 2006;59(6):922–8.
21. Lawn ND, Fletcher DD, Henderson RD, Wolter TD, Wijdicks EFM. Anticipating mechanical ventilation in Guillain-Barré syndrome. Arch Neurol. 2001;58(6):893–8.
22. Kouwenberg CV, Voermans NC, Quinlivan R, Van Den Engel-Hoek L. Mastication and oral motor function in McArdle disease: patient reported complaints. J Neuromuscul Dis. 2018;5(3):353–7.
23. Bollig G. McArdle's disease (glycogen storage disease type V) and anesthesia—a case report and review of the literature. Paediatr Anaesth. 2013;23(9):817–23.
24. British Metabolic Disease Group. Adult emergency management: long-chain fatty acid oxidation defects. 2018.; Available from: http://www.bimdg.org.uk/store/guidelines/ADULT_FAOD-rev_2015_428281_09012016.pdf.
25. Magoulas PL, El-Hattab AW. Systemic primary carnitine deficiency: an overview of clinical manifestations, diagnosis, and management. Orphanet J Rare Dis. 2012;7(1):2012.
26. Vockley J, Marsden D, McCracken E, DeWard S, Barone A, Hsu K, et al. Long-term major clinical outcomes in patients with long-chain fatty acid oxidation disorders before and after transition to triheptanoin treatment—a retrospective chart review. Mol Genet Metab. 2015;116:53–60.
27. Bollig G, Mohr S, Ræder J. McArdle's disease and anaesthesia: Case reports. Review of potential problems and association with malignant hyperthermia. Acta Anaesthesiol Scand. 2005;49(8):1077–83.
28. Boentert M, Prigent H, Vardi K, Jones HN, Mellies U, Simonds AK, et al. Practical recommendations for diagnosis and management of respiratory muscle weakness in late-onset Pompe disease. Int J Mol Sci. 2016;17(10):1735.

Chapter 13
Intensive Care Implications in Primary Mitochondrial Disease

Jelle van den Ameele, Yi Shiau Ng, Grainne S. Gorman, and Rita Horvath

Introduction

Mitochondria are organelles that play a key role in many different cellular processes. They are best known for their role in energy production through respiration but are also involved in maintenance of the redox balance, amino acid and lipid metabolism, calcium homeostasis, temperature regulation, apoptosis and much more.

Mitochondrial energy production occurs through oxidative phosphorylation, whereby electrons travel through four large complexes located at the inner mitochondrial membrane. Electrons enter the electron transport chain (ETC) through complex I or II and are donated to oxygen at complex IV. Complexes I, III and IV use the energy derived from these electrons to pump protons (H^+) from the matrix into the intermembrane space. This results in a proton gradient, used by the ATP synthase complex (complex V) to generate ATP from ADP.

J. van den Ameele
Department of Clinical Neurosciences, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK

MRC Mitochondrial Biology Unit, University of Cambridge, Cambridge, UK
e-mail: jv361@cam.ac.uk

Y. S. Ng · G. S. Gorman
Wellcome Centre for Mitochondrial Research, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK

NHS Highly Specialised Service for Rare Mitochondrial Disorders, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
e-mail: yi.ng@newcastle.ac.uk; grainne.gorman@ncl.ac.uk

R. Horvath (✉)
Department of Clinical Neurosciences, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK

John Van Geest Cambridge Centre for Brain Repair, University of Cambridge, Cambridge, UK
e-mail: rh732@medschl.cam.ac.uk

M. Damian, M. de Visser (eds.), *Emergencies in Neuromuscular Disorders*,
https://doi.org/10.1007/978-3-030-91932-0_13

Although defects in many mitochondrial processes may be involved in human disease, mitochondrial diseases are defined as genetic disorders that impair oxidative phosphorylation and mitochondrial ATP synthesis. Together, they affect about 1 in 5000 adults and children [1], and may lead to a range of well-defined, but overlapping, clinical syndromes (Table 13.1). However, the clinical diagnosis of a mitochondrial disease is often challenging. Many of the presenting symptoms are vague (e.g. chronic fatigue or abdominal discomfort), some of the typical complaints or signs are common in the general population (e.g. migraine or diabetes mellitus), and the range of phenotypes associated with mitochondrial disease is continuously expanding.

Diagnostic Work-Up in Suspected Mitochondrial Disease at the ICU

When a patient presents with one of the classical mitochondrial syndromes (see Table 13.1.), a clinical diagnosis can often be made and will then guide downstream targeted genetic analysis. However, most patients do not present with a clinically recognizable syndrome, and diagnosis is often difficult and delayed, both in children and adults [3]. Nevertheless, some symptoms, and in particular the co-occurrence of these symptoms in a patient or their family might raise suspicion of an underlying mitochondrial disease. For this purpose, mitochondrial disease criteria (MDC) have previously been established, based on scoring the presence of specific symptoms that are typically seen in patients [4] (Table 13.2). Traditionally, these criteria were used to decide on the need for invasive investigations like muscle biopsy. With the advent of next-generation sequencing, the diagnostic approach has changed significantly, but the same diagnostic criteria have recently been validated in a clinical context where both children and adults were diagnosed by whole exome or mtDNA sequencing [5]. A diagnostic flowchart including these criteria and current next-generation sequencing approaches is shown in Fig. 13.1 (adapted from [3]).

Neither the MDC nor the flowchart are routinely used in the everyday clinic, and they have not been validated in the emergency or intensive care context as far as we are aware. However, we believe that their value remains in raising clinical suspicion and guiding subsequent diagnostic work-up.

Genetics of Mitochondrial Disease

The proportion of genetic diagnosis in mitochondrial disease has significantly improved over recent years [3]. However, some patients do not yet receive a molecular genetic diagnosis, and clinical suspicion of mitochondrial disease is further supported only by biochemical or histological studies. Thanks to novel genotyping

Table 13.1 Typical[a] mitochondrial syndromes necessitating ICU admission

Syndrome	Commonly affected genes	Usual age of onset of symptoms	Clinical manifestations	Complications that may require critical care management
MELAS (Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episodes)	*MT-TL1* (m.3243A>G) and *POLG* Other mtDNA mutations	Children and adults (typically <40 years old)	Encephalopathy, stroke-like episodes and seizures, myopathy	Medically refractory/super-refractory seizures, mediating stroke-like episodes, arrhythmia, cardiomyopathy with heart failure, lactic acidemia, intestinal pseudo-obstruction, renal failure
MERRF (Myoclonic Epilepsy with Ragged Red Fibres)	*MT-TK* (m.8344A>G)	Children and adults	Encephalopathy, seizures and myoclonus, ataxia, optic atrophy	Generalized seizures, stroke-like episodes similar to MELAS (rare), cardiomyopathy with heart failure, arrhythmia, lactic acidaemia, respiratory failure (could be central-mediated or neuromuscular weakness)
Kearns-Sayre syndrome	Single, large-scale mtDNA deletion	Children and adolescents	Chronic progressive external ophthalmoparesis, retinitis pigmentosa, ataxia, heart block, short stature, deafness and dementia	Cardiac conduction defects (heart block), respiratory failure due to myopathy, complications of diabetes; seizures (cerebral folate deficiency) For other coauthors: Seizures are very uncommon in KSS, and cerebral folate deficiency and leukodystrophy are more commonly associated with cogntive impairment and hyperkinetic movement disorder

(continued)

Table 13.1 (continued)

Syndrome	Commonly affected genes	Usual age of onset of symptoms	Clinical manifestations	Complications that may require critical care management
Pearson syndrome	Single, large-scale mtDNA deletions	Infants	Lactic acidosis in infants, diarrhoea, abdominal pain, diabetes, pancreatic enzyme deficiency, sideroblastic anaemia, neutropenia, thrombocytopenia, bone marrow failure, hyperalaninemia, lactic aciduria, short stature, severe mineral and vitamin deficiencies	Transfusion-dependent anaemia, Life-threatening infections/bleeds (bone marrow failure); lactic acidosis; cardiac and liver failure
Leigh syndrome	Many nuclear and mtDNA mutations	Infants	Stepwise neurodevelopmental regression in children after infective illness	Central respiratory failure and other brainstem dysfunction
MNGIE (Mitochondrial Neuro-Gastro-Intestinal Encephalopathy)	*TYMP*	Childhood	Chronic progressive external ophthalmoparesis, gastrointestinal dysmotility, bacterial overgrowth, progressive weight loss and cachexia, peripheral neuropathy, hearing loss, leukoencephalopathy	Acute abdominal pain, intestinal pseudo-obstruction, aspiration pneumonia
Benign reversible myopathy	*MT-TE* (m.147674T>C/G)	Infants	Profound hypotonia, respiratory and feeding difficulties and lactic acidosis in infants	Severe lactic acidosis, respiratory insufficiency, feeding difficulties
Alpers-Huttenlocher syndrome	*POLG*, *TWNK* (rare)	Children	Refractory seizures, psychomotor regression, hepatopathy; valproic acid exposure inducing severe liver dysfunction; intestinal dysmotility; pancreatitis; cardiomyopathy (rare)	Medically refractory/super-refractory seizures, encephalopathy, liver failure, pancreatitis;,ventilation disorders

[a]Many other mitochondrial syndromes associated with specific genes or mutations have been described, and some of these have typical clinical presentations that may lead to ICU admission too. We refer the reader to more specialist literature [2]

Table 13.2 Mitochondrial disease criteria (MDC) (modified from Morava et al. 2006 [4, 5]) Every element scores 1 unless indicated differently. The severity of each finding is not taken into account due to the progressive nature of the disease. A score of 1 indicates unlikely mitochondrial disorder, score 2–4: possible mitochondrial disorder, score 5–7 probable mitochondrial disorder and score ≥ 8 definite mitochondrial disorder

Muscular	Myopathy or muscle weakness Muscle pain Ophthalmoplegia (chronic progressive, with ptosis) Exercise intolerance Abnormal EMG Motor developmental delay	Maximal score for muscular involvement is **2**
Neurological	Developmental delay Intellectual deficit Migraine Dystonia (extrapyramidal signs) Ataxia (cerebellar signs) Spasticity (pyramidal signs) Neuropathy Seizures/encephalopathy (stroke-like episodes)	Maximal score for neurological involvement is **2**
Multisystem	Any gastrointestinal tract disease Growth delay or failure to thrive Endocrine abnormalities (diabetes mellitus, hypothyroidism) Bone marrow failure Visual deficit (optic atrophy, retinitis pigmentosa, cataracts) Sensorineural hearing loss Renal tubular acidosis Cardiomyopathy or arrhythmia	Maximal score for multisystem involvement is **3**
Total clinical score		*Total clinical score is maximal 4*
Metabolic	Lactate high (at least on 2 occasions): 2 points Alanine high (at least on 2 occasions): 2 points Urinary Krebs' cycle intermediates or ethyl malonic and methyl malonic acid 3 methyl glutaconic acid Elevated CSF lactate, alanine: 2 points	Total score for metabolic and imaging signs is maximal **4**
Imaging /other	Leigh disease: 2 points Stroke like episodes: 2 points Basal ganglia/brain stem Lactate peak on MRS	
Total MDC score (clinical, metabolic, imaging)		*Total score without histology is maximal 8*

(continued)

Table 13.2 (continued)

Morphology[a]	Ragged red/blue fibres: Score 4 points COX-negative fibres: Score 4 points Reduced COX staining: Score 4 points Reduced SDH staining SDH positive blood vessels: Score 2 points Abnormal mitochondria on EM: Score 2 points	*Total morphology is maximal 4*
Total MDC score		*Total score is maximal 12*

Abbreviations: *CSF* Cerebrospinal fluid, *COX* Cytochrome c oxidase, *SDH* Succinate dehydrogenase, *EMG* Electromyography, *EM* Electron microscopy, *MRS* Magnetic resonance spectroscopy
[a]We aim to use the MDC score in bedside diagnostics for clinical decision-making and move away from invasive diagnostic procedures

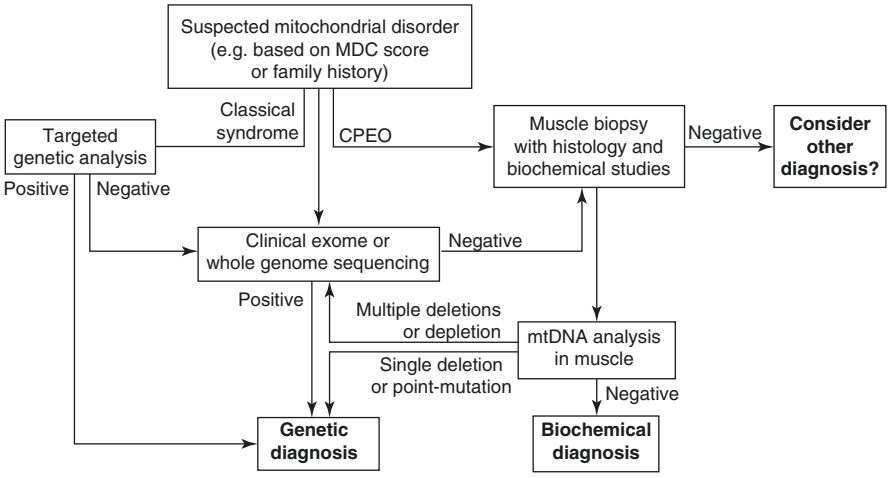


Fig. 13.1 Diagnostic flowchart for suspected mitochondrial disease (adapted from Schon et al. 2020 [3])

and phenotyping technologies, we expect this proportion to continue to decrease in the near future.

Currently (in 2020), over 300 nuclear genes [3, 6] are known to cause mitochondrial disease, with autosomal recessive, autosomal dominant and X-linked inheritance patterns, affecting both children and adults. However, in adult patients, mitochondrial disease is mainly caused by mutations in the mitochondrial genome (mtDNA) and then shows exclusive maternal inheritance. The mitochondrial genome is a 16.6 kb circular double-stranded DNA molecule that is located in the mitochondrial matrix and contains 37 intron-less genes: 13 genes encode essential peptides of 4 out of the 5 respiratory chain complexes (complex I, III, IV and V); the remaining genes are 12 transfer RNA (tRNA) and 2 ribosomal RNA (rRNA) genes required for local protein synthesis. Because every nucleated cell contains many

copies of mtDNA, cells can hold a mixture of different mitochondrial genomes, which is called heteroplasmy. Much of the mtDNA variation is neutral and does not cause disease, but when a deleterious variant arises, pathogenicity is determined in part, by the nature of the variant and the level of heteroplasmy required to manifest a biochemical defect or clinical phenotype. Heteroplasmy levels can differ between cells and tissues of a single individual, and it is this variability that likely contributes, in part, to the phenotypic heterogeneity encountered in mitochondrial disease.

MtDNA defects are not always inherited through the germline but can also arise during development and aging. This may lead to point mutations, large-scale deletions and progressive mtDNA depletion, usually as a consequence of primary defects in nuclear genes involved in maintenance and replication of the mtDNA. When these secondary mtDNA defects reach a high level in individual cells, they can cause a similar clinical phenotype to that seen for primary mtDNA disorders by directly affecting mitochondrial function.

General Approach to Critical Illness in Patients with Mitochondrial Disease

Preventing Acute Illness in Mitochondrial Disease

Because no curative treatment is available for mitochondrial diseases, a major aspect of their management is supportive therapies and the prevention of acute illness. Emergencies in mitochondrial disease are often related to deterioration of chronic conditions or to environmental changes that alter energy demands, like febrile infections, surgery and anaesthesia, dietary changes, prolonged fasting or specific medications (such as valproic acid [7]).

It is conceivable that stressors may induce a more catabolic state, whereby cells need to rewire metabolic pathways and increase utilization of intracellular stores of amino acids, fatty acids, nucleotides and carbohydrates. In the context of chronic mitochondrial dysfunction, this metabolic flexibility is often impaired and intracellular reserves are exhausted, resulting in increased production of toxic metabolites like reactive oxygen species that damage the cellular and extracellular environment. Together, this may lead to exacerbation of pre-existing conditions and even generalized multisystemic decompensation, particularly in children.

In order to prevent acute deterioration, most patients with mitochondrial disease will require life-long surveillance, involving multiple medical and allied-health disciplines. This is usually organized with input from specialist centres, experienced in the diagnosis and management of mitochondrial disease. Routine follow-up includes regular screening for recognized complications. Surgery needs to be properly planned, and patients need to be educated about avoiding precipitating factors, in particular specific medications (see below) [7], medication compliance and prolonged periods of fasting. End-of-life care planning should be integrated into a

framework for routine clinical practice for those with such life-limiting disorders. In addition, carrying an emergency care plan or a medical alert bracelet could be considered for some patients, which will help to guide decisions for clinicians in an acute care setting.

Management of Patients with Mitochondrial Disease in the Critical Care Setting

When patients are admitted to an ICU, they do not necessarily have a previous diagnosis of mitochondrial disease. Nevertheless, establishing a diagnosis of mitochondrial disease is important because the severity and chronicity of pre-existing problems, and the multi-system involvement will pose additional challenges that may require specialist expertise. Patients will often have respiratory insufficiency or dysphagia due to myopathy; they may have a cardiomyopathy or arrhythmia, suffer from gastrointestinal problems that lead to malnutrition and intestinal pseudo-obstruction, or have epilepsy, bone marrow failure or diabetes mellitus. In addition, mitochondrial dysfunction will further increase vulnerability of many other body systems when confronted with acute illness. Cardiac decompensation due to cardiomyopathy or arrhythmias, and acute cerebral events like seizures or stroke-like episodes (seizure-mediated) are well-recognized and are the leading causes of death in patients with mitochondrial disease [8]. Renal failure, acute liver failure, ventilator failure, encephalopathy with central respiratory depression, lactic acidaemia, and endocrine disturbances like diabetes, hypo- and hyperthyroidism, adrenal insufficiency or hypoparathyroidism, may all further contribute to the significant morbidity and threefold (for adults) or sixfold (for children) increased mortality in hospitalized patients with mitochondrial disease [9].

Once a diagnosis is made, there is little evidence to guide the specific management of patients with mitochondrial disease in the critical care setting [10]. Treatable metabolic conditions should of course be excluded (see Chap. 11), but in the absence of curative treatment for most mitochondrial diseases, recommendations are mainly based on expert-opinion guidelines.

Some general recommendations have been described in [11] and are copied here in Table 13.3. Advice on the specific management of more frequent acute complications of mitochondrial disease is described in the following chapters.

The Newcastle Mitochondrial Disease Clinical Guidelines provide expert guidance to health professionals about the management of various aspects of mitochondrial disease. They have been developed using consensus expert opinion sourced from the National Commissioning Group Service for Rare Mitochondrial Diseases for Adults and Children in Newcastle, UK, with associated experts from other hospitals. The guidelines are a very useful resource for any clinician involved in care for patients with mitochondrial disease and are available online at: https://www.newcastle-mitochondria.com/clinical-professional-homepage/clinical-publications/clinical-guidelines/

Table 13.3 General recommendations for critical illness in patients with mitochondrial disease (adapted from Parikh et al. 2017 [11])

1. Specific decisions about patient management including hospitalization require clinical judgment and should be case-specific. Decisions should reflect the individual patient's presentation as well as an understanding of the aetiology for the acute decompensation and the pathophysiology of the underlying mitochondrial disorder.
2. Patients with a mitochondrial disease should carry an emergency care plan that details their underlying disorder and provides management recommendations.
3. Patients with a mitochondrial disease should consider wearing a medical alert bracelet when appropriate, depending on their clinical symptomology.
4. Mitochondrial patients should take precautions to prevent entering catabolism, especially when exposed to medical stressors, including avoiding prolonged fasting and receiving dextrose-containing IV fluids before, during, and after procedures and surgeries.
5. Evaluation of a mitochondrial patient in the acute setting should include evaluation of routine chemistries, creatine kinase, glucose, transaminases, and lactate; all other testing is as clinically indicated, although one must keep in mind the potential for cardiac and neurologic decompensations in these patients.
6. Treatment during acute decompensation should include dextrose-containing* IV fluids, stopping exposure to potentially toxic medications, and correction of any metabolic derangements. IV fluid rate should be based on the clinical situation. Outpatient mitochondrial therapies should be continued when possible.
7. Lipids can be used when needed in mitochondrial patients, even in the presence of secondary fatty acid oxidation dysfunction.
8. Valproate should be avoided in patients with mitochondrial disease.
9. Repeat neuroimaging should be considered in any mitochondrial patient with an acute change in neurologic status.

Severe, Infantile Mitochondrial Disease

Genetic Causes and Pathophysiology

Mitochondrial diseases often manifest in infants, and there are several characteristic tissue specific and multisystem presentations reported in this age which require admission to the ICU. These diseases are both clinically and genetically very heterogeneous. For example, in a cohort of 42 infants with suspected mitochondrial disease, the molecular cause involved >10 different nuclear mitochondrial disease genes, subunits of mitochondrial respiratory chain enzymes, assembly genes, genes involved in mitochondrial translation, mtDNA maintenance or other mitochondrial functions [12]. However, there are several non-mitochondrial diseases with similar clinical presentation [11, 13, 14].

There is growing evidence that rare single gene disorders present in the neonatal period, therefore there is a need for rapid and comprehensive genetic testing in ICUs to assist acute and long-term clinical decision making [15]. In specialized centres rapid (turnaround time 2–3 weeks) whole genome sequencing has been used to identify the molecular diagnosis in 21% of infants in a large cohort of 567 samples. This study showed that the clinical presentation was a poor predictor of the

molecular diagnosis in 90% of cases, and the diagnosis affected the clinical management in more than 65% of patients (83% of neonates) including modification of treatments and care pathways or guiding palliative care decisions. Therefore, if biochemical or imaging studies do not highlight a specific diagnosis, WGS has the potential to be a first-line diagnostic tool in critically ill children in ICU [15].

Manifestations

There are a few phenotypes which need special attention, as treatment options may vary based on the exact molecular defect such as severe infantile muscle weakness (*floppy baby*), severe *lactic acidosis with metabolic crisis*, acute *infantile liver failure* (see under Liver failure in mitochondrial disease) and *multi-organ failure* in infants.

There are a number of non-mitochondrial neuromuscular (e.g. spinal muscular atrophy, congenital muscular dystrophies, congenital myopathies, congenital myasthenic syndromes) and metabolic (such as inborn errors of metabolism, congenital defects of glycosylation) diseases which can manifest in severely ill infants, therefore extensive investigation of these patients is important. Laboratory investigations include creatine kinase (CK), lactate (in serum and CSF), amino acids, organic acids, fatty acids, very long chain fatty acids, white cell enzymes and national newborn blood spot screening programmes and may identify some of the underlying causes. Neuroimaging may be also useful in the differential diagnosis, however rapid and unbiased genetic studies (trio exome/genome) in these infants are of utmost importance to achieve an early diagnosis enabling a timely treatment and guiding management decisions [15]. Although many of the severe infantile conditions are progressive and fatal, there are some rare treatable genetic forms [16] and some of these result in an infantile reversible disease presentation, albeit exceptionally rare [16, 17].

Management

Lactic acidaemia is frequent in infants with mitochondrial disease in ICU. Under stable clinical conditions, this process may remain well compensated and does not require specific therapy. However, especially in situations with altered energy demands, such as febrile infections or longer periods of fasting, children with mitochondrial disorders have a high risk of metabolic decompensation with exacerbation of hyperlactaemia and severe metabolic acidosis. Unfortunately, there are no controlled studies assessing the treatment of this critical condition, and clinical outcome is often unfavourable. There are some expert-based suggestions to treat lactic acidosis including dietary recommendations, buffering strategies and specific drug therapy using sodium bicarbonate, sodium citrate, THAM (Tris-hydroxymethyl-amino-methane) buffering or less frequently dichloroacetate [18].

These strategies can stabilize the metabolic crisis enabling time to achieve the genetic diagnosis, which will guide further treatment of these conditions.

Further options to support OXPHOS in critically ill infants are supplementation of respiratory chain cofactors, which may result in significant improvement in some conditions [16]. This includes thiamine, biotin, riboflavin, coenzyme Q10 or carnitine or ketogenic diet in defects of pyruvate dehydrogenase deficiency [18]. However, ketogenic diet is contraindicated in patients with known fatty acid oxidation disorders and pyruvate carboxylase deficiency [18].

Outcome

Many of the severe infantile mitochondrial diseases are progressive and do not recover. However, in contrast to fatal infantile mitochondrial and neuromuscular diseases (such as severe congenital myopathies or muscular dystrophies), patients with reversible infantile mitochondrial myopathy (m.14674T>C in mt-tRNA^{Glu}) or hepatopathy (*TRMU* mutations) have an excellent prognosis and spontaneously improve and recover after the 6–12 month of life, therefore these patients should receive all intensive care and life-sustaining measures. Mechanical ventilation, tube feeding, monitoring and treating other organ dysfunctions result in most cases in regression of clinical symptoms. Because some patients present with low levels of L-carnitine or mitochondrial cofactors (coenzyme Q10, thiamine, riboflavin), supplementing these factors may facilitate the clinical improvement of this condition. Low dietary cysteine intake has been suggested to compromize mitochondrial translation in infants carrying the homoplasmic m.14674T>C/G mutation, therefore supplementation with L-cysteine or N-acetyl-cysteine can be considered, especially in infants with clinical manifestations [19]. Furthermore, recent studies highlight the importance of nutrition in mitochondrial energy metabolism, therefore supplementation of critically ill infants with amino acids and nutrients may have a more important role than it has been suggested previously [20].

Case Vignette 1

A 3-months-old infant developed subacute severe muscle weakness, respiratory failure and feeding difficulties (floppy baby), requiring mechanical ventilation, tube feeding, and supportive treatment on ICU. Mitochondrial disease was suspected because of high lactate. Muscle biopsy showed numerous COX-negative RRFs and severe complex I and IV defects. Spontaneous improvement was observed at 6 months of age. Delayed motor milestones, some muscular hypotonia, but able to walk at 2.5 years of age. MtDNA analysis detected the homoplasmic m.14674T>C mutation, which was done by Sanger sequencing. Based on the clinical presentation and high lactate the clinicians wanted to screen directly for the genetic form leading to a reversible disease.

Learning Points
In infants with clinical signs of muscle weakness and high lactate, the reversible infantile form of mitochondrial disease has to be considered and tested as soon as possible. This has relevant implications about the prognosis and the ITU treatment of the patients.

Stroke-like Episodes and Epileptic Encephalopathy

Genetic Causes and Pathophysiology

Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes (MELAS) is one of the most severe syndromes in mitochondrial disease [21]. Stroke-like episodes, the acute presentation of MELAS syndrome, are clinically characterized by headache, nausea and vomiting, encephalopathy, focal-onset seizures with or without associated focal neurological deficits, with cortical and subcortical signal abnormalities that are usually cross-vascular territories identified on MRI brain. While stroke-like episodes were originally described in individuals under the age of 40, late-onset presentation is increasingly recognized [22]. The first genetic defect linked to MELAS was a heteroplasmic mitochondrial DNA mutation, m.3243A>G, which accounts for ~80% of the cases reported in the early literature [23]. Many other rarer mtDNA mutations such as m.3271T>C (*MT-TL1*) and m.13513G>A (MT-ND5) have also been linked to MELAS [24]. More recently, recessive mutations in the mitochondrial polymerase gamma (*POLG*) have emerged as another important cause of refractory/super-refractory seizures and stroke-like episodes [25–27].

Manifestations

The diagnosis of a stroke-like episode requires the combination of clinical assessment, cranial MRI and electroencephalogram (EEG). A mitochondrial stroke-like episode is a subacute event, driven by seizure activity in a patient with genetic mitochondrial disease [28]. It should not be confounded with a typical vascular stroke involving acute loss of function symptoms, and when this occurs in a patient with known mitochondrial disease, the presence of mitochondrial disease should not delay conventional evidence-based treatment for acute ischemic or haemorrhagic stroke. Instead, symptom onset is often subacute, may evolve over several days and is frequently accompanied by focal-onset seizures. Neurological symptoms are complex, may have positive (e.g. hallucinations or focal motor seizures) and negative (e.g. visual field defect, sensory deficit or motor weakness, apraxia and aphasia) signs, include neuropsychiatric disturbances, and are typically not limited to vascular territory.

These potentially treatable seizure-mediated episodes can present at any age and are typically associated with confluent cortical/subcortical MRI changes and EEG abnormalities. Potential triggers are often metabolic stressors including infection, gut dysmotility, dehydration, prolonged fasting or changes in anti-seizure medication. All patients with previous stroke-like episodes, as well as their carers, should be provided with an emergency personalized care plan which they can present to their local primary care and emergency services. An example care plan is shown in Fig. 13.2.

Management

The limitations in our understanding of disease mechanisms are reflected in the controversy surrounding the acute management of stroke-like episodes in clinical practice. There is no evidence that intravenous L-arginine works [29] and indeed it may delay instigation of appropriate therapies [30], although some clinicians do advocate its use in patients presenting with stroke-like episodes [31], based on the findings derived from a single open-label trial with a small number of patients [32] and other anecdotal case reports. There is consensus however that aggressive seizure management is too often still over-looked in patients presenting with stroke-like episodes, resulting in metabolic crisis and prolonged hospital admission [33–35].

A recent study used the modified Delphi process to harness the clinical expertise from a group of specialists in mitochondrial disease from five European countries to produce consensus guidance for acute management of stroke-like episodes and commonly associated complications [28].

Early anti-epileptic treatment with a benzodiazepine outside hospital, or an IV anti-epileptic drug (not valproate in the setting of known *POLG* mutations) should be the mainstay of treatment, as well as routine investigations aimed at treating potential triggers and preventing complications. Transferring patients to the intensive care unit is recommended in the following circumstances:

1. Generalized, convulsive status epilepticus
2. Intrusive, frequent focal motor seizures with breakthrough generalized seizures which fail to respond to IV AEDs (and titration of usual maintenance AEDs)
3. Severe encephalopathy (with breakthrough focal motor or generalized seizures) with a high risk of aspiration
4. Focal motor status epilepticus with retained consciousness failing to respond to benzodiazepine and two IV AEDs

Midazolam is often the first choice of general anaesthetic agent to treat refractory status epilepticus associated with stroke-like episodes. Anecdotal reports suggest that propofol, especially in the paediatric population, may lead to propofol infusion syndrome. However, propofol is not absolutely contraindicated in refractory status epilepticus associated with stroke-like episodes and oftentimes is required in combination with midazolam due to the refractory nature of the ictal activity. The decision to use propofol should be made on a case by case basis. Thiopentone sodium

PROPOSED ACUTE CARE PATHWAY

RE: NAME DOB: Hospital Number:

This patient has a diagnosis of mitochondrial disease due to the m.3243A>G mutation. She/he is at risk of developing recurrent seizures that cause a 'metabolic' stroke. Vigorous diagnosis and treatment of epilepsy is a major determinant of outcome.

Warning Signs

- Persistent headache with the presence of visual hallucinations/persistent visual flashing/colours (often unilateral).
- Any form of seizure activity e.g. focal seizures (persistent face/thumb/hand twitching) or generalised seizures.
- Evidence of loss of function such as visual field loss (development of a new hemianopia), difficulties with speech and/or weakness
- New onset drowsiness, disorientation, confusion and behavioural disturbance

Urgent Treatment at Home

- Give either buccal Midazolam (5-10mg) or oral Clobazam (10-20mg) immediately and seek urgent medical help.

Urgent Treatment in Hospital

- Thrombolysis is **NOT** indicated.
- Administer intravenous (IV) anti-epileptic drugs (AEDs) urgently.
- Identify and treat potential triggers including dehydration, sepsis, ileus/constipation, electrolyte imbalance and missed dose of usual AEDs.
- Early review of the nutritional and hydration needs of the patient is imperative.
- Ileus, gastroparesis and constipation can be problematic and also need to be managed from the outset.
- Arrange urgent EEG and MRI head scan.
- **Seek specialist advice urgently.**
- *At a glance guidelines* for the management of epilepsy, stroke like episodes and gut dysmotility are available at www.newcastle-mitochondria.com/service/patient-care-guidelines/.

Specialist advice is available from:
Name of Consultant clinician
Address of hospital with contact details (including out of hours)

Fig. 13.2 Example personalized care plan for patients with MELAS due to the m.3243A>G variant, as used at the Highly Specialized NHS Service for Rare Mitochondrial Disorders in Newcastle upon Tyne, UK. For POLG-related disease it also includes contraindication of Valproate

(high dose) remains an important drug in terminating refractory status epilepticus particularly in cases of POLG-related MELAS. However, recovery is slow from this anaesthesia and the need for intensive care is prolonged. Following general anaesthesia, continuous EEG monitoring of patients with stroke like episodes should be performed to ensure that no breakthrough seizures occur. If this is unavailable, EEG should be performed as soon as possible after induction of anaesthesia, and at regular intervals for the duration of anaesthesia.

Maintenance intravenous fluid should be administered for patients who are at risk of dehydration, especially in those presenting with vomiting due to intestinal pseudo-obstruction. Careful monitoring of fluid and electrolyte balance may be necessary in those patients with low body mass index, cardiomyopathy or chronic kidney disease as part of the multisystem mitochondrial disease.

Mild to moderate lactic acidosis (serum lactate level: 2.2–5.0 mmol/L with pH >7.30) often responds well to rehydration and does not require any buffering agent. Some patients with mitochondrial disease have baseline hyperlactaemia. Buffering agent such as sodium bicarbonate can be used with care in severe lactic acidosis (pH <7.1), but management of severe metabolic acidosis should be shared with the intensive care specialist or nephrologist. Dichloroacetate should not be used, as it has been shown to cause unacceptable levels of toxicity (neuropathy) that outweigh any potential benefits [36].

Early consultation with the nutritional team is recommended during admission for stroke-like episodes. Gastroparesis and small bowel intestinal pseudo-obstruction with recurrent vomiting can be particularly dangerous, certainly in patients at increased risk of aspiration—such as those with encephalopathy, seizures, or bulbar dysfunction. Prompt recognition of pseudo-obstruction based on clinical symptoms and radiological findings is crucial, so that drainage of the stomach content can be achieved with the insertion of a wide-bore nasogastric tube. Concomitant constipation often occurs and should be treated appropriately. Swallowing should be assessed and regularly monitored.

Acute neuropsychiatric symptoms (hallucinations, confusion) can be managed with anti-psychotic medications, but advice from the psychiatric service should be sought (Table 13.4).

Table 13.4 Recommended investigations for patients presenting with (suspected) stroke-like episode (adapted from Ng et al. 2019 [28])

Blood tests
• Full blood count
• Urea, creatinine and electrolytes
• Liver function test (LFT)
• Random glucose
• C-reactive protein (CRP)
• Creatine kinase (CK)
• Serum lactate (without tourniquet applied)
• Anti-epileptic drug level (e.g. phenytoin, carbamazepine, phenobarbitone) if applicable
• Coagulation screen (for patients with POLG pathogenic variants)
• HbA1c (for known diabetic patients)

(continued)

Table 13.4 (continued)

Additional laboratory and technical investigations: MRI head and EEG are essential for the diagnosis of a stroke-like episode
• Urinalysis and urine culture (septic screen)
• Blood culture (septic screen)
• Arterial blood gas (for pH if hyperlactataemia is present or respiratory insufficiency is suspected)
• MRI brain (should at least include T1, T2, FLAIR, DWI and ADC) CT brain can be performed if MRI is contraindicated
• Electroencephalogram (EEG)
• Chest radiography (if aspiration pneumonia is suspected)
• Abdominal radiography (abdominal X-ray, ultrasound or CT abdomen and pelvis if intestinal pseudo-obstruction is suspected)
• 12-lead electrocardiogram (ECG)

Outcome

The outcome of severe intractable stroke-like episodes can be fatal. The long-term consequence of recurrent stroke-like episodes is cognitive impairment due to neurodegeneration (Fig. 13.3).

Case Vignette 2

A 17-year-old woman presented to the emergency department with a 2-day history of a constant flashing light in her left hemi-visual field (also with eyes closed), blurred vision and worsening ataxia. She described experiencing intermittent blurred vision, a rainbow of coloured flashes with eyelid flickering lasting around 1 min and headache (described as her worst headache ever) for 2 weeks before attending the emergency department.

She had been diagnosed with recessive POLG-related mitochondrial disease characterized by ataxia, motor-sensory neuropathy and stable epilepsy at the age of 16 years. Her epilepsy was initially managed with topiramate which then changed to carbamazepine due to inefficacy, and levetiracetam was a subsequent add-on therapy. Gabapentin was started for neuropathic pain.

*On admission, her GCS was 15 and left homonymous hemianopia was evident. Other positive neurological findings were mild, distal ankle weakness, areflexia and sensory loss below the knee level. Stroke-like episode and prolonged occipital seizures were suspected; carbamazepine and levetiracetam were increased to 400 mg BD and 1750 mg, respectively, and clobazam 10 mg BD was added. MRI head performed a week after the onset of positive visual phenomena identified T2-signal abnormalities involving the right medial occipital lobe with cytotoxic changes (*Fig. 13.4a–d*). Her EEG demonstrated an active ictal focus over the right posterior quadrant with occasional epileptic discharges within the contra-lateral parieto-occipital region. A*

*decision for escalating to general anaesthesia treatment was made given the patient had developed refractory non-convulsive status epilepticus (occipital seizures) and unilateral visual field loss. Burst suppression pattern was achieved and maintained with the combined administration of midazolam (265 mg) and thiopentone (18,875 mg) over 3 days. She remained in a comatose state for 6 days after stopping thiopentone. Repeat MRI head (day 7) showed resolution of signal abnormalities in the right occipital lobe and corpus callosum (*Fig. 13.4e–h*). Her ICU stay was complicated by hospital-acquired pneumonia and clostridium difficile diarrhoea, which were treated with appropriate antibiotics. Extubation was successfully performed 10 days after ICU admission, and the patient was stepped down for rehabilitation on day 14. However, a left-sided visual field loss returned 5 days later, but without positive visual phenomena on this occasion. Her EEG only showed encephalopathic changes; repeat MRI head (day 22) showed a stroke-like lesion that had appeared in the same location as per the previous scan but without restricted diffusion (*Fig. 13.4i–l*).*

Learning Points

1. **Non-convulsive seizures originating from the occipital lobe could be misdiagnosed as migrainous visual aura.**
2. **Seizure management is challenging in POLG-related stroke-like episodes, and aggressive treatment is crucial to limit neuronal loss and development of significant disability.**

Severe Cardiac Complications in Mitochondrial Disease (Cardiomyopathy, Arrhythmia)

Genetic Causes and Pathophysiology

The heart heavily relies on mitochondrial respiration to produce energy required for contraction and electric conduction and is therefore amongst the most vulnerable tissues when confronted with mitochondrial dysfunction. Estimates of the prevalence of cardiac manifestations in mitochondrial disease vary [37–39], but overall, around 50–60% of patients are reported to be affected by some form of cardiac dysfunction. The prevalence and type of involvement are highly dependent on the underlying mutation (Table 13.5).

Cardiac manifestations are independent of the severity of other symptoms, and onset is most often insidious with clinical symptoms usually emerging after a diagnosis of mitochondrial disease has been made. However, in rare instances, a diagnosis of mitochondrial disease is made in ICU, when acute cardiovascular involvement is the initial and/or prevailing manifestation.

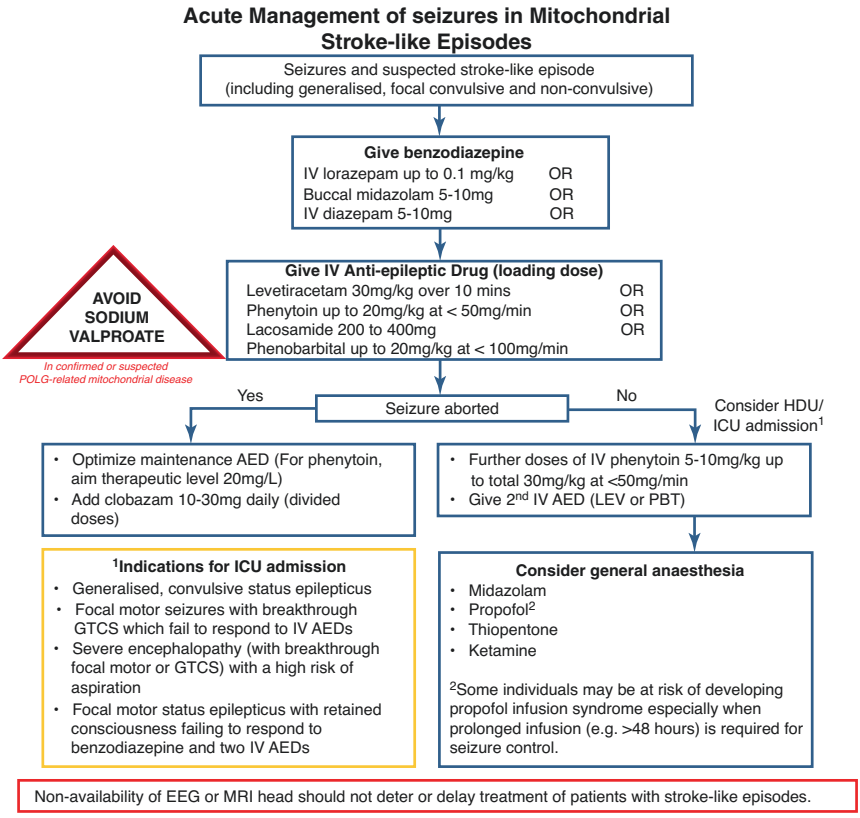


Fig. 13.3 Acute management workflow of seizures in mitochondrial stroke-like episodes, based on the "At a glance guidelines on the management of mitochondrial stroke-like episodes" used at the Highly Specialised NHS Service for Rare Mitochondrial Disorders in Newcastle upon Tyne, UK

Cardiac Manifestations

The most common manifestations of cardiac pathology in patients with mitochondrial disease are hypertrophic cardiomyopathy and conduction block often predicated by genotype. When a patient presents with these conditions to the emergency department and critical care unit, the absence of concomitant coronary artery disease, hypertension, valvular disease, or congenital heart disease might raise suspicion of an underlying metabolic or mitochondrial disorder. Nevertheless, many different cardiac manifestations have been reported in the context of mitochondrial disease, and presence of these certainly does not exclude this diagnosis.

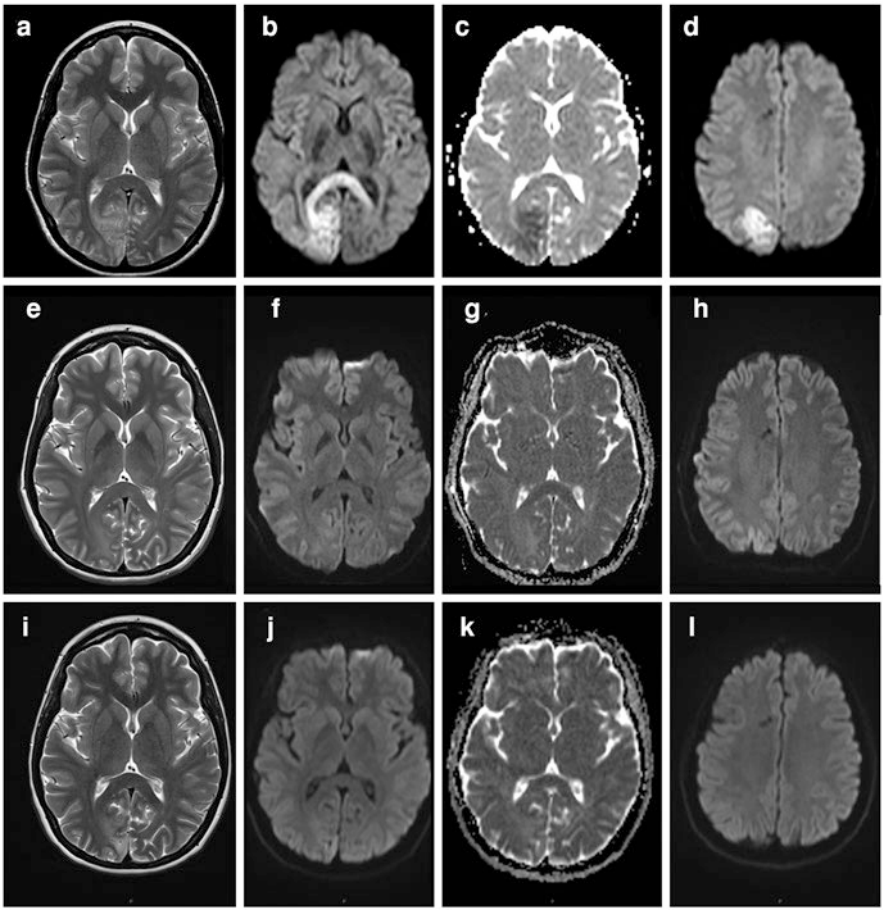


Fig. 13.4 Serial MRI scans from the patient described in case vignette 2. **a**, **e** and **i** = T2-weighted image; **b**, **f** and **j** + **d**, **h** and **l** = Diffusion-weighted image (DWI); **c**, **g** and **k** = apparent diffusion coefficient (ADC) image

Table 13.5 Mitochondrial diseases and typical cardiac complications

Syndrome	Most common mutations	Most frequent cardiac manifestations	Other frequent cardiac abnormalities
MELAS	m.3243A>G	Hypertrophic left-ventricular concentric cardiomyopathy	Wolff-Parkinson-White syndrome and tachyarrythmia
MERRF	m.8344A>G	Wolff-Parkinson-White syndrome	Hypertrophic and dilated cardiomyopathies
KSS/CPEO	Single large-scale mtDNA deletions	Conduction defects	

(continued)

Table 13.5 (continued)

Syndrome	Most common mutations	Most frequent cardiac manifestations	Other frequent cardiac abnormalities
Barth syndrome	*TAZ*	Dilated cardiomyopathy	Left ventricular noncompaction, arrhythmia
Senger's syndrome	*AGK*	Hypertrophic cardiomyopathy	
Cardio(encephalo) Myopathy	*AARS2, MTO1, SCO2*	Hypertrophic cardiomyopathy	

Structural Defects

Hypertrophic cardiomyopathy (HCM) is the most common structural abnormality found in mitochondrial disease and can sometimes even be seen on prenatal ultrasound [40]. Patients often remain asymptomatic for a long time before chest pain, dyspnoea, palpitations or syncope develop. Diagnosis is supported by ECG and 2D-echocardiogram (and/or cardiac MRI).

Overall, HCM is most frequently associated with autosomal dominant mutations in genes encoding cardiac sarcomere proteins. Only a minority of cases are caused by pathogenic mitochondrial disease variants, but the signs in Table 13.2 (MDC score) should raise suspicion and initiate a diagnostic work-up for mitochondrial disease as in Fig. 13.1 (flowchart). Specific patterns on cardiac ultrasound or magnetic resonance imaging (MRI) may be preferentially associated with particular syndromes or genetic mutations and guide further diagnostic investigations. For example, concentric left ventricular hypertrophy with patchy non-ischemic (intramural) late gadolinium enhancement in multiple segments on cardiac MRI is thought to be more suggestive of m.3243A>G-associated cadiomyopathy [39]. However, these patterns are not diagnostic, and phenotypes are most likely further confounded by variability in heteroplasmy levels.

Arrhythmias

Arrhythmias caused by mitochondrial dysfunction may include various degrees of atrio-ventricular conduction block, sick sinus syndrome, left or right bundle branch blocks, intra-ventricular delays, Wolff-Parkinson-White tachyarrhythmia or left ventricular pre-excitation [41, 42].

Diagnosis of arrhythmias is usually based on history and 12-lead resting or longer-term ECG. Brady-arrhythmias can be asymptomatic, but with persistent or severe abnormalities, symptoms are common and include easy fatigability, reduced exercise capacity, dizziness, dyspnoea, presyncope and syncope. Tachycardia will usually produce symptoms and may result in palpitations, fatigue, light-headedness, chest pain, dyspnoea and less commonly syncope.

Conduction blocks are most frequently seen in association with heteroplasmic large-scale deletions of mtDNA, leading to CPEO and Kearns-Sayre Syndrome (KSS). Additional symptoms of KSS are a pigmentary retinopathy, often accompanied by ataxia, deafness and dementia. Severe cardiac manifestations of KSS include complete heart block and sudden death; therefore cardiac monitoring and considering defibrillator or pacemaker implantation in at-risk patients are of primordial importance in the follow-up of these patients. Patients with m.8344A>G [43] or m.3243A>G mutations [37] in contrast have a higher incidence of tachy arrhythmias such as Wolff-Parkinson-White Syndrome.

Management

All patients with a suspected or confirmed diagnosis of mtDNA-related mitochondrial disease and/or those considered susceptible to cardiac involvement should undergo repeated assessment to ensure early detection and treatment of cardiac pathology [11]. Guidelines suggest blood pressure measurement, ECG and cardiac ultrasound at the initial visit, and afterwards 1- to 2-yearly follow-up for the first 5 years. Further screening then depends on findings and symptoms but could be extended to once every 3 years if investigations are normal. Frequent (every 3–6 months) Holter monitoring should be considered in those patients with high risk of conduction abnormalities, in particular single deletions leading to CPEO and Kearns-Sayre Syndrome. Asymptomatic carriers should be screened as well, as even low levels of heteroplasmy may lead to cardiac abnormalities, but the intervals can be tailored to individual mutations and symptoms.

When acute cardiac pathology is the primary manifestation, and patients have not had a diagnosis as yet, more advanced imaging modalities, for example through cardiac MRI or MRS, may aid in excluding other possible causes of apparent ventricular hypertrophy and can guide further testing and genetic analysis [44]. Endomyocardial biopsy may aid in the differential diagnosis of various forms of hypertrophic cardiomyopathy, but in the current era of genomics, the risks often outweigh the possible benefits.

Good guidelines exist for management of hypertrophic cardiomyopathy, including from the European Society of Cardiology (ESC) [45], and these are applicable to patients with mitochondrial disease also. Cardiac arrhythmias should be investigated and treated accordingly, and ablation in Wolff-Parkinson-White syndrome and pacemakers or implantable defibrillators should be considered where appropriate. When patients are at high risk of completed heart block (e.g. KSS), current guidelines suggest to follow the same approach as for other patients without genetic conditions [46, 47].

Heart transplantation as a treatment for intractable heart failure caused by mitochondrial hypertrophic or dilated cardiomyopathy may be considered too. Several case reports [48–50] and one larger series of 11 patients [51] have been published describing successful heart transplants in adult patients with mitochondrial disease. In children, heart transplantation has a similarly favourable outcome [52–54], and

overall survival seems comparable to children without mitochondrial disease. Nevertheless, mitochondrial disease does confer a greater risk of complications and longer hospital stay both in children and adults [54].

Prognosis

In adults with mitochondrial disease, sudden death is sometimes reported in the family history of patients [38, 55]. Nevertheless, life-threatening cardiovascular complications are relatively rare and when properly treated, the prognosis of cardiac involvement is overall good. In one series of 32 adult patients with mitochondrial disease, 5-year cardiovascular event free survival was 67%. Four out of 32 patients received invasive treatment (heart transplant, pacemaker or ablation) and none died of cardiovascular disease [38]. In children, cardiovascular involvement is less frequent than in adults, but when cardiomyopathy is present, it is a significant contributor to mortality. It increased mortality risk almost three times (up to 71%) in hospitalized children with mitochondrial disease [56].

Case Vignette 3

A 32-year-old man with a 6-year history of sensorineural hearing loss presented to the emergency department with intermittent vague chest pain for 3 weeks. Troponin I was slightly raised (94 ng/L; ref. 0–56) with lateral T-wave inversion and infero-lateral ST-depression on ECG. He was hyperglycaemic and HbA1c was 89 mmol/mol (ref. <48 mmol/mol). Serum lactate was increased (3.1 mmol/L; ref. 0.6–1.4) and it was noted that 6 months previously, on a routine blood test, this also was raised to 3.3 mmol/L. Troponin I remained stable between 69 and 94 ng/L over the next 3 days. Echocardiogram and CT coronary angiogram were normal, but CT chest showed mild thickening of the left ventricular myocardium. Two weeks later, he experienced palpitations from sleep and was admitted the same day after a pre-syncopal episode. Holter monitoring was repeatedly normal. Clinical examination only suggested mild bilateral ptosis that was not reported by the patient.

His grandmother and maternal uncle were known to have hearing problems, and his mother was previously diagnosed with type II diabetes. Mitochondrial disease was suspected, and he was referred for outpatient cardiac MRI and genetic testing. Cardiac MRI confirmed minor concentric left ventricular hypertrophy up to 12 mm with normal ventricle size and systolic function, and he was found to carry the common m.3243A>G mutation at 34% heteroplasmy in blood. A diagnosis of maternal inherited diabetes and deafness (MIDD) was made. Ophthalmology screening showed bilateral macula pattern-like dystrophy without visual symptoms. Ramipril 2.5 mg daily, Aspirin 75 mg daily and subcutaneous insulin were started, and further follow-up with yearly ECG, 24-h ECG and echocardiogram have been stable.

Learning Points
Acute or subacute heart disease can be a presenting feature in mitochondrial disease. Attention for other signs and symptoms in patients and teir families, even when they are very common in the population (like diabetes, migraine or hearing problems), may point to an underlying genetic mitochondrial disease. Long-term screening and standard treatment of cardiac disease should then be initiated.

Liver Failure in Mitochondrial Disease

Genetic Causes and Pathophysiology

Liver failure is a life-threatening critical illness, often leading to admission to intensive care. Symptoms include jaundice, encephalopathy, bleeding, fatigue and lactic acidosis. Although the cause of liver failure is often unknown, inherited disorders of mitochondrial oxidative phosphorylation may be responsible, especially in infancy and young children <2 years of age [57]. In general, mitochondrial liver disease often occurs with extra-hepatic involvement [58]. However, isolated hepatic failure may also be related to mitochondrial dysfunction caused by defects of mitochondrial DNA (mtDNA) maintenance such as mtDNA deletion (Pearson syndrome) and depletion [58]. Genetic forms of mtDNA depletion and liver failure can be associated with autosomal recessive mutations in *DGUOK* [59], *MPV17* [60], *TWNK* [61], *SUCLG1* [62] or *POLG* (Alpers-Huttenlocher syndrome) [57, 63]. Patients with mutations in *POLG* are at high risk for developing valproate induced liver failure. Low mtDNA copy number has also been detected in patients (often infants) with acute liver failure without a specific mitochondrial genetic diagnosis [57, 64], and these patients may have a good prognosis and do not develop other symptoms, suggesting that low liver mtDNA copy number may be a secondary phenomenon caused by various liver pathologies in infants [57].

Severe infantile liver failure can also be caused by dysfunction of mitochondrial transcription and translation [65]. Pathogenic mutations in *TFAM* cause infantile-onset progressive fatal liver failure, while intrauterine growth restriction and severe hepatopathy was reported in patients with mutations in translation elongation factors *GFM1* and *TSFM* [65].

In contrast to these progressive and often fatal conditions, a unique reversible infantile hepatopathy has been shown in association with mutations in the mitochondrial tRNA modifying factor *TRMU* [66, 67]. Considering that acute infantile liver failure may be reversible is of utmost importance in treating patients with liver failure in ICU. These patients need rapid diagnostic testing and consideration of active therapeutic interventions including liver transplantation [51].

Rare cases of liver dysfunction in single respiratory chain complex deficiencies were reported due to mutations in *SCO1* (complex IV assembly factor) and *BCS1L*

(complex III assembly factor) [58]. Biallelic mutations in *NBAS* have been identified as a new molecular cause of acute recurrent liver failure and dysmorphic signs with onset in infancy [68].

Manifestations

Mitochondrial liver failure often presents in early infancy [57]. Liver biopsy often shows cirrhosis, micro- and macrovesicular steatosis and cholestasis and abnormal mitochondrial morphology on electron microscopy as well as low mtDNA copy number. Liver crises are triggered by febrile infections; they become less frequent with age but are not restricted to childhood. Complete recovery is typical for *TRMU* mutations, but acute crises can be fatal in other genetic forms, such as POLG mutations (see above). Furthermore, respiratory chain abnormalities were frequently detected in liver samples of patients with severe liver failure requiring transplantation due to various forms of non-mitochondrial liver diseases [64].

Management

Treatment of liver failure in *NBAS* deficiency is symptomatic, antipyretic therapy and induction of anabolism including glucose and parenteral lipids effectively ameliorate the course of liver crises [69]. Patients with biallelic *TRMU* mutations usually recover spontaneously after 1–2 years of age [67]. Active intensive care support of these patients is of utmost importance, as they have a good prognosis, although long-term follow up data are not available in many cases.

Liver transplantation can be lifesaving in severe cases [61, 70]. Liver transplantation has been performed in patients with liver failure due to mutations in *DGUOK* or *POLG* [59, 60, 71], but may be considered in isolated or predominant severe liver presentations of other forms of mitochondrial diseases [72, 73]. Liver transplantation has been effective in stabilizing symptoms and nearly normalizing thymidine levels in patients with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) [72]. These patients do not have acute liver failure, but the donor liver produces wild-type TYMP enzyme, and even a small increase in enzyme activity enables elimination of toxic thymidine nucleotides in MNGIE. Therefore, liver transplantation may have an improved safety profile over hematopoietic stem cell transplant in this condition [72].

Outcome

A significant proportion of patients benefit from liver transplantation with long-term survival and a stabilization of neurological features despite initial neurological abnormalities [60, 71]. Decisions to list a patient with mitochondrial disease for

liver transplant should be taken in the light of other comorbidities and the natural history of the specific mitochondrial disease [51].

Case Vignette 4

Acute liver failure and muscle weakness in a 4-months-old child. Diagnostic work-up revealed a female infant with skin icterus, enlarged liver, body weight was under the third percentile. Laboratory investigations showed lactic acidosis (12.4 mmol/L, normal<2.2 mmol/L) with pH 7.3, BE-13 mmol/L, bicarbonate 14 mmol/L and hypoglycaemia (12 mg/dL, normal 60–100 mg/dL), elevated liver enzymes (AST 1310 U/L, normal<80 U/L; ALT 1364 U/L, normal <65 U/L; LDH 709 U/L, normal 158–353 U/L), elevated total bilirubin (6.3 mg/dL, normal 0.2–1.0 mg/dL) with elevated direct bilirubin (4.8 mg/dL, normal <0.2 mg/dL) and normal indirect bilirubin (0.5 mg/dL) as well as an impaired liver synthesis (PTT 160 s, normal 25–60 s; TPZ 17%, normal range 70–120%, AT III 17%, normal range 80–123%) and thrombocytopenia (60/nL, normal 200–480/nL). On the intensive care unit symptomatic therapy was started immediately, comprising invasive ventilation, volume substitution, glucose infusion, substitution with sodium bicarbonate, platelets and erythrocytes and fresh frozen plasma. Antibiotic and antiviral therapy (Cefotaxim, Ampicillin, acyclovir) were initiated. Muscle and liver biopsy showed combined complex I and IV deficiency and normal mtDNA copy number. WES detected compound heterozygous TRMU mutations. The child recovered at 12 months of age after careful management of liver failure and doing well at 10 years of age.

Learning Points

Severe infantile liver failure can be reversible, therefore diagnosing *TRMU* mutations is of utmost importance, as these patients have a very good prognosis.

Acute Gastrointestinal Manifestations in Mitochondrial Disease

Causes and Manifestations

Gastrointestinal involvement in mitochondrial disease is common, affecting more than 50% of patients and their presentation may vary considerably between syndromes and individuals. Although well recognized in patients with *TYMP* mutations causing Mitochondrial NeuroGastro-Intestinal Encephalopathy (MNGIE), gastrointestinal symptoms are often underappreciated in other patients with mitochondrial disease. Common features include chronic constipation or diarrhoea, poor appetite with weight loss, nausea, recurrent vomiting, dysphagia, and

sphincter dysfunction causing reflux or rarely achalasia. Many of these symptoms could be attributed to smooth muscle myopathy related to mitochondrial dysfunction, but they may also be a sign of underlying neuropathy, central nervous system problems, or even mood disturbance [74]. Chronic gastrointestinal symptoms can lead to acute complications such as aspiration pneumonia due to dysphagia, or electrolyte disturbances associated with chronic diarrhoea and vomiting. In addition, they may complicate care for patients with mitochondrial disease hospitalized for other conditions, in particular in patients with MELAS and stroke-like episodes.

One of the most severe manifestations of gastrointestinal dysmotility is chronic intestinal pseudo-obstruction (IPO), which is particularly common in patients with MELAS. IPO is characterized by more than 6 months of recurrent episodes of bowel obstruction in absence of a mechanical cause. Symptoms include abdominal distension and pain, nausea and vomiting with evidence of a dilated bowel on clinical examination or radiography (abdominal X-ray, ultrasound or CT scan). In a retrospective study from a tertiary care centre, up to 19% of patients with IPO were found to have an underlying mitochondrial disorder [75], and these patients were more likely to have severe nutritional deficiency requiring parenteral nutrition and multisystem complications leading to premature death [74, 75]. Importantly, acute exacerbations of IPO may accompany or precipitate stroke-like episodes in patients with MELAS [74].

Management of Acute Pseudo-Obstruction

(Sub-)Acute intestinal pseudo-obstruction should be managed aggressively after exclusion of a mechanical obstruction (e.g. volvulus, adhesion, tumour or impacted stool). Patients should be kept nil by mouth until the pseudo-obstruction is resolved, while maintaining adequate IV hydration with dextrose (see Table 13.3). For patients who present with predominantly gastroparesis and small bowel involvement, prompt gastric drainage and decompression is crucial to circumvent severe aspiration. Parenteral nutrition should be considered, in particular when the episode is long-lasting and patients are already underweight. Water-soluble enemas and flatus tubes may help to relieve distal small bowel and large bowel pseudo-obstruction. Medications that may have precipitated the acute deterioration should be withdrawn and accompanying urinary retention treated accordingly. Surgical resection should only be a last resort, in case of true obstruction or complications requiring surgery like perforation, after consultation with specialized gastroenterologists and clinicians with experience in treating patients with mitochondrial disease. Certainly in patients with MELAS, close monitoring for other multisystem manifestations and neurologic decline is required.

In patients with MNGIE, several treatments have been proposed, including allogeneic hematopoietic stem cell transplantation [76], carrier erythrocyte entrapped thymidine phosphorylase therapy [77] or liver [72] transplantation. However, the outcome of these invasive therapies is worse in patients with significant comorbidity and more advanced disease: pre-transplant liver disease or a history of IPO are negative predictors of outcome and overall survival [76].

Safe Use of Medications in Patients with Mitochondrial Disease

Traditionally, patients with mitochondrial disease are given a long list of medications that should be avoided if at all possible. Although this cautionary approach has certainly helped to raise awareness of the risk for medication- or stressor-induced metabolic decompensation, for example in the perioperative period, there is very little evidence that most of these medications actually cause any harm to these patients.

Recently, a mitochondrial expert panel followed a Delphi method to establish consensus guidelines for the safe use of medications in patients with mitochondrial disease [7]. Their main conclusions are summarized in Table 13.6 [7]. The key recommendations regarding use of medications in patients with mitochondrial disease are the following:

1. Valproate should be avoided in patients with POLG-related mitochondrial disease.
2. Prolonged use of specific drugs (see Table 13.6) should be avoided if good alternative treatment options are available.
3. The usual standards of good practice prevail when prescribing any drug, irrespective of the drug's mitochondrial toxicity potential or profile (e.g. corticosteroids may cause muscle toxicity or spironolactone may cause metabolic acidosis, independent of an underlying mitochondrial disease or not).

Table 13.6 Expert recommendations regarding safe use of medications in patients with mitochondrial disease adapted from De Vries et al. 2020 [7]

Specific drug/drug group/clinical condition/genotype	Points of attention
Aminoglycosides	The mitochondrial 12S rRNA is a hot spot for mutations associated with both aminoglycoside-induced and non-syndromic hearing loss. Screening for these mtDNA mutations is strongly recommended before elective long-term treatment is planned. The benefits of the drug in emergency treatment, as a very effective broad-spectrum antibiotic, outweigh the risks in these situations.

(continued)

Table 13.6 (continued)

Specific drug/drug group/clinical condition/genotype	Points of attention
Valproic acid	Should be used only in exceptional circumstances. The drug is absolutely contraindicated in patients with mitochondrial disease due to POLG mutations. Valproic acid should not be used in patients with known liver disease and/or clinical signs suspicious for POLG disease.
Neuromuscular blocking agents	Extra caution and monitoring should be performed for patients manifesting a predominantly myopathic phenotype.
General anaesthesia and surgery	Catabolism should be prevented by minimizing preoperative fasting and administering intravenous glucose perioperatively during prolonged anaesthesia, unless the patient is on a ketogenic diet.
Duration of treatment	The duration of drug administration may play a role in whether or not side effects develop. Duration of treatment should be guided by individual patient needs and their response to specific treatments.
Renal impairment	Many patients with a mitochondrial disease have renal impairment; drug dose adjustment should be considered particularly when active drug moieties are renally cleared.
Metabolic acidosis (lactic acidosis)	Metabolic acidosis (lactic acidosis) may occur in patients with mitochondrial disease, therefore drugs that can cause acidosis (e.g. metformin) should be prescribed with caution. Regular clinical review and monitoring of acid-base status in blood is recommended.

Self Assessment Questions

1. Mitochondrial diseases frequently present with a clinically recognizable syndrome.

   (a) True.
   (b) False (*)

2. Which of the following examination findings is most characteristic for mitochondrial myopathy?

   (a) Delayed tonic pupillary reaction on light stimuli.
   (b) External ophthalmoplegia. (*)
   (c) Muscle weakness fluctuating within 5 min.
   (d) Painful cramps with fasciculations.

3. Which of the following symptoms should raise a suspicion of a mitochondrial disease if there is no other explanation?

   (a) Burning feet.
   (b) Kinesiogenic dystonia.
   (c) Paroxysmal vertigo.
   (d) Sensorineural hearing loss. (*)

4. Abnormalities in which type of DNA cause a mitochondrial disease?

   (a) Only in mitochondrial DNA.
   (b) Only in nuclear DNA.
   (c) Both in mitochondrial and nuclear DNA. (*)

5. What is the most common inheritance pattern in adult-onset mitochondrial disease?

   (a) Autosomal dominant.
   (b) Autosomal recessive.
   (c) X-linked.
   (d) Maternally-inherited. (*)

6. What is the most common inheritance pattern in paediatric mitochondrial disease?

   (a) Autosomal dominant.
   (b) Autosomal recessive. (*)
   (c) X-linked.
   (d) Maternally-inherited.

7. A patient with a mitochondrial cytopathy should avoid fasting for the prevention of an acute deterioration.

   (a) True. (*)
   (b) False.

8. Which of the following problems may be seen in the context of a mitochondrial disease?

   (a) Cardiac arrhythmias.
   (b) Heart failure.
   (c) Seizures.
   (d) Stroke-like episodes.
   (e) All of the above. (*)

9. Which of the following are generally recommended for nutrition of a mitochondrial patient in the ICU?

   (a) Avoidance of lipids.
   (b) Dextrose containing IV fluids. (*)
   (c) L-arginine infusion

10. All severe infantile mitochondrial diseases are progressive and do not recover.

    (a) True.
    (b) False. (*)

11. Which of the following anti-epileptic drugs should be avoided in a patient with a mitochondrial cytopathy?

    (a) Carbamazepine.
    (b) Lamotrigine.
    (c) Levetiracetam.
    (d) Valproate. (*)

12. Which is the first choice general anaesthetic agent to treat a refractory status epilepticus in a patient with mitochondrial cytopathy?

    (a) Midazolam. (*)
    (b) Thiopentone.
    (c) Ketamine.
    (d) Propofol.

13. Which is the best way to treat a mild lactic acidosis in a patient with mitochondrial cytopathy?

    (a) Acetozolamide.
    (b) Glucose.
    (c) Rehydration. (*)
    (d) Sodium bicarbonate.

14. Which antibiotic agent should be used with caution in patients with predisposing mtDNA mutations for ototoxicity.

    (a) Aminoglycosides. (*)
    (b) Cephalosporins.
    (c) Macrolides.
    (d) Penicillin.

15. Life-threatening cardiovascular complications are common in all forms of mitochondrial disease.

    (a) True.
    (b) False. (*)

References

1. Gorman GS, et al. Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease. Ann Neurol. 2015.
2. Chinnery PF, Keogh MJ. Clinical mitochondrial medicine. Cambridge University Press; 2018.
3. Schon K, Ratnaike T, van den Ameele J, Horvath R, Chinnery PF. Mitochondrial diseases: a diagnostic revolution. Trends Genet. 2020.
4. Morava E, et al. Mitochondrial disease criteria: diagnostic applications in children. Neurology. 2006.
5. Witters P, et al. Revisiting mitochondrial diagnostic criteria in the new era of genomics. Genet Med. 2018.

6. Stenton SL, Prokisch H. Genetics of mitochondrial diseases: identifying mutations to help diagnosis. EBioMedicine. 2020.
7. De Vries MC, et al. Safety of drug use in patients with a primary mitochondrial disease: an international Delphi-based consensus. J Inherit Metab Dis. 2020.
8. Barends M, et al. Causes of death in adults with mitochondrial disease. JIMD Rep. 2016.
9. McCormack SE, et al. Hospitalizations for mitochondrial disease across the lifespan in the U.S. Mol Genet Metab. 2017.
10. Howard RS, et al. Management of mitochondrial disease on an intensive care unit. QJM. 1995.
11. Parikh S, et al. Patient care standards for primary mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. Genet Med. 2017.
12. Calvo SE, et al. Molecular diagnosis of infantile mitochondrial disease with targeted next-generation sequencing. Sci Transl Med. 2012.
13. Pyle A, et al. Respiratory chain deficiency in nonmitochondrial disease. Neurol Genet. 2015.
14. Parikh S, et al. Diagnosis of possible' mitochondrial disease: an existential crisis. J Med Genet. 2019.
15. C.E., F., et al. Whole genome sequencing reveals that genetic conditions are frequent in intensively ill children. Intensive Care Med. 2019.
16. Distelmaier F, Haack TB, Wortmann SB, Mayr JA, Prokisch H. Treatable mitochondrial diseases: cofactor metabolism and beyond. Brain. 2017.
17. Boczonadi V, Bansagi B, Horvath R. Reversible infantile mitochondrial diseases. J Inherit Metab Dis. 2015.
18. Danhauser K, et al. Treatment options for lactic acidosis and metabolic crisis in children with mitochondrial disease. J Inherit Metab Dis. 2015.
19. Boczonadi V, et al. Altered 2-thiouridylation impairs mitochondrial translation in reversible infantile respiratory chain deficiency. Hum Mol Genet. 2013.
20. Hathazi D, et al. Metabolic shift underlies recovery in reversible infantile respiratory chain deficiency. EMBO J. 2020;39(23):e105364.
21. Goto YI, Nonaka I, Horai S. A mutation in the tRNALeu(UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. Nature. 1990.
22. Hirano M, et al. MELAS: An original case and clinical criteria for diagnosis. Neuromuscul Disord. 1992.
23. Yu-Ichi G, et al. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes(MELAS): a correlative study of the clinical features and mitochondrial DNA mutation. Neurology. 1992.
24. Shanske S, et al. The G13513A mutation in the ND5 gene of mitochondrial DNA as a common cause of MELAS or Leigh syndrome: evidence from 12 cases. Arch Neurol. 2008.
25. Deschauer M, et al. MELAS associated with mutations in the POLG1 gene. Neurology. 2007.
26. Tzoulis C, et al. Localized cerebral energy failure in DNA polymerase gamma-associated encephalopathy syndromes. Brain. 2010.
27. Engelsen BA, et al. POLG1 mutations cause a syndromic epilepsy with occipital lobe predilection. Brain. 2008.
28. Ng YS, et al. Consensus-based statements for the management of mitochondrial stroke-like episodes. Wellcome Open Res. 2019.
29. Stefanetti RJ, Ng YS, Errington L, Blain AP, McFarland R, Gorman GS. L-arginine in mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes: a systematic review. Neurology. 2022;98(23):e2318–28.
30. Kitamura M, et al. L-arginine intervention at hyper-acute phase protects the prolonged MRI abnormality in MELAS. J Neurol. 2016.
31. Koenig MK, et al. Recommendations for the management of strokelike episodes in patients with mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes. JAMA Neurol. 2016.
32. Koga Y, et al. L-arginine improves the symptoms of strokelike episodes in MELAS. Neurology. 2005.

33. Whittaker RG, et al. Epilepsy in adults with mitochondrial disease: a cohort study. Ann Neurol. 2015.
34. Kaufman KR, Zuber N, Rueda-Lara MA, Tobia A. MELAS with recurrent complex partial seizures, nonconvulsive status epilepticus, psychosis, and behavioral disturbances: case analysis with literature review. Epilepsy Behav. 2010.
35. Lee HN, et al. Epilepsy characteristics and clinical outcome in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Pediatr Neurol. 2016.
36. Kaufmann P, et al. Dichloroacetate causes toxic neuropathy in MELAS: a randomized, controlled clinical trial. Neurology. 2006.
37. Anan R, et al. Cardiac involvement in mitochondrial diseases: a study on 17 patients with documented mitochondrial DNA defects. Circulation. 1995.
38. Limongelli G, et al. Prevalence and natural history of heart disease in adults with primary mitochondrial respiratory chain disease. Eur J Heart Fail. 2010.
39. Florian A, et al. Characteristic cardiac phenotypes are detected by cardiovascular magnetic resonance in patients with different clinical phenotypes and genotypes of mitochondrial myopathy. J Cardiovasc Magn Reson. 2015.
40. García-Díaz L, Coserria F, Antiñolo G. Hypertrophic cardiomyopathy due to mitochondrial disease: prenatal diagnosis, management, and outcome. Case Rep Obstet Gynecol. 2013.
41. Kabunga P, et al. Systematic review of cardiac electrical disease in Kearns-Sayre syndrome and mitochondrial cytopathy. Int J Cardiol. 2015.
42. Wahbi K, et al. Long-term cardiac prognosis and risk stratification in 260 adults presenting with mitochondrial diseases. Eur Heart J. 2015.
43. Wahbi K, et al. Cardiac involvement is frequent in patients with the m.8344A>G mutation of mitochondrial DNA. Neurology. 2010.
44. Partington SL, Givertz MM, Gupta S, Kwong RY. Cardiac magnetic resonance aids in the diagnosis of mitochondrial cardiomyopathy. Circulation. 2011.
45. Elliott PM, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy. Eur Heart J. 2014.
46. Brignole M, et al. 213 ESC guidelines on cardiac pacing and cardiac resynchronization therapy. Eur Heart J. 2013.
47. Brugada J, et al. 2019 ESC guidelines for the management of patients with supraventricular tachycardia the task force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). Eur Heart J. 2019.
48. Homan DJ, et al. Heart transplantation for a patient with Kearns-Sayre syndrome and end-stage heart failure. Congest Heart Fail. 2011.
49. Tranchant C, et al. Cardiac transplantation in an incomplete Kearns-Sayre syndrome with mitochondrial DNA deletion. Neuromuscul Disord. 1993.
50. Bhati RS, Sheridan BC, Mill MR, Selzman CH. Heart transplantation for progressive cardiomyopathy as a manifestation of MELAS syndrome. J Heart Lung Transpl. 2005.
51. Parikh S, et al. Solid organ transplantation in primary mitochondrial disease: proceed with caution. Mol Genet Metab. 2016.
52. Santorelli FM, et al. Hypertrophic cardiomyopathy and mtDNA depletion. Successful treatment with heart transplantation. Neuromuscul Disord. 2002.
53. Golden AS, Law YM, Shurtleff H, Warner M, Saneto RP. Mitochondrial electron transport chain deficiency, cardiomyopathy, and long-term cardiac transplant outcome. Pediatr Transplant. 2012.
54. Weiner JG, et al. Heart transplantation in children with mitochondrial disease. J Pediatr. 2020;217:46–51.e4.
55. Ng YS, et al. Sudden adult death syndrome in m.3243A>G-related mitochondrial disease: an unrecognized clinical entity in young, asymptomatic adults. Eur Heart J. 2016.
56. Holmgren D, et al. Cardiomyopathy in children with mitochondrial disease: clinical course and cardiological findings. Eur Heart J. 2003.
57. McKiernan P, et al. Incidence of primary mitochondrial disease in children younger than 2 years presenting with acute liver failure. J Pediatr Gastroenterol Nutr. 2016.

58. Rahman S. Gastrointestinal and hepatic manifestations of mitochondrial disorders. J Inherit Metab Dis. 2013.
59. Dimmock DP, et al. Abnormal neurological features predict poor survival and should preclude liver transplantation in patients with deoxyguanosine kinase deficiency. Liver Transpl. 2008.
60. Hynynen J, et al. Acute liver failure after valproate exposure in patients with POLG1 mutations and the prognosis after liver transplantation. Liver Transpl. 2014.
61. Fellman V, Kotarsky H. Mitochondrial hepatopathies in the newborn period. Semin Fetal Neonatal Med. 2011.
62. Van Hove JLK, et al. Succinyl-coa ligase deficiency: a mitochondrial hepatoencephalomyopathy. Pediatr Res. 2010.
63. Naviaux RK, Nguyen KV. POLG mutations associated with Alpers' syndrome and mitochondrial DNA depletion. Ann Neurol. 2004.
64. Lane M, et al. Mitochondrial dysfunction in liver failure requiring transplantation. J Inherit Metab Dis. 2016.
65. Boczonadi V, Ricci G, Horvath R. Mitochondrial DNA transcription and translation: clinical syndromes. Essays Biochem. 2018.
66. Zeharia A, et al. Acute infantile liver failure due to mutations in the TRMU gene. Am J Hum Genet. 2009.
67. Schara U, et al. Acute liver failure with subsequent cirrhosis as the primary manifestation of TRMU mutations. J Inherit Metab Dis. 2011.
68. Carli D, et al. NBAS pathogenic variants: defining the associated clinical and facial phenotype and genotype–phenotype correlations. Hum Mutat. 2019.
69. Staufner C, et al. Recurrent acute liver failure due to NBAS deficiency: phenotypic spectrum, disease mechanisms, and therapeutic concepts. J Inherit Metab Dis. 2016.
70. Chinnery PF, DiMauro S. Mitochondrial hepatopathies. J Hepatol. 2005.
71. Grabhorn E, et al. Long-term outcomes after liver transplantation for deoxyguanosine kinase deficiency: a single-center experience and a review of the literature. Liver Transpl. 2014.
72. Kripps KA, et al. Successful liver transplantation in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). Mol Genet Metab. 2020.
73. Parikh S, et al. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. Genet Med. 2015.
74. Ng YS, et al. Pseudo-obstruction, stroke, and mitochondrial dysfunction: a lethal combination. Ann Neurol. 2016.
75. Amiot A, et al. Frequency of mitochondrial defects in patients with chronic intestinal pseudo-obstruction. Gastroenterology. 2009.
76. Halter JP, et al. Allogeneic haematopoietic stem cell transplantation for mitochondrial neurogastrointestinal encephalomyopathy. Brain. 2015.
77. Levene M, et al. Safety and efficacy of erythrocyte encapsulated thymidine phosphorylase in mitochondrial neurogastrointestinal encephalomyopathy. J Clin Med. 2019.

Chapter 14
ICU-Related Neuromuscular Weakness and Neuromuscular Differential Diagnoses in the ICU

Janneke Horn and Nicola Latronico

Introduction

Patients admitted to the Intensive Care Unit (ICU) are critically ill. The survival rate of patients admitted to the ICU has increased, revealing the long-term consequences of surviving a critical illness. Survival often comes with the cost of injuries to multiple organ systems, including the central and peripheral nervous system. The combination of physical, cognitive and mental sequelae seen in patients with a prolonged ICU stay is called the post intensive care syndrome (PICS) [1]. Generalized muscle weakness is one of the main issues in PICS. This weakness, nowadays called ICU-acquired weakness (ICUAW), is caused by a variety of pathologies, including critical illness myopathy (CIM), critical illness polyneuropathy (CIP), or a combination of critical illness neuromyopathy (CIPNM) [2]. The many different terminologies used in the past hampered studies on ICUAW. Therefore, in 2009, criteria for ICUAW were established in a consensus meeting [3]. ICUAW is a very serious condition, it leads to prolonged mechanical ventilation [4], increased hospital stay and increased morbidity and mortality [5–7].

J. Horn (✉)
Amsterdam University Medical Centres, location Academic Medical Centre, Amsterdam, the Netherlands
e-mail: j.horn@amsterdamumc.nl

N. Latronico
Spedali Civili University Hospital, Brescia, Italy
e-mail: nicola.latronico@unibs.it

M. Damian, M. de Visser (eds.), *Emergencies in Neuromuscular Disorders*,
https://doi.org/10.1007/978-3-030-91932-0_14

Epidemiology

In 1984, Bolton et al. described five relatively young patients developing severe weakness during ICU admission [8]. The patients were admitted to the ICU for different reasons but all developed profound limb weakness and decreased tendon reflexes. Electrophysiological studies showed a sensory-motor axonal polyneuropathy, which was defined as CIP. Later studies showed that an acute primary myopathy, the CIM, was as common as CIP and was frequently associated with CIP [9]. Over the years, the syndrome of weakness in the ICU was recognized and described by many groups. The incidence reported varies, but overall 40% of ICU patients develop ICUAW [5, 10–14]. The incidence rates depend on the group of ICU patients studied and the criteria used for the diagnoses. For example, in ICU patients with sepsis, the incidence of ICUAW is much higher, up to 64%, compared to patients with other diseases [15, 16]. Appleton et al. reported a substantially lower incidence when using clinical examination for diagnosis (32%) compared to the use of electrophysiological techniques (47%) [17].

Pathophysiology and Risk Factors of ICUAW

ICUAW occurs most often in severely ill ICU patients with multi-organ failure. Therefore, ICUAW has been considered as a part of the multi-organ failure syndrome, involving the nerves and muscles [18–21]. The pathophysiological mechanisms leading to ICUAW are multifactorial and partly unknown [21]. For thorough research on this topic, nerve and muscle tissue should be investigated at different time points during the disease. This is problematic in ICU patients who often have coagulation disorders, and the test results do not lead to changes in therapy [9]. If nerve biopsies are performed, pure sensory nerves such as the sural nerve or superficial peroneal nerve are sampled [9]. This is suboptimal, as ICUAW primarily affects strength. Motor nerves have rarely been investigated and post-mortem tests lead to a selection bias of the more severely ill patients [22, 23]. Biopsy of the motor nerve to the gracilis muscle, a superficial muscle that is located on the medial surface of the thigh whose action overlaps that of stronger muscles, may be considered for research purposes or complex differential diagnoses [24].

One of the factors leading to muscle weakness is bed rest. In healthy elderly patients, a period of 10 days of bed rest was found to lead to a significant decrease in muscle mass, muscle strength and physical condition [25, 26]. A study following 222 ICU survivors reported a 3–11% relative decrease in muscle strength for every additional day of bed rest in the ICU, after adjusting for other potential risk factors contributing to long-term weakness [27]. In ICU patients, bed rest is combined with a strong inflammatory response, severe metabolic derangements, microvascular changes leading to increased permeability, altered energy delivery, mitochondrial dysfunction and possibly channelopathies [2]. Reduced excitability of motor nerves as a consequence of inactivation of sodium channels is a major event causing muscle weakness during critical illness. This acquired channelopathy involves

voltage-gated Na^+-channels (VGSC) and is one of the earliest consequences of critical illness [28]. Dysfunction of alpha motor neurons during repetitive firing can be an even earlier event preceding the electrical failure of peripheral axons and causing inadequate muscle force generation in the early phases of sepsis at a time when nerve conduction is still normal. Furthermore, in CIM, muscle atrophy results from increased protein degradation not compensated by protein synthesis [29].

Diaphragm weakness has been considered an integral part of ICUAW since its initial description. Historically, difficulty in weaning from the ventilator and limb muscle weakness with decreased or absent deep tendon reflexes were described as the typical presentation of the syndrome [8]. A recent study showed that diaphragm weakness can be twice as common as limb weakness, suggesting that weakness of the diaphragm and limbs might represent two distinct entities [30]. However, differences in the diagnostic method used to document diaphragm and limb weakness may have played a role. The pathophysiological mechanisms leading to diaphragm weakness are similar to ICUAW, but mechanical ventilation-induced diaphragm inactivity in itself is another contributing factor [31, 32].

Given these pathophysiological mechanisms leading to ICUAW, the most important risk factors are bed rest, sepsis, hyperinflammatory states and multiple organ failure [18–20, 33–37]. Furthermore, hyperglycemia, a condition frequently found in ICU patients, is also an independent risk factor for ICUAW. Controlling hyperglycemia to a normal range with intensive insulin therapy possibly reduces the incidence of ICUAW, but the risk of hypoglycemia with slightly but significantly increased mortality outweighs the potential benefits [33, 38–40] (Fig. 14.1).

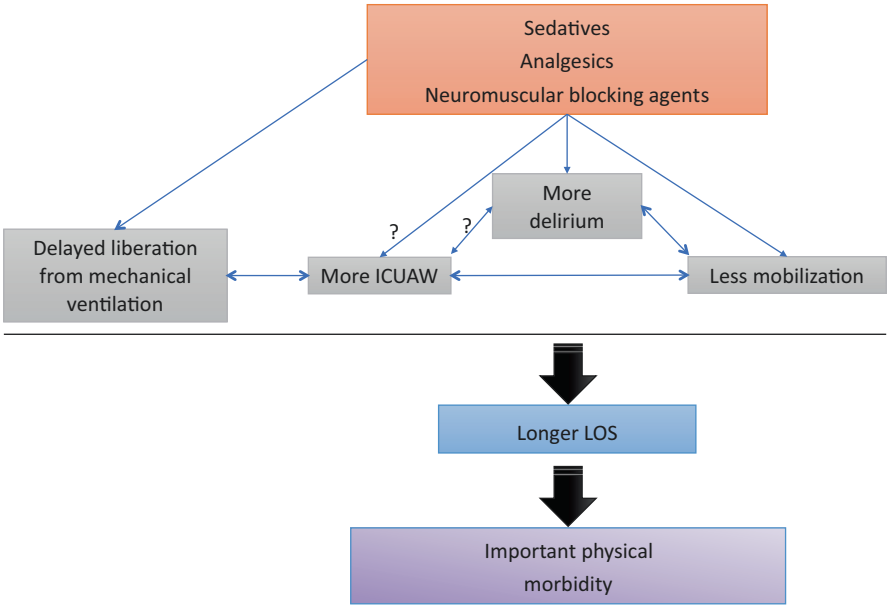


Fig. 14.1 Potential impact of sedatives, analgesics, and neuromuscular blocking agents on ICU-acquired weakness (ICUAW), delirium, and mobilization [41]

Several case reports suggested a link between ICUAW and administration of corticosteroids and prolonged administration of neuromuscular blocking agents [12, 20, 36, 39]. However, other prospective studies could not confirm these relations [19, 27, 33, 35, 38, 39, 42–44]. Finally, age was described as a factor independently related with ICUAW [20, 38].

Clinical Features and Diagnosis

ICUAW is a syndrome of generalized limb weakness that develops during the ICU stay for which there is no alternative explanation other than the critical illness itself (Case Vignette 1) [3, 16].

Case Vignette 1

A 62-year-old man with a medical history of diabetes mellitus type 2 and hypertension is admitted to the intensive care unit (ICU) with a severe pneumonia. Pneumococci turn out to be the cause, and the condition of patient deteriorates rapidly into a full blown sepsis. Besides treatment with adequate antibiotics, hemodynamic support with noradrenaline is needed, and hydrocortisone is administered. The lungs are severely affected, so mechanical ventilation in prone position is needed for several days. To enable this, sedative drugs are administered in quite high doses. Neuromuscular blockage is only needed for several hours.

After 5 days the situation gradually improves, proning is no longer needed and with decreasing intensity of mechanical ventilation the sedation can be tapered. Due to a temporarily deteriorated kidney function, it takes a while before he starts to wake up. When he is able to follow commands, it turns out that he has ICU acquired weakness (ICUAW), with severe, diffuse, symmetric muscle weakness involving all four limbs and sparing of facial muscles.

As this is thought to be caused by the severe inflammatory response that occurred during the sepsis and no special treatment options are currently available, no diagnostic tests are done. Physical therapy including bed cycling and mobilization in a chair is initiated and intensified over the days. A tracheostomy is placed and weaning off the ventilator is also started. After a week, the ICU nurse and physical therapists report that there is only minimal improvement. Are we sure that ICU-AW is the cause?

Electroneurography and electromyography are performed. A combined axonal neuropathy and myopathy are found with involvement of both proximal and distal muscles and nerves in all four limbs. At the level of the neuromuscular junction, no abnormalities are found. As this is supportive for a severe critical illness neuromyopathy, the treatment as initiated is continued. Gradually, over weeks, the patient improves and is discharged from the hospital to a rehabilitation unit.

Learning Points

1. **Severe generalized limb muscle weakness developing in a patient admitted to the ICU because of severe pneumonia necessitating mechanical ventilation is most likely ICU-acquired weakness (ICUAW).**
2. **Recovery of muscle strength may take weeks.**
3. **Specific treatment strategy to prevent or cure ICUAW is currently not available. Physical therapy, weaning off the ventilator and appropriate feeding are key.**

Limb muscle involvement is symmetric and is more pronounced in the lower extremities [45]. Facial muscles are usually spared. The recent ATS clinical practice guidelines emphasize the importance of clinical examination using the "Medical Council Research" (MRC)-scale. The consensus is that for a diagnosis of ICUAW the MRC-scores for six different bilaterally tested muscle-groups should be summed (the so-called "MRC-sum score" or MRCSS) [3, 16, 46].

An MRC-SS <48 indicates significant ICUAW, whereas a score below 36 is considered severe ICUAW [47]. However, already a mild reduction in muscle strength, with MRC-SS ≤55, is associated with decreased survival [48]. Importantly, ICUAW is not limited to ICU patients as it may represent a spectrum of weakness which can occur in any serious illness irrespective of the care location [41].

Both proximal and distal muscle groups should be tested whenever possible, including deltoids, biceps, wrist extensors, iliopsoas, quadriceps and ankle dorsiflexor muscles. In patients in whom it is impossible to bilaterally test all six muscle groups, an average MRC score <4 can be used. Testing strength using handgrip dynamometry has been described, but reliability and optimal cut-off values of this method need to be validated [11, 49, 50].

For optimal testing of muscle strength, the patient should be awake and alert. Many ICU patients have a decreased level of consciousness or delirium. Electrophysiological testing might be a preferable method in these patients. In daily clinical practice, the use of electromyography (EMG) and nerve conduction studies (NCS) were found to be variable [16]. Furthermore, variations in the timing (early or late after ICU admission), the number of nerves and muscles tested and diagnostic thresholds were described [51, 52].

More recently, ultrasound of nerves and muscles has been described as a possible method to diagnose ICUAW [53]. This easy-to-use bedside available diagnostic tool could enable easily repeated investigations of limb muscles, even in patients unable to cooperate in strength assessment. However, only limited studies combining ultrasound and strength assessment are available [54]. Therefore, the clinical relevance of ultrasound in ICUAW needs to be determined.

For evaluation of diaphragm function, the standard test is measurement of transdiaphragmatic twitch pressure (PdiTw) generated in response to bilateral anterior magnetic phrenic nerve stimulation [31]. Furthermore, ultrasound of the diaphragm can be used [55].

In the patient with the classical clinical picture of ICUAW a "wait and see" diagnostic policy is appropriate, but if any abnormalities outside the usual spectrum are found, other diagnoses should be excluded. Additional testing should be performed, especially if other clinical conditions with possible therapeutic options are considered (see Table 14.1 for an overview of conditions to consider). A useful diagnostic algorithm was described by Latronico et al., and the acronym "MUSCLES" as

Table 14.1 Differential diagnosis of ICU-acquired weakness (ICUAW)

Brain disorders
Brainstem infarcts
Brainstem encephalitis
Central pontine myelinolysis
Spinal cord and anterior horn disorders
Anterior spinal artery thrombosis
Acute transverse myelitis (immune-mediated)
Infective myelitis (West Nile, polio, cytomegalovirus, HIV)
Postinfective myelitis (zoster, West Nile)
Acute spinal cord compression (epidural abscess, metastasis)
Hopkins syndrome
Neuropathies
Critical illness polyneuropathy
Guillain–Barré syndrome and postinfective and paraneoplastic radiculitis
Toxic neuropathy
Vasculitic neuropathy
Neuromuscular junction diseases
Myasthenia gravis and myasthenic syndromes
Prolonged neuromuscular blockade
Hypermagnesemia
Myopathies
Critical illness myopathy
Drug-induced rhabdomyolysis
Myositis and pyomyositis
Toxic myopathies
Metabolic myopathies, unmasked (CPT, mitochondrial)
Compartment syndrome
Propofol syndrome
Unmasking of subclinical myopathy
Cachexia and disuse
Phrenic neuropathy (idiopathic)
Infective radiculitis (cytomegalovirus)
Lymphomatous and carcinomatous infiltration
General medical conditions
Electrolyte disturbances (hyponatremia, hypokalemia, hypophosphatemia)
Porphyria
Paraneoplastic disorders

suggested by Marramattom et al. can be helpful to remember the most common causes of generalized weakness in the ICU [2, 56].

Furthermore, undiagnosed neuromuscular disorders already existing before ICU admission can be a diagnostic pitfall (Case Vignette 2) [57]. As some of these diseases can present with respiratory insufficiency as first symptom and could have therapeutic options, it is crucial to quickly establish the correct diagnosis.

Case Vignette 2

A 46-year-old man is admitted to the ICU for observation after a fall from the stairs, leading to several broken ribs and a pneumothorax on the right side. He used to work as a truck driver but due to problems with his back, he stopped a year ago. Despite drain placement for the pneumothorax, the respiratory situation deteriorates after 2 days and a chest X-ray shows a massive atelectasis of the right lung. Also, the patient develops fever and laboratory abnormalities indicative of an infection are found, so antibiotic treatment for a possible pneumonia is started. Intubation is needed to enable bronchoscopy in order to solve the atelectasis. After a successful bronchoscopy, the patient is extubated. However, after several hours he fails, and reintubation is needed. This is quite unexpected. It is considered too soon after admission, and no severe sepsis has occurred so there are no real risk factors for ICU-AW. Is anything else wrong with this patient? The nurse taking care of the patient that day mentions that she had noticed that the patient had difficulty swallowing before intubation.

Further history is obtained from the patient's partner. She explains that apart from the back problems, the patient also had slowly increasing weakness in the limbs and difficulty walking. To illustrate this, she shows some holiday videos of the patient walking in a park. A typical walking pattern suggestive of proximal muscle weakness is seen. This information raises the suspicion of a pre-existing neuromuscular disease. Further diagnostics, including electroneurography and electromyography are performed. Nerve conduction studies do not show abnormalities, but needle electromyography indicates a generalized myopathy with fibrillation potentials and positive sharp waves. Furthermore, laboratory testing reveals increased serum creatine kinase activity and a deficiency of GAA enzyme activity leading to a diagnosis of late Pompe disease. Knowing this, a prolonged weaning from mechanical ventilation is expected, and a tracheostomy is performed. Despite several efforts, ventilatory support remains needed and the patient is transferred to a long-term ventilation facility.

Learning Points

1. **If a patient is not able to breathe independently after extubation, an as-yet undiagnosed disorder involving the diaphragm should be suspected.**
2. **Thorough history taking from the patient and family is paramount.**
3. **Late onset Pompe disease manifests with slowly progressive muscle weakness, which often goes unnoticed.**

Muscle biopsy may be required in case of diagnostic uncertainty or if muscle weakness persists despite rehabilitation and may be useful to improve prognostication. Thick filament myopathy with selective loss of myosin filaments is the hallmark of CIM in the early stage of the ICU stay [58]. It is due to increased catabolic and reduced anabolic muscle activity, and portends a good prognosis [59]. Prognosis is worse in case of myofiber necrosis, which is usually scattered. Rarely, a diffuse necrotizing myopathy is documented in patients with severe conditions and is associated with marked elevated serum CK levels and poor prognosis [60, 61]. Disuse atrophy, mainly affecting type 2 fibers, or denervation atrophy (due to concomitant CIP) is also common and may coexist with myosin loss or muscle necrosis. Sustained muscle atrophy in survivors of critical illness with persistent weakness is associated with decreased satellite cell content and impaired muscle regrowth, suggesting diminished regenerative capacity [62].

General Principles of Management

A specific treatment strategy to prevent or cure ICUAW is currently not available [47, 63]. Rapid and adequate treatment of the critical illness leading to the ICU admission and optimal supportive care are the most important first steps. Furthermore, additional injury should be prevented by protective ICU treatment strategies wherever possible. For example, by using lung protective ventilation further damage to the lungs, diaphragm and other respiratory muscles can possibly be minimized [31, 32]. There is ongoing debate about the optimal feeding strategy and the effects of enteral and parenteral feeding on ICUAW [64]. As bed rest is such an important risk factor for muscle weakness, early mobilization strategies have been investigated extensively. So far, results have been conflicting and the quality of evidence is low due to methodological limitations of the studies performed [47]. For optimal early mobilization, minimization of sedation is necessary [41, 65].

Theoretically, electrical muscle stimulation could preserve muscle strength in patients incapable of physical exercise. The studies performed in this field were recently reviewed [66]. No benefit in global muscle strength, ICU mortality, or ICU length of stay in comparison with usual care alone was found.

Short- and Long-Term Consequences

ICUAW was found to be associated with an increased risk for extubation failure, necessitating reintubation [47, 67]. Therefore, patients with ICUAW should be observed carefully for respiratory insufficiency for a prolonged period after extubation. Several factors seem to play a role in the extubation failure in patients with ICUAW: insufficient cough strength, increased risk for pulmonary atelectasis, swallowing disorders and (aspiration) pneumonia [68]. Furthermore, ICUAW leads to a

prolonged need for mechanical ventilation, ICU and hospital admission and increased mortality [47]. This increased risk for mortality is not limited to the ICU admission period, but extends to the period after ICU discharge and even long after hospital discharge [6, 48].

Conclusive Remarks

ICUAW is a common complication of critical illness and has a major impact on clinical course, survival, and long-term sequelae of the ICU stay. Diagnosis is clinical, though electrophysiological and ultrasound investigations of peripheral nerves and muscles are increasingly considered in these patients to better define etiology. As such, it is vital that neurologists and intensive care physicians fully appreciate the diagnostic approach to the weak ICU patient. Pathophysiological mechanisms are increasingly emerging, particularly nerve-muscle membrane sodium channelopathy, severe metabolic derangements, microvascular changes, altered energy delivery and use, and possibly central motor neuron dysfunction. Pharmacological treatments are lacking, but early rehabilitation with minimization of sedation may reduce muscle wasting and weakness, thus facilitating the patients weaning from the ventilation and recovery of physical function. Future research is needed to fully elucidate the pathophysiology of ICU-associated neuromuscular disorders and to make specific treatments available in this important field of medicine.

Self Assessment Questions

1. Which of the following factors is—as far as we know—most important in the development of ICU-acquired weakness?

   (a) Breakdown of actin-myosin interaction.
   (b) Damage of the neuromuscular junction.
   (c) Disorder of sodium channels in motor nerves. (*)
   (d) Disturbance of the muscular T-tubuli system.

2. Which of the following is—as far as we know—most probably the earliest event in ICU-acquired weakness?

   (a) Breakdown of signal propagation in nerves.
   (b) Dysfunction of alpha motor neurons. (*)
   (c) Protein degradation in muscles.

3. Long-lasting mechanical ventilation leads to intrinsic diaphragm weakness.

   (a) True. (*)
   (b) False.

4. Which of the following factors is most contributing to ICU-acquired weakness?

   (a) Hyperglycemia. (*)
   (b) Hypokalemia.
   (c) Hypoxemia.
   (d) Hypernatremia.

5. Sepsis is a major risk factor for ICUAW in patients who are mechanically ventilated in the ICU.

   (a) True. (*)
   (b) False.

6. Which of the following agents is most *probably* involved in the development of ICU-acquired weakness?

   (a) Antipsychotic agents.
   (b) Calcium-entry-blocker.
   (c) Neuromuscular blocking agents. (*)
   (d) Tranquilizers.

7. Which of the following agents is most *probably* involved in the development of ICU-acquired weakness?

   (a) Antibiotics.
   (b) Antiviral drugs.
   (c) Corticosteroids. (*)
   (d) Non-steroid anti-inflammatory agents.

8. Which muscle group is generally most affected in ICU-acquired weakness?

   (a) Facial muscles.
   (b) Lower limb muscles. (*)
   (c) Upper limb muscles.

9. Which component of the muscle fibre is characteristically most severely involved in ICU-myopathy?

   (a) Myosin. (*)
   (b) The nucleus.
   (c) The sarcolemma.
   (d) The sarcoplasmatic reticulum.

10. Electrical muscle stimulation was shown to be useful for preserving muscle strength in patients incapable of physical exercise.

    (a) True.
    (b) False. (*)

11. ICU acquired weakness leads to a prolonged need for mechanical ventilation.

    (a) True.
    (b) False. (*)

12. ICU acquired weakness leads to an increased risk for mortality. When?

    (a) During stay in the ICU.
    (b) During stay in the hospital after ICU.
    (c) Even long after hospital discharge.
    (d) A-C are all true. (*)

References

1. Needham DM, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. Crit Care Med. 2012;40(2):502–9.
2. Latronico N, Bolton CF. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. Lancet Neurol. 2011;10(10):931–41.
3. Stevens RD, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. Crit Care Med. 2009;37(10 Suppl):S299–308.
4. De Jonghe B, et al. Does ICU-acquired paresis lengthen weaning from mechanical ventilation? Intensive Care Med. 2004;30(6):1117–21.
5. Sharshar T, et al. Presence and severity of intensive care unit-acquired paresis at time of awakening are associated with increased intensive care unit and hospital mortality. Crit Care Med. 2009;37(12):3047–53.
6. Wieske L, et al. Impact of ICU-acquired weakness on post-ICU physical functioning: a follow-up study. Crit Care. 2015;19:196.
7. Hermans G, et al. Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. Am J Resp Crit Care Med. 2014;190(4):410–20.
8. Bolton CF, et al. Polyneuropathy in critically ill patients. J Neurol Neurosurg Psychiatry. 1984;47(11):1223–31.
9. Latronico N, et al. Critical illness myopathy and neuropathy. Lancet. 1996;347(9015):1579–82.
10. Stevens RD, et al. Neuromuscular dysfunction acquired in critical illness: a systematic review. Intensive Care Med. 2007;33(11):1876–91.
11. Ali NA, et al. Acquired weakness, handgrip strength, and mortality in critically ill patients. Am J Resp Crit Care Med. 2008;178(3):261–8.
12. De Jonghe B, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA. 2002;288(22):2859–67.
13. Mirzakhani H, et al. Muscle weakness predicts pharyngeal dysfunction and symptomatic aspiration in long-term ventilated patients. Anesthesiology. 2013;119(2):389–97.
14. Bercker S, et al. Critical illness polyneuropathy and myopathy in patients with acute respiratory distress syndrome. Crit Care Med. 2005;33(4):711–5.
15. Bolton CF. Neuromuscular manifestations of critical illness. Muscle Nerve. 2005;32(2):140–63.
16. Fan E, et al. An official American Thoracic Society clinical practice guideline: the diagnosis of intensive care unit-acquired weakness in adults. Am J Resp Crit Care Med. 2014;190(12):1437–46.
17. Appleton RT, Kinsella J, Quasim T. The incidence of intensive care unit-acquired weakness syndromes: a systematic review. J Intensive Care Soc. 2015;16(2):126–36.
18. Garnacho-Montero J, et al. Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients. Intensive Care Med. 2001;27(8):1288–96.
19. Nanas S, et al. Predisposing factors for critical illness polyneuromyopathy in a multidisciplinary intensive care unit. Acta Neurol Scand. 2008;118(3):175–81.
20. Hermans G, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med. 2013;1(8):621–9.

21. Friedrich O, et al. The sick and the weak: neuropathies/myopathies in the critically ill. Physiol Rev. 2015;95(3):1025–109.
22. Zochodne DW, et al. Critical illness polyneuropathy: a complication of sepsis and multiple organ failure. Brain. 1987;110:819–41.
23. Witteveen E, et al. Muscle and nerve inflammation in intensive care unit-acquired weakness: a systematic translational review. J Neurol Sci. 2014;345(1–2):15–25.
24. Corbo M, et al. Motor nerve biopsy studies in motor neuropathy and motor neuron disease. Muscle Nerve. 1997;20(1):15–21.
25. Coker RH, et al. Bed rest promotes reductions in walking speed, functional parameters, and aerobic fitness in older, healthy adults. J Gerontol A Biol Sci Med Sci. 2015;70(1):91–6.
26. Kortebein P, et al. Functional impact of 10 days of bed rest in healthy older adults. J Gerontol A Biol Sci Med Sci. 2008;63(10):1076–81.
27. Fan E, et al. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. Crit Care Med. 2014;42(4):849–59.
28. Latronico N, Friedrich O. Electrophysiological investigations of peripheral nerves and muscles: a method for looking at cell dysfunction in the critically ill patients. Crit Care. 2019;23(1):33.
29. Batt J, Santos CCD, Herridge MS. Muscle injury during critical illness. JAMA. 2013;310(15):1569–70.
30. Dres M, et al. Coexistence and impact of limb muscle and diaphragm weakness at time of liberation from mechanical ventilation in medical intensive care unit patients. Am J Respir Crit Care Med. 2017;195(1):57–66.
31. Supinski GS, et al. Diaphragm dysfunction in critical illness. Chest. 2018;153(4):1040–51.
32. Hussain SN, et al. Prolonged controlled mechanical ventilation in humans triggers myofibrillar contractile dysfunction and myofilament protein loss in the diaphragm. Thorax. 2016;71(5):436–45.
33. Van Den Berghe G, et al. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology. 2005;64(8):1348–53.
34. Van Den Berghe G, et al. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359–67.
35. Weber-Carstens S, et al. Risk factors in critical illness myopathy during the early course of critical illness: a prospective observational study. Crit Care. 2010;14(3):R119.
36. Campellone JV, et al. Acute myopathy after liver transplantation. Neurology. 1998;50(1):46–53.
37. De Letter MACJ, et al. Risk factors for the development of polyneuropathy and myopathy in critically ill patients. Crit Care Med. 2001;29(12):2281–6.
38. Patel BK, et al. Impact of early mobilization on glycemic control and ICU-acquired weakness in critically ill patients who are mechanically ventilated. Chest. 2014;146(3):583–9.
39. Hermans G, et al. Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. Am J Resp Crit Care Med. 2007;175(5):480–9.
40. Investigators N-SS, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283–97.
41. Latronico N, et al. The ICM research agenda on intensive care unit-acquired weakness. Intensive Care Med. 2017;43(9):1270–81.
42. Bednarík J, et al. Risk factors for critical illness polyneuromyopathy. J Neurol. 2005;252(3):343–51.
43. Steinberg KP, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med. 2006;354(16):1671–84.
44. Papazian L, et al. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010;363(12):1107–16.
45. Argov Z, Latronico N. Neuromuscular complications in intensive care patients. Handb Clin Neurol. 2014;121:1673–85.
46. Sharshar T, et al. Neurological examination of critically ill patients: a pragmatic approach. Report of an ESICM expert panel. Intensive Care Med. 2014;40(484):495.

47. Vanhorebeek I, Latronico N, Van den Berghe G. ICU-acquired weakness. Intensive Care Med. 2020;46(4):637–53.
48. Van Aerde N, et al. Five-year impact of ICU-acquired neuromuscular complications: a prospective, observational study. Intensive Care Med. 2020;46(6):1184–93.
49. Hermans G, et al. Interobserver agreement of Medical Research Council sum-score and handgrip strength in the intensive care unit. Muscle Nerve. 2012;45(1):18–25.
50. Parry SM, et al. A new two-tier strength assessment approach to the diagnosis of weakness in intensive care: an observational study. Crit Care. 2015;19:52.
51. Latronico N, et al. Validation of the peroneal nerve test to diagnose critical illness polyneuropathy and myopathy in the intensive care unit: the multicentre Italian CRIMYNE-2 diagnostic accuracy study. F1000Res. 2014;3:127.
52. Wieske L, et al. Feasibility and diagnostic accuracy of early electrophysiological recordings for ICU-acquired weakness: an observational cohort study. Neurocrit Care. 2015;22(3):385–94.
53. Bunnell A, et al. Quantitative neuromuscular ultrasound in intensive care unit-acquired weakness: a systematic review. Muscle Nerve. 2015;52(5):701–8.
54. Witteveen E, et al. Diagnostic accuracy of quantitative neuromuscular ultrasound for the diagnosis of intensive care unit-acquired weakness: a cross-sectional observational study. Ann Intensive Care. 2017;7(1):40.
55. Zambon M, et al. Assessment of diaphragmatic dysfunction in the critically ill patient with ultrasound: a systematic review. Intensive Care Med. 2017;43(1):29–38.
56. Maramattom BV, Wijdicks EFM. Acute neuromuscular weakness in the intensive care unit. Crit Care Med. 2006;34(11):2835–41.
57. Damian MS, Wijdicks EFM. The clinical management of neuromuscular disorders in intensive care. Neuromuscul Disord. 2019;29(2):85–96.
58. Wollersheim T, et al. Dynamics of myosin degradation in intensive care unit-acquired weakness during severe critical illness. Intensive Care Med. 2014;40(4):528–38.
59. Friedrich O, Diermeier S, Larsson L. Weak by the machines: muscle motor protein dysfunction - a side effect of intensive care unit treatment. Acta Physiol (Oxf). 2018;222(1).
60. Ramsay DA, et al. A syndrome of acute severe muscle necrosis in intensive care unit patients. J Neuropathol Exp Neurol. 1993;52(4):387–98.
61. Zochodne DW, et al. Acute necrotizing myopathy of intensive care: electrophysiological studies. Muscle Nerve. 1994;17(3):285–92.
62. Dos Santos C, et al. Mechanisms of chronic muscle wasting and dysfunction after an intensive care unit stay. A pilot study. Am J Respir Crit Care Med. 2016;194(7):821–30.
63. Shepherd SJ, et al. Pharmacological therapy for the prevention and treatment of weakness after critical illness: a systematic review. Crit Care Med. 2016;44(6):1198–205.
64. Gunst J, Van den Berghe G. Intensive care nutrition and post-intensive care recovery. Crit Care Clin. 2018;34(4):573–83.
65. Schaller SJ, et al. Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. Lancet. 2016;388(10052):1377–88.
66. Zayed Y, et al. Effects of neuromuscular electrical stimulation in critically ill patients: a systematic review and meta-analysis of randomised controlled trials. Aust Crit Care. 2020;33(2):203–10.
67. Dres M, et al. Critical illness-associated diaphragm weakness. Intensive Care Med. 2017;43(10):1441–52.
68. Zuercher P, et al. Dysphagia in the intensive care unit: epidemiology, mechanisms, and clinical management. Crit Care. 2019;23(1):103.

Chapter 15
Neuromuscular Emergencies from a Low- and Middle-Income Countries Perspective

Gentle Sunder Shrestha, Gaurav Nepal, and Rajeev Ojha

Introduction

According to the World Bank, low- and middle-income countries (LMICS) includes those nations with gross national income (GNI) per capita below $12,535. LMICS includes low-income economies with a GNI per capita below $1035, lower-middle-income economies with a GNI per capita of $1036 to $4045, and upper-middle-income economies with a GNI per capita between $4046 and $12,535. LMICS have been plagued by a colossal array of communicable and non-communicable diseases since perpetuity. However, only infectious diseases, nutritional disorders, and some common non-communicable diseases come under the radar of concerned authorities. Neurological disorders remain one of the most neglected disease conditions in LMICS, including neuromuscular emergencies.

Despite being under-reported, the burden of neuromuscular emergencies in LMICS remains high. Although neuromuscular emergencies in LMICS deserve special attention, policymakers and major stakeholders, the international community, clinicians, and researchers are hardly aware of them. Compared with high-income countries (HIC), managing neuromuscular emergencies in LMICS is perplexing due to religious belief and superstitions, intricate road networks, unavailability of transportation, unavailability of emergency services, lack of specialized training among physicians, restricted access to advanced diagnostic facilities,

G. S. Shrestha (✉)
Department of Critical Care Medicine, Tribhuvan University Teaching Hospital, Kathmandu, Nepal

G. Nepal
Department of Internal Medicine, Tribhuvan University Teaching Hospital, Kathmandu, Nepal

R. Ojha
Department of Neurology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal

M. Damian, M. de Visser (eds.), *Emergencies in Neuromuscular Disorders*,
https://doi.org/10.1007/978-3-030-91932-0_15

unavailability and unaffordability of treatment, lack of intensive care units (ICU) and ventilators, and lack of access to neuromonitoring. LMICS further differs from HIC as they encounter unique neuromuscular emergencies such as tetanus, organophosphate poisoning, neuroparalytic snakebite, diphtheria polyneuropathy, arsenic poisoning, Japanese encephalitis, poliomyelitis, and West Nile encephalitis [1–6]. Data and research are limited regarding these diseases, and clinicians treat them based on their clinical judgment and experience.

Given the grim situation of neuromuscular emergencies in LMICS, the outcome of patients with such disorders is usually poor. Due to poor transportation, most of the patients die even before reaching the hospital, while others die due to unavailability of emergency service, unavailability, and unaffordability of drugs, monitoring beds, and ventilators. A quarter of those who survive often have residual weakness and disability, pushing them into a vicious cycle of poverty and disability.

In this chapter, we provide an overall perspective of neurological emergencies in LMICS. The first part deals with how clinicians manage a typical neuromuscular crisis (Guillain-Barré syndrome) in LMICS. The rest of the parts deals with the management of neuromuscular emergencies unique to LMICS.

Guillain-Barré Syndrome in LMICS

Case Vignette 1

A 26-year-old male presents to the emergency department with complaints of weakness in his legs. Symptoms began 2 days prior when he failed to put on his slippers. It was also associated with a tingling sensation in his feet. This morning, the patient was having difficulty walking upstairs, and by early afternoon he was having difficulty walking on the floor. He also reports numbness in his legs, which is minor in comparison to his motor complaints. He said having few diarrhea episodes 2 weeks back, which was relieved by self-medication from a local pharmacy. He had no history of trauma, recent vaccination, fever, headache, nausea, and vomiting. His bladder and bowel function was normal. He denies low back pain and shooting pain. On examination, his blood pressure was 140/80 mm of Hg, pulse rate was 96 bpm, respiratory rate was 20/min, and he was afebrile. He didn't have pallor, icterus, lymphadenopathy, cyanosis, clubbing, edema, or dehydration. The patient was conscious, alert, and oriented. On nervous system examination, toe flexion and extension are 1/5 bilaterally, ankle and knee flexion and extension are 2/5, and hip flexion and extension are 3/5. Muscle bulk was regular, the tone was flaccid, and reflexes were absent in the lower extremities. Upper extremities were normal to bulk, power, tone, and reflexes. He had no spine sensory level. Meningeal irritation signs and upper motor neuron signs were negative. A systemic examination yielded no remarkable findings. His higher

mental function was intact. The patient was admitted to the neurology ward. The results of baseline laboratory investigations were unremarkable. USG abdomen and pelvis were normal. The cervical spine and head computed tomography scan were normal. Lumbar puncture was done, and cerebrospinal fluid (CSF) analysis revealed albuminocytological dissociation.

The patient could not afford magnetic resonance imaging of his spine. The electrodiagnostic test was not available in the city. Based on the prodrome, clinical features, and CSF studies, a diagnosis of Guillain-Barré syndrome was made. Due to the intensive care unit's unavailability, he was admitted to the medicine ward; and a monitor was attached to measure physiological parameters. The patient could not afford intravenous immunoglobulin and plasmapheresis; therefore, methylprednisolone was started. The patient showed gradual improvement in motor function over 3 months and received intense physiotherapy during this time. The patient did not develop respiratory paralysis and dysautonomia during the hospital stay. He was discharged after 4 months of hospital stay with residual weakness.

Learning Points

- **In LMICS, the diagnosis of Guillain-Barré syndrome is wholly based on clinical findings and, if available, with supportive evidence from cerebrospinal fluid studies.**
- **A diagnostic facility like magnetic resonance imaging and electrophysiological tests are not available easily.**
- **Most of the time, treatment is supportive only due to the unavailability and unaffordability of immunomodulating therapies.**
- **Clinicians from LMICS have tried various low-cost alternatives for the management of Guillain-Barré syndrome. However, they have hardly been studied in a clinical trial due to a lack of economic and scientific support.**

Introduction

Guillain-Barré syndrome (GBS) is one of the common neuromuscular emergencies worldwide and in LMICS. It manifests as rapid motor weakness and sensory disturbance, involving the limbs, face, bulbar, and respiratory muscles. GBS is a neuroimmunological disorder causing demyelination or axonal damage in the peripheral nervous system [7]. Acute inflammatory demyelinating polyneuropathy (AIDP) is the most common form of GBS, but other forms are frequently reported, such as acute motor axon neuropathy (AMAN), acute motor-sensory axon neuropathy (AMSAN), and Miller-Fisher syndrome [8]. GBS's weakness usually progresses quickly, and most GBS patients reach their maximum disability within 2 weeks. It is also one of the most common causes of neuromuscular respiratory failure, with

17%–30% of patients requiring mechanical ventilation [9]. In addition to motor weakness, GBS patients can also develop fatal arrhythmias and blood pressure fluctuations due to autonomic nervous system involvement [10]. So far, GBS's exact cause is unclear, but two-thirds of patients report having some kind of infection within the preceding 6 weeks [7, 10]. There is currently no cure for GBS, but immunomodulating therapies can relieve symptoms and speed up motor recovery. Compared with GBS patients in the West, the prognosis of GBS patients in LMICS is poor because of difficulties in diagnosis, referral, transportation, and availability and affordability of treatment.

Diagnosis

Clinical Assessment

The diagnosis of GBS in LMICS is challenging, and the diagnosis depends solely on clinical features. The heterogeneous clinical manifestations further complicate the diagnosis. Electrodiagnostic tests and neuroimaging tests are not readily available in LMICS, and most clinicians may have to rely on the clinical diagnostic criteria (Table 15.1) along with cerebrospinal fluid (CSF) studies [10, 11]. An infectious prodrome can provide a hint for diagnosis, and about two-thirds of patients who develop GBS report symptoms of infection in the 6 weeks preceding the onset of the condition. Commonly involved infectious etiologies include *Campylobacter jejuni* diarrhea, cytomegalovirus, *Mycoplasma pneumoniae* pneumonia, Epstein-Barr virus, and Zika virus disease. GBS's most important diagnostic feature is acute flaccid paralysis, but this feature overlaps with other common diseases, such as transverse myelitis, polio, traumatic neuritis, hypokalemia/hyperkalemia, neuroparalytic snake bite, and Japanese encephalitis. Other uncommon causes include acute poisoning (arsenic and organophosphate), myasthenic crisis, West Nile encephalitis, and diphtheria polyneuropathy. In most cases, clinical features and readily available laboratory tests can effectively rule out these conditions (Table 15.2).

Cerebrospinal Fluid (CSF) Examination

CSF examination is available in selected government hospitals, private health centers, and academic institutes; however, it is not required for GBS's clinical diagnosis and should not delay treatment. CSF albuminocytological dissociation (raised CSF protein level and CSF total white blood cell count <50 cells/ mm^3) provides supporting evidence for GBS diagnosis. However, normal protein levels and cell counts do not exclude GBS. In GBS, >50% of patients show albuminocytological dissociation within the first week, and >75% of patients show albuminocytological dissociation within the third week. Therefore, CSF studies done within a week of symptom onset might show a normal result. If the diagnosis remains uncertain, a repeat CSF

Table 15.1 Commonly used criteria for the diagnosis of GBS in LMICS

Features needed for diagnosis of Guillain-Barré syndrome (and variants) in clinical practice	Progressive weakness in legs and/or arms
	Areflexia or hyporeflexia in weak limbs
Supportive features	The progressive phase lasts days to 4 weeks
	Symmetrical weakness
	Paresthesia or numbness in the extremities
	Pain
	Cranial nerve involvement (bulbar/facial palsy, ophthalmoplegia)
	Ataxia
	Autonomic dysfunction
Features making the diagnosis of GBS suspicious	Severe pulmonary dysfunction with little or no limb weakness at the onset
	Severe sensory signs with little or no weakness at the onset
	Bladder or bowel dysfunction at onset or persistent bladder or bowel dysfunction
	Fever at the onset
	Nadir <24 h
	Clinical progression for >4 weeks
	The slow progression of weakness and without respiratory involvement
	Hyperreflexia or clonus
	Extensor plantar responses
	Sharp spinal cord sensory level
	Marked, persistent asymmetry of weakness

examination may be performed at the second or third week of symptom onset. The presence of mononuclear or polymorphonuclear cells >50 cells/mm^3 makes GBS diagnosis unlikely [10].

Electrophysiological Tests

Except for a few academic institutions and private health centers, these tests are not readily available in LMICS. If available, electrophysiological testing can help improve GBS's diagnostic certainty and can also classify GBS subtypes. AIDP exhibits demyelination characteristics, such as decreased motor nerve conduction velocity, prolonged distal motor latency, increased F wave latency, conduction block, and temporal dispersion. AMAN, an axonal form, shows distal compound muscle action potential (CMAP) amplitude <80% of the lower limits of normal, the F wave is absent, and the proximal to distal amplitude ratio is <0.7 [10]. A transient motor nerve conduction block may also exist in the axonal form. Besides, the electrophysiological test can also help rule out other common causes of acute flaccid paralysis.

Table 15.2 Differential diagnosis of acute flaccid palsy in LMICS and their clinical features

Differential diagnosis	Clinical features
Poliomyelitis	Only in Pakistan, Afghanistan, and Nigeria. Febrile illness with a sore throat, headache, and acute flaccid palsy. • Spinal polio (most typical): Involves the trunk, limbs, and the intercostal muscles. Weakness is asymmetrical and proximal, and any limb or combination of limbs may be affected. Bowel/bladder involvement is present. • Bulbospinal polio (rare): It is also called respiratory type, and the virus affects the upper part of the cervical spinal cord, paralyzing the diaphragm along with bulbar neuron causing pharyngeal paralysis. • Bulbar polio (very rare): It involves bulbar neurons in brain stem, causing pharyngeal paralysis. The involvement of the medullary centers can be fatal. CSF studies show lymphocytic pleocytosis and raised protein.
Transverse myelitis	Fever absent. Acute symmetrical weakness involving the lower limb. Cranial nerves are not involved. Bowel/bladder involved. Band-like sensation in the trunk at the level of lesion that feels like a tight strap.
Traumatic neuritis	History of trauma, spine bruising, tenderness.
Hypo/hyperkalemia	Altered K^+ level and electrocardiography changes.
Japanese encephalitis (JE)	This occurs in Asia and the pacific rim, common in the rainy season. Common in the pediatric age group. Fever, chills, headache, myalgia, and neck stiffness are present. Rapidly progressive encephalopathy, seizure, and focal neurological sign. Acute asymmetrical and mainly proximal weakness. CSF lymphocytic pleocytosis and raised protein. JE IgM in serum or CSF.
Elapidae snake bite (Cobra, Krait, Mamba)	Hypersalivation Bilateral ptosis and persistently dilated pupils and ophthalmoplegia Inability to open mouth, tongue extrusion, inability to swallow, inability to hold neck (broken neck sign), and loss of gag reflex Limb weakness, flaccid paralysis, and loss of deep tendon reflexes Paralysis of intercostals and diaphragm
Acute arsenic poisoning	History of taking ayurvedic or homeopathic medicine, and drinking contaminated well water Garlicky breath, nausea, vomiting, rice water diarrhea, and colicky abdominal pain Arrhythmia and acute kidney injury Symmetrical sensorimotor polyneuropathy described as distal paresthesia, followed by rapidly ascending sensory loss and weakness

Table 15.2 (continued)

Differential diagnosis	Clinical features
Organophosphate poisoning	History of exposure to organophosphate insecticide: Accidental/suicidal. Muscarinic signs: Hypersalivation, lacrimation, urination, diaphoresis, gastrointestinal upset, emesis, bronchospasm, bronchorrhea, blurred vision, bradycardia or tachycardia, hypotension, confusion, and shock. Nicotinic effects: Skeletal muscle fasciculation, cramps, weakness, and paralysis
Myasthenia gravis	Initially blurred vision, diplopia, or lid ptosis Passive elevation of each eyelid, in turn, unmasks or exaggerates ptosis in the contralateral lid (curtain sign) Improvement of ptosis in response to eyelid cooling (ice pack test) Progress to difficulty chewing, swallowing, or talking (nasal speech) Progress to an isolated limb or axial muscle weakness The hallmark is the progression of muscle weakness with repeated use.
West Nile encephalitis	Distributed in Africa, the middle east, Europe, and the Americas, common in the elderly Fever, chills, headache, skin rash on the trunk, and lymphadenopathy are present Rapidly progressive encephalopathy, seizure, and focal neurological sign Acute asymmetrical and mainly proximal weakness; paresthesia absent, pain present CSF lymphocytic pleocytosis and raised protein Bowel/bladder involvement present
Diphtheria polyneuropathy	Fever, sore throat, difficulty swallowing, hoarseness Bull neck appearance Pseudo-membrane in the pharynx Arrhythmia

Treatment

General

GBS is a potentially life-threatening disorder. Supportive medical care and monitoring and evaluation and administration of immunomodulating therapy needs should be carried out quickly and simultaneously. Because of the associated risks of respiratory failure and autonomic dysfunction, supportive treatment for GBS patients is extremely important. Patients in the progressive phase of GBS require close monitoring of respiration, blood pressure, heart rate, and dysphagia, if possible, in Intensive care units (ICU) [10, 11]. In LMICS, ICU is not easily available; in such cases, any bed with a monitor can be used. Clinicians should remain vigilant to prevent complications such as venous thromboembolism, lung infections, and urinary tract infections. Nutritional support, pain management, psychosocial support, and physical therapy are invaluable in early recovery.

Specific

Plasma exchange or intravenous immunoglobulin (IVIG) therapy is recommended for the majority of GBS patients on account of accelerated clinical recovery. IVIG is as effective as therapeutic plasma exchange, and the choice of treatment should be based on availability, cost, and feasibility of administration. If immunomodulating therapy is given to the right patient at the right time, it can provide a remarkable clinical benefit. In non-ambulatory patients, they must be administered as early as 2 weeks and not beyond 4 weeks from the onset of symptoms. In ambulatory patients who are not yet recovering by 4 weeks of symptom onset should also be started on immunotherapy [10]. IVIG and plasma exchange, despite being the standard of care for GBS, patients from LMICS can barely meet the treatment standards due to their unaffordability. The cost of treatment with IVIG or plasma exchange sums $5000 to 10,000, and for those with an annual income abiding around $1000, it is impossible to afford this cost. Plasma exchange is relatively cheaper than IVIG and is the first option for those who aim to afford the treatment cost. For those who can't cope, steroids are still a hope. Steroids are still widely used in the treatment of GBS in South Asian and African countries. Although they have shown no role in randomized controlled trials [12]; steroids have shown to have suboptimal effects in GBS treatment in real-world practice. Plasma exchange with replacement fluid as frozen plasma and normal saline is also a reasonable alternative when the patient can't afford albumin [13, 14]. Small volume plasma exchange is regularly being used in specific centers of few South Asian and South East Asian countries. They are available at a low cost and validated by prospective studies and clinical trials [15, 16]. Exchange blood transfusions have also been used to treat GBS in children in some LMICSs and have shown to be effective. More research is needed to find cost-effective alternatives for the treatment of GBS. Industry-sponsored randomized controlled trials, selecting a narrow range of patients, done in the developed country's exorbitant setup, are less likely to be useful both clinically and economically in LMICS.

Organophosphate Poisoning

Case Vignette 2
A 42-year-old male farmer presented to the emergency department in a comatose state. There was a garlicky odor coming from his body. On inquiry with his wife, she said that her husband was stressed about the financial crisis 2 days back due to the poor harvest this year. Today she found her husband lying on the floor unconscious and with an insecticide bottle nearby. On

examination, he had profuse salivation, excessive lacrimation, was diaphoretic, had fixed pinpoint pupils, had incontinence, fasciculations, and was unresponsive to deep pain. His blood pressure was 150/90 mm Hg, temperature 101 °F, pulse 58 beats/min, and had an oxygen saturation of 94% at room air. His chest revealed crackles on examination. Cardiac and gastrointestinal examinations were unremarkable. His Glasgow come scale was 8/15, with reduced movements of all four limbs. The plantar reflex was extensor bilaterally. Deep tendon reflexes were sluggish. Investigations at admission showed regular renal function tests, liver function tests with leukocytosis. Serum or red blood cell cholinesterase could not be analyzed due to a lack of a testing facility. Based on clinical features and examination of the insecticide bottle, a diagnosis of methyl-parathion poisoning was made. Secretions were suctioned from the oral cavity, and the patient was intubated, and ventilatory support was instituted. Continuous cardiac monitoring and pulse oximeter was established. Gastric lavage was performed with 200 ml of normal saline, and 50-g activated charcoal was administered. Atropine was given as 2 mg bolus and then doubled every 5 min as per the clinical response and signs of atropinization, which includes clear chest on auscultation with no wheeze, pulse >80 beats/min, non-pinpoint pupil, dry skin, and systolic blood pressure >80 mm of Hg. At the fourth bolus, atropinization was reached with a total of 30 mg atropine. Atropine infusion was started at a dose of 6 mg/h, and the infusion dose was reduced by 20% every 4 h based on auscultatory findings and oxygenation. After 8 h, the patient had dried pulmonary secretions and adequate oxygenations, so atropine was stopped. Pralidoxime was also administered concurrently at a loading dose of 2 g over 30 min, followed by continuous infusion of 8–10 mg/kg/h until atropinization. The patient regained spontaneous respirations and consciousness after 22 h and was subsequently extubated and closely monitored for the next 48 h. His motor functions recovered utterly, and he revealed to us that he consumed insecticide due to financial pressure. A psychiatric consultation was done, and he was transferred to the psychiatry ward with no residual weakness.

Learning Points

- **Suicidal organophosphorus pesticide poisoning is one of the most common causes of neuromuscular emergencies in LMICS.**
- **The effects of muscarinic involvement appear soon after ingestion, followed by nicotinic effects like fasciculations, cramps, and paralysis.**
- **Supportive treatment, along with antidotes like atropine and pralidoxime, is used to manage organophosphorus poisoning.**
- **Patients with neuromuscular weakness will eventually require endotracheal intubation and mechanical ventilation.**

Introduction

Organophosphorus (OP) pesticide poisoning is mainly suicidal and rarely accidental. It is the most common cause of poisoning in the developing world, and about 2,000,000 people each year succumb to OP poisoning [17]. Besides, it is one of the most common causes of neuromuscular emergencies in LMICS, especially in South Asia. OPs are usually used for pest control in agriculture. In South Asian countries/regions, these compounds are easily available in local stores, and their supply is unrestricted. Commonly used compounds include methyl parathion, malathion, fenthion, chlorpyrifos, quinalphos, and diazinon [18]. They can be quickly absorbed through the skin and mucous membranes or by inhalation. The primary mechanism of action of organophosphate pesticides is the inhibition of carboxyl ester hydrolase, especially acetylcholinesterase (AChE), by phosphorylation of the serine hydroxyl group at the active site of AChE. This occurs in the peripheral nicotinic and muscarinic, central nervous system (CNS) muscarinic nerve terminals and junctions. Inhibition of the AChE enzyme leads to the accumulation of acetylcholine (ACh) and excessive cholinergic stimulation of nicotinic and muscarinic receptors [19, 20].

Clinical Features

Depending on the amount of OP exposure and the site of exposure, the clinical features are evident from a few minutes to a few hours. Clinical characteristics can be classified according to the receptors involved (Table 15.3). The effects of

Table 15.3 Clinical manifestations of organophosphate poisoning based on receptors involved

Receptor involved	Receptor subtype and clinical manifestations		
Nicotinic	N1 (neuromuscular junction)	Fasciculations, twitching, cramps, and paralysis	
	N2 (autonomic ganglia and adrenal medulla)	Tachycardia and hypertension	
Muscarinic	M1–M5 (central nervous system)	Anxiety, agitation, emotional liability, confusion, seizures, ataxia, coma, respiratory depression, circulatory collapse	
	M2	Heart	Bradycardia
	M3	Smooth muscles	Due to an increase in intracellular calcium: Bronchospasm, abdominal cramp, urinary incontinence, and miosis Due to increased Nitric oxide synthesis in vascular endothelial cells: Hypotension
		Exocrine glands	Lacrimation, salivation, rhinorrhea, bronchorrhea, and sweating

muscarinic involvement include excessive salivation, tearing, urination, sweating, gastrointestinal discomfort, vomiting, bronchospasm, bronchorrhea, blurred vision, bradycardia or tachycardia, hypotension, shock, anxiety, restlessness, encephalopathy, seizures, and central respiratory failure. Muscarinic effects occur immediately after exposure, and symptoms may last up to several days, depending on the amount of OP [21]. The nicotinic effect, also known as intermediate syndrome, follows the muscarinic effect. Acetylcholine overstimulates neuromuscular junctions at first, causing fasciculations and cramping, and then neuromuscular paralysis due to receptor desensitization. Its onset usually occurs after 24 h and may last up to 3 weeks [21, 22].

Neuromuscular Emergency

Type I Paralysis

In the first 24 h of poisoning, during the cholinergic crisis, type I paralysis or acute paralysis ensues. Due to the inhibition of AChE, a large amount of ACh accumulates in the neuromuscular junction (NMJ), leading to continuous depolarization of the nicotinic receptors on the NMJ, resulting in muscle fasciculations, cramps, and sometimes paralysis [21].

Type II Paralysis

Also known as the intermediate syndrome, it appears 24 h after being poisoned, and the patient seems to have recovered from the cholinergic crisis. Prolonged depolarization of NMJ's nicotinic receptors can lead to receptor desensitization and, eventually, paralysis. Patients who recover from type I paralysis can also develop type II paralysis [22].

Type III Paralysis

It is a rare type of paralysis caused by OP, which manifests after 3 weeks of poisoning. It is also known as organophosphate-induced delayed-onset polyneuropathy (OPIDP), a distally dominant sensorimotor axonal polyneuropathy that can develop rapidly to cause respiratory insufficiency. OPIDN can mimic Guillain-Barré syndrome because of it of long latency and similar clinical pictures. OPIDN is caused by the covalent inhibition of neuropathic target esterase (NTE) [23].

Diagnosis

The diagnosis is based on the history of pesticide intake, the presence of pesticide bottles on-site, suicidal history, characteristic clinical signs, the smell of pesticides (garlicky), and laboratory tests. Ideally, OP poisoning should be diagnosed by measuring plasma butyrylcholinesterase or red blood cell acetylcholinesterase. However, these tests should not delay treatment. When the clinical manifestations are suspicious, and enzyme assay is not possible, the atropine challenge test can be used to diagnose OP poisoning. When administered to a person with regular AChE activity, atropine at a dose of 1–2 mg will show anticholinergic effects. However, in patients with OP poisoning, the anticholinergic effect is absent. The most crucial anticholinergic effect in clinical practice is to increase the heart rate by more than 25 beats/min or to cause skin flushing [17, 19].

Management of Non-Neuromuscular Manifestations

General

Patients with acute OP poisoning should be immediately evaluated to manage the airway, breathing, and circulatory disorders. Medical staff must use personal protective equipment as OP is quickly absorbed from the patient's skin and body secretions. The oral cavity should be suctioned to remove the accumulation of saliva and froth. The patient should be placed in the left decubitus position to reduce the risk of gastric aspiration. High flow oxygen should be provided in all patients. Intubation may be necessary for respiratory distress due to laryngospasm, bronchospasm, bronchorrhea, central respiratory depression, or seizures. During intubation, succinylcholine should be avoided as it is degraded by AChE and may result in prolonged paralysis. Continuous cardiac monitoring and pulse oximetry should be established. OP can cause fatal arrhythmias and seizures and should be treated accordingly. The eyes should be flushed with an isotonic solution.

Two venous lines should be opened, and blood samples should be sent for hematology, biochemistry, and enzyme assay [17]. In patients with agitation, 10 mg of diazepam can be used intravenously, and 30–40 mg can be repeated every 24 h [19]. The patient should be decontaminated by removing all clothing and washing the skin with soap and water. Forced vomiting is not recommended. Gastric lavage should be performed as soon as possible. Due to its high risk of aspiration, it should only be performed in calm consenting or unconscious intubated patients. Gastric lavage is recommended only after the administration of an antidote. Lavage should not exceed 300 ml as it may push poison into the intestine [18, 19]. Although strong evidence is lacking, activated charcoal (1 g per kilogram, up to 50 g) can be used for patients who arrive hospital within 1 h of exposure [19].

Antidotes

Atropine

Atropine is the only proven effective antidote for OP poisoning. The atropine regimen is not uniform, and different clinicians used different treatment regimens. The most widely followed regimen is a bolus loading dose followed by boluses every 5 min till atropinization. The initial dose of atropine is usually low (1–2 mg) and then escalated every 5 min (doubled each time) to achieve atropinization. Atropinization criteria are clear chest on auscultation with no wheeze, pulse >80 beats/min, non-pinpoint pupil, dry skin, and systolic blood pressure > 80 mm of Hg. Once atropinization is reached, atropine infusion is started at a dose of 20% of the total atropine required for atropinization. The infusion dose is reduced by 20% every 4 h based on auscultatory findings and oxygenation. Pulse, pupil size, skin finding, and systolic blood pressure should not be used to titrate atropine dose once atropinization is reached. The endpoint of atropine administration is dried pulmonary secretions and adequate oxygenations [19, 24].

Pralidoxime

It is usually used with atropine and helps reactivation of AChE. However, it must be administered before the aging of AChE as aged AChE cannot be reactivated by oximes. Aging is a conformational change that makes the bond between OP and AChE irreversible. Pralidoxime is useful for up to 12 h in dimethyl OP and up to 5 days in diethyl OP. It is usually given at a loading dose of 2 g (30 mg/kg) over 30 min, followed by continuous infusion of 8–10 mg/kg/h, until atropinization or 7 days later, whichever is later [18].

Management of Neuromuscular Manifestations

Because atropine does act on nicotinic receptors on the NMJ, it has no clinical effect in paralysis treatment. However, pralidoxime can reverse neuromuscular blockade by reactivating inhibited AChE. Magnesium sulfate can also be trialed as it can block the presynaptic ligand-gated calcium channel, resulting in a decrease in the release of ACh from the presynaptic terminal, thereby restoring NMJ [25]. However, none of them have optimal clinical benefit. A large number of patients, following acute OP poisoning, will require prolonged ventilatory support in the intensive care unit (ICU) due to neuromuscular weakness. Since the ICU is not easily available in LMICS, bag and masks ventilation is usually performed after intubation. Besides, respiratory failure caused by neuromuscular palsy may overlap with respiratory

failure caused by laryngospasm, bronchospasm, bronchorrhea, or central respiratory depression. All these possible causes should be identified in time and managed accordingly.

Neuroparalytic Snake Bite

Clinical Vignette 3

A 48-year-old female farmer was brought to the regional hospital's emergency department with a history of snakebite. At arrival, she was frothing, could hardly open her eyes and mouth, could not hold her neck straight, and was barely walking. Farmers from her village killed the snake and brought it to the hospital. Based on the signs of envenomation and identification of the dead snake, a diagnosis of cobra envenomation was made. She was admitted to the emergency ward, her oral secretions were suctioned, and oropharyngeal airway was placed and bag valve mask ventilation was started. Her blood pressure, pulse, breathing, temperature, and hemoglobin oxygen saturation were monitored. On admission, her blood pressure was 120/80 mm Hg, respiratory rate was 90/min, the temperature was 38 °C, and oxygen saturation was 98% with room air. On examination on her left leg, there were six puncture wounds, suggesting multiple bites. There was no swelling, blistering, and cellulitis. The bite wound was irrigated with normal saline, and the leg was pressure immobilized. Tetanus toxoid was given, and dextrose normal saline was started. Her hemogram, coagulation profile, liver function tests, and renal function tests came out to be normal. On reviewing the history, that morning on the way to her farm, she accidentally stepped on a snake and sustained a snake bite.

As noticed, she was taken back home and planned to be transported to a traditional healer. But one of the educated villagers suggested not to waste time on traditional therapy and rush her to a nearby hospital. Subsequently, she was transported to a regional hospital, 10 km away on a motorbike. It took 3 h to reach the hospital due to a difficult road network. She was immediately given ten vials of polyvalent anti-snake venom (ASV) along with neostigmine and atropine. As her saturation was dropping and she was having breathing difficulty, a repeat dose of ten vials of ASV was given. Her vitals and local wound were regularly monitored. After the last dose of ASV, her weakness remained stable. Bag valve mask ventilation was continued for 4 h, following which she had improvement in weakness, and her breathing improved. Pupil size became normal, ptosis improved, she could raise her neck, open her mouth, and protrude her tongue. She was monitored for 48 h and subsequently discharged with oral antibiotics and analgesics.

Learning Points

- **Cobra and krait bites are common neuromuscular emergencies in LMICS, especially in tropical and subtropical regions.**
- **Neurotoxins injected by such snakes alters the neuronal transmission at the neuromuscular junction leading to weakness and paralysis.**
- **Weakness develops in descending motor order, initially involving the eyelid muscles followed by weakness of facial muscles, tongue, neck, bulbar muscles, and limb muscles. Eventually, intercostal and diaphragm muscle paralysis will lead to respiratory failure.**
- **Rapid transport to the health care facility, supportive care, and anti-snake venom administration will cause immediate recovery.**
- **Failure to receive anti-snake venom will unanimously cause respiratory failure and death.**

Introduction

Neuroparalytic snakebite is one of the common neuromuscular emergencies seen by physicians practicing in rural areas of tropical and subtropical countries. Through a lack of proper epidemiological studies, the exact burden of a neuroparalytic snakebite is unclear. Neuroparalytic snakes mainly belong to the Elapidae family, which is endemic to tropical and subtropical regions worldwide, with terrestrial and marine forms [26]. Elapid snakes include cobras, kraits, sea snakes, coral snakes, taipans, tiger snakes, death adders, and mambas. Among them, cobras and kraits are responsible for most of the neuroparalytic envenomation, mainly in South Asia, Southeast Asia, and sub-Saharan Africa [26–28]. This region is prosperous in agriculture, with a hot climate, abundant seasonal rainfall, dense natural vegetation, rich in rodents, and amphibians, providing an ideal habitat for snakes to live. People living in this region mainly depend on agriculture, which increases the contact between humans and snakes, leading to snake bites. Besides, poor housing and the habit of sleeping on the floor make these people vulnerable to snake bites [27].

Neuroparalytic snake venom does not contain a single toxin, rather a mixture of enzymes, peptides, nucleotides, and other substances, many of which may have different neurotoxicities. They mainly target the neuromuscular junction, where nerve terminals (presynaptic) and nicotinic acetylcholine receptors of the motor endplate (postsynaptic) are the main target sites. Cobratoxin of cobra and α-bungarotoxin of krait act postsynaptically by binding to acetylcholine receptors on the motor endplate while β-bungarotoxin of krait act presynaptically and prevent the release of acetylcholine at the neuromuscular junction. These toxins cause ptosis, ophthalmoplegia, facial, palatal, tongue paralysis, neck muscle paralysis, and limb paralysis heralding acute flaccid palsy. Respiratory failure caused by paralysis of intercostal muscles and diaphragm muscles is the leading cause of death in neuroparalytic snakebite [29, 30].

Clinical Features

The clinical manifestations of neuroparalytic snake bite depend on the type of snake, the amount of venom injected, the bite's season, the location of the bite, the dry or incomplete bites, and multiple bites' vascular territory, the victim's build, and the time elapsed. Local signs include fang marks, local swelling, and tenderness. Systemic features include nausea and vomiting, abdominal pain, discomfort, drowsiness, prostration, and hypersalivation [27]. Neuroparalytic snake bite typically develops with descending motor weakness, initially involving the eyelid muscles, clinically manifested as bilateral ptosis, usually within a few hours after biting. The second phase is external ophthalmoplegia, continuous dilation of pupils and diplopia, weakness of facial muscles with slurred speech, inability to open the mouth, protruding the tongue, and inability to hold the neck (broken neck sign). The paralysis then descends to the bulbar muscles, causing difficulty swallowing and impairing airway protection. Later, limb weakness ensues, which rapidly progresses to flaccid paralysis with loss of deep tendon reflexes. Finally, intercostal and diaphragm muscle paralysis will lead to respiratory failure. The recovery of neuromuscular function usually follows the reverse order of muscle involvement. Ptosis and ophthalmoplegia are the last neurological symptoms that disappear [31, 32].

Diagnosis

There are no clear diagnostic markers or kits available for diagnosing neuroparalytic snake bite; therefore, the exact diagnosis requires identification of snakes and observation of the clinical manifestations of snake venom. In most cases, fang marks may be noticeable, which can be a single puncture, double or multiple, or only scratch. However, it should not be relied upon for the diagnosis because the Krait bite may leave no fang marks at all. Neuroparalytic snake bites usually cause no signs of local inflammation, and there is little pain. Besides, most of the krait bite occurs at night, while sleeping on the floor, mostly on the trunk, which may not be noticed. Due to submucosal bleeding in the gut, abdominal pain may be the only initial clue to krait envenomation. Krait bites often present in the early morning with paralysis that can be mistaken for a stroke. Cobra bites usually leave large fang marks with significant local inflammation manifested as pain, tenderness, swelling, and local tissue damage [27].

Treatment

Since the cobra injects a large volume of venom, paralysis has a rapid clinical onset, and respiratory failure may occur within 30 min after being bitten. Although more lethal than cobra venom, the development of symptoms is relatively late in Krait

bite because it injects a small venom volume. Similarly, in the case of a cobra bite, the recovery after treatment is faster, reflecting the reversibility of postsynaptic neurotoxicity. In contrast, the presynaptic neurotoxins found in krait venom can cause irreversible nerve damage, and clinical recovery is usually delayed as it requires axon repair.

At the Site of a Snake Bite

After a snake bite, it is wise to identify or take a picture of the snake. It is recommended not to kill snakes for the sake of identification. However, if killed accidentally, it's astute to take the snake to the hospital. Active movement should be as little as possible. The bitten part should be fixed with a splint or sling. If the equipment is available, pressure immobilization can be applied. Tourniquets and compression bandages are contraindicated because they can cause limb ischemia, gangrene, peripheral nerve paralysis, and increased local toxicity. It is contraindicated to cut and suck the bite site or use locally available traditional medicines or chemicals. The techniques mentioned above were historically a part of snakebite management; however, with time, they have been discouraged and removed from snake bite guidelines nationally and globally. Delay should not be done seeking the advice of a traditional healer. The patient should be assured and transferred to the nearest hospital as soon as possible as the most common cause of death in neuroparalytic snakebites is delayed arrival to the hospital. Therefore, all measures should be taken to send the patient to the hospital as soon as possible. The patient should not be allowed to eat or drink as it might increase the risk of aspiration [26, 28].

Rapid Clinical Assessment and Resuscitation at the Hospital

Any snakebite should be considered poisonous. The clinician must record the time of the bite, the type of snake, and check the photos (if any). All snakebite patients must undergo a quick assessment upon arrival at the hospital. The airway, breathing, and circulation should be evaluated and managed appropriately. If the patient has airway obstruction or respiratory failure due to neuromuscular weakness, immediate airway support is required. Oral secretions should be cleared, and the oropharyngeal airway can be utilized if the patient can't protect the airway. If the patient is not breathing adequately, bag valve mask ventilation should be performed. If available, the patient should be intubated, and a mechanical ventilator or artificial respiration through a bag valve mask should be used [26, 33]. The bite site should be examined, irrigated with normal saline, and splinted. All patients who are bitten by a snake must be vaccinated against tetanus immediately. Pulse, blood pressure, respiratory rate, saturation, local swelling, or tissue damage should be monitored every hour. If the patient shows no signs of being poisoned, they are kept awake and monitored for 24 h.

Definitive Treatment

Timely administration of anti-snake venom (ASV) and cardiopulmonary support is the only effective treatment for neuroparalytic snakebite. As soon as the patient develops features of envenomation, ASV should be administered. Since ASV only neutralizes the free-flowing venom in the blood, it is barely effective when applied after the venom reaches the target. In a neuroparalytic snake bite, the ASV indications are ptosis, ophthalmoplegia, inability to open the mouth and protruding tongue, difficulty swallowing, broken neck sign, and difficulty breathing. In most Asian countries, polyvalent ASV is available to neutralize common venomous snake bites. Although ASV can significantly improve the outcome, its use carries the risk of anaphylaxis and should only be used after skin testing. Prophylactic epinephrine is usually given before ASV is administered. However, it should not be given to patients with coronary heart disease or cerebrovascular disease. Repeat administration of ASV is not recommended if neurological signs persist. However, it should be repeated if the neurological status begins to deteriorate [26–28].

Delayed administration of ASV and sometimes even early administration cannot prevent the development of respiratory paralysis. In such a case, the patient should be intubated and artificially ventilated. If there is no ventilator, the patient can be transferred to a fully equipped hospital after using the ASV. In the worst case, when a ventilator is not available, bag valve mask ventilation should be performed [27]. Neostigmine has also been used to treat neuroparalytic snakebites. The recommended dose is 0.01 mg/kg up to 0.5 mg IV or IM every 30 min until neuroparalytic features improve. Neostigmine must be given together with atropine to block muscarinic side effects [26, 27, 34]. In case of non-availability of ASV, we recommend using neostigmine and artificial ventilation. Even in the absence of ASV, complete recovery has been observed after a few days of artificial ventilation.

Tetanus

Clinical Vignette 4

A 45-year-old male farmer, recently diagnosed to have hypertension, non-smoker but chew tobacco, with a history of significant alcohol consumption for the last 20 years presented with a history of difficulty in opening mouth and swallowing for 5 days. He had neck and throat tightening and pain on eating or drinking for 5 days and tightening of the whole body for 4 days. Due to stiffness and pain of lower limbs, he was unable to walk. He further developed pain over the lower jaws, back, and upper limbs. However, he didn't give a history of fever, headache, vomiting, ear discharge, loss of consciousness, altered sensorium, abnormal body movement. He had normal bladder and

bowel habits. He had a history of injury over the right foot's medial aspect, allegedly sustained with a bamboo stick 25 days back. The wound developed into a red, tender, pus-filled lesion over 3 days and was treated at a local health center by drainage of pus and oral medications. The patient had no history of immunization later except birth immunization. There was no history of regular dressing post-injury and after surgical drainage. He was not given human tetanus immunoglobulin as it was not available at the center. According to the patient's family member, the reason for the difficulty in follow-up in the local health center was the geographical location being in the village and the need to walk 2 h from his home to the regional center.

On examination, his blood pressure was 140/80 mm of Hg, pulse rate was 96 bpm, respiratory rate was 20/min, and he was afebrile. He didn't have pallor, icterus, lymphadenopathy, cyanosis, clubbing, edema, or dehydration. He had an approximately 0.5 cm long healed scar on the medial aspect of the right foot at the great toe base. On systemic examination, his Glasgow coma scale (GCS) was E4V5M6, oriented to time, place, and person. He had trismus with a mouth opening of less than one finger. He had rigidity of neck muscles and bilateral lower limbs. However, tone and power were normal on his upper limbs. He had no sensory signs or signs of cranial nerve involvement. The examination of the pulmonary, cardiovascular, and gastrointestinal system was regular. On laboratory investigation, liver function tests, renal function tests were regular. Total leukocyte counts were 17,900/mm^3 with a neutrophilic predominance (87%). His arterial blood gas analysis showed partially compensated respiratory alkalosis.

The patient was admitted to ICU and was treated with intramuscular human anti-tetanus immunoglobulin, intravenous diazepam, magnesium sulfate infusion, and intravenous metronidazole. He had profuse pulmonary secretions during the hospital stay and could not maintain oxygen saturation despite medications and frequent suctioning, so he was electively intubated on the sixth day of ICU admission. He also developed septic shock and was kept on inotrope support. His sputum sample revealed a Staphylococcus aureus infection, and he was treated according to drug sensitivity. Inotropes were tapered and stopped after 2 days, and he was extubated on the tenth day. He also developed delirium 10 days after ICU admission. The patient's spasm and tightness gradually started to decrease, and then, tapering of diazepam was started while stopping magnesium sulfate infusion. The patient was then shifted to high care bed from ICU on the 13th day of admission, and delirium was improved. The patient gradually improved and was discharged on the 20th day of admission with a mild oral diazepam dose. The patient couldn't come to the center for follow-up due to geographical constraints; instead, he contacted us via telephone that he had improved entirely.

Learning Points

- **Tetanus is acquired through infection of a cut or wound with the spores of the bacterium Clostridium tetani. Tetanus is unique among the vaccine-preventable diseases in that it is not communicable.**
- **Tetanus can be prevented through immunization with tetanus-toxoid-containing vaccines.**
- **The spores of tetanus germinate and produce toxins that block the release of the inhibitory neurotransmitters glycine and gamma-amino-butyric acid in the spinal cord. Consequently, lower motor neuron inhibition is reduced, which results in the characteristic spasms of tetanus.**
- **Generalized tetanus is the most common form of tetanus, presenting with trismus (lockjaw), facial grimacing (risus sardonicus), dysphagia, opisthotonus, spasms, back and neck stiffness, muscle rigidity, dysautonomia, and respiratory failure.**
- **Treatment includes aggressive wound care, isolation, administration of human tetanus immunoglobulin and tetanus toxoid, airway maintenance and respiratory support, control of muscle spasms and dysautonomia, and nutritional support.**

Introduction

Tetanus is a vaccine-preventable disease that still commonly occurs in many low and middle-income countries (LMICS), although it is rare in high-income countries. It is a neuromuscular disorder contracted through exposure to the bacterium's spores, *Clostridium tetani*, which live in soil, dust, and manure. It is a gram-positive, spore-forming, obligate anaerobic bacillus. The organism is found worldwide; it is frequently encountered in a tropical region where the soil is rich with organic matter [35]. *C. tetani* may enter the human body through a blunt or sharp wound. Once the bacterial spore enters the body, it germinates in the wound under anaerobic conditions and releases a highly toxic neurotoxin, Tetanospasmin. Tetanospasmin binds to presynaptic membranes at neuromuscular junctions and is subsequently internalized and transported retrogradely in the motor neuron via endogenous microtubule-based axonal pathways. The toxin undergoes transcytosis and is taken up by the inhibitory GABAergic and/or glycinergic neurons that control the lower motor neurons' activity. The neurotoxin then alters cytosolic proteins (vesicle-associated membrane protein 2 or synaptobrevin-2) necessary for synaptic vesicle docking and neurotransmitter release. This prevents the release of inhibitory neurotransmitters, and consequently, lower motor neuron inhibition is reduced, which results in the characteristic spasms of tetanus [35, 36]. Tetanus can be prevented by good wound care and vaccination with tetanus toxoid. The primary series of three doses should be given in infancy, with a booster dose at age 4–7 years and another booster at 12–15 years. Those who have received the primary series plus two booster doses are unlikely to get tetanus [37].

Clinical Features

Tetanus symptoms usually present following contamination of a wound with soil, rusted metal, or manure. Possible entry routes include minor skin abrasions, puncture wounds, burns, fractures, or umbilical cord stumps (in neonates). The average incubation period, i.e., the time from presumed injury to the first symptom's appearance, is 8 days, ranging from 3 to 21 days. The duration from the appearance of symptoms to the onset of muscle spasms usually lasts 1–7 days [35].

Based on the clinical presentation, tetanus can be described in four categories:

(a) Generalized tetanus
(b) Neonatal tetanus
(c) Localized tetanus
(d) Cephalic tetanus

Generalized Tetanus

Generalized tetanus is the most common and severe form of tetanus, characterized by the triad of stiffness, muscle spasms, and dysautonomia [36]. Trismus is the first and most common manifestation of tetanus caused by masseter muscle spasms. Facial muscle spasm causes typical facial expression, the 'risus sardonicus'. The disease then progresses in a descending manner, causing rigidity of the neck muscles (neck retraction), trunk muscles (opisthotonus), abdominal muscles (board abdomen), and chest wall muscles. Opisthotonus occurs in tetanus because trunk extensors' contractions tend to be stronger than that of the flexor muscles. In addition to muscle rigidity, episodic muscle spasm also occurs, including agonists and antagonist muscle groups, which mimic seizures. They may be spontaneous or triggered by tactile, visual, and auditory stimuli. The spasm may be strong enough to cause a fracture or tendon rupture.

Additionally, tetanic contractions of the diaphragm and the pharyngeal/laryngeal muscles may also lead to respiratory failure. These spasms are predominant in the first week of illness and continue for up to 3 weeks [36, 38]. The action of tetanus toxin is not confined to the motor system. The entry of tetanus toxin into preganglionic nerve terminals of the sympathetic nervous system can cause autonomic dysfunction. In fact, sudden cardiac death is now the commonest cause of death in patients with tetanus. Autonomic features usually peak in the second week of illness [36, 39].

Neonatal Tetanus

Any neonate with a normal ability to suck and cry during the first 2 days of life and who, between 3 days and 28 days of age, cannot suck normally and becomes stiff or has spasms (i.e., jerking of the muscles) is considered a confirmed case of neonatal tetanus. It can be regarded as a subset of generalized tetanus occurring in neonates.

Using an unsterile blade and sickle to cut the umbilical cord and applying cow dung in the umbilical wound have been implicated in contributing to this condition. The average incubation period for neonatal tetanus is shorter than that of non-neonatal tetanus. The onset and progression of disease are also more rapid in neonatal tetanus, attributed to the shorter axonal length. Like in generalized tetanus, the disease begins with trismus and lip muscle rigidity, which interfere with normal sucking and feeding; this is the hallmark of disease onset. The spasms then descend caudally, initially only occurring with sensory stimuli but later progressing to excruciating and prolonged tonic contractions [40].

Localized Tetanus

It is a relatively uncommon form of tetanus characterized by tonic or spastic muscle contractions in the region of the body (usually a limb) around the area of the initial injury. It can arise due to a low toxin load inadequate to spread and create generalized symptoms. It can often also merely be the predecessor to generalized tetanus. In its localized form, it can often be hard to detect and is rarely ever fatal.

Cephalic Tetanus

Cephalic tetanus can be understood as a form of local tetanus affecting the head and the neck. It is usually known to occur after head trauma. Like other localized forms, it can also progress to generalized tetanus. However, before this progression, it may present with symptoms of neck stiffness, dysphagia, trismus, retracted eyelids, deviated gaze, and risus sardonicus. Focal cranial neuropathies are common, with the facial nerve being most frequently involved.

Diagnosis

Clinical Assessment

The diagnosis of tetanus is made exclusively from the clinical features. History of deep wound followed by generalized muscular rigidity, risus sardonicus, trismus, dysphagia, opisthotonus, or combinations thereof strongly point towards the diagnosis. The presentation of generalized tetanus is so characteristic that the diagnosis can be made rather straightforwardly once the condition is considered. It is more challenging to identify localized tetanus early in its progression. Though not as easy to recognize in the initial presentation, the neonatal form becomes very obvious in quite a short period. In those who present without a history of immunization or with a history of incomplete immunization, the clinical index of suspicion should

be higher. In contrast, in patients who have completed primary series of immunizations and have properly maintained all the boosters, tetanus should not be considered the primary diagnosis until all the other differential diagnoses have been ruled out [35].

Gram Stain and Culture of the Wound

It is important to note that diagnosis does not depend upon bacteriological confirmation by grain staining or culture. Gram stains of the wound demonstrate *C. tetani* in <30% of tetanus patients. Furthermore, its presence could simply refer to it being part of the wound flora, even in patients who do not have tetanus. Besides, the morphology of *C. tetani* is similar to other anaerobic bacteria and can lead to false interpretation, so Gram staining cannot confirm the diagnosis; instead, it is only supportive of the diagnosis. Likewise, wound anaerobic cultures are of limited value since C. tetani are not recovered in more than two-third of tetanus patients. Toxigenic *C. tetani* can even be isolated from wounds in patients without tetanus, so its presence is only supportive of the diagnosis [35].

Spatula Test

The 'spatula' test is a simple diagnostic bedside test for tetanus that involves stroking the posterior pharyngeal wall with a soft-tipped instrument like a spatula or tongue blade and then observing the result. Under normal circumstances, there is the elicitation of a gag reflex with the individual attempting to expel the foreign object, i.e., a negative test result. However, if the patient has tetanus, there is a reflex spasm of the masseters leading to the contraction of the jaw, and the patient bites the spatula, i.e., a positive test result. This test has a high sensitivity (94% of the infected patients demonstrated positive test results) and high specificity (zero false-positive test result) to clinically diagnose tetanus [41].

Differential Diagnosis

The signs and symptoms of tetanus may overlap with many diseases that have to be excluded before making the diagnosis of tetanus, including orofacial infection, drug-induced dystonia (e.g., phenothiazines, metoclopramide), strychnine poisoning, malignant neuroleptic syndrome, stiff-person syndrome, hypocalcemia, rabies, cerebral malaria, and status epilepticus. Strychnine poisoning can truly mimic tetanus. However, muscle rigidity between spasms and trismus is absent in strychnine poisoning; poisoning can be confirmed by the presence of strychnine in blood, urine, and tissues [36, 42].

Treatment

General Management

A separate quiet ward/room should be chosen for tetanus patients. It should be a shaded area with protection from tactile and auditory stimulation as they can precipitate spasms. All the wounds should be cleaned with saline, and the wounds should undergo debridement to eradicate spores and necrotic tissues. Antibiotics play a minor role in the management of tetanus. Metronidazole at a dose of 500 mg can be given intravenously every 6–8 h for 7–10 days. Intravenous penicillin G at a dose of two to four million units every 4–6 h for 7–10 days can also be used [43].

Neutralization of Toxin and Active Immunization

Only the unbound toxin is available for neutralization as tetanus toxin irreversibly binds to tissues. The use of passive immunization is considered standard treatment, which improves survival. Human Tetanus Immune Globulin (HTIG) is the preparation of choice. A single dose of 500 units IM is recommended, which is administered as soon as tetanus is diagnosed with part of the dose infiltrated around the wound, and it should not be administered in the same site as tetanus toxoid. As an alternative to HTIG, intravenous immune globulin may be administered. Equine antitoxin is used IM or IV, where HTIG is not readily available. At first, 0.1 ml in a 1:10 dilution is administered intradermally to evaluate hypersensitivity reactions before giving the full dose. The type of immunization required following injury depends on the nature of the lesion and the history of previous immunizations. In previously non-immunized patients, active immunization with a complete series of tetanus toxoids is recommended. For previously immunized patients, a booster dose is needed if the last dose of the primary series, or subsequent booster injections, was given more than 5 years ago for dirty wounds or more than 10 years ago for clean wounds [35, 43].

Management of Complications

1. *Airway management:* Drugs used to sedate and control spasms in tetanus can cause central respiratory depression and subsequent respiratory failure. Furthermore, spasm of the laryngeal and diaphragmatic muscle can also cause respiratory failure. So airways should be secured in severe cases of tetanus either by endotracheal intubation or by tracheostomy. Tetanus usually requires prolonged intubation, so the patients must be referred to a tertiary care center equipped with a mechanical ventilator.
2. *Control of muscle spasm:* Generalized muscle spasm may lead to respiratory failure, aspiration, and induce generalized exhaustion to the patient. As benzodi-

azepines are cheaper and readily available, they are the preferred drug to control the tetanus muscle spasm. Propofol, vecuronium, and intrathecal baclofen can also be used for the same purpose if facility and expertise are available [44].

3. *Management of dysautonomia:* Patients with generalized tetanus are at risk of developing fatal dysautonomia and must be admitted to the intensive care unit. If unavailable, any bed with monitors attached can be utilized for the same purpose. Several drugs have been used to produce adrenergic blockade and suppress autonomic hyperactivity in tetanus like magnesium sulfate, dexmedetomidine, atropine, clonidine, epidural bupivacaine, labetalol, and morphine [45], but only treatment with magnesium sulfate has been studied in clinical trials [46]. Furthermore, magnesium sulfate is readily available in all hospitals (for management of eclampsia) and cheaper, making it the drug of choice for managing tetanus dysautonomia in LMICS.
4. *Supportive measures:* As energy demands in patients with tetanus are very high, early nutritional support is mandatory, enhancing chances of survival. Enteral feeding might be preferred. Prophylactic treatment with sucralfate or acid blockers might be used to prevent gastroesophageal hemorrhage from stress ulceration. Also, prophylaxis of thromboembolism with heparin or other anticoagulants should be administered early. Since tetanus patients often are left with disability from prolonged muscle wasting and contracture, physical therapy should be started as soon as the muscle spasm ceases.

Conclusion

Inequity exists in access to standard treatment around the globe and particularly in LMICSs. In the LMICSs, billions of people have no, or limited, access to urgently needed healthcare, leading to poor or sub-optimal health outcomes. The situation of neuromuscular emergencies in LMICS is grim, and the outcome of patients with such disorders is usually poor. Although it is tough to change the status of neuromuscular emergencies in LMICS, some fundamental problems need to be identified and solved to improve the situation. These issues should be addressed by policymakers and stakeholders, international societies as well as clinicians and researchers. Policymakers and stakeholders can contribute by developing appropriate road networks and extending them to rural areas, ensuring the provision of ambulance services, expanding and improving emergency services, upgrading diagnostic facilities, establishing ICUs with ventilators in all government health centers, establishing the public medical insurance system, and providing essential medicines at reasonable prices. International societies can play a role in providing training opportunities to physicians and other health care workers from LMICS, contributing to uplifting the diagnostic facility in LMICS, donating drugs and devices required for management of neuromuscular emergencies, and supporting and funding quality research locally. Currently, most of the drug therapies and guidelines for

managing neuromuscular emergencies are targeted to HIC, and they do not fit well for LMICS. Thus, clinicians from LMICS are compelled to use a pick-and-mix approach that dips into various guidelines according to disease, diagnostic facility, availability, and affordability of therapy. Further, treatment guidelines for the management of neuromuscular emergencies common in LMICS are lacking. Clinicians and researchers can play a role in researching cost-effective alternative drugs, development of cost-effective neuromonitoring devices and ventilators, formulating non-HIC centric treatment guidelines that are generalizable to all or forming an LMICS oriented guideline as done in some other diseases [47], and discouraging industry-sponsored studies on expensive drugs for common neurological disorders.

Self Assessment Questions

1. Neuromuscular emergencies do present a significant burden of disease in low and middle income countries (LMICs).

   (a) True. (*)
   (b) False.

2. Suicidal organophosphate poisoning is a common cause of neuromuscular weakness in LMICs.

   (a) True. (*)
   (b) False.

3. Which of the following types of polio is most common?

   (a) Bulbar polio.
   (b) Bulbospinal polio.
   (c) Spinal polio. (*)

4. Which of the following is the cornerstone in the diagnosis of Japanese encephalitis?

   (a) The characteristic clinical picture.
   (b) Electro-encephalography.
   (c) IgM in serum and CSF. (*)
   (d) Typical findings on brain CT.

5. How can CSF analysis differentiate between polio and GBS? Contrary to in GBS in polio…….

   (a) non-traumatic erythrocytosis is found.
   (b) lymphocytic pleiocytosis is found. (*)
   (c) raised protein is found.

6. Which of the following symptoms is often encountered after a snake bite?

   (a) Acute diarrhoea.
   (b) Hypersalivation. (*)
   (c) Profuse sweating.
   (d) Urine retention.

7. Which of the following symptoms is often part of a syndrome caused by a snake bite?

   (a) External ophthalmoplegia. (*)
   (b) Miosis.
   (c) Pseudobulbar weakness.
   (d) Spasticity.

8. Which of the following is the most important cause of arsenic poisoning in developing countries?

   (a) Attempted murder.
   (b) Eating poisoned fish.
   (c) Insect bite.
   (d) Traditional medication. (*)

9. Which of the following is the most important internal complication of acute arsenic poisoning?

   (a) Cardiac arrhythmia. (*)
   (b) Distributive shock.
   (c) Liver failure.
   (d) Obstipation.

10. What is the characteristic breath odor in arsenic poisoning?

    (a) Acetone-like.
    (b) Alcohol-like.
    (c) Garlic-like. (*)
    (d) Tobacco-like.

11. Neuroparalytic snake bite by cobra may cause respiratory failure within 30 min.

    (a) True. (*)
    (b) False.

12. Protrusion of the tongue should raise the suspicion of……

    (a) diphtheria polyneuropathy.
    (b) organophosphate poisoning.
    (c) poliomyelitis.
    (d) a snake bite. (*)

13. Which of the following is a feature of West Nile encephalitis?

    (a) Bluish nails.
    (b) Palmar erythema.
    (c) Peripheral edema.
    (d) Skin rash. (*).

14. Which of the following is a feature of Diphteria infection?

    (a) Bull neck. (*)
    (b) Protruding tongue.
    (c) Broken neck sign.
    (d) Miosis.

15. Which of the following therapies is widely used in the treatment of GBS in South Asian and African countries?

    (a) Corticosteroids. (*)
    (b) Intravenous immunoglobulin.
    (c) Monoclonal antibodies.
    (d) Plasma-exchange.

There are several stages of paralysis after organo-phosphate poisoning. The last one occurs after a couple of weeks.

16. What is the best description of this post-poisoning syndrome?

    (a) Encephalitic.
    (b) GBS-like. (*)
    (c) Myasthenic.
    (d) Parkinsonian.

Pralidoxime is used in the treatment of organophosphate poisoning.

17. What is the action mechanism of this drug?

    (a) Blocking peripheral nerve endings.
    (b) Competitive binding on the acetylcholine receptor.
    (c) Inhibition of acetylcholinesterase.
    (d) Reactivation of acetylcholinesterase. (*)

18. Excision of the wound area is an important first measure after snake bit, even before initiating transport.

    (a) True.
    (b) False. (*)

19. Which of the following causes irreversible presynaptic damage?

    (a) Cobra venom.
    (b) Krait venom. (*)
    (c) Both do.
    (d) None of these both does.

20. Neuroparalytic snake venom usually contains one single toxin.

    (a) True.
    (b) False. (*)

21. Clinical manifestations of neuroparalytic snake bite may depend on several factors. Which of the following belongs to these?

    (a) The altitude of the scene.
    (b) The bite's season. (*)
    (c) The day's temperature.
    (d) The environmental humidity.

22. Neuroparalytic snake typically develops in a characteristic way. How?

    (a) From distal to proximal regions.
    (b) From proximal to distal regions.
    (c) With ascending motor weakness.
    (d) With descending motor weakness. (*)

23. Inability to hold the neck should raise the suspicion of……

    (a) diphtheria.
    (b) organophosphate poisoning.
    (c) poliomyelitis.
    (d) a snake bite. (*)

24. Inability to open the mouth should raise the suspicion of……

    (a) a snake bite. (*)
    (b) diphtheria polyneuropathy.
    (c) organophosphate poisoning.
    (d) poliomyelitis.

25. What is the most significant risk of using an anti-snake venom?

    (a) Anaphylactic shock. (*)
    (b) Ascending paralysis.
    (c) Laryngeal stridor.
    (d) Encephalomyelitis after anti-venom treatment.

26. Which therapy is—apart from anti-snake venom—most promising to treat symptoms of a paralysing snakebite?

    (a) Anticholinesterases. (*)
    (b) Beta-adrenergic agents.
    (c) Depolarizing relaxants.
    (d) Parasympathicolytics.

27. The "spatula test" is a sensitive and specific bedside test for tetanus.

    (a) True. (*)
    (b) False.

28. Minimizing tactile and auditory stimulation remains an important part of general management for tetanus.

    (a) True. (*)
    (b) False.

29. Active immunization is pointless once symptoms of tetanus develop.

    (a) True.
    (b) False. (*)

30. Dysautonomia is the commonest cause of death in patients with tetanus.

    (a) True. (*)
    (b) False.

31. Neonatal tetanus is a consequence of traditional medicine.

    (a) True. (*)
    (b) False.

32. Which of the following treatments is most effective for the treatment of dysautonomia in Tetanus?

    (a) Atropine.
    (b) Magnesium sulfate. (*)
    (c) Metoprolol.
    (d) Sildenafil.

33. Which of the following antibiotics is effective in Tetanus?

    (a) Ceftazidime.
    (b) Doxycyline.
    (c) Metronidazole. (*)
    (d) Tobramycine.

References

1. Mateen FJ, Bahl S, Khera A, Sutter RW. Detection of diphtheritic polyneuropathy by acute flaccid paralysis surveillance, India. Emerg Infect Dis. 2013;19(9):1368–73.
2. Rahman MM, Chowdhury UK, Mukherjee SC, Mondal BK, Paul K, Lodh D, et al. Chronic arsenic toxicity in Bangladesh and West Bengal, India--a review and commentary. J Toxicol Clin Toxicol. 2001;39(7):683–700.
3. Eddleston M, Mohamed F, Davies JOJ, Eyer P, Worek F, Sheriff MHR, et al. Respiratory failure in acute organophosphorus pesticide self-poisoning. QJM. 2006;99(8):513–22.
4. Nathanson N, Kew OM. From emergence to eradication: the epidemiology of poliomyelitis deconstructed. Am J Epidemiol. 2010;172(11):1213–29.
5. Misra UK, Kalita J. Overview: Japanese encephalitis. Prog Neurobiol. 2010;91(2):108–20.
6. Sejvar JJ, Leis AA, Stokic DS, Van Gerpen JA, Marfin AA, Webb R, et al. Acute flaccid paralysis and West Nile virus infection. Emerg Infect Dis. 2003;9(7):788–93.

7. Yuki N, Hartung H-P. Guillain–Barré Syndrome. N Engl J Med. 2012;366(24):2294–304.
8. Fokke C, Van Den Berg B, Drenthen J, Walgaard C, van Doorn PA, Jacobs BC. Diagnosis of Guillain-Barre syndrome and validation of Brighton criteria. Brain. 2014;137(Pt 1):33–43.
9. Lawn ND, Fletcher DD, Henderson RD, Wolter TD, Wijdicks EF. Anticipating mechanical ventilation in Guillain-Barré syndrome. Arch Neurol. 2001;58(6):893–8.
10. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barré syndrome. Lancet. 2016;388(10045):717–27.
11. Leonhard SE, Mandarakas MR, Gondim FAA, Bateman K, Ferreira MLB, Cornblath DR, et al. Diagnosis and management of Guillain-Barré syndrome in ten steps. Nat Rev Neurol. 2019;15(11):671–83.
12. Hughes RA, Brassington R, Gunn AA, van Doorn PA. Corticosteroids for Guillain-Barré syndrome. Cochrane Database Syst Rev. 2016;10(10):CD001446.
13. French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Efficiency of plasma exchange in Guillain-Barré syndrome: role of replacement fluids. Ann Neurol. 1987;22(6):753–61.
14. The French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Appropriate number of plasma exchanges in Guillain-Barré syndrome. Ann Neurol. 1997;41(3):298–306.
15. Islam B, Islam Z, Rahman S, Endtz HP, Vos MC, Van Der Jagt M, et al. Small volume plasma exchange for Guillain-Barré syndrome in resource-limited settings: a phase II safety and feasibility study. BMJ Open. 2018;8(8):1–10.
16. Tharakan J, Jayaprakash PA, Iyer VP. Small volume plasma exchange in Guillain-Barre syndrome: experience in 25 patients. J Assoc Physicians India. 1990;38(8):550–3.
17. Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. Lancet. 2008;371(9612):597–607.
18. WHO. Clinical management of acute pesticide intoxication: prevention of suicidal behaviours. Geneva: World Health Organization; 2008. https://www.who.int/mental_health/prevention/suicide/pesticides_intoxication.pdf.
19. Bajracharya SR, Prasad PN, Ghimire R. Management of Organophosphorus Poisoning. J Nepal Health Res Counc. 2016;14(34):131–8.
20. Paudyal BP. Organophosphorus poisoning. J Nepal Med Assoc. 2008;47(172):251–8.
21. Peter JV, Sudarsan TI, Moran JL. Clinical features of organophosphate poisoning: a review of different classification systems and approaches. Indian J Crit Care Med. 2014;18(11):735–45. https://pubmed.ncbi.nlm.nih.gov/25425841.
22. Jayawardane P, Dawson AH, Weerasinghe V, Karalliedde L, Buckley NA, Senanayake N. The spectrum of intermediate syndrome following acute organophosphate poisoning: a prospective cohort study from Sri Lanka. PLOS Med. 2008;5(7):e147.
23. Jokanovic M, Stukalov PV, Kosanovic M. Organophosphate induced delayed polyneuropathy. Curr Drug Targets CNS Neurol Disord. 2002;1(6):593–602.
24. Roberts DM, Aaron CK. Management of acute organophosphorus pesticide poisoning. BMJ. 2007;334(7594):629–34.
25. Brvar M, Chan MY, Dawson AH, Ribchester RR, Eddleston M. Magnesium sulfate and calcium channel blocking drugs as antidotes for acute organophosphorus insecticide poisoning - a systematic review and meta-analysis. Clin Toxicol. 2018;56(8):725–36.
26. WHO. Guidelines for the management of snakebites. 2nd ed. New Delhi: World Health Organization, Regional Office for South-East Asia; 2016.
27. Epidemiology and Disease Control Division. National guidelines for snakebite management in Nepal. Teku: Department of Health Services, Ministry of Health and Population, Government of Nepal; 2019.
28. Ministry of Health & Family Welfare. Management of snake bite. Delhi: Ministry of Health & Family Welfare, Government of India; 2016.
29. Silva A, Hodgson WC, Isbister GK. Antivenom for neuromuscular paralysis resulting from snake envenoming. Toxins (Basel). 2017;9(4):143.

30. Oh AMF, Tan CH, Ariaranee GC, Quraishi N, Tan NH. Venomics of Bungarus caeruleus (Indian Krait): comparable venom profiles, variable immunoreactivities among specimens from Sri Lanka, India and Pakistan. J Proteomics. 2017;164:1–18.
31. Silva A, Maduwage K, Sedgwick M, Pilapitiya S, Weerawansa P, Dahanayaka NJ, et al. Neuromuscular effects of common krait (Bungarus caeruleus) envenoming in Sri Lanka. PLoS Negl Trop Dis. 2016;10(2):e0004368.
32. Del Brutto OH, Del Brutto VJ. Neurological complications of venomous snake bites: a review. Acta Neurol Scand. 2012;125(6):363–72.
33. Agrawal P, Aggarwal A, Gupta D, Behera D, Prabhakar S, Jindal S. Management of respiratory failure in severe neuroparalytic snake envenomation. Neurol India. 2001;49(1):25–8.
34. Anil A, Singh S, Bhalla A, Sharma N, Agarwal R, Simpson ID. Role of neostigmine and polyvalent antivenom in Indian common krait (Bungarus caeruleus) bite. J Infect Public Health. 2010;3(2):83–7.
35. Yen LM, Thwaites CL. Tetanus. Lancet. 2019;393(10181):1657–68.
36. Cook TM, Protheroe RT, Handel JM. Tetanus: a review of the literature. BJA Br J Anaesth. 2001;87(3):477–87.
37. WHO. Tetanus fact sheets [Internet]. WHO; 2018. Accessed 3 Oct 2020.
38. Richardson JP, Knight AL. The management and prevention of tetanus. J Emerg Med. 1993;11(6):737–42.
39. Wright DK, Lalloo UG, Nayiager S, Govender P. Autonomic nervous system dysfunction in severe tetanus: current perspectives. Crit Care Med. 1989;17(4):371–5.
40. Roper MH, Vandelaer JH, Gasse FL. Maternal and neonatal tetanus. Lancet. 2007;370(9603):1947–59.
41. Apte NM, Karnad DR. Short report: the spatula test: a simple bedside test to diagnose tetanus. Am J Trop Med Hyg. 1995;53(4):386–7.
42. Van Driessche A, Janssens B, Coppens Y, Bachmann C, Donck J. Tetanus: a diagnostic challenge in the Western world. Acta Clin Belg. 2013;68(6):416–20.
43. WHO Communicable Diseases Working Group on Emergencies. Current recommendations for treatment of tetanus during humanitarian emergencies [Internet]. Geneva: World Health Organization; 2010. https://www.who.int/diseasecontrol_emergencies/who_hse_gar_dce_2010_en.pdf.
44. Rodrigo C, Fernando D, Rajapakse S. Pharmacological management of tetanus: an evidence-based review. Crit Care. 2014;18(2):217. https://pubmed.ncbi.nlm.nih.gov/25029486.
45. Sutton DN, Tremlett MR, Woodcock TE, Nielsen MS. Management of autonomic dysfunction in severe tetanus: the use of magnesium sulphate and clonidine. Intensive Care Med. 1990;16(2):75–80.
46. Thwaites CL, Yen LM, Loan HT, Thuy TTD, Thwaites GE, Stepniewska K, et al. Magnesium sulphate for treatment of severe tetanus: a randomised controlled trial. Lancet. 2006;368(9545):1436–43.
47. Dünser MW, Festic E, Dondorp A, Kissoon N, Ganbat T, Kwizera A, et al. Recommendations for sepsis management in resource-limited settings. Intensive Care Med. 2012;38(4):557–74.

Chapter 16
Neuromuscular Disorders and Palliative Care in Adults

Derek Willis, Tracey Willis, and Marianne de Visser

Introduction

Neuromuscular disorders and adult palliative care is an area that is developing and is very much still in its infancy. Both 'worlds' have changed a lot over the past decades. As far as adult neuromuscular palliative care goes, previously the overlap between the two worlds was slight. Recent experience and research are changing that position. This chapter will discuss

- Palliative care in patients with motor neurone disease
- Adult palliative care in hereditary neuromuscular diseases with onset in childhood or adolescence—what the model is now and how the specialty has changed—and the differences between adult and children's hospices
- Neuromuscular care—how the change in the care and treatment of these disorders is making adult palliative care needed
- Symptom control—what are the emerging symptom control issues for patients within this group?
- Advance care planning—what does this have to offer and what does this process involve in such patients?

D. Willis (✉)
Severn Hospice, Apley Castle, Telford, UK
e-mail: derekw@severnhospice.org.uk

T. Willis
The Muscle Team, Robert Jones and Agnes Hunt Hospital, Oswestry, UK
e-mail: tracey.willis1@nhs.net

M. de Visser
Amsterdam University Medical Centres, location Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands
e-mail: m.devisser@amsterdamumc.nl

M. Damian, M. de Visser (eds.), *Emergencies in Neuromuscular Disorders*,
https://doi.org/10.1007/978-3-030-91932-0_16

- Ethical elements—are there particular ethical challenges that face this group of patients and their clinicians?
- The Oswestry Model—how can tertiary centres deliver symptom control and palliative care with regional centres? We discuss our hub and spoke model for delivering this along with the Oswestry red flag model for determining patients with neuromuscular disorders who need palliative care input.

Throughout this chapter, we will use illustrations of the type of patients that we have experience of delivering joint care for. We, as a medical community are still very much at the early stages with this model of care, but our patients are helping us discern and describe what adult palliative care for this group looks like. The patients' names have been changed and certain details about them altered—but permission has been sought from them and their families to describe their care and our experience.

Motor Neurone Disease: A Paradigmatic Disease for Palliative Care

The WHO definition of palliative care describes it as 'an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual' [1].

Initally palliative care was felt to be solely related to be delivered for patients with cancer. Motor neurone disease (MND) was the first neuromuscular disease in which palliative care was integrated early in the disease trajectory. Some even call MND a paradigmatic disease for palliative care [2]. There is evidence that palliative care with wide involvement of a multidisciplinary team leads to improvement of symptoms and quality of life of the patients and families [3]. MND is unique in the sense that rapid progression of muscle weakness requires discussing personal values, life goals, and preferences regarding medical care right after diagnosis [4]. In this regard, the disease differs from the chronic progressive neuromuscular diseases which are addressed in this chapter and which have an onset in childhood or adolescence.

MND, i.e. amyotrophic lateral sclerosis (ALS) and progressive muscular atrophy (PMA), are associated with a considerable disease burden and a shortened life expectancy. In ALS, 50% of patients die within 36 months after symptom onset as a result of respiratory failure due to progressive muscle weakness.

MND is an 'incurable' disease but this is not synomynous with 'untreatable'. Therefore, palliative care—a customized treatment plan—should start right after the diagnosis has been communicated [5]. In MND palliative care should not be postponed to the terminal stage of the disease in which only end-of-life issues can

be discussed. During the follow-up visits much attention should be given to frequently occurring symptoms such as fatigue, pain, dyspnoea, and nutritional issues. Not only physical symptoms but also psychosocial and existential distress require appropriate palliation [4]. Supportive interventions including feeding via a gastrostomy tube and non-invasive ventilation do not prevent severe and progressive disability but are associated with prolonged survival and/or improved health-related quality of life and therefore recommended to be offered to patients with MND in a shared decision setting.: The multi-system symptom control, the rapid progression of the disease compared to other neuromuscular conditions and experience of positive experience of advance care planning in tailor-made discussions on treatment options and deciding sealing of care and preferred place of death are now considered standard of care and gradually integrated in the clinical practice.

Given this positive experience for this neuromuscular condition, the question remains why other NMDs do not have the same service. The rest of this chapter tries to find an answer to this—and also to suggest ways in which patients with specific NMDS may have their needs addressed.

Case Vignette 1: 'Jack'
'Jack' is a young gentleman in his 20s with a diagnosis of Duchenne Muscular Dystrophy. He was well known to the local children's hospice but had become too old to be under their care. The neuromuscular clinic in the regional centre referred to the local palliative care specialist for advice re his pain. 'Jack' was in a wheelchair and suffered from quite severe pain within his back and in his side. To start with, the team looked at this by altering his cushion and his wheelchair. It was clear that the pain was musculo-skeletal in origin. These measures didn't work so the team added in low dose buprenorphine patches. 'Jack' got on with these patches well to begin with. However, his pain developed and it was clear he was getting bony pain within his hip itself. It was X-rayed and the film was reported as normal. 'Jack' was started on Naproxen once a day and this improved his symptoms. The team had discussions with the cardiologist who were not keen for him to have NSAIDs. The decision was reached by him and his mum that the pain was much better with the NSAIDs and therefore his quality of life was much better with it.

Palliative Care

The traditional historical delivery of palliative care services for those with neuromuscular disorders has been focussed on children, generally with a diagnosis of Duchenne Muscular Dystrophy delivered through children's hospices. It may seem strange to now talk about adult hospices being able and needed to deliver services. This strangeness comes for two reasons:

1. The external perception of adult hospices and what it is that they deliver—this is generally the barrier to neuromuscular centres involving adult palliative care services.
2. The perception of neuromuscular diseases by palliative care services—either that they are exclusively diagnoses of children and are fatal in childhood (e.g. Duchene Muscular Dystrophy)—or so rare that a general palliative care physician is not likely to see any patient with such a diagnosis.

Hospice Perception

There is often a public and professional perception that what adult hospices are for exclusively is to be a safe place where patients go to die. It is the place you 'never come out of'. There is some truth regarding having a role in end-of-life care, and it is also true that what the hospice movement was set up initially was to show to how to deliver good care for people at the end of their life. It is true that the first hospice and palliative care services were originally designed by Dame Cicely Saunders to show how end-of-life care could be done with the public health care system, with the aim that public services would take these over. Palliative care has changed and advanced since the first hospice was set up in 1967 in London. A full specialty has developed with a specific training programme attached to it and the remit of what and how the specialty looks after itself has changed significantly. This is both because

(a) The hospice and palliative care movement has started to see a greater need for services not just for those who have a cancer diagnosis—but to extend this out to those with other non-malignant life limiting conditions. A lot of hospices would now routinely see patients with motor neurone disease, heart failure and chronic obstructive pulmonary disease—and the list of diagnoses continues to expand
(b) The palliative care movement has started to see that there is a lot of work required for patients with symptom control before the patient reaches end of life. The patient may have a life limiting condition, but the time of their death may be some time off. The patient may have pain, nausea, vomiting etc. and palliative care specialists have a role in alleviating the symptoms that patients may have while they continue

Palliative Care:

- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends neither to hasten or postpone death
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help the family cope during the patient's illness and in their own bereavement

- Uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated
- Will enhance quality of life, and may also positively influence the course of illness
- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage symptomatic complications' [1]

As can be seen from the above—there is an emphasis on the holistic care of the patient and the family inherent in the palliative care model. Holism does not just include the physical aspects of a patient's disease but the spiritual and psychological aspects of their care.

What is also not generally understood is the difference between children's and adult hospice services. To a certain extent, each hospice is an individual charity—so there is bound to be a large regional difference between the two—but generally

- Children's hospices have an emphasis on provision of respite care—most adult hospices would not provide this service anymore. Many patients who become too old for children's hospice services expect that they will be able to get a referral to adult services and they will be eligible for respite. This is often not the case
- The nature of the diseases that the two different types of hospices deal with are different. Adult hospices will generally still take patients with cancer diagnosis as most of their work—and their involvement with patients will still be over a relatively short time. There has been an emphasis on provision of services for children with long term neurological or metabolic conditions. The nature of the disease mean that families will likely to be well known to the staff of a children's hospice as they will have known them for a long time
- Specialty trained doctors/consultants are more unusual in children's palliative care than adult palliative care. There are more training posts and consultants in adult palliative care and indeed there is still a lot of adult consultant jobs which are fallow in adult palliative care
- The focus of children's palliative care is that it concerns a family that includes parents or guardians. It is obvious—but in adult palliative care generally the patients can be parents or grandparents themselves. The family and social dynamics within the two different client groups can be very different.

Change in Neuromuscular Disorders

Neuromuscular disorders in the last decade have seen a dramatic change in standards of care and quality of life and length of life in what previously had been childhood diseases. Whilst some of this is due to better standards of care and coordination of services, some is due to novel treatments, earlier diagnoses and improvement in technologies; such as non-invasive ventilation and internal defibrillators.

Duchenne Muscular Dystrophy (DMD)

Duchenne muscular dystrophy (DMD) affects approximately 1/5000 live male births and is a progressive muscle wasting condition, causing respiratory failure and cardiomyopathy. The average life expectancy is now around 26 years, although some live into their 30s and 40s. This has improved dramatically over the last two decades and a study by Eagle et al. [6] highlighted the change over the last few decades with the advent of ventilation via non-invasive techniques, spinal surgery and then the introduction of steroids as a 'gold standard' treatment in the care of DMD [7, 8].

Children now presenting with a diagnosis of DMD will expect to be treated aggressively with steroids to improve length of ambulation and many will have the opportunity to enter into clinical trials for disease modifying treatments; such as exon skipping therapy trials; some of these medications are part of managed access programmes or early access to medicine schemes (EAMs). Some have been approved by the FDA (Federal Drug Administration) and not by the EMA (European Medicines Agency) and therefore are controversial, anti-fibrotic agents to decrease fibrosis, early cardiac therapy to prevent the development of the cardiomyopathy early on, Idebenone (Raxone) to slow down the respiratory decline; available for some on an EAMs for those not on a glucocorticoid. Clinical trials still on-going with the same therapy for boys/men on steroids. There are also trials on-going to determine the correct regime for steroid treatment (FORDMD) and trials looking at alternatives to Prednisolone and Deflazacort, sparing the effects of conventional steroids, such as the VISION trial and POLARIS trial.

This is in addition to the improved standards of care; cardiac—proactive cardiac monitoring and treatment of cardiac changes, sensitive cardiac MRI, improvement in pharmacology and commencement early, the insertion of devices in the 'right' patient.

Respiratory—the measurement and monitoring of FVC (Forced vital capacity) every 6 months, sleep studies and commencement of non-invasive ventilation at the appropriate time, with an increasing sophistication in both interfaces available as well as ventilators.

There has now been many studies looking at exercise; both from a well-being point of view as well as managing patients and keeping them active and ambulant. Along with excellent monitoring of bone health, renal function, seating, technology in the home and general standards of care, all these measures together have improved the longevity as well as quality of life of DMD patients, and we are now seeing adult DMD patients walking into clinic rather than being non-ambulant.

This therefore has changed the field of neuromuscular medicine and whilst this is all very positive, these patients are still at risk of early death and can die unexpectedly. It is therefore important to address this part of their condition, and as with all the other aspects of care, to discuss what their choices and wishes would be if they should have a sudden collapse, cardiac event or severe sepsis/chest infection and whether they would want all the treatment that could be offered or a modified

treatment pathway. This is best done outside the ITU environment and with the support of family and when your patient is well and can be objective, rather than leaving this to the ITU consultant to discuss at an emotive time.

There is also the converse; some patients may present with a first acute presentation to ITU and because of their age and diagnosis may not be thought to be salvageable, and indeed this may be a young man with a good quality of life, good cardiac function and pre-ITU, excellent mobility and respiratory function. This also needs to be conveyed as the ITU staff need to have all this information to make a reasoned decision with treatments offered.

Case Vignette 2: 'Tom'
This is Tom, an 18 year old with DMD admitted to his local hospital with a possible chest infection. Up to this point he has been well, non-ambulant since the age of 12 years, but no respiratory issues and minimal cardiac changes on his last ECHO scan. It is his first admission with his chest. Approximately 6 weeks prior to this, he had his annual sleep study which was borderline, and he was transitioning over to adults, so there had been discussion about commencing night time ventilation. This has not started yet, but Tom has no symptoms. He has secured a place at University which he is hoping take up in September, 2 months' time. Whilst on the general medical ward Tom has a bout of coughing and 'plugs off', he desaturates and requires suction and the 'crash team' are called. He is intubated and taken to ITU. Discussions in ITU are had, and it agreed that as he is 18 years old with DMD that should he fail extubation, this was not unexpected. Unfortunately, he did fail extubation and did so a number of times, before the muscle team were contacted. With the involvement of them and arrangement to send to a specialist weaning unit, he successfully went on to get off the ventilator and is now 25 years old on his night time ventilator but lives independently with carers and went to college. At the time, he did not have an emergency/advance care plan; he has now, and this is reviewed every year—lessons were learnt.

Spinal Muscular Atrophy

Spinal muscular atrophy affects 1 per 8000 to 10,000 people worldwide. Spinal muscular atrophy type I is the most common type, accounting for about half of all cases. Types II and III are the next most common and types 0 and IV are rare. The patients that survive into adulthood have typically been SMA type II and III, with type II having the more severe respiratory issues and scoliosis.

More recently with the advent of new treatments this landscape may be changing. SMA is caused by mutations in the SMN1 gene, this causes all types of spinal muscular atrophy described above. The number of copies of the SMN2 gene

however is thought to modify the severity of the condition and helps determine which type develops, with the more copy numbers of SMN2 being associated with a better outcome.

The SMN1 and SMN2 genes both provide instructions for making a protein called the survival motor neuron (SMN) protein. Normally, most functional SMN protein is produced from the SMN1 gene, with a small amount produced from the SMN2 gene.

This is what has been used to develop technologies to improve the outcome in SMA, with an increase in the number of SMN2 copy numbers from therapies such as intrathecal Nusinersen, now approved for adult patients (Type II and ambulant type III) and Risdiplam, available in the UK under a "managed access agreement". Gene therapy with Onasemnogene abeparvovec is approved for patients with SMA type I that fulfil strictly defined criteria.

As these young people now have increased longevity but represent a complex patient, it is important to discuss future treatments at appropriate times, and wishes and desires, if they are in an emergency situation. Whilst we are actively treating these young people, we are still aware that in parallel we need to plan for emergencies and possible death. As this is an ever-changing field, we are discovering that whilst cardiac features were not thought of as a part of SMA, there is increasing evidence that we need to monitor this, particularly for conduction defects.

- New treatments therefore bring new challenges and new emerging phenotypes, in an already complex situation.

Myotonic Dystrophy

In myotonic dystrophy type 1 (DM1) is truly a progressive multisystem disorder, affecting not just the skeletal muscles, but also the heart, respiratory system, endocrine, central nervous system, gastrointestinal system, skin, ocular and causes psychiatric issues. It is due to a CTG triplet repeat expansion, and as a result of this, is also subject to anticipation, the phenomenon of increasing severity of the phenotype with each generation. Generally, the bigger the expansion the more severe the phenotype [4], ranging from severe neonatal (congenital) forms through to mild adult forms that are often not recognised until later on in adulthood.

One of the main issues in DM1 is conduction disturbances, and tachyarrhythmias are common in DM1 and contribute significantly to the morbidity and mortality of the disease [9–13]. The cardiac histopathology demonstrates fibrosis, particularly of the conducting system and sinoatrial node [9].

In a 10-year follow-up study by Mathieu et al. [14], there was a 7.3 times greater mortality in DM1 than the general population. Mean age of death was 53 years. There was a positive correlation between age of onset and age at death. Thirty percent of the deaths were due to cardiac complications and 40% were due to respiratory complications. The cardiac abnormalities included sudden unexpected death,

presumed to be due to a malignant arrhythmia, progressive left ventricular dysfunction and ischaemic heart disease.

Weakness and/or myotonia of the diaphragm and a susceptibility to aspiration from swallowing problems increase the risk of respiratory compromise and aspiration pneumonia, usually in individuals with advanced disease and swallowing difficulties [15].

New advances in treatment have been slow with regards to human trials although animal studies have been promising, and advances are being made now that we understand the genetics behind DM1 and also DM2, the milder phenotype. Many of these techniques are adopting the antisense oligonucleotide approach seen being used in both DMD and SMA treatments. This being said, many of our severely affected adults still die within their fifth decade due acute cardiac events or respiratory compromise. Some of this is secondary to their lack of motivation and regular clinic attendance and adherence to advice, part of the cognitive issues inherent in DM1.

Whilst great advances have been made both in standards of care, guidelines and new novel treatments, these patients do still continue to have a palliative or 'life limiting' diagnosis, in that their life span is shortened. At any point, these patients experience a sudden deterioration, particularly in their respiratory status or cardiac status, regardless of the new technologies and drug therapies.

As a neuromuscular team, we need to be prepared and prepare the patients and their families for this. As part of that preparation, it is helpful to review your patient lists to see who may be more at risk of this and therefore approach the subject in a coordinated and empathic way. The patients and family often need time to think about these issues and therefore whilst they welcome a professional broaching this, and are often aware and fearful of the discussion, many find it a relief to eventually discuss the "what ifs". As Abbott et al. highlighted many young men with DMD did want to talk about this but wanted the professional to start the conversation [16]. This is essential whilst the patient is well and can articulate or indicate what their wishes are. It is best done by the multidisciplinary team that has known them for years, they have trust in and who know the family. This subject is often difficult to broach and very often needs a follow up visit or in many cases a home visit by the specialist nurse to go over again their wishes before both the professional and the patient agree and sign.

It is often once the subject has been broached and a discussion had, that all feel relieved to have the 'issue on the table' and many feel that this is the last part of their care being put into place, alongside their pain control, home adaptations and benefits.

It can be seen as an empowering and positive experience, as often this is giving the patient control over what they want to happen in an emergency and that will not 'be given up on' by a team who does not know them when they are well and just sees a diagnosis.

What we are now finding is that palliative care requirements for patients with neuromuscular disease now falls into the two distinct areas:

1. Palliative care for those patients who previously had diseases that were fatal in childhood are now becoming adult diseases. So, the disease itself could now be viewed as an 'adult' life limiting disease. As patients are living longer, there is also a growing number of them who are developing adult diseases (e.g. breast cancer) along with their muscular dystrophy.
2. Palliative care for patients with diseases that have always been life limiting in adulthood, who now are coming under the umbrella of adult palliative care as adult palliative care branches into those patients with non-malignant conditions.

Case Vignette 3: 'Mitch'
'Mitch' was a 40-year old man with severe cardiac and respiratory complications of Duchenne Muscular Dystrophy. There was no further treatment available and no reversible element to his condition. He lived some 40 miles from the neuromuscular centre, and it was his expressed wish that he should die at home. Honest conversations had been had with him, his wife and his family and it was clear that he understood where in his disease stage he had reached. He wanted to have his ICD discontinued. The catchment area of the hospice where he lived in was outside of the palliative care physician attached to the clinic. The palliative care doctor liaised with the hospice local to Mitch, and he was referred to that hospice's local community support team. Mitch had his ICD deactivated and he died with his family—well supported from a symptom control perspective, at home.

Advance Care Planning

Advance care planning (ACP) has both a future and an immediate effect. By involving a patient in discussion about their future health care it makes patients feel empowered and not as if they will be 'given up on' just because they have a neuromuscular condition. Research within young adults, specifically with Duchenne Muscular Dystrophy, has shown this [16]. ACPs have generally been used within an oncology setting and in ALS care—and generally, given the steep and often predictable decline of patients with these diseases involve discussions on treatment options, e.g. in cancer another cycle of chemotherapy, and in MND insertion of a PEG or non-invasive ventilation. Equally important is the discussion of what will happen during a precipitous event (i.e. where would you like to die—hospital, hospice/nursing home or home?). With the advent of sealing of care documents with the DNACPR (e.g. RESPECT) and the widening of ACP discussions to those diseases with a more variable course—ACPs have become more complex than simply where a person wishes to die (preferred place of death (PPD)). Despite this complexity ACP's have been shown to reduce grief-related symptoms in the carers during the bereavement phase [17].

So why bother at all with ACPs?

- The best way to illustrate what a difference ACPs can make is to provide the histories of patient A where end-of-life care because for an ACP went well and patient B where it did not and an ACP could have made a difference.

'Mrs A' is divorced and she has three adult children. She was referred because of a slurred speech and forced laughter and on examination she was found to have fasciculations. She was diagnosed with bulbar-onset ALS. She was prescribed Riluzol—an evidence-based disease-modifying drug for ALS—and accepted a 3-monthly follow-up by her treating physician and the multidisciplinary team at the ALS Centre. At one such a visit, she admitted that she had lost weight (4 kg in 3 months), that the meals took considerably longer and that she was not able to chew and swallow steaks anymore. Initially, she refused a PEG, but when VC dropped further (to 50%) and the meals took more than 1 h, she changed her mind. She moved into her daughter's house and the occupational therapist provided all sorts of aids in the house. Once, at a follow-up visit, she mentioned that she was opting for euthanasia. She explained that she was afraid to choke and that talking about euthanasia would be a relief. At that time there was no nocturnal hypoventilation, albeit she was somewhat dyspnoeic. She received information about non-invasive ventilation, but she decided to refrain from this intervention and she and her neurologist discussed her preferences with regard to end-of-life issues. She was at that time wheelchair-bound and after consultation of her children she was clear about her wish not to have any life-extending intervention. She stayed at home under the care of her daughter and professional care, and she received low dosages of opioids and oxygen when the dyspnoea worsened. After a few days, 17 months after diagnosis she died peacefully at home, in the presence of her children.

'Mr B' was a 74-year-old retired gardener who was directly admitted at the ICU because of progressive dyspnea. Onset had been 1 year earlier with weakness of arms and legs. Subsequently he developed weakness of his axial muscles (dropped head, bent spine) and he complained about swallowing difficulty. On admission, he was found to have nocturnal hypoventilation, tachypnoea, a VC of 1,6 L when sitting in a chair and dropping to <1 L in a supine position. pCO2 was just above the upper level of normal. He was urgently referred to the Home Mechanical Ventilation Centre where various options were disussed, i.e. withholding artificial ventilation and treatment of the dyspnoea and non-invasive ventilation. He was in an advanced stage of the disease but was still ambulatory using a walker so the patient and his wife opted for non-invasive ventilation (NIV). He was able to go home on NIV and died 3 months later.

Both cases are illustrate how helfpul early discussion of advance care planning can be. The first patient was diagnosed early and there was ample time for advance care planning (ACP) including shared decision making. She was able to discusss her treatment preferences in light of her personal values and wishes. The second patient

was referred at a very late stage of the disease with severe involvement of his respiratory muscles which led to an emergency admission to the ITU. This hampered careful advance discussion of his treatment preferences, albeit the treating physician at the Home Mechanical Ventilation Centre did discuss different treatment options, including withholding artificial ventilation, and administration of morphine and oxygen if required.

We would contend that ACP conversations and subsequent documentation contain three distinct elements within them

A. Do not attempt resuscitation order
B. Advance refusal of treatments
C. Advance description of preferences

- A

  DNACPR comes into place at a very specific moment—i.e. when the patient has died. Under these specific circumstances the decision reached either as an intervention that the patient does not want or as a procedure which is not felt to produce benefit (i.e. CPR will not work or if successful the patient's condition will be significantly worse.) It must be remembered that CPR for patients with no pre-existing health conditions—generally has a good success rate. The type of patient where a DNACPR order is discussed are those people whose underlying medical conditions mean that CPR would not be successful. Following the legal case called the 'Tracey' judgement [18], made it clear that a DNACPR needs to be discussed with the patient, and that it needs to be a multidisciplinary team decision, at which point the patients can gain a second opinion. It is clear that a DNACPR order is ultimately a medical decision—but that the patient must know that this has been done and has a right to appeal this decision. Hence it is argued that the discussion that is had with the patient is more akin to an information giving discussion rather than a consent discussion.
- B

  Refusal of treatment has the clearest legal standing and is a 'negative freedom' as described by Berlin. Such negative freedoms are the right to not have my liberty interfered with [19]. To put this in medical terms I have a right only to that treatment that I consent to. Non-consensual treatment is legally termed as assault—where this causes harm however, it is termed 'battery'. So, if I refuse a treatment but you give it to me anyway—you have assaulted me and potentially may have committed battery if by that treatment you are deemed to have harmed me. So, what an ACP tries to capture are those things that in the future I would not want you to give to me as a person. For example, if I have a stroke in the future, I may write an ACP that describes how I would not want intravenous antibiotics. Our experience of using these with patients who have Duchenne Muscular Dystrophy is that it is generally urinary catheters that are refused in advance by these patients.
- C

Preferences - these refer to positive freedoms (again in reference to Berlin [19]) which are things that I would like to happen to me. In medical terms, this is not a refusal but a request. These are not as strongly supported by law as I may request something that is a) not a possibility for me (either does not work or is not available) b) may harm others c) or does not exist yet. For example, I may want not to die in a hospice setting—but there may be no hospice near me, a bed may not be available, or someone may need the bed more than I do. I can't require the hospice to take me—even if this is recorded on an ACP—but I can request it. Sometimes a false expectation can be created by the way ACPs are filled in, as if one is talking about a choice. Choice implies that at times there are positive options available to me and sometimes this is not true. Preferences give a better description of what this part of an ACP covers and allows us to order how our future care may look. So, to use my example of PPD—I may prefer to die in a hospice as my strongest preference, however if not there, then at home and failing that, in a hospital. Choice is too strong a word and implies that we can deliver what the patients ask for. Preferences enable us to give some form of 'hierarchy' of what I might want in the future.

ACPs are therefore a mixture of types of decision. The tendency can be to develop a form of nihilism as soon as an ACP is seen—as well as judging that a person with a neuromuscular condition is never for active treatment. For example, a person may not be for resuscitation—but this does not mean they are for no active treatment at all. DNACPR is a specific treatment decision under a specific circumstance. It is not a blanket 'do nothing order'. Such a patient may be entirely appropriate for intra-venous antibiotics and for hospital admission and indeed may do well on these in an inpatient setting. Certain neuromuscular conditions also do well in ITU—so again DNACPR may have a 'ceiling of care' that involves some form of intervention in an ITU setting. The nature of the muscle weakness may be that the patient has something that exacerbates dyspnoea—but this is reversible. Emergencies within patients who are in the palliative stage of their disease may seem like an oxymoron. However, hospital treatment in this group of patients can provide good symptom control and indeed extend and improve quality of life. ACPs can help with recording and clarifying what the wishes of patients are and keeping the carers and relatives of the patient informed.

Which brings us onto what the value of ACPs are. If I fill in an ACP—the time when it is used would generally be when I am unable to voice my preferences. If I was able to state what I wanted at the time a decision needed to be made, then you could have a conversation with me as normal. ACPs are used when the patient can't tell you what their care should look like. So, the good of the ACP for the patients can't be the outcome—i.e. if I didn't want to go into hospital and this was respected—I could not be aware that this is happening to benefit from this. Under these circumstances it is the relatives and the health-care staff who gain the benefit (we know we

did what he would have wanted). The benefit for the patient is having the conversation in the first place, and being reassured that they are involved and able to decide what their future care will be. Therefore, these conversations are not something to be avoided, even though they are difficult, they are the 'good' that ACPs are meant for and not necessarily the outcome itself for the patient.

Ethics

Space does not allow for a full description of the ethics involved in palliative care and neuromuscular disorders—but given the subject matter of the book, we will briefly discuss the ethics of withdrawal and withholding.

Two brief initial notes. There is a perception that DNACPR orders are euthanasia in everything but name. Part of the problem is ensuring that we have a coherent description of what euthanasia is, as the word is used to describe different clinical situations, mostly incorrectly.

For euthanasia to be said to have occurred it must be administered to

(a) A patient who is alive at the time.
(b) There must be some form of positive action that brings about the death of the patient (i.e. to distinguish it from assisted suicide where a person enables but does not administer the death of another).
(c) There must be intention to bring about the death of the person.

Even if someone disagrees with some of those descriptions—it is easy to see how DNACPR is not euthanasia as there is nothing involved in this application where the death of a person is hastened—it only comes into action when the patient has died and involves not actioning a treatment that will not work.

Opiates

There is also a perception that when patients are given morphine or other strong pain killers within a palliative care setting—that this hastens death. The doctrine of double effect (DDE) used to be discussed in relation to these circumstances. The doctrine justified this risk as the medication relieved pain and that when prescribed it was justified if death was not the intended outcome. Recent studies have shown that opiates do not hasten death—in fact if appropriately prescribed they appear to lengthen average life expectancy [20]. Opiates are dangerous in overdose and if not prescribed according to guidelines but if prescribed appropriately they are not seen to shorten life. DDE has a role in medical practice but not in relation to pain relief.

Withdrawal of Treatment

We have already touched on the ability of people to refuse treatment in ACPs. If I don't consent to treatment and yet you still give this treatment to me, it is classed as assault. This is the case even if the treatment is life-saving. The harm to me of invading my personal liberty is felt to be a greater harm than refusing medical treatment. We can make 'unwise decisions'—given the proviso that I have capacity to make that specific decision. As detailed in the Mental Capacity Act [21]—capacity is:

(a) Decision Contingent, i.e. just because I have no capacity for one decision does not mean I have no capacity for any decision. A diagnosis is not proof of a lack of capacity. For example, a person with learning disability may have no capacity to make decisions regarding treatment, but may have capacity to decide where their future care should take place.
(b) Process driven—capacity is not dependent on the outcome (i.e. I deem you to have no capacity if you do not accept the treatment that I am offering to you). Rather it is dependent on the process that you reach to arrive at the decision—detailed in the five stage process within the Act.

As stated above, ACPs are a way of capturing the above so that if a patient becomes unable to tell us that they do not want a treatment—we know what their wishes would have been.

All this is fine when it is definitely a treatment one is talking about—but what about interventions such as PEG feeding? Certain interventions that we provide for a patient are termed 'basic care' which a patient can refuse but as health-care professionals we cannot withdraw, e.g., providing food and ensuring warmth. Peg feeding, it could be argued, is a form of feeding, i.e. it is a form of basic care. This obviously has implication for those in 'unresponsive wakefulness syndrome' and minimally conscious state. The landmark case of Bland [22] clarified that legally the use of a peg feed was classed as a treatment so could be withdrawn. In the Bland case the patient who was being given peg feed had no hope of improvement—so the treatment was felt to be a burden rather than a benefit—so it was deemed legal to stop the feed.

Case Vignette 4: 'Elaine'
Elaine is a 55-year-old lady with myotonic dystrophy who was referred to the joint palliative care clinic. She had been getting recurrent chest infections but did not like going into hospital because she felt that she was ignored there. Her husband was sole carer with no equipment at home and had refused any help with carers. The team referred to the local hospice for an inpatient assessment. She was given iv antibiotics there, had assessment by occupational therapy and physio and had full multi-professional assessment. She was discharged with a commode delivered to her home along with a hospital bed.

The community clinical nurse specialist from the hospice continued to visit her and helped her and her husband write an advance care plan. They attend the day unit and the husband carers support meetings. This was the third adult with myotonic dystrophy that the hospice had looked after. Both Elaine and her husband liked the hospice as they felt supported and heard there.

The Oswestry Model

Given that neuromuscular centres are tertiary if not quaternary referral centres—the centre potentially has multiple hospices that the service catchment area is responsible for. We have piloted a hub and spoke model for palliative care involvement within the neuromuscular centre where the patient is seen in the clinic, then advice and support are given to the patient in their community via local palliative care services [23]. A lot of hospices are very nervous about having neuromuscular patients as part of their workload—but with support both from an expert in neuromuscular patients and in palliative care, we have found that this model works. We have also developed a traffic light system which makes it clear, which patients should be referred for review at the palliative care / symptom control clinic (see Appendix 1 and [24]). ITU and hospital specialists should be encouraged to refer on to hospices—or to check that the patients is not already know to any adult services.

Case Vignette 5: 'Bob and Barbara'
Bob is a 67-year-old gentle man with Becker muscular dystrophy (BMD). He was referred to the joint palliative/symptom control clinic due to worsening heart failure and lymphoedema. He had also had a long standing history of bleeding piles and subsequent anaemia which also troubled him significantly and caused breathlessness with anaemia and dizziness. His wife Barbara was his sole carer, however as Bob's mobility has decreased due to his BMD and she has her own health issues, there was a danger of this fragile home situation breaking down. As a part of the clinic appointment, the palliative care physician was able to liaise with the local hospice, which was a day hospice, to arrange day care and release Barbara from continuing care to go shopping and have some 'me' time. They were also able to arrange the heart failure nurse to see Bob in the hospice and continue monitoring his treatment, rather than repeated hospital visits, and arrange his blood infusions due to his continual bleeding piles. Between the Hospice nursing team, the neuromuscular consultant and neuromuscular specialist nurse, we have completed Bob's ACP and ECP and both Bob and Barbara feel that they now have a good package of care, an expectation of the level of care and Bob does not feel that

he will be treated inappropriately if an emergency occurs and that he will remain at home if appropriate. Their quality of life has improved as they now do not have the number of hospital visits, but have local support from the hospice as required.

These clinics are in their infancy but our ambition is wide—we feel every patient who wishes or is indicated for this—should have access to palliative care services. As described in the All-Party Paper 2018—covering national access to psychological services and palliative care.

> *'I would like every hospice in the country to have access to a specialist in palliative medicine.*
>
> *I want every patient with a neuromuscular disease, irrespective of diagnosis, to have access to someone who can give them advice. And I would also like hospitals to start working in partnership with hospices and charities, not just saying that hospices take over the role, but seriously working in partnership with hospitals to do this effectively. We've found that the crossover between the palliative care person and the psychologist has really helped patients to express where they wish to die. And this has prevented unnecessary hospital admissions, where people are dying in hospital when they don't want to [die there]'[25].*

Self Assessment Questions

1. Motor neuron disease (MND) is an untreatable disease.

   (a) True.
   (b) False. (*)

2. Some persuasion may be suitable and necessary in ALS patients with severe swallowing difficulty refusing *percutaneous endoscopic gastrostomy (*PEG) in order to avoid further complications.

   (a) True.
   (b) False. (*)

3. Hospice centres for NMD patients are only considered with the end of life in sight.

   (a) True.
   (b) False. (*)

4. Palliative care never intends to hasten death.

   (a) True. (*)
   (b) False.

5. Palliative care may positively influence the course of illness.

   (a) True. (*)
   (b) False.

6. With the advance of new treatment new intrinsic complications of NMDs, not expected before, become overt.

   (a) True. (*)
   (b) False.

7. Palliative care in patients with motor neuron disease should be postponed to the terminal stage of the disease.

   (a) True.
   (b) False. (*)

8. The discussion of end-of-life issues should be postponed to the terminal stage of the disease.

   (a) True.
   (b) False. (*)

9. Palliative care provides relief from pain and other distressing symptoms.

   (a) True. (*)
   (b) False.

10. Approaching NMD patients, not seeking help by themselves, as for example maybe the case in patients with Myotonic Dystrophy, is considered good care by the authors of this chapter.

    (a) True. (*)
    (b) False.

11. Caregivers should realize that patients with a NMD may expect the professional to start a conversation about certain aspects of their disease ~~and thus do so~~.

    (a) True. (*)
    (b) False.

12. Advance care planning by involving a patient in a discussion about his future health should be avoided in early stages of a terminal disease as it entails the risk of mood problems.

    (a) True.
    (b) False. (*)

13. Prescription of opiates should be discouraged as a policy in palliative care of NMD since this hastens death.

    (a) True.
    (b) False. (*)

14. Legally the use of a PEG feed is considered a treatment so if a patient has no hope of improvement it is deemed legal to stop the PEG feed.

    (a) True. (*)
    (b) False.

Appendix 1 Red Flag System for Referral to Palliative Care Service

	Blue	Green	Events	Amber	Events	Red	Events
Respiratory		No respiratory support		Overnight NIV, significantly reduced lung function	Starting overnight NIV	Daytime NIV, unrecordable peak flow	Starting NIV during day
Cardiac		Normal cardiac function or mild cardiomyopathy		Moderate cardiomyopathy	Insertion of ICD	Severe cardiomyopath arrhythmias	
Locomotor		Ambulant, or wheelchair user, able to transfer	Loss of ambulation	Wheelchair user, unable to transfer		Unable to self-feed, dependen for all care	
GI		Orally feeding		Supplemental gastrostomy feeds	Insertion of gastrostomy	Dysphagia, at risk of aspiratio	
Acute hospital admissions		Occasional admission only		Increasing frequency		With life threatening event	ICU admission
Prognosis	Condition not expected to be life limiting.	Condition expected to be life limiting. Expected to have a period of stability, not expected to die within the next few years		You would not be surprised if this patient dies within the next few years. And/or patient has significant palliative comorbidity.		You would not be surprised if this patient die in the next 12 months? And/or patient has significant palliative comorbidity.	

References

1. https://www.who.int/cancer/palliative/definition/en/.
2. Borasio GD, Shaw PJ, Hardiman O, Ludolph AC, Sales Luis ML, Silani V, European ALS Study Group. Standards of palliative care for patients with amyotrophic lateral sclerosis: results of a European survey. Amyotroph Lateral Scler Other Motor Neuron Disord. 2001;2(3):159–64.
3. Oliver DJ, Borasio GD, Caraceni A, de Visser M, Grisold W, et al. A consensus review on the development of palliative care for patients with chronic and progressive neurological disease. Eur J Neurol. 2016;23(1):30–8.
4. NICE. Motor neurone disease: assessment and management. NICE guideline NG42. Methods, evidence and recommendations. 2016.
5. Seeber AA, Pols AJ, Hijdra A, Grupstra HF, Willems DL, de Visser M. Advance care planning in progressive neurological diseases: lessons from ALS. BMC Palliat Care. 2019;18(1):50.
6. Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscul Disord. 2002;12(10):926–9.
7. Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Brumbaugh MPHD, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol. 2018;17(3):251–67.

8. de Temmerman N, Sermon K, Seneca S, et al. Intergenerational instability of the expanded CTG repeat in the DMPK gene: studies in human gametes and preimplantation embryos. Am J Hum Genet. 2004;75:325–9.
9. Bassez G, Lazarus A, Desguerre I, et al. Severe cardiac arrhythmias in young patients with myotonic dystrophy type 1. Neurology. 2004;63:1939–41.
10. Chebel S, Ben Hamda K, Boughammoura A, et al. Cardiac involvement in Steinert's myotonic dystrophy (in French). Rev Neurol. 2005;161:932–9.
11. Dello Russo A, Pelargonio G, Parisi Q, et al. Widespread electroanatomic alterations of right cardiac chambers in patients with myotonic dystrophy type 1. J Cardiovasc Electrophysiol. 2006;17:34–40.
12. Montella L, Caraglia M, Addeo R, et al. Atrial fibrillation following chemotherapy for stage IIIE diffuse large B-cell gastric lymphoma in a patient with myotonic dystrophy (Steinert's disease). Ann Hematol. 2005;84:192–3.
13. Phillips MF, Harper PS. Cardiac disease in myotonic dystrophy. Cardiovasc Res. 1997;33:13–22.
14. Mathieu J, Allard P, Potvin L, et al. 10-year study of mortality in a cohort of patients with myotonic dystrophy. Neurology. 1999;52:1658–62.
15. Howard RS, Wiles CM, Hirsch NP, et al. Respiratory involvement in primary muscle disease: assessment and management. Q J Med. 1993;86:175–89.
16. Abbott DWF, Prescott H, Forbes K, Fraser J, Majumdar A. Men with Duchenne muscular dystrophy and end of life planning. Neuromuscul Disord. 2017;27(1):38–44.
17. Chhetri SK, Bradley BF, Callagher P, Addison-Jones R, Bennett W, et al. Choosing the place of death: empowering motor neurone disease/amyotrophic lateral sclerosis patients in end-of-life care decision making. Pall Med. 2015;29(7):667–8.
18. R (David Tracey) v (1) Cambridge University Hospitals NHS Foundation Trust (2) Secretary of State for Health. www.judiciary.uk.
19. Berlin I. Two concepts of liberty. Liberty Oxford University Press; 2002.
20. Scofield G, Baker I, Bullock R, Clare H, Clark P, Willis D, Gannon C, George R. Palliative opioid use, palliative sedation and euthanasia: reaffirming the distinction. J Med Ethics. 2020;46(1):48–50.
21. Mental Capacity Act 2005. http://www.legislation.gov.uk/ukpga/2005/9.
22. Airedale N.H.S. Trust v bland, A.C. 789 House of Lords 1993.
23. Macfarlane M, Willis TA, Easthope-Mowatt Y, Bassie C, Willis D. Adult neuromuscular disorders: a joint palliative/neuromuscular clinic. BMJ Support Palliat Care. 2019.
24. https://spcare.bmj.com/content/early/2020/06/08/bmjspcare-2020-002336.
25. https://www.musculardystrophyuk.org/wp-content/uploads/2018/11/MDUK-APPG-report-141118_final-lo-res.pdf.

Useful Links

Links to the respect document. https://www.resus.org.uk/respect/.
Link to the collaborative ACP. http://cypacp.uk/.
APM guidance for withdrawal of ventilation specifically for MND but is useful for other neurological conditions. https://apmonline.org/wp-content/uploads/2015/02/APM-Guidance-on-Withdrawal-of-Assisted-Ventilation-Consultation-1st-May-2015.pdf.

Index

M. Damian, M. de Visser (eds.), *Emergencies in Neuromuscular Disorders*,
https://doi.org/10.1007/978-3-030-91932-0

N