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Atlas of Neuromuscular Diseases

A Practical Guideline

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Printed in Austria
SpringerWienNewYork is a part of Springer Science+Business Media
springeronline.com

Typesetting: Grafik Rödl, 2486 Pottendorf, Austria
Printing and Binding: Druckerei Theiss GmbH, 9431 St. Stefan, Austria, www.theiss.at

Printed on acid-free and chlorine-free bleached paper
SPIN 10845698

Library of Congress Control Number: 2004109783

With partly coloured Figures

ISBN 3-211-83819-8 SpringerWienNewYork

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Dedication

This book is dedicated to Professor P. K. Thomas (London, UK), our friend, teacher and leader in neuromuscular diseases and to our families whose help and support made this book possible.

Special acknowledgements are made to Dr. Mila Blaivas (Michigan), Dr. Andrea Vass (Vienna), Ms. Judy Boldt, Ms. Denice Janus, Ms. Piya Mahendru (Michigan), Ms. Claudia Steffek (Vienna), and Mr. Petri Wieder from Springer.
The authors are grateful to Mr. James Hiller who provided financial assistance for the colour photographs.

Contents

Introduction

The authors of this book are American and European neurologists. This book is termed a "neuromuscular atlas" and is designed to help in the diagnosis of neuromuscular diseases at all levels of the peripheral nervous system. This book is written for students, residents, physicians and neurologists who do not specialize in neuromuscular diseases.

The first chapter describes the numerous tools used in the diagnosis of neuromuscular disease. These include history taking, the physical examination, laboratory values, electrophysiology, biopsy and genetics. It should help the reader gain an overview of the commonly used methods.

The clinical chapters start with cranial nerves, followed by radiculopathies, plexopathies, mononeuropathies of upper extremities, trunk, lower extremities and polyneuropathies. This is followed by disorders of neuromuscular transmission, muscle and myotonic diseases and motor neuron disease.

The final chapter is called a general disease finder, which helps to identify neuromuscular symptoms and signs associated with general disease.

Each section has a "tool" bar, giving an outline of which examination techniques are most useful. This is followed by anatomical localization, symptoms and signs. The different etiologies are described and are followed by a description of useful diagnostic tests, differential diagnosis, therapy and prognosis. This structured approach occurs through the whole book and allows the reader to follow the same pattern in all sections. A few key references are provided.

Figures and clinical pictures are an essential part of the book. The figures are simple and focus on the essential features of the peripheral structures. We were fortunate to work with artist Jeanette Schulz who put our anatomical requests into clear and distinct figures.

The pictures are of two categories: histological pictures and pictures of patients and diseases. The histologicical pictures were mostly provided by Dr. James Russel who also received neuropathological help from Dr. Mila Blaivas. The clinical pictures were mostly taken by Drs. Grisold and Zifko and reflect a large series of photographic clinical documentation, that was accumulated over the years.

We are aware that for many entities like polyneuropathies, myopathies, and mononeuropathies several excellent monographs and teaching books have been written. However we found no other book which provides a complete overview in a structured and easily comprehensive pattern supported by figures and pictures.

While writing for this book the authors have had fruitful discussions about several disease entities with individuals from the different schools of diagnosis, treatment and teaching in the US and in Europe. We hope that this book will be of clinical help for all physicians working with patients with neuromuscular disease.

E. Feldman
W. Grisold
J. W. Russel
U. A. Zifko

Tools

Several important diagnostic tools are necessary for the proper evaluation of a patient with a suspected neuromuscular disorder. Each individual chapter in this book is headed by a "tool bar", indicating the usefulness of various diagnostic tests for the particular condition discussed in the chapter. For example, genetic testing is necessary for the diagnosis of hereditary neuropathy and hereditary myopathy, while nerve conduction velocity (NCV) and electromyography (EMG) can be important but are less specific for these diseases. Conversely, NCV and EMG are the predominate diagnostic tools for a local entrapment neuropathy like carpal tunnel syndrome. Some conditions will require autonomic testing or laboratory tests.

The patient with neuromuscular disease

The evaluation of a patient with neuromuscular disease includes a thorough history of the symptoms, duration of the present illness, past medical history, social history, family history, and details about the patient's occupation, behaviors, and habits. Much can be learned from the distribution of the symptoms and their temporal development. The types of symptoms (motor, sensory, autonomic, and pain) need to be addressed in detail.

The history is followed by a clinical examination, which will assess signs of muscle weakness, reflex and sensory abnormalities, and autonomic changes, as well as give information about pain and impairment. The clinical examination is of utmost importance for several reasons. The findings will correlate with the patient's symptoms, and the distribution of the signs (e.g. muscle atrophy in muscle disease) may be a significant diagnostic clue. Documentation of the course of signs and symptoms will be useful in monitoring disease progression, and may guide therapeutic decisions.

Documentation of the progression of neuromuscular disease (especially chronic diseases) should not be limited to changes measured by the ancillary tests described later in this section. Depending upon the disease, measurement of muscle strength, sensory measurements (e.g., vibration threshold, Semmes-Weinstein filaments, etc.), and sketches of the patterns of atrophy and weakness may be helpful. Digital imaging, video clips, and photographs of patients provide a precise documentation of the patient's movement capabilities, but may not be possible due to legal, ethical, and other concerns for the patient.

The diagnostic hypothesis developed by the history and clinical exam can be confirmed by ancillary testing. Ancillary tests can also be used to monitor the stabilization or progression of the disease, and the impact of therapies. Standard electrophysiological tests include NCV, EMG, and repetitive nerve stimulation. Laboratory tests, such as creatine kinase, electrolyte assessment, and antibody testing (e.g. myasthenia gravis, MG) may also be necessary. Genetic testing has become an important tool in the last twenty years, and can be used in many diseases to confirm a precise diagnosis. Some other tests, like autonomic testing (such as the Ewing battery and others) and quantitative sensory testing may not be available in some areas. Finally, neuroimaging can also provide information. MRI can be used to assess muscle inflammation and atrophy, and compression or swelling of peripheral nerves.

The following description of diagnostic tools is intended to be a brief overview, with references for further reading.

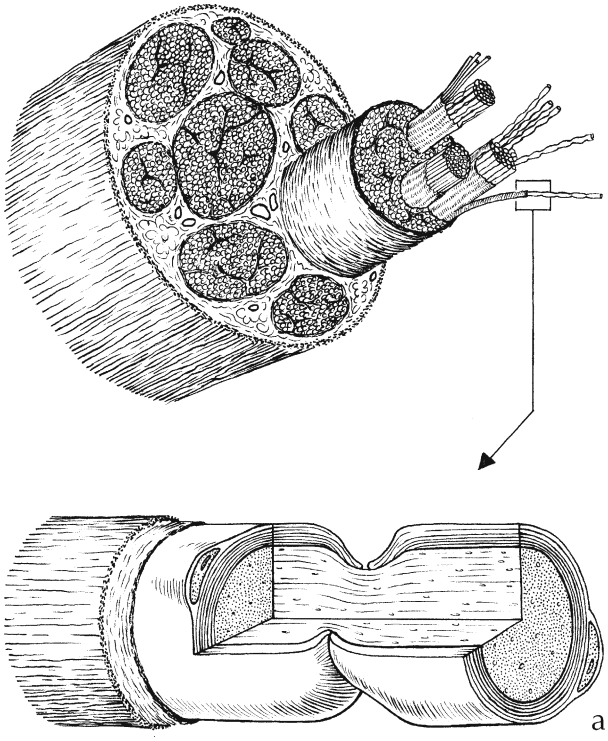

Fig. 1. Anatomy of peripheral nerve. A peripheral nerve consists of bundles of axons surrounded by and embedded in a collagen matrix. The outer connective tissue covering is called the epineurium. The inner connective tissue that divides the axons into bundles is called the perineurium. The innermost layer of connective tissue surrounding the individual axons is called the endoneurium. Blood vessels and connective tissue cells such as macrophages, fibroblasts and mast cells are also contained within the peripheral nerve. The arrow (*a*) indicates an enlarged view of an individual axon and its surrounding Schwann cells. A node of Ranvier, the space between adjacent Schwann cells is depicted as the narrowing of the sheath surrounding the axon. Each internode is formed by a single Schwann cell

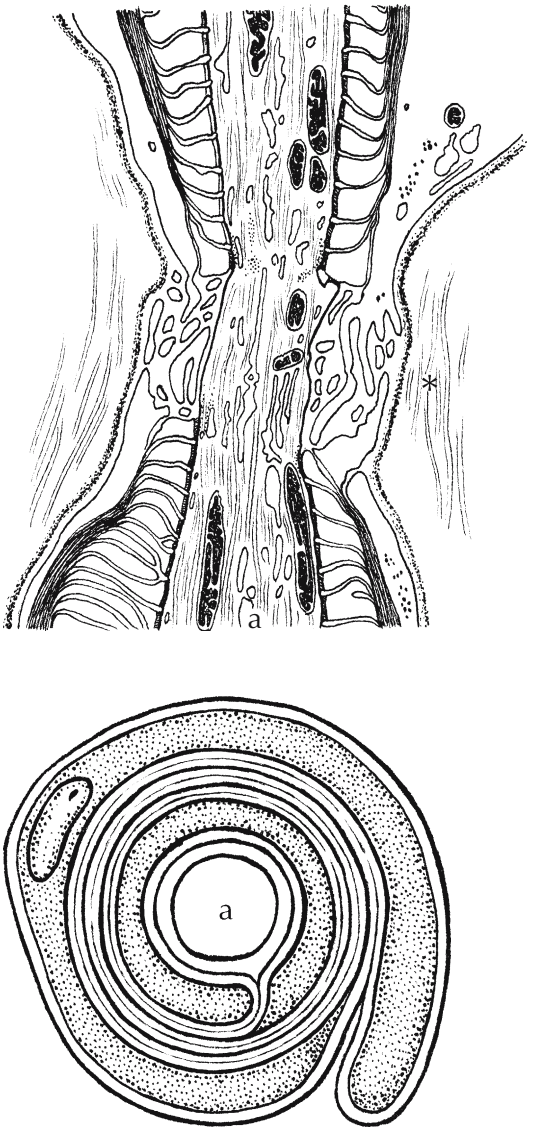

Fig. 2. Below: The axon (*a*) is surrounded by layers of Schwann cell cytoplasm and membranes. The Schwann cell cytoplasm is squeezed into the outer portion of the Schwann cell leaving the plasmalemmae of the Schwann cell in close apposition. These layers of Schwann cell membrane contain specialized proteins and lipids and are known as the myelin sheath. Above: Peripheral axons are surrounded by as series of Schwann cells. The space between adjacent Schwann cells are called Nodes of Ranvier (*). The nodes contain no myelin but are covered by the outer layers of the Schwann cell cytoplasm. The area covered by the Schwann cell is known as the internode

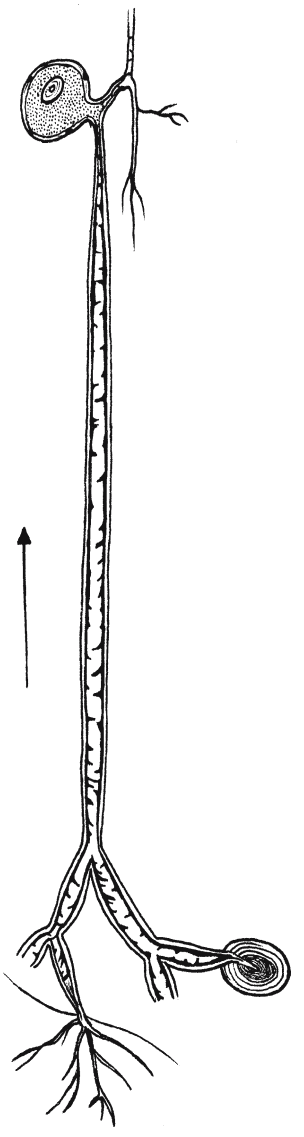

Fig. 3. Sensory information is relayed from the periphery towards the central nervous system through special sensory neurons. These are pseudo-unipolar neurons located within the dorsal root ganglia along the spinal cord. Mechanical, temperature and noxious stimuli are transduced by special receptors in the skin into action potentials that are transmitted to the sensory neuron. This neuron then relays the impulse to the dorsal horn of the spinal cord

General examination

As already pointed out above, the case history is the basis of the clinical examination. Before assessing the patient in detail, the general examination may give clues to underlying disease (e.g., diabetes, thyroid disease, toxic or nutritional problems). The family history may suggest genetic diseases. Changes of the skeletal system (e.g., kyphosis, scoliosis, atrophy, hypertrophy, and abnormal muscle movements) may indicate neuromuscular disease. Skin changes to watch for include signs of vasculitis, café-au-lait spots, patchy changes from leprosy or radiation, and the characteristic changes associated with dermatomyositis.

Neuromuscular clinical phenomenology

Motor function

Motor dysfunction is one of the most prominent features of neuromuscular disease. The patient's symptoms may include weakness, fatigue, muscle cramps, atrophy, and abnormal muscle movements like fasciculations or myokymia. Weakness often results in disability, depending on the muscle groups involved. Depending on the onset and progression, weakness may be acute and debilitating, or may remain discrete for a long time. As a rule, lower extremity weakness is noticed earlier due to difficulties in climbing stairs or walking. The distribution of weakness is characteristic for some diseases, and proximal and distal weakness are generally associated with different etiologies. Fluctuation of muscle weakness is often a sign of neuromuscular junction disorders.

Weakness and atrophy have to be assessed more precisely in mononeuropathies, because the site of the lesion can be pinpointed by mapping the locations of functional and non-functional nerve twigs leaving the main nerve trunk.

Muscle strength can be evaluated clinically by manual and functional testing. Typically, the British Medical Research Council (BMRC) scale is used. This simple grading gives a good general impression, but is inaccurate between grades 3 and 5 (3 = sufficient force to hold against gravity, 5 = maximal muscle force). A modified version of the scale has subdivisions between grades 3 and 5. A composite BMRC scale can be used for longitudinal assessment of disease. Quantitative assessment of muscle power is more difficult because a group of muscles is usually involved in the disease, and cannot really be assessed accurately. Handgrip strength can be measured by a myometer, and can be useful in patients with generalized muscle weakness involving the upper extremities.

Fatigability is present in many neuromuscular disorders. It can be objectively noted in neuromuscular transmission disorders like myasthenia gravis (e.g., ptosis), and is also present in neuromuscular diseases like amyotrophic lateral sclerosis (ALS), muscular dystrophies, and metabolic myopathies, where it appears to be caused by activity.

Muscle wasting can be generalized or focal, and may be difficult to assess in infants and obese patients. Asymmetric weakness is usually noted earlier, in particular, the intrinsic muscles of the hand and foot. Muscle wasting may also occur in immobilization (either due to medical conditions like fractures, or persistent immobility from rheumatoid diseases with joint impairment) and in wasting due to malnutrition or cachexia caused by malignant disease.

Muscle hypertrophy is much rarer than atrophy and may be generalized, as in myotonia congenita, or localized, as in the "pseudohypertrophy" of the calf muscles in some types of muscular dystrophy and glycogen storage diseases. Focal hypertrophy is even rarer and may occur in muscle tumors, focal myositis, amyloidosis, or infection. Also, ruptured muscles may mimic a local hypertrophy during contraction.

Abnormal muscle movements

Abnormal muscle movements can be the hallmark of a neuromuscular condition and should be observed at rest, during and after contraction, and after percussion.

- Fasciculations are brief asynchronous twitches of muscle fibers usually apparent at rest. They may occur in healthy individuals after exercise, or after caffeine or other stimulant intake. Cholinesterase inhibitors or theophylline can provoke fasciculations. Fasciculations are often associated with motor neuron disease [ALS, spinal muscular atrophy (SMA)], but can also occur in polyneuropathies, and be localized in radiculopathies. Contraction fasciculations appear during muscle contraction, and are less frequent.
- Myokymia is defined as involuntary, repeated, worm-like contractions that can be clearly seen under the skin ("a bag of worms"). EMG shows abundant activity of single or grouped, normal-appearing muscle unit potentials, and is different from fasciculations. Myokymia is rare and appears in neuromuscular disease with "continuous muscle fiber activity", such as Isaac's syndrome, and in CNS disease (e.g. brainstem glioma). Myokymia may be a sequel of radiation injury to the peripheral nerves, most frequently seen in radiation plexopathies of the brachial plexus.
- Neuromyotonia, or continuous muscle fiber activity (CMFA), is rare. It results in muscle stiffness and a myotonic appearance of movements after contraction. Rarely, bulbar muscles can be involved, resulting in a changed speech pattern. The condition can be idiopathic, appear on a toxic basis (e.g., gold therapy) or on an autoimmune basis.
- Myoedema occurs after percussion of a muscle and results in a ridge-like mounding of a muscle portion, lasting 1–3 seconds. It is a rare finding and can be seen in hypothyroidism, cachexia, or rippling muscle disease.
- Rippling muscle is a self-propagating rolling or rippling of muscle that can be elicited by passive muscle stretch. It is an extremely rare phenomenon. Percussion can induce mounding of the muscle (mimicking myoedema). The rippling muscle movement is associated with electrical silence during EMG.
- Myotonia occurs when a muscle is unable to relax after voluntary contraction, and is caused by repetitive depolarizations of the muscle membrane. Myotonia is well characterized by EMG. It occurs in myotonic dystrophies and myotonias.
- Action myotonia is most commonly observed. The patient is unable to relax the muscles after a voluntary action (e.g. handgrip). This phenomenon can last up to one minute, but is usually shorter (10–15 seconds). Action myotonia diminishes after repeated exercise (warm up phenomenon), but may conversely worsen in paramyotonia congenita.
- Percussion myotonia can be seen in all affected muscles, but most often the thenar eminence, forearm extensors, tibialis anterior muscle or the tongue

are examined. The relaxation is delayed and a local dimple caused by the percussion appears, lasting about 10 seconds.

- Pseudoathetosis is a characteristic of deafferentiation and loss of position sense. Fine motor tasks are impaired or markedly slowed, and result in a writhing and undulating movement pattern of outstretched fingers, aggravated with eye closure. Pseudoathetosis appears in sensory neuropathies, posterior column degeneration, and tabes dorsalis.
- Moving toes: Length dependent distal neuropathies may be associated with moving toes. This sign may be due to large sensory fiber loss, and has been observed in cisplatinum induced neuropathies.
- Neuropathic tremor resembles orthostatic tremor and has a frequency of 3–6 Hz. It occurs in asscociation with demyelinating neuropathies.
- Muscle cramps are painful involuntary contractions of a part or the whole muscle. At the site of the contraction a palpable mass can be felt. EMG reveals bursts of motor units in an irregular pattern. Cramps often occur in the calves, and can be relieved by stretching. Cramps may occur in metabolic conditions (electrolyte changes), motor neuron disease, some myopathies, and some types of polyneuropathy.
- Stiff person syndrome is characterized by muscle stiffness and spasms due to synchronous activation, predominantly of trunk muscles. EMG reveals normal muscle unit potentials firing continuously. This disease, though producing muscle symptoms, is a central disease due to a disinhibited gaba receptor. It occurs in autoimmune or paraneoplastic disease.

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Reflex testing

The long reflex arch tested by the deep tendon reflex is useful for neuromuscular diagnosis, as it reflects both the function of sensory and motor divisions of the local segment tested. It also provides information about the status of the central influence on the local segment being assessed by the quality of the reflex (exaggerated, brisk, normal, diminished). In polyneuropathies the reflexes tend to be diminished or absent, with a tendency towards distal loss in length-dependent neuropathies. A mosaic pattern of reflex activity may point to multifocal neuropathies or multisegmental disorders. Reflexes in myopathies are usually preserved until late stages of the disease (in Duchenne's dystrophy, knee jerks are often absent prior to ankle jerks). Exaggerated and brisk reflexes in combination with weakness and atrophy are suggestive of a combined lesion of lower and upper motor neurons, as in ALS.

Reflexes may be absent at rest and reappear after contraction or repeated tapping ("facilitation") as seen characteristically in the Lambert Eaton syndrome. The reflex pattern pinpoints the site of the lesion, such as with radiculopathies and cervical or lumbar stenosis, where the pattern of elicitable and

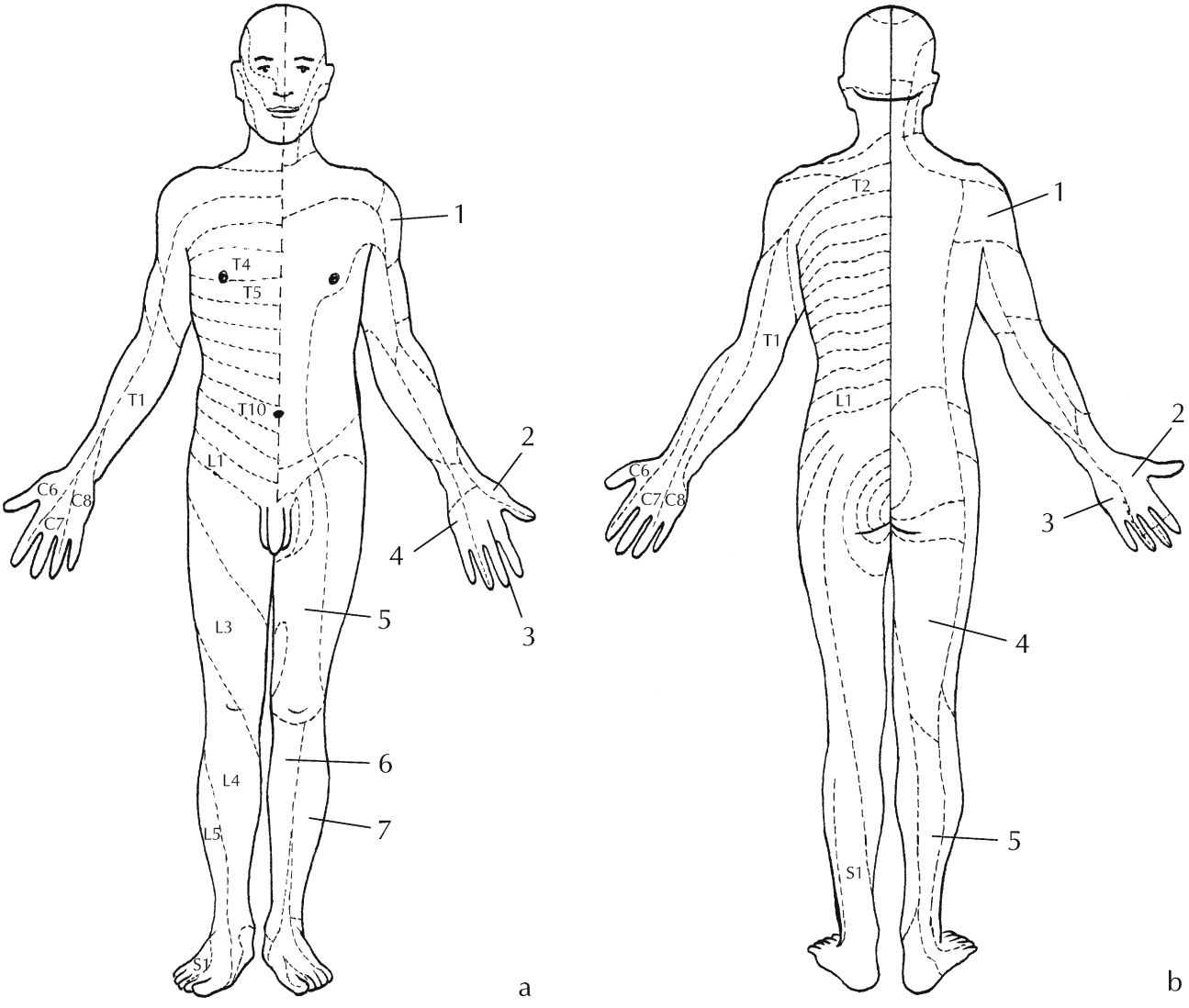

Fig. 4. a *1* Axillary nerve, *2* Superficial radial nerve, *3* Median nerve, *4* Ulnar nerve, *5* Femoral *nerve, 6* Sapheneous nerve, *7* Peroneal nerve. **b** *1* Axillary nerve, *2* Superficial radial nerve, *3* Ulnar nerve, *4* Cutaneous femoris posterior nerve, *5* Sural nerve

absent reflexes (inversion) or combination with long tract signs gives important clues.

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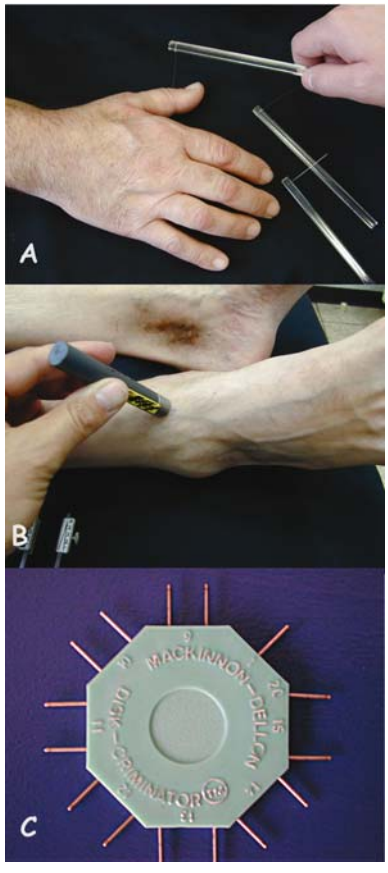
Muscle tone

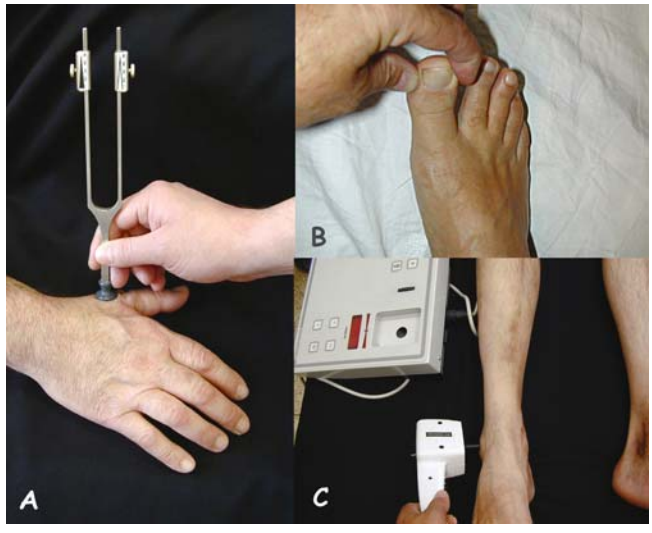
Muscle tone is an important issue in neuromuscular disease in ALS patients and "the floppy infant".

Sensory disturbances

Sensory disturbances signal disease of the peripheral nerve or dorsal root ganglia and include a spectrum of positive and negative phenomena. The patient is asked to provide a precise description and boundaries of sensory loss (or parasthesias). Reports of permanent, undulating, or ictal (transient) loss or sensations should be noted.



A Weinstein filaments; **B** Simple test for temperature discrimination; **C** Graeulich „star" for two point discrimination



A Vibration can be assessed with a Rydel Seiffert tuning fork; **B** Clinical assessment of position sense; **C** Vibrometer allows quantitative assessment of vibration threshhold

a Small fiber, testing by thermal theshhold. The finger is put on a device, which changes temperature. The patient is requested to report changes of temperature or pain. **b** Vibration threshhold can be assessed electronically and displayed on the screen

Fig. 5. Sensory testing mehtods

Table 1.

Sensory quality	Method*	Fiber type
Light touch	Brush, examiner's finger tips	All types
Pressure	Semmes Weinstein filaments	Small and large fibers – quantification possible
Pain	Pin prick	Small fibers
Temperature	Temperature threshold devices	Small fibers
Vibration	Tuning fork	Large fibers
Position sense		Large fibers
Two point discrimination	Graeulich device	Large fibers

*See Fig. 5

Qualities

- Negative symptoms are numbness, loss of feeling, perception, and even anesthesia.
- Positive symptoms are paresthesia, pins and needles, tingling, dysesthesia (uncomfortable feeling) or hyperpathia (painful perception of a non-painful stimulus). Inadequate sensory stimuli can result in allodynia.

The type of sensory disturbance gives a clue to the affected fibers. Loss of temperature and pain perception points to small fiber loss, whereas large fiber loss manifests itself in loss of vibration perception and position sense (Table 1).

The distribution of the sensory symptoms can follow a peripheral nerve (mononeuropathy), a single root (radiculopathy) or in most polyneuropathies, a stocking glove distribution. The sensory trigeminal nerve distribution can suggest a lesion of a branch (e.g., numb chin syndrome) or a ganglionopathy. Maps of dermatomes and peripheral nerve distributions can be used to distinguish and classify the patterns found (Fig. 4).

Transient sensory symptoms can be elicited by local pressure on a nerve, resulting in neurapraxia. In patients who have a history of repeated numbness in a mononeuropathic distribution or permanent symptoms, a hereditary neuropathy with pressure palsy has to be considered. Some transient sensory changes are characteristic but difficult to assess, such as perioral sensations in hypocalciemia or hyperventilation.

A characteristic sign of sensory neuropathy is the Tinel's sign, which is a distally radiating sensation spreading in the direction of a percussed nerve. It is believed to be a sign of reinnervation by sensory fibers, but may also occur in a normal peripheral nerve when vigorously tapped.

Quantitative sensory testing includes sensory NCV, testing of small fibers by cooling, and large fibers by vibration threshold.

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Table 2. Characteristics of dysesthetic and nerve trunk pain

Dysesthetic pain	Nerve trunk pain
Symptoms Burning, raw, crawling, drawing, "electric"	Aching, "knife like"
Distribution Usually distal, superficial	Deep
Time perspective Often intermittent, shooting, lancinating	Continuous, with waxing and waning
Syndromes Small fiber neuropathy, causalgia	Root compression, plexopathy

Myalgia and pain

Myalgia (muscle pain) occurs in neuromuscular diseases in several settings. It can occur at rest (polymyositis), and may be the leading symptom in polymyalgia rheumatica. Focal muscle pain in association with exercise-induced ischemia is observed in occlusive vascular disease. Local, often severe, pain is the hallmark of a compartment syndrome occuring after exercise or ischemia. Exercise-induced muscle pain in association with muscle cramps can be seen in metabolic disease.

Neuropathic pain

Neuropathic pain can result from a damaged peripheral nerve. It can be divided into dysesthetic or nerve trunk pain (Table 2).

Trigeminal neuralgia, sometimes overlapping with "atypical facial " pain are good examples of neuropathic pain.

Reflex sympathetic dystrophy (RSD) is a burning pain in the extremity associated with autonomic changes, allodynia, and trophic and motor abnormalities. It is associatied with local osteoporosis (Sudeck's atrophy), and the pain causes a reduced range of motion and leads to contractures.

The definition and characterization of neuropathic pain has several implications. Firstly, a possible cause-effect relationship, or "symptomatic" cause needs to be ruled out. Secondly, neuropathic pain needs particular treatment considerations, which include a number of drugs and different mechanisms usually not considered for nociceptive pain.

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Autonomic findings

Autonomic findings are often neglected and include orthostatic hypotension, tachyarrhythmias, ileus, urinary retention, impotence, incontinence and pupillary abnormalities. In some polyneuropathies and mononeuropathies the autonomic changes are revealed by skin changes at examination. The dry, anhidrotic skin in diabetic neuropathy is a good example. Skin changes in peripheral nerve lesions can include pale, dry, and glossy skin, and changes of the nailbeds. The methods suggested for testing include RR variation testing, the sympathetic skin response, and the Ewing battery.

Gait, coordination

The gait can be a definite clue to the cause of the neuromuscular disease. Proximal weakness (if symmetric) causes a waddling gait. Unilateral pelvic tilt toward the swinging leg is caused by weakness of contralateral hip abductors.

Hyperextension of the knee may be compensatory for quadriceps weakness. If proximal weakness has progressed, hip flexion can be replaced by circumduction of the hyperextended knee. Distal neuropathies often include weakness of the peroneal muscles, resulting in a steppage gait. Loss of position sense due to large fiber damage results in sensory ataxia, with a broad-based gait and worsening of symptoms with eyes closed (Romberg's sign).

NCV/EMG/ autonomic testing and miscellaneous electrophysiologic tests

Motor NCV studies

Motor NCV are one of the basic investigations in peripheral neurology. A peripheral nerve is stimulated at one or more points to record a compound action potential (CMAP) from a muscle innervated by this nerve. The amount of time between the stimulation of a motor nerve and a muscle response (distal latency) includes the conduction time along the unmyelinated axonal endings and the neuromuscular transmission time. The difference in latency between two points of stimulation is used to calculate the nerve conduction velocity in m/sec. The amplitude of the CMAP in the muscle reflects the number of innervated muscle fibers. This method can discriminate between axonal and demyelinating neuropathies, and correlates well with morphological findings.

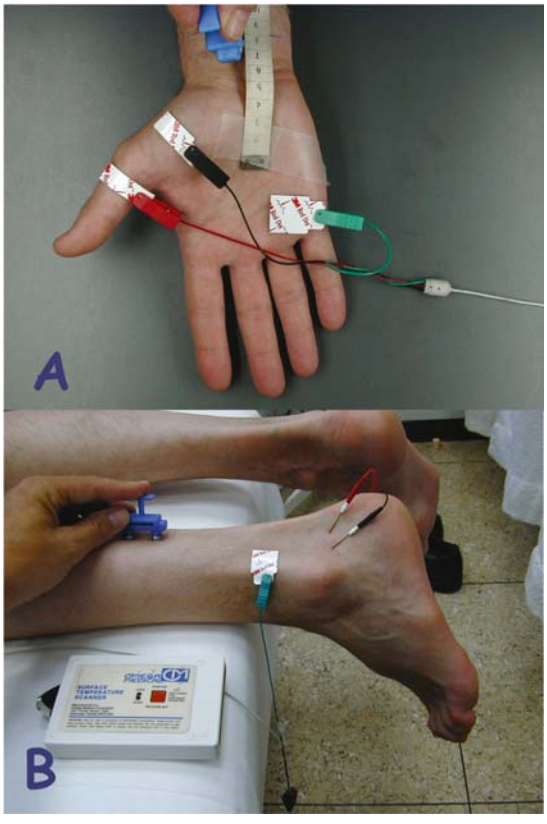

Fig. 6. NCV studies. **A** Motor nerve conduction of the median nerve; **B** Sural nerve conduction, with near nerve needle electrodes

NCV can be used to locate the site of entrapment in mononeuropathies. Local slowing and local impulse blockade of sensory fibers, and decreased or absent sensory nerve action potentials with stimulation proximal and distal of a lesion can be observed. Several techniques are used to detect these changes, including stimulation at different sites, comparison of conduction properties in adjacent nerves (median/ulnar) and the "inching" technique.

NCV can be used intraoperatively, mainly by orthopedic and neurosurgeons, to facilitate decisions in surgery and nerve surgery.

While the measurement of motor nerves at the extremities is methodologically easy, the measurement of NCVs of proximal nerve segments is problematic. For some proximal motor nerves, like the long thoracic and femoral nerves, only the latencies can be assessed with certainty. Age, height, and temperature are also factors that have to be considered.

Sensory NCV studies

Unlike motor conduction, where a terminal branch and synapse contribute to latency, no synapse occurs between the stimulating site and recording site in a sensory nerve. Sensory nerve action potentials (SNAPs) can be measured in both the orthodromic and the antidromic direction. This means that stimulation of the main (mixed) nerve trunk results in a signal at the distal sensory nerve, or conversely stimulation of the distal sensory branch yields a signal at the nerve trunk.

The studies can be done with surface recordings, or recording with needle electrodes using a near-nerve technique. Antidromic techniques with surface recording are commonly used. Near-nerve recordings are time-consuming but are able to pick up even low signals, and allow the assessment of several populations conducting at different velocities (dispersion), which may be necessary for diagnosis in sensory neuropathies.

Sensory nerve studies are more sensitive than motor studies at detecting nerve pathology.

Sensory responses are more sensitive to temperature than motor responses in regard to conduction velocity, but not to nerve action potential amplitude. Correction factors or warming of the extremity must be considered.

Radiculopathies do not affect the sensory potentials, as the dorsal root ganglion, which lies within or outside the neural foramen, is not affected. This can be useful if electrophysiology is needed to distinguish between radiculopathy and plexopathy or neuropathy.

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Late responses

Late responses (e.g. F wave) are techniques to obtain information about the proximal portions of the nerve and nerve roots. This is important because few studies permit access to proximal parts of the PNS.

- The A wave (axon reflex) is a small amplitude potential of short latency (10–20 ms) and high persistence, usually elicited by submaximal stimulation. It is generated by normal or pathologic axon branching. It may occur in neuropathies, possibly due to sprouting.
- The F wave is an antidromic/orthodromic motor response and can be generated from any motor nerve. It has a variable latency and amplitude and can be confused with A waves. It is clinically used to evaluate proximal portions of the nerves.
- The H reflex is an orthodromic sensory/orthodromic motor response and is usually obtained in the L5/S1 portion, evaluating a S1 radiculopathy.
- The blink reflex and the masseteric reflex are used in the evaluation of cranial nerve and brainstem function. The blink reflex has a reflex arc consisting of an orthodromic trigeminal nerve and an orthodromic motor facial nerve loop. Primary and secondary uni- and contralateral responses reveal reflex patterns in the brain stem. The masseteric reflex is induced by tapping on the chin, and results in a response in the masseteric muscle.

Proximal nerve stimulation studies

Proximal nerve stimulation studies are more difficult than the "standard" NCV studies. Proximal stimulation can be performed near-nerve with electrical or magnetic stimulation. The proximal parts of nerves like the long thoracic, phrenic, spinal acessory, suprascapular, axillary, musculocutaneous, femoral and sciatic nerves can be evaluated by this method.

Short segment studies

Short segment studies are used for short nerve segments, like the carpal tunnel syndrome (inching), the ulnar nerve over the elbow, and the peroneal nerve over the fibular head.

Repetitive nerve stimulation

Repetitive nerve stimulation is most commonly used to investigate the function of the neuromuscular junction. A train of stimuli is given to a peripheral nerve in a defined frequency. The resulting CMAP amplitudes and areas are recorded and measured. Repetitive nerve stimulation allows a distinction between pre- and postsynaptic transmission disorders. MG is usually detected at low frequency 3 Hz stimulation, whereas high frequency stimulation (20 Hz) leads to an incremental response in the Lambert Eaton Myasthenic syndrome (LEMS). Although this technique is extremely useful, decremental and incremental responses can be observed in other conditions.

Evoked responses

Evoked responses, in particular somatosensory evoked responses, allow measurement of central structures like the posterior columns, and provide additional insight into peripheral-central conduction properties.

Magnetic stimulation techniques

Magnetic stimulation techniques are usually performed with a coil and can be used to measure central conduction time as a parameter for central motor function. Stimulation at the vertebral column and in proximal nerve segments allows measurement of these difficult to approach segments.

Electromyography

Electromyography (EMG) is the basic method to study skeletal muscle function. In Europe, concentric needle electrodes are mainly used, while in the USA monopolar needles in combination with surface reference electrodes are used. The application of surface electrodes for the assessment of muscle function is still a matter of debate.

Three different steps of evaluation of the electrical activity are usually taken:

– **Insertional activity** is created by small movements of the needle electrode, and results in amorphous discharges with short durations. It is usually increased in neuropathic processes, but is difficult to quantify, and often labeled "irritability". Strictly speaking, pathologic conditions like myotonia, neuromyotonia, myokymia, and complex repetitive discharges (CRDs) belong in that category, but are usually considered spontaneous activity.

– **Activity at rest (spontaneous activity)**
A normal muscle has no spontaneous activity, other than at the end plate region. The end plate region has typical short negative spikes. Potentials generated from single muscle fibers are called fibrillations and positive sharp waves. More complex discharges from the motor unit are fasciculations, myokymia, neuromyotonia, and the discharges of muscle-cramps and tetany. CRDs stem from electrically linked muscle fibers, firing in a synchronous pattern.

– **Voluntary activity**
Voluntary innervation generates muscle unit action potentials (MUAPs). These MUAPs have a variable duration, depending on the method of assessment (concentric needle, monopolar, or single fiber technique), and depend on the muscle and the age of the patient. At mild contraction the duration is usually in the range of 5 to 15 ms, has up to four phases, and an amplitude between 300–3000 µV. For the assessment of MUAPs, duration is more constant and reliable than amplitude.
Maximum contraction produces overlapping MUAPs, called an interference pattern under normal conditions. The spectrum of pathologic abnormalities ranges from individual MUAPs firing in neurogenic conditions, to a full interference pattern with low amplitude in myopathies.

Types of pathological discharges:

Fasciculations resemble MUAPs in configuration, but have an irregular discharge pattern. They may be linked with a visible or palpable muscle twitch. They can be benign, or occur as part of a neuromuscular condition and are notably increased in ALS.

CRDs ("bizarre high frequency discharges") are caused by groups of adjacent muscle fibers discharging with ephaptic spread from one fiber to another. They are usually seen in chronic neurogenic and myopathic disease processes. They typically begin and end abruptly, and have a frequency of 5–100 Hz. The frequency does not change and contrasts with the waning and waxing pattern of myotonia.

Myotonic discharges are induced by mechanical provocation (needle, percussion). They are independent repetitive discharges of muscle fibers at rates of 20 to 80 Hz. The amplitude and frequency wane characteristically. The sound is

often compared to a "dive bomber". They occur in myotonic dystrophy, myotonia congenita, paramyotonia congenita, hyperkalemic periodic paralysis, acid maltase deficiency, and myotubular myopathy.

Neuromyotonia are bursts of multiple spikes, discharging in high frequency (up to 300 Hz). The frequency remains constant, but the amplitude slowly decreases. Sometimes groups of normal appearing MUAPs are called neuromyotonia, but may also be classified as myokymia.

Myokymia is a burst of motor unit potentials (resembling normal MUAPs), and appearing in groups separated by intervals of silence. The frequency of the spikes is 5–60 Hz. They may appear focal or generalized. Focal myokymia is often associated with radiation damage.

Cramp discharges are involuntary muscle discharges, consisting of multiple MUAPs that originate from an involuntary tetanic contraction. The discharge rate is between 20–150 Hz.

EMG techniques

- Quantitative EMG: Usually 20 MUAPs are analyzed for this technique. Automated or semi-automated methods are available on most new EMG machines. Decomposition techniques can extract single MUAPs from an interference pattern. For analysis of the interference pattern, a turn amplitude system is available in most programs
- Single fiber (SF) EMG is performed with a special needle (SFEMG-needle), a special filter setting, and special analysis programs. The SFEMG technique permits the study of the fiber density and the time relationship between discharges of fibers. This allows measurement of "jitter", which depends on the functional state of neuromuscular transmission. These studies can be used for disorders of neuromuscular transmission, but also provide insight into the stability of the neuromuscular system (reinnervation, denervation).
- Macro-EMG provides an overview of a motor unit. It is the combination of a single fiber port with a needle electrode, capturing as many potentials from the motor unit as possible. Macro area, amplitude, and duration can be measured.
- Scanning EMG: This technique also uses a single fiber electrode to detect muscle fibers firing nearby. The concentric needle is slowly and mechanically withdrawn, which allows rastered sweeps to correlate with the topographic distribution of the motor unit.

- **Special applications:**
  - Investigations of the respiratory system (diaphragm) (see Fig. 8)
  - Sphincteric EMG
  - EMG of the vocal cords (also monitoring of thyroid surgery)
  - Intraoperative techniques
  - Surface EMG

How to interpret EMG

The interpretation of EMG is based on activity at rest, spontaneous activity, characteristics of MUAPs, and the pattern at maximum contraction. The concept of EMG is based on the fact that diseases of the neuromuscular system often induce changes in the architecture of the motor unit, which induces

morphologic changes and the changes of electrical activity observed in EMG. The EMG is used to show normal, myopathic and neurogenic changes. Specific (or almost specific) phenomena can appear, as well evidence of denervation, reinnervation, and acute or stable conditions. The advantage of this technology is that it is an easily available and useful application for the diagnosis of pathophysiologic conditions. EMG is still but one step in the clinical picture, which also must take into account symptoms, signs, and other ancillary findings.

The specific patterns of abnormality found with needle EMG are subsequently described in the individual disease chapters.

Autonomic testing

The sympathetic and parasympathetic autonomic systems can be tested with various methods. Cardiovascular function, thermoregulatory tests (Fig. 7), and combined tests are available.

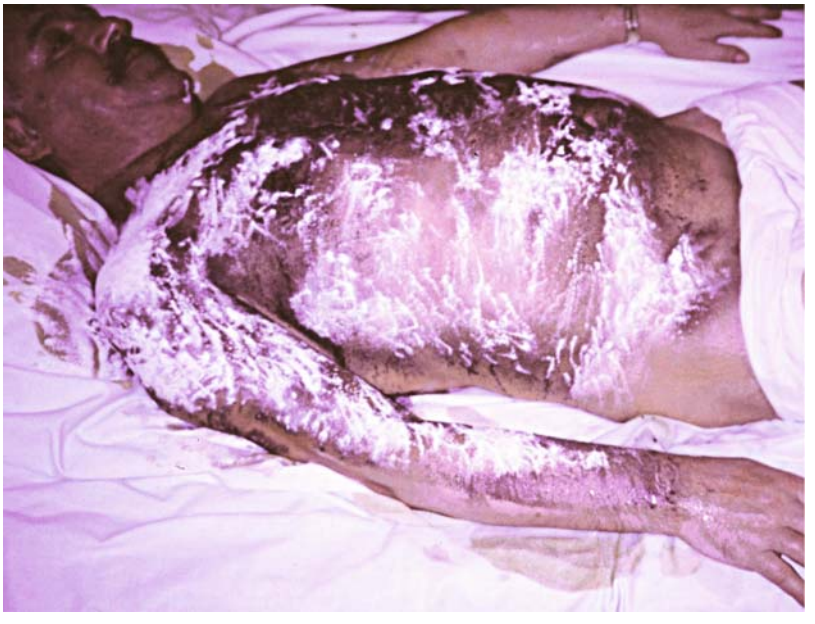

Fig. 7. Sweat test. Sweat secretion test with the iodine-starch method (Minor test). Foto documentation has to be performed when perspiration begins

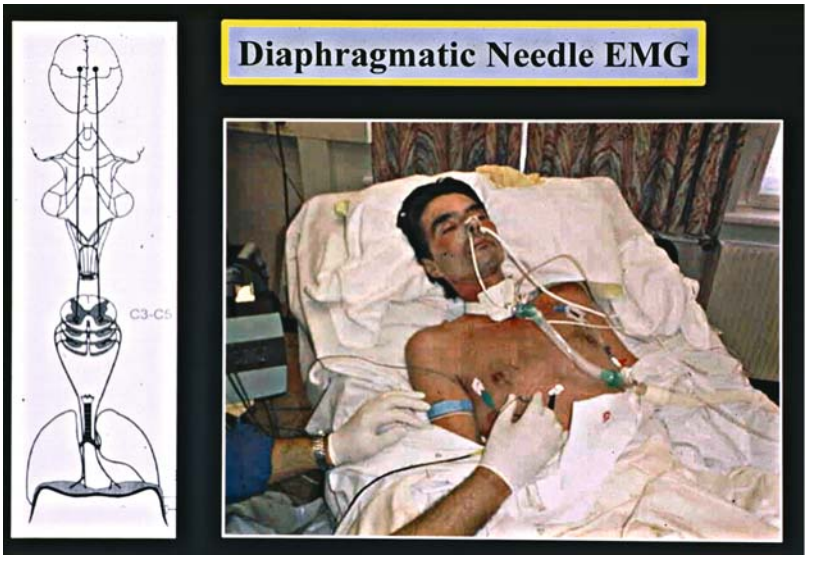

Fig. 8. EMG of the diaphragm. Left side shows the anatomic course of the nerve. The right side shows the position of the patient and examiner during the EMG

Most often the RR intervals and the sympathetic skin response are used in clinical practice. Tests of sudomotor function, like the quantitative sudomotor axon reflex test (QSART), or the thermoregulatory sweat test (Fig. 7), are more readily available in research than in clinical practice.

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Laboratory tests, biochemistry, and immunology

- **Laboratory and muscle enzymes**
- **CSF studies**
- **Autoantibodies**

- Laboratory tests are an essential part of investigations of neuromuscular diseases. Abnormal liver or renal function, endocrine function, blood glucose, and electrolyte abnormalities may be important clues for dysfunction of the neuromuscular system.
- Investigations to identify vasculitic neuropathy are clinically guided by asymmetric (multiplex) neuropathy. Laboratory tests are needed to confirm the diagnosis. Autoimmune disease (in particular rheumatoid arthritis (RA) or collagen vascular disease, association with hepatitis B antigen, and clues for hypersensitivity angiitis) can be identified by laboratory tests.
  Elevated sedimentation rate (ESR), nuclear antigens, antinuclear antibody test (ANA), rheumatoid factor (RF), antineutrophil cytoplasmic antibodies (ANCA), and cryoglobulins can be assayed along with serum and urine electrophoresis, immunoelectrophoresis, and HIV testing. The final diagnosis of vasculitis is finally confirmed by nerve (and muscle) biopsy.
  Neuromuscular diseases are associated with polyarteritis nodosa, Churg-Strauss syndrome, Wegener's granulomatosis, hypersensitivity angiitis, and, rarely, isolated vasculitis of the peripheral nervous system.

One important laboratory test is the measurement of creatine kinase (CK). This single, reliable test is usually associated with myopathies, rather than neurogenic disorders. However, transient CK elevation is also observed after exercise, muscle trauma, surgery, seizures and acute psychosis. Asymptomatic CK elevations occur more often in people of African descent with large muscle mass. The syndrome of idiopathic hyperCKemia is a persistent CK elevation without a definable neuromuscular disease.

Other enzymes which can be affected in neuromuscular diseases are aminotransferases, lactate dehydrogenase, aldolase, carbonic anhydrase-III, pyruvate kinase and muscle specific enolase.

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CSF studies

The CSF is often studied in polyneuropathies, particularly in acute and chronic polyradiculoneuropathies. Often, inflammatory or cellular responses can be ruled out, and the elevated protein levels remain the only significant finding.

Table 3. Radiculitis and CSF findings

Infection	Cell count	Cell type	Clinical manifestation	Other tests
Borreliosis, Lyme disease	Up to 200/µl	Lymphocytic, lymphomonocytic, many activated lymphocytes	Cranial nerve: VII Meningoradicular syndrome	Antibody detection by ELISA, Immunoblotting, PCR
Herpes zoster	300/µl	Lymphocytic	Monoradicular (also myotomal) lesions	Serology
HIV Seroconversion	8/µl	Polymorphonuclear cells	AIDP, CIDP	Serology
CMV-Radiculitis	8/µl	Mixed cell population	Cauda equina-syndrome	
Syphillis	Early: 25–2000/µl IgG≫ Late: may be normal	Lymphomonocytic cell count	Painful polyneuropathy Tabes dorsalis	Specific test
Brucellosis	15–700/µl cells	Lymphocytic, granulomatous meningitis	CN: VII, lumbar radiculopathies polyradiculopathies	
West Nile fever	Pleocytosis Protein elevation	Lymphocytic cell distribution	AIDP-like polyneuropathy	
FSME ("Central European Tick Encephalitis")	60–2000/µl	Lymphocytes: 20–60% lymphocytes and 40–80% PMN	Radiculitis, Myelitis, Poliomyelitis-like, CN	Antibody testing

PCR Polymerase chain reaction; *AIDP* acute inflammatory demyelinating polyneuropathy; *CIPD* chronic inflammatory demyelinating polyneuropathy; *CMV* cytomegalovirus; *PMN* polymorphonuclear cells; *CN* cranial nerves.

Inflammatory conditions like neuroborreliosis ("Lyme's disease") have a characteristic inflammatory pattern, which can be confirmed by serologic studies.

Several serologic and immunologic tests of CSF are available. Table 3 gives an overview of expected CSF findings in radiculitis.

Immunologic studies

Autoantibodies have been described in several disease entities, like polyneuropathies, disorders of the neuromuscular junction, paraneoplastic disease and muscle disease. The antibodies can be detected by immunofluorescence methods, enzyme linked immunosorbent assays (ELISA), western blotting, radioimmunoassays, thin layer chromatography, and immunofixation electrophoresis.

Autoantibodies and immune polyneuropathies

In the most frequently occuring conditions, like acute and chronic polyradiculoneuropathy (AIDP, CIDP), no constant autoantibody pattern is found. There is a high frequency of anti-GM1 antibodies in multifocal motor neuropathy with conduction block (80%). The antimyelin associated glycoprotein (MAG) neuropathy is a typical syndrome with MAG positivity in 50–70%. GM1 and GD1 autoantibodies occur in about 50% of cases with AIDP. The GQ1b antibody is recorded in 95% of patients with the rare Miller-Fisher syndrome. Also, there are several autoantibodies described against sulfatides, GM2, GalNAc-GD1a, GD1b. In most cases, the role and frequency of occurrence for these antibodies is uncertain.

In paraneoplastic polyneuropathies, the association with anti-Hu antibodies and sensory neuronopathy is common. In Sjögren's syndrome, IgG against SS-A and SS-B has been described. However, most of these autoantibodies seem to be an epiphenomenon, rather than a pathologic cause for the neuropathy.

Paraproteinemia can occur without pathological significance, or point to hematologic diseases like multiple myeloma, Waldenstrom's disease, osteosclerotic myeloma, or lymphoma. Electrophoresis, immunofixation, and often bone marrow biopsies are needed, in addition to skeletal X-ray, and nerve biopsies.

Amyloidosis of peripheral nerves and muscle can develop in hematologic diseases, which can be confirmed with biopsy.

Reference

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Autoimmune testing in neuromuscular transmission and muscle disorders

The prototype of neuromuscular junction disorders are MG and LEMS. The pathology of MG is localized to the postsynaptic membrane. In the majority of patients (in particular with generalized MG – about 90%) antibodies against the nicotinic acetylcholine receptor (AchR) can be detected. The yield in ocular MG is lower (60–70%). There is a poor correlation between antibody titers and disease severity, but they have a high specificity for MG. About 10% of typical generalized MGs are seronegative; for these, the presence of anti-muscle specific tyrosine kinase (MUSK) autoantibodies have been described. Striatal antibodies lack specifity for MG, but may be helpful in thymoma detection. Other autoantibodies like titin and RyR may point to epitopes in a thymoma.

In LEMS, a presynaptic disorder, calcium channel autoantibodies directed against the P/Q type channels have been described. These autoantibodies are

detected in nearly 100% of patients with LEMS. Antibodies against the N-type channel are detected in 74% of LEMS patients.

Neuronal acetylcholine receptor antibodies are directed against AchR in autonomic ganglia, resulting in autonomic dysfunction.

Patients with MG or LEMS have a higher association with other autoantibodies, like thyroid peroxidase, thyreoglobulin, gastric parietal cell, and glutamic acid decarboxylase (GAD).

Autoantibodies have been described in syndromes with increased muscle activity, such as rippling muscle syndrome and neuromyotonia. Neuromyotonia can be caused by an antibody against voltage-gated potassium channels at the paranodal and terminal regions of myelinated axons of peripheral nerves. The acquired type of rippling muscle disease has been described in association with thymoma and an antibody against the ryanodin receptor.

In various types of myositis, antibodies like anti-Jo 1, anti-PL 7, anti-PL 12, anti-OJ, anti-EJ, anti-KS, and several others have been described. Some of them may help to predict disease, prognosis and response to therapy. Another spectrum of autoantibodies can be found in the myositis overlap syndrome. Unlike the autoantibodies in MG and LEMS, the pathogenic role of these is not well understood, though they serve, with the exception of some myositis specific antibodies, diagnostic purposes.

Genetic testing

Genetic testing has become an important tool in the diagnosis and research of neuromuscular diseases. Molecular diagnosis has helped divide conditions into inherited and non-inherited neurologic diseases. Presently in many genetic diseases a precise diagnosis can be offered, which is the basis for genetic counseling. The identification of the responsible biochemical defect gives hope that these pathological processes can be halted or cured.

Several techniques are presently available, and some are being developed.

- Cytogenetics is used to visualize large genetic anomalies like aneuploidies, and some nonaneuploid or euploid cytogentic abnormalities. The flourescent in situ hybridization (FISH) method adds an additional level of resolution, and can be used to detect deletions, duplications, and rearrangements.
- DNA mutation tests:
  Deletion test (presence or abscence of exons), tested by polymerase chain reaction (PCR) or Southern blot.
  Restriction fragment length polymorphism: a method to detect point mutations
  Amplification refractory mutation system
  Single strand conformational polymorphism
- New technologies:
  Microarrays
  Denaturing high pressure liquid chromatography (DHPLC)

A problem for clinical practice is that for some diseases, one common mutation has been described, and the available tests are directed to detect this defect. Thus, finding a different mutation in a patient with a clearly defined clinical syndrome that is negative for the common mutation can be difficult and time consuming. It is not routine to sequence the entire gene of a patient with a negative result, and thus the physician needs to interpret negative results with care.

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Neuroimaging techniques

MR has become the method of choice for many conditions, although CT remains superior in the imaging of bones and calcified structures. Ultrasound has the ability to view dynamic processes (e.g., movement of the diaphragm).

Imaging of the spine and vertebral column

MR techniques are gradually replacing classic methods like the plain X ray, myelography, CT, and CT myelography, although CT still has a role in detecting osseus changes.

MR spinal cord imaging has become the method of choice for degenerative disc disease, and is a valuable method to discriminate disk bulges and herniations. It is also used to show degenerative diseases of the facets and vertebral joints.

Spinal stenosis, epidural abscess, or other spinal infections can also be detected, as well as arachnoiditis, neoplasms, and malformations.

In some diseases, the paravertebral muscle may undergo changes that can also be seen with MR.

Imaging of peripheral nerves

MR neurography is becoming an important method to identify small focal lesions. Using MR to detect optic neuritis has become routine in MS patients. Other nerves, like the inferior alveolar and mandibular nerves, can be checked for swelling or disruption.

The brachial plexus, which is difficult to assess by other methods, can now be imaged to detect swelling and inflammation, tumors, or discriminate between radiation induced and neoplastic neuropathy. This is also true for the lumbar and sacral plexuses, where the structures of the nerve tissue and surrounding structures can be observed.

MR studies are also advocated in entrapment neuropathies like carpal tunnel syndrome, ulnar nerve lesion (proximal or distal), and peroneal nerve lesion. Currently, the relationship between MR findings and conventional neurophysiologic methods for these conditions is not clear.

The list of indications for neuroimaging of peripheral nerve structures is growing, and includes nerve trauma (demonstrating discontinuities), follow up of nerve grafting procedures, and nerve tumors (for example, neurofibromatosis [NF]).

A few reports suggest MR may have a role in the diagnosis of some polyneuropathies, like multifocal motor neuropathy with conduction block, CIDP, and perhaps focal lesions in nerve trunk pathology (such as in vasculitis).

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Imaging of muscle

MR can help identify the degree and distribution of muscle abnormalities. However, many diverse conditions that affect muscle have similar or overlap-

ping appearances on MR. These include denervation, trauma, infections, and inflammatory conditions.

In inflammatory muscle disease the MR findings are not specific, showing a patchy distribution. MR may help in selecting and guiding a biopsy necessary to establish the diagnosis in these cases. Focal nodular myositis is a rare condition, where MR imaging can be used to distinguish this from other causes of muscle swelling.

Sarcoidosis and amyloidosis of muscle are conditions where MR may also help to establish the diagnosis.

MR is helpful in identifying denervated muscle, and can differentiate between subacute and chronic conditions. Hypertrophy or pseudohypertrophy can be seen in the calf muscles, as well as in the masseter, neck, back, thenar and hypothenar muscles.

Imaging studies can be used in the dystrophies, to detect the extent of the disease and to monitor progression.

MR can be useful in the diagnosis of infectious conditions of the muscle (more frequent in tropical regions), exercise-induced changes, compartment syndromes (either due to exercise or vascular disease), radiation damage, and muscle infarction (as in diabetes).

Ultrasound imaging can be used to indicate the location of on-site or intraoperative biopsy sites. The dynamic aspect of ultrasound has been used to monitor the function of the diaphragm.

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Tissue diagnosis: muscle/nerve/skin biopsy

Nerve and muscle biopsy are important tools in the diagnosis of neuromuscular disease. Precise clinical, electrophysiological, and laboratory diagnostics must be done and assessed before a biopsy is done. The tissue taken must be selected from the right place; the nerve and muscles are selected to obtain optimal results. A neuropathologist experienced in processing samples of the neuromuscular system should be involved, and optimal tissue processing by the most current methods must be applied. There is rarely an acute indication for biopsy, except in the suspicion of peripheral nerve vasculitis or florid polymyositis. According to our own experience, the number of nerve biopsies seems to be decreasing due to the increased power of genetic testing, or the sufficiency of clinical and immunological criteria for some diseases like CIDP.

Imaging studies are becoming increasingly important as a precursor to biopsy. Particularly in muscle disease, imaging allows estimation of the pattern of distribution of the disease in various muscles. In patients with considerable muscle atrophy and fatty replacement, imaging helps in the selection of the muscle to be biopsied.

Nerve biopsy

The sural nerve is the most frequently biopsied nerve. Some schools prefer the superficial peroneal nerve, and biopsies from other nerves such as the superfi-

cial radial or pectoral nerves can be obtained. The nerve should be fixed in formalin, prepared for electron microscopy, and a special segment should be kept ready if nerve teasing is indicated. Immunologic studies can be best obtained on a frozen section.

More material for serial sections may be necessary in cases of vasculitis.

The histologic examination includes hematoxilyn eosin (HE) sections, staining for myelin, and special stainings depending on the case. A morphometric analysis can be used to define the population of myelinated fibers, which is bimodal in the normal nerve. Plastic embedded sections and preparations for teased fibers should be available. The analysis of the biopsy can distinguish between axonal pathology, demyelination, regeneration, inflammation, and rare conditions such as neoplastic involvement or deposition of amyloid.

Muscle biopsy

Muscle tissue can be examined by several histologic techniques, including light microscopy, electron microscopy, and histochemistry. Immunohistochemistry uses available antibodies to detect immunologic alterations or defined structures. Molecular diagnosis, studying the cytoskeleton and its interaction with the sarcolemma, extracellular matrix, and transmembrane proteins, has been applied in the diagnosis of dystrophies.

There is a long list of myopathies that warrant a biopsy, either for morphological, molecular, or biochemical analysis.

In clinical practice, a biopsy is often performed to discover or confirm inflammatory conditions (dermato-, polymyositis), structural abnormalities, and finding additional morphologic indication of neuromuscular disease.

Simultaneous muscle and nerve biopsies are recommended in cases of suspected vasculitic neuropathies. The likelihood of detecting inflammatory changes is higher by using both techniques together.

Skin biopsy

Skin biopsy allows an estimation of epidermal innervation. It has been advocated in diabetic polyneuropathy by several studies. So far, it has not become a routine method.

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Assessment and treatment of neuromuscular disorders

Quantification of function, impairment, disability, treatment outcome, and quality of life are some of the parameters which need thorough, statistically valid, efficient, sensitive, and specific methods. These instruments are prerequisites for clinical studies and outcome measures, and the elected methodology may contribute significantly to the result of a study.

Some of the available scales are listed below.

- Motor scales: MRC scale, dynamometry (e.g., maximal voluntary isometric contraction), Appel ALS scale, Norris ALS scale, Rivermead motor assessment, Trunk control test
- Sensory scales: quantitative sensory testing, sensory NCVs
- Spasticity scales: Modified Ashworth scale
- Respiratory scales: Forced vital capacity, slow vital capacity, tidal volume, maximum inspiratory/expiratory pressures
- Disability scales: ALS functional rating scale, neuropathy disability scale, Rankin scale, Barthel index
- Diabetic neuropathy: neuropathy impairment score (NIS), neuropathy symptom score (NSS)
- ALS: ALS functional rating scale
- MG: myasthenic muscular score, myasthenia severity scale, myasthenic functional score, quantitative MG score, MG activities of daily living score
- Quality of life: Short form 36, Short form 12, sickness impact profile, schedule for the evaluation of individual quality of life measure (SEIQoL)

Reference

Rosenfeld J, Jackson CE (2002) Quantitative assessment and outcome measures in neuromuscular disease. In: Katirji B, Kaminski HJ, Preston DC, Ruff RL, Shapiro B (eds) Neuromuscular disorders. Butterworth Heinemann, Boston Oxford, pp 309–343

Cranial nerves

Olfactory nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy	Clinical testing Smell/Taste
			+		

Function

Mediates olfaction defined as the sense of smell.

Anatomy

Olfactory receptors are present in the superior nasal conchae and nasal septum. The unmyelinated axons pass through the cribiform plate to synapse in the olfactory bulb.

The olfactory bulb is located beneath the surface of the frontal lobe. Axons leave the olfactory bulb as the olfactory tract and connect to prepyriform cortex.

Symptoms

The term parosmia describes a qualitative change in smell while total loss of smell is known as anosmia. Disorders of smell usually develop slowly and insidiously (except in traumatic brain injury) and are commonly associated with impaired taste. Olfactory hallucinations may accompany seizures or psychosis.

Signs

Altered smell is difficult to quantitate on examination. Each nostril is tested separately for the patient's ability to smell coffee, peppermint oil, oil of cloves and/or camphorated oil.

Ammonia provokes a painful sensation and can be used to diagnose fictitious anosmia. In acute trauma, nasal bleeding and swelling may impede examination.

Pathogenesis

Parosmia and anosmia are most frequently due to trauma. Approximately 7% of head injuries involve altered smell. Impact from a fall causes anterior-posterior brain movement and olfactory fibers may be literally "pulled out." This may occur without or with a skull fracture. An anteroposterior skull fracture can cause tearing of the olfactory fibers that traverse the cribriform plate with loss of ipsilateral olfaction. Other traumatic etiologies include missile injuries and inadvertant postsurgical damage. Other less frequent causes are listed in Table 1.

Diagnosis

Diagnosis is made by history, signs upon clinical testing and in rare cases olfactory evoked potentials. If loss of taste accompanies loss of smell, electrogustometria is used.

Functional MRI – may be useful in the future.

Table 1. Etiologies of parosmia and anosmia

Vascular	Metabolic	Toxic	Infection	Inflammatory	Mass	Degenerative and aging	Genetic
Anterior cerebral artery giant cell aneurysm	Renal insufficiency Diabetes Hypothyroidism	Drugs[1]	Meningitis Herpes Influenza Diphtheria TB Postinfectious	Granuloma[2] TB Syphillis Rhinoscleroma	Tumor[3]	Alzheimers's disease Jakob Creutzfeldt disease (new variant) Huntington's disease Korsakow syndrome Parkinson's disease	Congential and hereditary

[1] Drugs include antihelmintic, local anesthetics, statins, antibiotics (amphotericin B, ampicillin, ethambutol, lincomycin, tetracyclin), cytostatics (doxorubicin, methotrexate, carmustin, vincristine), immunosuppressants (azothioprine), allopurinol, colchicine, analgesics, diuretics, muscle relaxants, opiates.
[2] Wegener's granulomatous, sarcoid.
[3] Tumors include abscesses, aesthesioneuroepithelioma (blastoma), craniopharyngioma, meningiomas, olfactory meningioma, nasopharyngeal tumors, mucocele, olfactory neuroblastoma, tuberculum sellae tumors.

Differential diagnosis

The perception of loss or altered smell may be actually due to altered taste secondary to dysfunction in the glossopharyngeal nerve (CN IX).

Therapy

Therapy depends upon etiology and in cases of trauma is usually supportive.

Prognosis

When the loss of smell is due to trauma, more than one third of individuals have full recovery within 3 months.

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Optic nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Other clinical tests Color vision
	Visual evoked potentials (VEP) Electroretinogram (ERG)		CT, MRI, plain X-ray +	

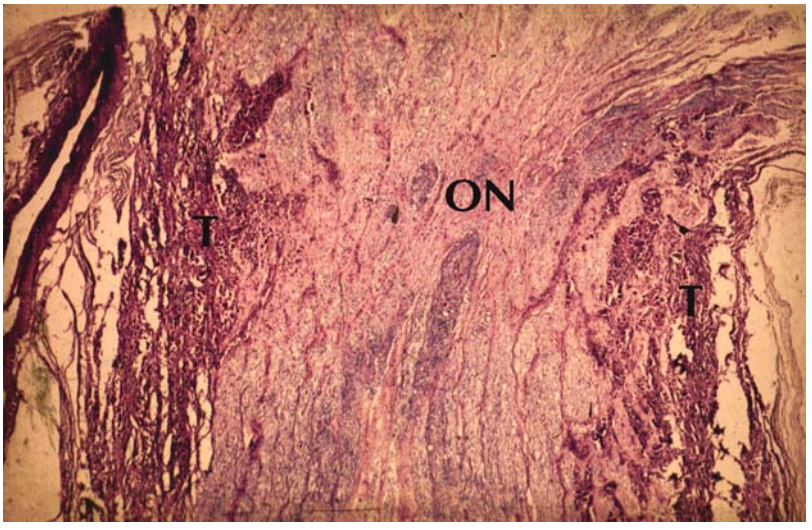

Fig. 1. Optic nerve (photomicrograph). The nerve is compressed by tumor cells in meningeal carcinomatosis, resulting in blindness of the patient. *ON* Optic nerv. *T* Tumor

Quality

Special sensory: visual information from the retina

Anatomy

Light energy is transduced into electrical signals in the posterior layer of the retina by receptor cells called rods and cones. Primary sensory neurons called bipolar cells receive signals from the rods and cones. Bipolar cells pass these signals onto secondary sensory neurons called ganglion cells, which are found in the most anterior layer of the retina. The axons of the ganglion cells traverse the retina and converge at the optic disc near the center of the retina. The macula contains no traversing ganglion cell axons, in order to diminish interference with central vision. At the optic disc, the axons turn posteriorly through the lamina cribiformis of the sclera and exit the eyeball as the optic nerve. The optic nerve leaves the orbit through the optic canal (lesser wing of the sphenoid bone), in close proximity to the ophthalmic artery and the cavernous sinus.

The optic nerve enters the middle cranial fossa and joins the optic nerve from the other eye to form the optic chiasm.

Location of lesions

Lesions of the optic nerve can be divided into three categories:

a) anterior to the chiasm (monocular field defect or blindness)
b) medial and temporal compression of chiasm (hemianopias)
c) posterior to the chiasm (hemianopias)

Central lesions and papillary dysfunction will not be discussed here.

Symptoms

Loss of vision.

Signs

While direct pupillary reaction to light is absent, the pupillary reaction can be evoked indirectly.

Pathogenesis

Metabolic:
Diabetes, thyrotoxicosis, uremia.

Toxic optic neuropathy:
Alcohol
Anilin dye
Amoproxan
Ara C (high dose)
Arsenic
Aspidium (antihelmintic drug)
Cafergot
Carbon disulfide
Carbon tetrarchloride
Chinin
Chinolin derivates
Chlorambucil (edema of the retina)
Chloramphenicol
Digitalis
Disulfiram
Docetaxel: may cause visual sensations (“visual field flash”)
Ethambutol
Isoniazid
Lead
Mercury (Hg)
Nitrosurea and radiation
Nitrous oxide (N_2O)
Thallium
Vincristine

Vascular:
Ischemic optic neuropathy due to:
Amyloidosis
Arteritis cranialis
Herpes zoster
Retrobulbar optic neuropathy
Systemic lupus erythematosis (SLE)

Infectious:
Meningitis
Sarcoid
Syphilis
Tuberculosis

Focal infection:
Granulomatous disease
Sinusitis

Inflammatory:
Optic neuritis due to demyelinating diseases (MS, neuromyelitis optica)

Nutritive:
Alcohol ingestion
B12 anemia
Cuban neuropathy
Methylol toxicity
Strachan's syndrome
Tobacco alcohol amblyopia

Compression:
Apoplexy of the pituitary
Carotid aneurysm
Endocrine orbitopathy
Orbital tumors
Inflammatory causes of compression: syphilis, tuberculosis, arachnitis opto-chiasmatica

Tumors:
Metastases
Melanocytoma
Meningeal carcinomatosis (see Fig. 1)
Nasopharyngeal tumor
Neurofibromatosis (NF 1)
Optic nerve glioma
Retinal infiltration: leukemia

Compression of the optic chiasm by tumors in the sella results in visual field defects and a swollen optic disc. Compression occurs in 50% of pituitary adenomas; other potential causes include craniopharyngeoma (in childhood), meningeoma of the tuberculum sellae, aneurysm, tumors of the chiasm itself (spongioblastoma, meningioma, neuronoma, or retinoblastoma).

Paraneoplastic:
Rarely involved in paraneoplastic dysfunction: CAR (carcinomatous retinopathy)

Hereditary:
Charcot-Marie-Tooth (CMT)
Leber's disease
Lysosomal disease
Storage disease (Tay Sachs)
Spinocerebellar disease

Ataxias:
Friedreich's ataxia
Mitochondrial – NARP Syndrome: (**N**europathy; **A**taxia; **R**etinitis **P**igmentosa)
Posterior column ataxia + Retinitis pigmentosa

Iatrogenic:
Pressure on the eye bulb caused by anesthesia (ischemic optic nerve neuropathy), blepharoplasty, fractures of the orbit, or surgery of the nasal sinus.

Radiation:
Radiation therapy of brain tumors, pituitary tumors, metastases, or ENT tumors can cause uni- or bilateral loss of vision with long latencies. Progressive optic nerve atrophy is seen within 6 weeks of exposure to 70 Gy (units of gray).

Trauma:
"Blow out" fractures
Gunshot wounds
Penetrating trauma
Trauma of the orbit
Traumatic optic neuropathy

Diagnosis

Diagnosis is based on X-ray, CT, or MRI imaging, visual function and color discrimination tests, ophthalmoscopic exam, visual evoked potentials (VEP), and electroretinogram (ERG).

Differential diagnosis

Other causes of papilledema should be considered, including increased intracranial pressure (ICP) and pseudotumor cerebri.

Therapy

Treatment depends upon the cause of the lesion.

Prognosis

Depending on the etiology.

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Oculomotor nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy	Lee screen
	(PNP: NCV)	+ (Diabetes)	++		+

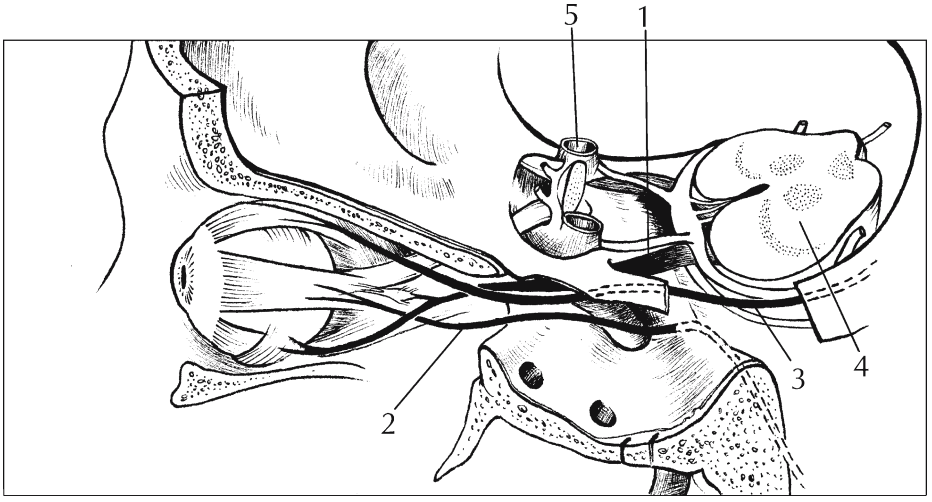

Fig. 2. *1* Oculomotor nerve, *2* Abducens nerve, *3* Trochlear nerve, *4* Cross section through brainstem, *5* Internal carotid artery

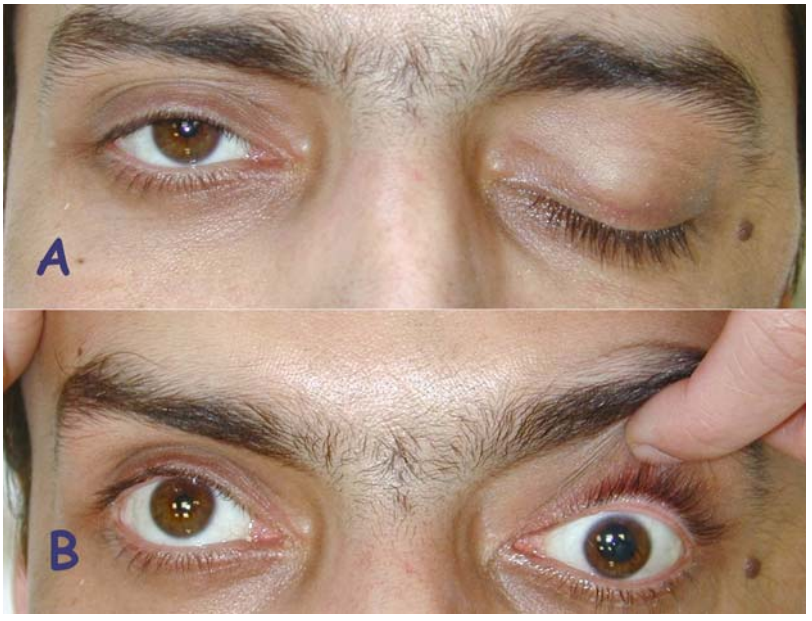

Fig. 3. Oculomotor nerve paresis: **A** Complete ptosis; **B** Upon lifting of the lid lateral deviation of left bulbus. Pupillary dilatation (mydriasis) signals the parasympathetic fibers for the sphincter pupillae are affected

Qualities

Somatic motor

Extraocular eye muscles except superior oblique muscle and lateral rectus muscle.

Visceral motor

Parasympathetic to the constrictor pupillae and ciliary muscles.

Anatomy

The nucleus of the oculomotor nerve is located in the midbrain, ventral to the cerebral aqueduct. The nerve fibers course ventrally in the tegmentum, through the red nucleus and the medial aspect of the peduncles, emerging in the fossa interpeduncularis. The nerve passes the posterior cerebral and superior cerebellar arteries as it courses anteriori. It pierces through the dura and enters the cavernous sinus, where it runs along the lateral wall superior to the trochlear nerve. The nerve then passes the superior orbital fossa and through the tendinous ring. In the orbit, it divides into a superior portion (innervating the superior rectus and levator palpebrae superioris) and inferior portion (innervating the inferior rectus, inferior oblique, and medial rectus). The visceral fibers (originating in the Edinger-Westphal nucleus of the oculomotor nucleus complex) are also found in the inferior portion and terminate in the ciliary ganglion (see Fig. 2).

Topographical location of lesions

Nuclear lesions:
Nuclear lesions are rare, and usually of vascular etiology.

Fascicular lesions:
Concomitant with lesions of the pyramidal tract and cerebellar fibers.

Intracranial pathway:
Posterior communicating aneurysm- often with pupillary involvement. However, the pupil can be spared.
Other causes: meningitis, trauma, compression.

Transtentorial herniation:
With impairment of consciousness and other signs of raised ICP.

Clivus and plica petroclinoidea:
In herniation.

Cavernous sinus:
Associated with other CN involvement (IV, V, VI).
The pupil can be spared.
“Pseudopupillary sparing” means that pupillary involvement by an oculomotor nerve lesion is masked by a concomitant Horner’s syndrome.

Extracranial pathway/orbit:
Superior division (levator and superior rectus).
Inferior division (inferior oblique, inferior rectus, medial rectus, pupillary muscle).

Orbital lesion:
Often associated with proptosis and optic nerve dysfunction.

Symptoms

Patients with third nerve palsies have diplopia and unilateral ptosis. Complete ptosis may mask diplopia. Patients have difficulty viewing near objects because convergence is impaired.

Signs

Partial or complete ipsilateral ptosis occurs. The pupil can be dilated and poorly reactive or nonreactive to light and accomodation. Examination reveals ipsilateral adduction, elevation, and depression deficit of the bulbus. If the deficit of adduction is significant, there will be a primary position exotropia that is worse when the gaze is directed towards the paretic medial rectus muscle. If the levator muscles (e.g., superior rectus or inferior oblique muscles) are involved, ipsilateral hypotropia occurs. If the inferior rectus muscle is involved, ipsilateral hypertropia occurs.

Complete paresis of both inferior and superior divisions of the nerve causes ptosis, downward and outward deviation of the eye, and mydriasis (with preserved consensual pupilary reaction contralaterally) (see Fig. 3).

Internal oculomotor ophthalmoplegia involves the parasympathetic pupillary fibers exclusively.

External oculomotor ophthalmoplegia involves only the extraocular eye muscles, while sparing the parasympathetic fibers.

Pathogenesis

Cranial nerve III is the second most frequently affected of the ocular muscle nerves. Incomplete lesions are more common. 60–70% of lesions are isolated, the rest being associated with a lesion of CN IV and/or VI.

Metabolic:
Diabetes: often painful, with sparing of the pupil.

Toxic:
Botulism

Vascular:
Aneurysm: often painful and involves the pupil.
Brainstem infarcts can cause nuclear and fascicular lesions.

Inflammation:
AIDP (rare)
Meningitis – with other cranial nerve involvement
Syphilis
Tuberculosis

Compressive:
Herniation of the temporal lobe
Neurosurgical procedures
Pathologic conditions in the cavernous sinus

Tumor:
Base of the skull metastasis
Leptomeningeal carcinomatosis
Multiple myeloma
Neuroma

Trauma:
Cranial trauma with or without fracture
Traumatic aneurysm

In trauma impairment of orbital movements due to generalized swelling may occur.

Regeneration after trauma:
May be aberrant and posttraumatic innervation may cause erroneous innervation of adjacent muscles.

Others causes:

Migraine:
Ophthalmoplegic migraine

Pediatric oculomotor lesions:
Congenital, traumatic, and inflammatory causes are most common.

Diagnosis

Fasting glucose
Imaging, especially to exclude aneurysm

Differential diagnosis

Botulism (pupils)
Brainstem disorders and Miller Fisher Syndrome
Congenital lesions
Hereditary conditions
Myopathy – chronic progressive external ophthalmoplegia
Myasthenia Gravis

Therapy

Long duration of defects may require prism therapy or strabismus surgery.

Prognosis

Depends on the treatment of the underlying pathology. If the lesion is of vascular etiology, resolution occurs usually within 4–6 months.

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Richards BW, Jones FRI, Young BR (1992) Causes and prognosis in 4278 cases of paralysis of oculomotor, trochlear and abducens cranial nerve. Am J Ophthalmol 113: 489–496

Trochlear nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
		+	+	

Qualities

Somatic motor to the superior oblique muscle.

Anatomy

The trochlear nucleus is located in the tegmentum of the midbrain at the inferior colliculus, near the midline and ventral to the aqueduct. Axons leave the nucleus and course dorsally around the aqueduct and decussate within the superior medullary velum (thus, each superior oblique muscle is innervated by the contralateral trochlear nucleus). The axons exit from the midbrain on its dorsal surface and travel around the cerebral peduncle, emerging between the posterior cerebral and superior cerebellar arteries with the oculomotor nerve. The trochlear nerve pierces the dura at the angle between the free and attached borders of the tentorium cerebelli. It then enters the lateral wall of the cavernous sinus, along with the ophthalmic nerve (V1), CN III, and sometimes the maxillary nerve (V2). It enters the superior orbital fissure, passes above the tendinous ring, crossing medially along the roof of the orbit, then diagonally across the levator palpebrae. The nerve breaks into three or more branches as it enters the superior oblique muscle.

Topographical localization of lesion

Lesion sites include the midbrain, subarachnoid space, cavernous sinus, superior orbital fissure, or orbit.

Symptoms

Patients experience vertical diplopia that increases when the gaze is directed downwards and medially.

Signs

The affected eye is sometimes extorted (although this may not be apparent to the observer) and exhibits poor depression during adduction. Hypertropia may occur if the weakness is severe.

Pathogenesis

Isolated lesion of the trochlear nerve is rare, although it is the most common cause of vertical diplopia. More often trochlear nerve dysfunction is observed in association with lesions of CN III and CN VI.

Metabolic:
Diabetes

Vascular:
Hypertension
Subarachnoid hemorrhage

Uncertain: microvascular infarction
Vascular arteriosclerosis, diabetes (painless diplopia)

Infection:
Mastoiditis
Meningitis

Inflammatory:
Ophthalmoplegia or diplopia associated with giant cell arteritis

Compression:
Cavernous sinus, orbital fissure lesions
Inflammatory aneurysms (posterior cerebral artery, anterior superior cerebellar artery)

Trauma:
Head trauma causing compression at the tentorial edge
Lumbar puncture or spinal anesthesia
Surgery
The trochlear nerve is the most commonly injured cranial nerve in head trauma.

Neoplastic:
Carcinomatous meningitis
Cerebellar hemangioblastoma
Ependymoma
Meningioma
Metastasis
Neurilemmoma
Pineal tumors
Trochlear nerve sheath tumors

Others:
Superior oblique myokymia

Pediatric: congenital, traumatic and idiopathic are the most frequent causes**.**

Diagnosis

Diagnosis can be facilitated by the Bielschowsky test:

1. Hypertropia of the affected eye
2. Diplopia is exacerbated when the affected eye is turned nasally
3. Diplopia is exacerbated by gazing downward
4. Diplopia is improved by tilting the head away from the affected eye

Also, when viewing a horizontal line, the patient sees two lines. The lower line is tilted and comes closest to the upper line on the side towards to the affected eye.

Subtle diagnosis: “Cross over” or Maddox rod techniques

Differential diagnosis

Skew deviation, a disparity in the vertical positioning of the eyes of supra-nuclear origin, can mimic trochlear palsy. Myasthenia gravis, disorders of the extraocular muscles, thyroid disease, and oculomotor palsy that affects the superior rectus can also cause similar effects.

Therapy

The vertical diplopia may be alleviated by the patching of one eye or the use of prisms. Surgery could be indicated to remove compression or repair trauma.

Prognosis

The recovery rate over 6 months was observed to be higher in cases of diabetic etiology than other non-selected cases.

References

Berlit P (1991) Isolated and combined pareses of cranial nerves III, IV, and VI. A retrospective study of 412 patients. J Neurol Sci 103: 10–15
Jacobson DM, Marshfield DI, Moster ML, et al (2000) Isolated trochlear nerve palsy in patients with multiple sclerosis. Neurology 55: 321–322
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Rush JA, Younge BR (1981) Paralysis of cranial nerves III, IV, and VI. Arch Ophthalmol 99: 76–79

Trigeminal nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+ Somatosensory evoked potentials Reflexes: masseteric, corneal reflex, EMG	+	++	

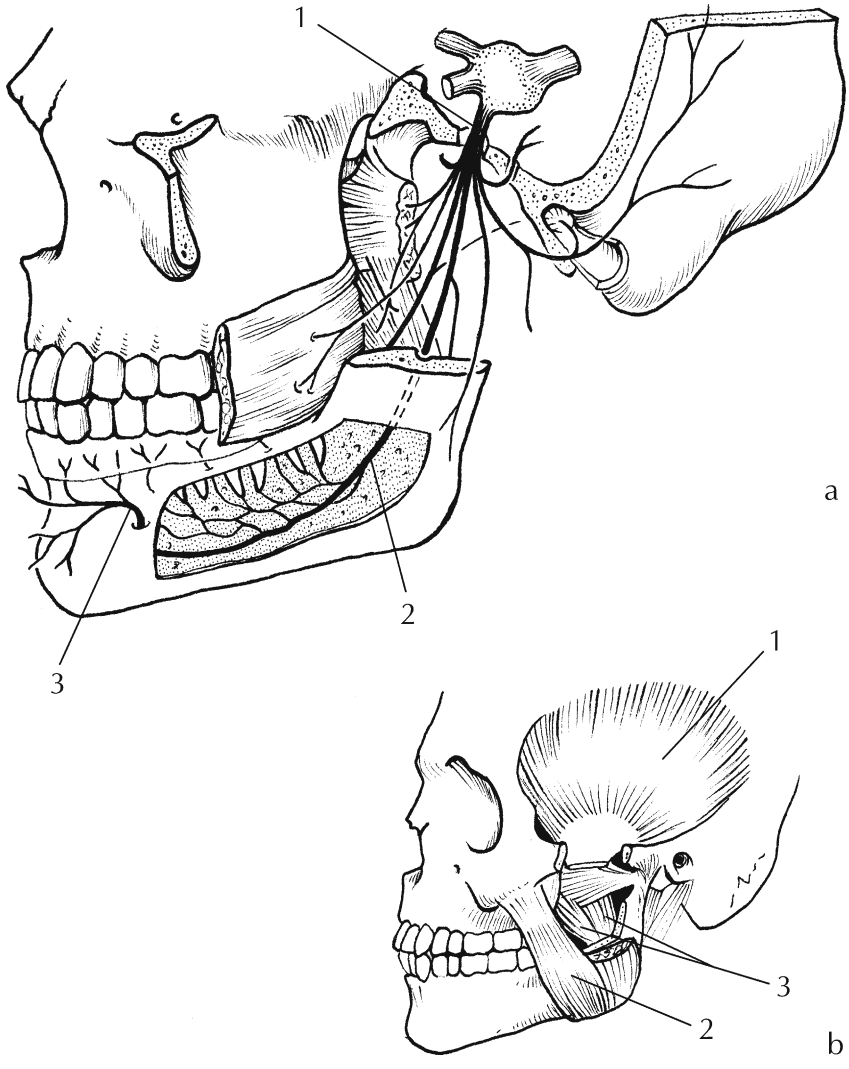

Fig. 4. a *1* Mandibular nerve, *2* Inferior alveolar nerve, *3* Mental nerve. **b** *1* Temporal muscle, *2* Masseteric muscle, *3* pterygoid muscles.

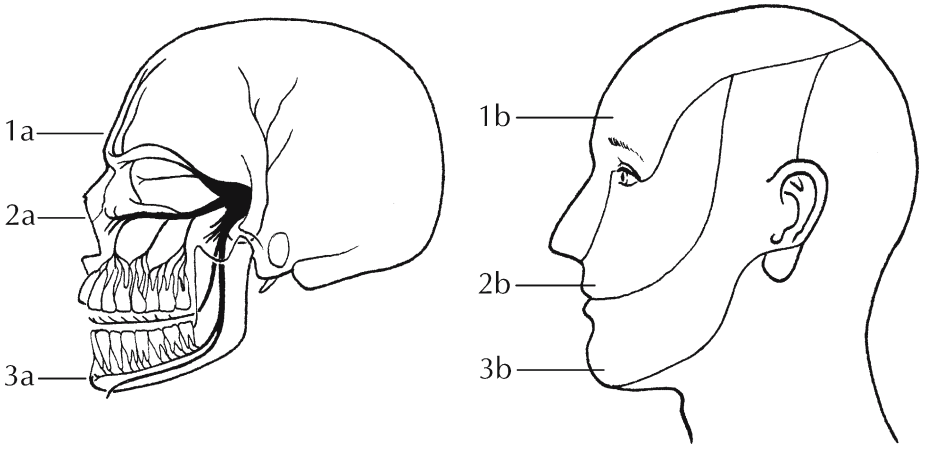

Fig. 5. *1a* Ophthalmic nerve, *2a* Maxillary nerve, *3a* Mandibular nerve, *1b–3b* Sensory distribution

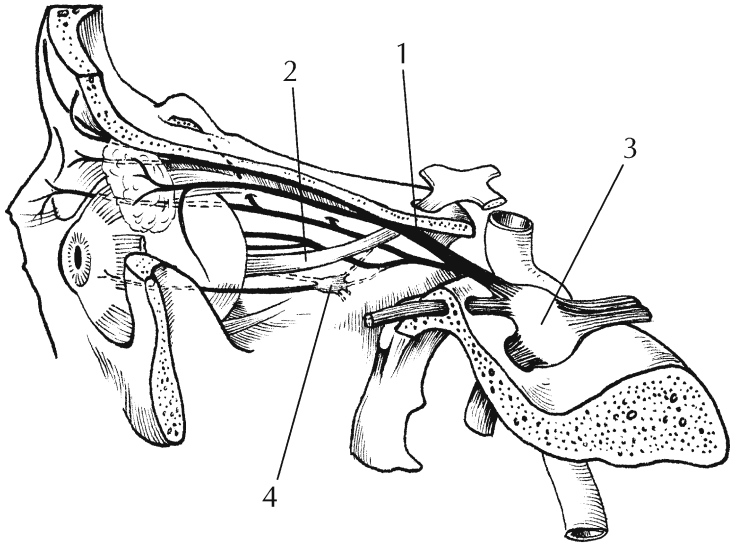

Fig. 6. *1* Ophthalmic nerve, *2* Optic nerve, *3* Trigeminal ganglion, *4* Ciliary ganglion

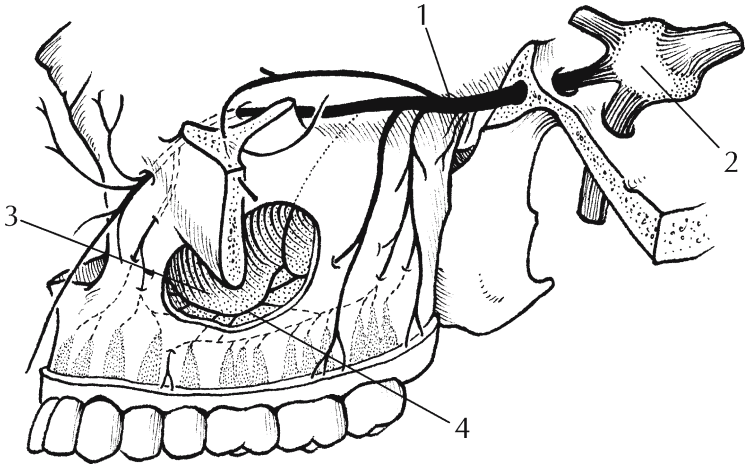

Fig. 7. *1* Maxillary nerve, *2* Trigeminal ganglion, *3* The maxilla (bone removed), *4* Branch of superior alveolar nerve

Qualities

Branchial motor: mastication, tensor tympani muscle, tensor veli palatini muscle, myohyoid muscle, anterior belly of digastric muscle.

General sensory:
Face, scalp, conjunctiva, bulb of eye, mucous membranes of paranasal sinus, nasal and oral cavity, tongue, teeth, part of external aspect of tympanic membrane, meninges of anterior, and middle cranial fossa.

Anatomy

The trigeminal nuclei consist of a motor nucleus, a large sensory nucleus, a mesencephalic nucleus, the pontine trigeminal nucleus, and the nucleus of the spinal tract. The nerve emerges from the midlateral surface of the pons as a large sensory root and a smaller motor root. It ascends over the temporal bone to reach its sensory ganglion, the trigeminal or semilunar ganglion. The branchial motor branch lies beneath the ganglion and exits via the foramen rotundum. The sensory ganglion is located in the trigeminal (Meckle's) cave in the floor of the middle cranial fossa. The three major divisions of the trigeminal nerve, ophthalmic nerve (V1), maxillary nerve (V2), and mandibular nerve (V3), exit the skull through the superior orbital fissure, the foramen rotundum and the foramen ovale, respectively. V1 (and in rare instances, V2) passes through the cavernous sinus (see Fig. 4 through Fig. 7).

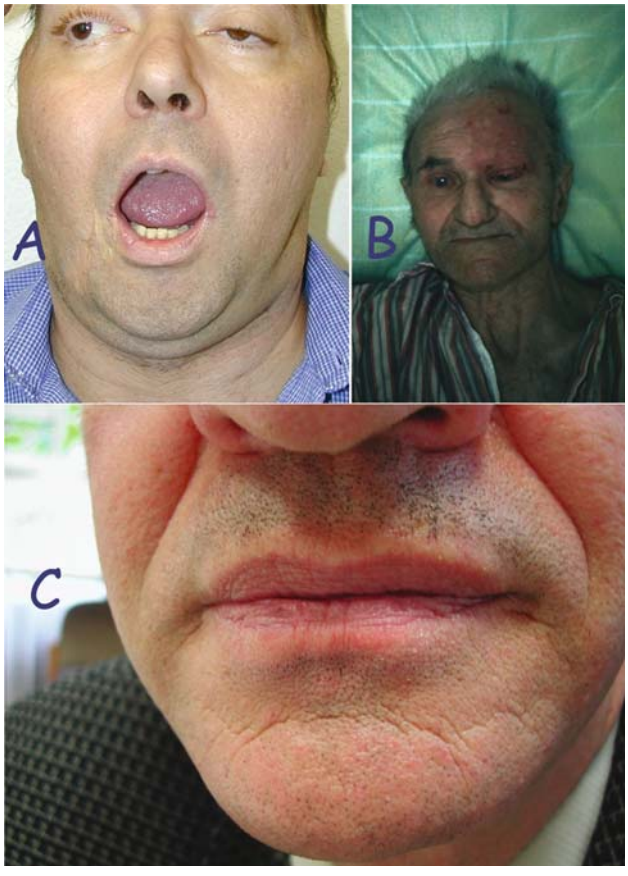

Fig. 8. Some features of trigeminal neuropathy: **A** Motor lesion of the right trigeminal nerve. The jaw deviates to the ipsilateral side upon opening the mouth. **B** Left ophthalmic zoster. **C** The patient suffers from trigeminal neuralgia. Shaving above the mouth induces attack. Note the unshaved patch, that corresponds to the area, where the attack is elicited

The extracranial pathway has three major divisions:

1. **V1, the ophthalmic nerve:**
   The ophthalmic nerve is positioned on the lateral side of the cavernous sinus, and enters the orbit through the superior orbital fissure. It has three major branches, the frontal, lacrimal, and nasociliary nerves. Intracranially, V1 sends a sensory branch to the tentorium cerebelli.
   The frontal nerve and its branches can be damaged during surgery and fractures .
2. **V2, the maxillary nerve:**
   The maxillary nerve has three branches: the infraorbital, zygomatic, and pterygopalatinal nerves. It passes below the cavernous sinus and gives off some meningeal branches.
   Lesions: V2 is most frequently affected in trauma. Sensory loss of cheek and lip are common symptoms. V2 can also be injured during facial surgery.
3. **V3, the mandibular nerve:**
   The mandibular nerve's major branches are the auriculotemporal, inferior alveolar, and lingual nerves. A separate motor division innervates the masseteric muscles and the tensor tympani and veli palatini muscles. The mandibular nerve also has meningeal branches.
   Lesions of the V3 may result from dentistry, implantation, mandible resection, hematoma of lower lip, or bites.

Symptoms

The symptoms of trigeminal nerve lesions are predominantly sensory and rarely motor. Pain in the distribution of the trigeminal nerve can vary widely from symptomatic pain to neuralgia.

Signs

Sensory loss can be demonstrated by sensory examination of all qualities. The corneal reflex may be absent. Complete sensory loss, or loss of pain and temperature, may lead to ulcers on the skin, mucous membranes and the cornea. Sensory lesions in trigeminal nerve distribution may be also caused by central lesions and follow an "onion skin" pattern (Fig. 8B, C). Some neuralgic trigeminal pain syndromes may be associated with redness of the eye or abnormal tearing during the attack.

Motor lesions are rarely symptomatic and could cause a mono- or diplegia masticatoria. When the patient's mouth is opened widely, the jaw will deviate to the affected side (Fig. 8A).

Pathogenesis

Toxic:
Trichloroethylene (TCE)

Vascular:
Medullary infarction may cause trigeminal sensory deficits (e.g. "onion skin" distribution) and pain.

Infectious:
Herpes zoster ophthalmicus: may rarely be associated with corneal ulcer, iridocyclitis, retinal and arterial occlusions, optic nerve lesions, and oculomotor nerve lesions.

Inflammatory, immune mediated:
Sensory trigeminal neuropathy subacute sensory neuropathy, sensory trigeminal neuropathy (connective tissue disease), Sjögren is syndrome, scleroderma, SLE, progressive sclerosis, mixed connective tissue disease. Characterized by abrupt onset, usually affecting one or two branches unilaterally, numbness (may disturb motor coordination of speech), and pain.
"Numb chin syndrome"or mental neuropathy has been described as an idiopathic neuropathy or resulting from mandibular metastasis.

Compressive:
Compressive lesion of the trigeminal nerve in the intracranial portion by vascular loops (posterior inferior cerebellar artery, superior cerebellar artery, arteriovenous malformation) is considered to be a major cause of trigeminal neuralgia.

Trauma:
Cranial fractures often cause local lesions of the supratrochlear, supraorbital and infraorbital nerves (e.g., facial lacerations and orbital fractures). Trigeminal injury caused by fractures of the base of the skull is usually combined with injury to the abducens and facial nerves. Injury to the maxillary and ophthalmic divisions results in facial numbness, and involvement of the mandibular branch causes weakness of the mastication muscles.

Neoplastic:
"Amyloidoma"
Cholesteatoma
Chordoma
Leptomeningeal carcinomatosis may compress or invade the nerve or trigeminal ganglion, either intracranially or extracranially.
Metastasis
Neuroma

Iatrogenic:
Pressure and compression of infra- and supraorbital nerves by oxygen masks during operations. Excessive pressure during operating procedures on the mandibular joint may affect the lingual nerve. The infraorbital nerve may be damaged by maxillary surgery. The lingual nerve can be affected by dental surgery (extraction of 2nd or 3rd molar tooth from the medial side, and wisdom teeth). Bronchoscopy can rarely lead to lingual nerve damage. Also abscesses and osteosynthetic procedures of the mandibula can affect the lingual nerve.
Clinically, patients suffer from hypesthesia of the tongue, floor of the mouth, and lingual gingiva. Patients have difficulties with eating, drinking and taste. Neuralgias may occur.

Others:
Association of the trigeminal nerve with polyneuropathies:
AIDP (acute inflammatory demyelinating polyneuropathies)
Amyloidosis
Diphtheria
Leprosy
Waldenstroem's macroglobulinemia
Syphilis
Thallium neuropathies

Cavernous sinus lesions:
The ophthalmic nerve can be injured by all diseases of the cavernous sinus. Neoplastic lesions can be caused by sphenoid tumors, myeloma, metastases, lymphoma, and tumors of the nasopharynx. Typically, other cranial nerves, particularly the oculomotor nerves, are also involved.

Gradenigo syndrome: Lesion of the apex of the pyramid (from middle ear infection) causes a combination of injury to CN V and VI, and potentially CN VII.

Other conditions are the paratrigeminal ("Raeder") syndrome, characterized by unilateral facial pain, sensory loss, Horner's syndrome, and oculomotor motility disturbances.
Aneurysm of the internal carotid artery may also damage the cavernous sinus accompanied by concomitant headache, diplopia and ptosis.

Trigeminal neuralgia:
Can be separated into symptomatic and the more common asymptomatic forms.

Idiopathic trigeminal neuralgia:
Has an incidence of 4 per 100,000. The average age of onset is 52–58 years. The neuralgia affects mostly the second and third divisions.
Clinically patients suffer from the typical "tic doloreux". Trigger mechanisms can vary but are often specific movements such as chewing, biting or speaking. The neurologic examination is normal, and ancillary investigations show no specific changes. Vascular causes, like arterial loops in direct contact of the intracranial nerve roots, are implicated as causal factors.
Therapies include medication (anticonvulsants), decompression or lesion of the ganglion, vascular surgery in the posterior fossa, and medullary trigeminal tractotomy.

Symptomatic trigeminal neuralgia:
May be caused by structural lesion of the trigeminal nerve or ganglion, by surgical procedures, tumors of the cerebellopontine angle, meningitis, and mutiple sclerosis.
If the ophthalmic divison is involved, keratitis neuroparalytica, hyperemia, ulcers and perforation of the cornea may result.

Diagnosis:
Neuroimaging is guided by the clinical symptoms and may include CT to detect bony changes, and MRI to investigate intracranial and extracranial tissue spaces.
Neurophysiologic techniques rely on sensory conduction velocities and reflex techniques (masseteric, blink reflex). Trigeminal SEP techniques can also be used. Motor impairment of the temporal and masseter muscles can be confirmed by EMG.
Blink reflex responses can be interpreted topographically.

Therapy

Treatment is dependent upon the underlying cause. Neuralgias are usually treated with drugs, and sometimes surgery. Symptomatic care is required when protective reflexes, like the corneal reflex, are impaired and may lead to ulceration.

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Abducens nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy	CSF
		+	MRI CT Angiography		

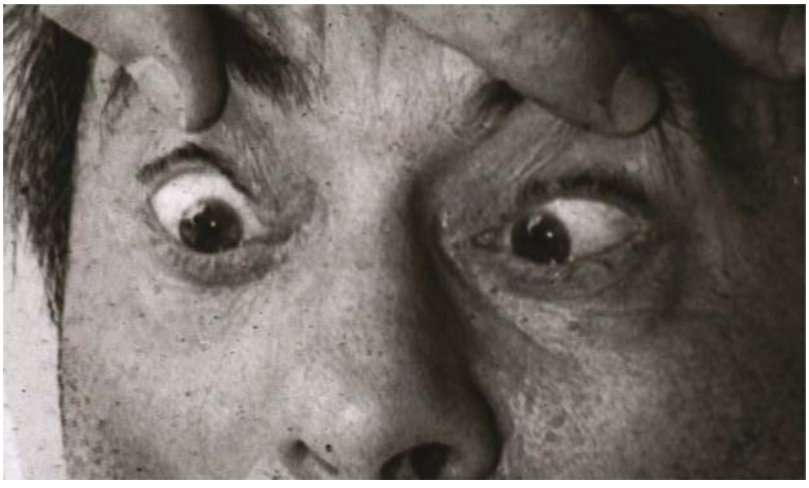

Fig. 9. Bilateral abducens nerve paresis. Inward gaze of bulbi. This patient suffered a fall with subsequent head trauma

Quality

Somatic motor, innervation of lateral rectus muscle

Anatomy

The abducens nucleus is located in the pontine tegmentum close to the midline, and ventral to the fourth ventricle. Axons from cranial nerve VII loop around the abducens nucleus, forming the bulge of the fourth ventricle. Axons from the abducens nucleus course ventrally through the pontine tegmentum to emerge from the ventral surface of the brainstem at the junction of the pons and the pyramid of the medulla. The nerve runs anterior and lateral in the subarachnoid space of the posterior fossa, to piercing the dura lateral to the dorsum sellae of the sphenoid bone. The nerve continues forward between the dura and the apex of the petrous temporal bone. Here it takes a sharp right angle, bending over the apex of the temporal bone to enter the cavernous sinus. The nerve lies lateral to the carotid artery, and medial to CN III, IV, V1 and V2. Finally, the abducens nerve enters the orbit at the medial end of the superior orbital fissure.

Symptoms

Patients report binocular horizontal diplopia that worsens when looking in the direction of the paretic lateral rectus muscle and when looking at distant objects.

Signs

An isolated paralysis of lateral rectus muscle causes the affected eye to be adducted at rest. Abduction of the affected eye is highly reduced or impossible, while gaze to the unaffected side is normal (see Fig. 9).

Pathogenesis

Lateral rectus paralysis is the most frequently encountered paralysis of an extraocular muscle. 80% of cases exhibit isolated paralysis of the lateral rectus, while 20% of cases are in association with CN III or IV.

Topographically:

Nuclear:	Infarction, tumor, Wernicke's disease, Moebius and Duane's syndrome (rare).
Fascicular lesion:	Demyelination, infarction, tumor.
Subarachnoid:	Meningitis, subarachnoid hemorrhage, clivus tumor (meningioma, chordoma), trauma, basilar aneurysm.
Petrous apex:	Mastoid infection, skull fracture, raised ICP, trigeminal Schwannoma.
Uncertain:	Microvascular infarction, migraine

Metabolic:
Rarely diabetes

Toxic:
Vincristine therapy

Vascular:
Aneurysms of the posterior inferior cerebellar, basilar or internal carotid arteries

Infections:
CMV encephalitis
Cryptococcal meningitis
Cysticercosis
HIV
Lyme disease
Syphilis
Tuberculosis
Ventriculitis of the fourth ventricle

Inflammatory-immune mediated:
Vasculitis, sarcoidosis, systemic lupus erythematosus (SLE)

Trauma:
Fractures of the base of the skull

Neoplastic:
Abducens nerve tumor
Cerebellopontine angle tumor
Clivus tumor
Leptomeningeal carcinomatosis
Leukemia
Metastasis (base of the skull)

Congenital:
Duane's syndrome

Compressive:
Lesions of the cavernous sinus (e.g. thrombosis)

Abducens palsy is a common sign of increased cranial pressure caused by:
Hydrocephalus
Pseudotumor cerebri
Tumors

Most frequent causes:
Multiple Sclerosis (MS)
Syphilis
Vascular, diabetes
Undetermined cause

Most frequent causes in pediatric cases:

Neoplasm	39%
Trauma	20%
Inflammatory	18%

Bilateral CN VI palsy:
Meningitis, AIDP, Wernicke's encephalopathy, pontine glioma

Diagnosis

Diagnosis is achieved by assessing the patient's metabolic situation (DM), imaging to exclude tumors or vascular conditions, and checking the CSF and serology for signs of infection.

Differential diagnosis

Convergence spasm
Duane's syndrome
Internuclear ophthalmoplegia
Myasthenia gravis
Pseudo VI nerve palsy (thalamic and subthalamic region)
Thyroid disease

Therapy

Treatment is dependent upon the underlying cause.

Prognosis

The most frequent "idiopathic" type in adults usually remits within 4–12 weeks.

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Facial nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Clinical exam Taste Hearing
	++	+	MRI	

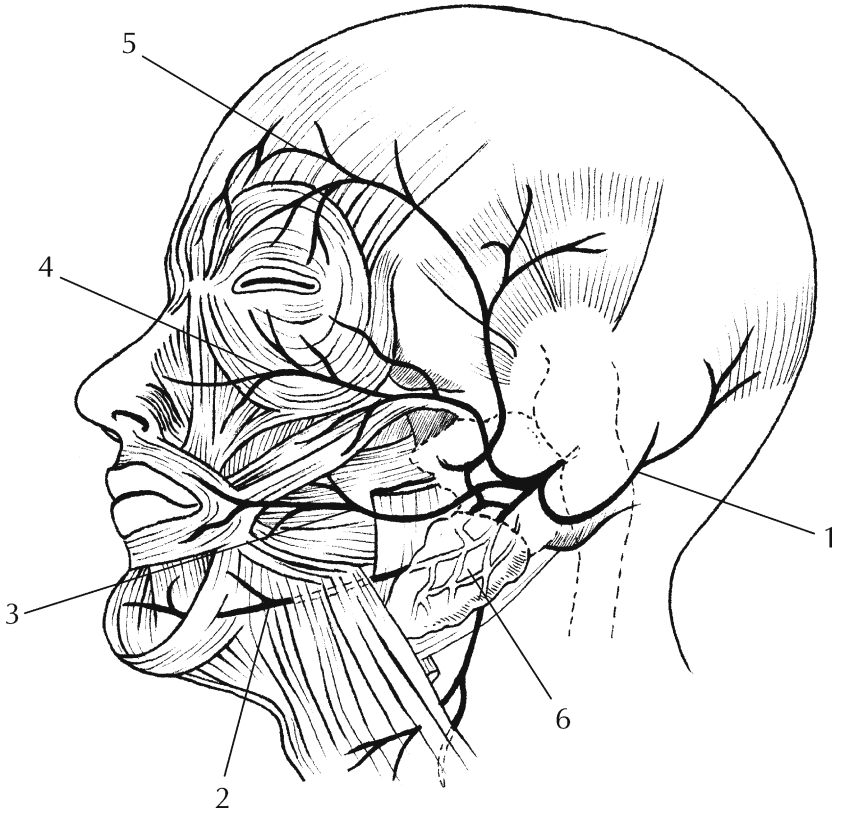

Fig. 10. Facial nerve: *1* Posterior auricular nerve, *2* Mandibular branch, *3* Buccal branch, *4* Zygomatic branch, *5* Temporal branch, *6* Parotid gland

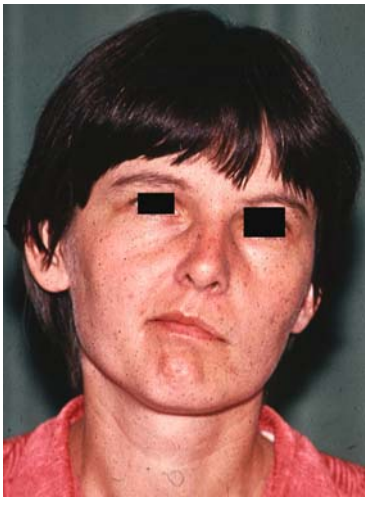

Fig. 11. Facial nerve palsy: This patient suffered from a right sided Bell's palsy, which resulted in a contracture of the facial muscles. Note the deviated mouth

Qualities

Branchial motor

Stapedius, stylohyoid, posterior belly of disgastric, muscles of facial expression, including buccinator, platysma, and occipitalis muscles.

Visceral motor

Lacrimal, submandibular, sublingual glands, as well as mucous membranes of the nose and hard and soft palate.

General sensory

Skin of concha of auricle, small area of skin behind ear. Trigeminal nerve-V3 supplies the wall of the acoustic meatus and external tympanic membrane.

Special sensory

Taste of anterior two thirds of tongue and hard and soft palate

Major branches

Large petrosal: salivation and lacrimation
Nerve to the stapedius muscle
Chorda tympani: taste
Motor branches
Sensory: ear

Anatomy

Branchial motor fibers originate from the facial motor nucleus in the pons, lateral and caudal to the VIth nerve nucleus. The fibers exit the nucleus medially, and wrap laterally around the VIth nerve nucleus in an arc called the internal genu. The superior salivatory nucleus is the origin of the preganglionic parasympathetic fibers. The spinal nucleus of the trigeminal nerve is where the small general sensory component synapses. Taste fibers synapse in the rostral gustatory portion of the nucleus solitarius. All four groups of fibers leave the brainstem at the base of the pons and enter the internal auditory meatus. The visceral motor, general sensory, and special sensory fibers collectively form the nervus intermedius. Within the petrous portion of the temporal bone, the nerve swells to form the geniculate ganglion (the site of the cell bodies for the taste and general sensory fibers). The nerve splits within the petrous portion of the temporal bone. First, the greater petrosal nerve carries the parasympathetic fibers to the lacrimal gland and nasal mucosa (the pterygopalatine ganglion is found along its course). The chorda tympani nerve exits through the petrotympanic fissure, and brings parasympathetic fibers to the sublingual and submandibular salivary glands, as well as the taste sensory fibers to the tongue. The nerve to the stapedius innervates the stapedius muscle. The remaining part of the facial nerve, carrying branchial motor and general sensory fibers, exits via the stylomastoid foramen. The motor fibers branch to innervate the facial muscles, with many branches passing through the parotid gland (see Fig. 10).

Topographic lesions

1. Supranuclear lesion
2. Nuclear and brainstem lesions
3. Cerebellopontine angle
4. Canalis nervi facialis
5. Exit of cranial vault and peripheral twigs

Symptoms

Lesion of the facial nerve results predominantly in loss of motor function characterized by acute onset of facial paresis, sometimes associated with pain

and/or numbness around the ear. Loss of visceral function results in loss of tearing or submandibular salivary flow (10 % of cases), loss of taste (25%), and hyperacusis (though patients rarely complain of this).

Signs

Central lesions

Supranuclear: Because the facial motor nuclei receive cortical input concerning the upper facial muscles bilaterally, but the lower face muscles unilaterally, a supranuclear lesion often results in paresis of a single lower quandrant of the face (contralateral to the lesion).
Pyramidal facial weakness: lower face paresis with voluntary motion.
Emotional: face paralysis with emotion (location: dorsolateral pons- anterior cerebellar artery).
Pontine lesion: associated lesion of neighboring structures: nucleus of CN VI, conjugate ocular movements, hemiparesis.

Peripheral lesions

Mimic and voluntary movements of the facial muscles are impaired or absent. Dropping of corner of mouth, lagophthalmos. Patients are unable to whistle, frown, or show teeth. Motor function is assessed by the symmetry and degree of various facial movements. With paralysis of the posterior belly of the disgastric, the jaw is deviated to the healthy side. With pterygoid paralysis, the opposite is true.

Location of peripheral lesion

a) Internal auditory meatus: geniculate ganglion-reduced salivation and lacrimation. Loss of taste on anterior 2/3 of tongue. Hyperacusis.
b) Between internal auditory meatus and stapedius nerve: Facial paralysis without impairment of lacrimation, however salivation, loss of taste and hyperacusis.
c) Between stapedius nerve and chorda tympani: facial paralysis, intact lacrimation, reduced salivation and taste. No hyperacusis.
d) Distal to the chorda tympani: facial paralysis, no impairment of salivation, lacrimation or hyperacusis.
e) After exit from the stylomastoid foramen: lesions of singular branches.
f) Muscle disease: myopathic face

Partial peripheral lesion

Symptoms and signs depend upon the site of the lesion. Perifacial nerve twigs can be damaged with neurosurgical procedures. Parotid surgery may damage one or several twigs, and a paresis of the caudal perioral muscle is seen in carotid surgery.

Bell's palsy

Prevalence 6–7/100,000 – 23/100,000. Increases with age.
Development: Paralysis progresses from 3–72 hours. About half of the patients have pain (mastoid, ear). Some (30%) have excess tearing. Other symptoms include dysgeusia.
Facial weakness is complete in 70% of cases.
Stapedius dysfunction occurs in 30% of cases.
Mild lacrimation and taste problems are rare.
Some patients complain of ill-defined sensory symptoms in the trigeminal distribution.
Improvement occurs in 4–6 weeks, for about 80% (see Fig. 11).

Symptoms may persist and contractures or synkineses may develop.
Pathogenesis is not clear, but may be viral or inflammatory.
Associated diseases: diabetes.

Therapy

Acyclovir, steroids, and surgery were compared: Results show better outcome from steroid treated vs. non-steroid treated patients. Steroids with acyclovir are also effective.
Surgery: 104 cases were evaluated. 71 showed complete recovery, 84% with near nomal function.
Important additional measures to consider: eye care, eye-lid surgery, facial rehabilitation, botulinus toxin injections for symptomatic synkineses.

Differential diagnosis for Bell's palsy

Sarcoid and granulomatous disease
Infection (leprosy, otitis media, Lyme disease, Ramsay Hunt syndrome)
Neoplasm or mass
Trauma
Cardiofacial syndrome (lower lip palsy)

Pathogenesis

Polyneuropathies:
AIDP (often bilateral)

Neoplastic:
Leptomeningeal carcinomatosis

Infection:
Leprosy
Lyme disease (often bilateral)
Otitis media, acute or chronic, cholesteatoma
Ramsey Hunt syndrome

Birth trauma:
Cardiofacial syndrome
Congenital dysfunction
Hemifacial microsomia
Mobius syndrome
Prenatally: face compression aginst mother's sacrum, abnormal posture.

Iatrogenic:
Oxygen mask used in anesthesia (mandibular branch)

Trauma:
Extracranial: parotid surgery, gunshot, knife wound, carotid endartectomy
Intratemporal: motor vehicle accidents – 70–80% from longitudinal fractures.
Intracranial: surgery.
Temporal bone fractures: In about 50% of cases of transverse temporal bone fractures, the facial nerve within the internal auditory canal is damaged. Facial nerve injury occurs in about 50% of cases and the labyrinth is usually damaged by the fracture. 65% to 80% of fractures are neither longitudinal nor transverse, but rather oblique. Severe head injury can also avulse the nerve root from the brainstem.

Tumors:
Predominantly cerebellopontine angle
Acoustic neuroma
Base of the skull tumors: dermoids, large meningiomas, metastasis

Other conditions:
Infection: Botulism, Polio, Syphillis, tetanus
Heerfort syndrome
Paget's disease
Myeloma
Porphyria

Regeneration may result in involuntary movements and similar conditions:
Blepharospasm
Contracture (postparalytic facial dysfunction) (see Fig. 11)
Facial myokymia
Hemifacial spasm
Synkinesis
Tick

Association with Polyneuropathy:
AIDP, Lyme disease, polyradiculopathies, sarcoid

Periocular weakness, without extraocular movement disturbance:
Congenital myopathies
Muscular Dystrophies: Myotonic, Facioscapulohumeral, Oculopharyngeal
Polymyositis

MND/ALS:
ALS, bulbospinal muscular atrophy, motor neuron syndromes

Bilateral facial paralysis:
AIDP
Leprosy
Lyme disease
Melkersson-Rosenthal syndrome
ALS
Moebius syndrome
Myopathies
Sarcoid

Diagnosis

Along with the clinical examination, laboratory tests that may be helpful include: ESR, glucose, ANA, RF, Lyme serology, HIV, angiotensin converting enzyme (for sarcoidosis), serology, virology, microbial tests.
CSF should be examined if an intracranial inflammatory lesion is suspected. Other tests include CT and MRI, EMG (facial nerve CMAP, needle EMG), blink reflex and magnetic stimulation.

Therapy

For Bell's palsy, steroids and decompression may be helpful, along with supportive care.

Prognosis

In Bell's palsy, improvement typically occurs 10 days to 2 months after onset.
Plateau is reached at 6 weeks to 9 months.
Recurrence is possible in up to 10%.

Prognosis based on electrophysiologic tests:
CMAP in comparison side to side: good
Blink: uncertain
Needle EMG: limited

Qualities associated with a better prognosis for Bell's palsy include:
Incomplete paralysis
Early improvement
Slow progression
Younger age
Normal salivary flow
Normal taste
Results of the electrodiagnostic tests

Residual signs may occur with Bell's palsy. These include:
Synkinesis (50%)
Facial weakness (30%)
Contracture (20%)
Crocodile tears (6%)

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Acoustic nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy	Hearing tests
Familial	Auditory evoked potentials	+	MRI, CT		+

Quality

Special sensory: auditory information from the cochlea.

Anatomy

Cell bodies of afferent neurons are located in the spiral ganglia in the inner ear and receive input from the cochlea.

The central processes of the nerve travel through the internal auditory meatus with the facial nerve. The eighth nerve enters the medulla just at the junction of the pons and lateral to the facial nerve. Fibers of the auditory nerve bifurcate on entering the brain stem, sending a branch to both the dorsal and ventral divisions of the cochlear nucleus. From here, the path to the auditory cortex is not well understood and includes several pathways: superior olivary complex, nuclei of the lateral lemniscus, the trapezoid body, the dorsal acoustic striae, and the inferior colliculi.

A small number of efferent axons are found in the eighth nerve, projecting from the superior olivary complex to the hair cells of the cochlea bilaterally. The function of this projection is not clear.

Symptoms

Hearing loss predominates (slow onset or acute), possibly associated with tinnitus.

Signs

Damage can cause hearing loss ranging from mild to complete deafness.

Pathogenesis

Metabolic:
Diabetes, hypothyroidism

Toxic
Aniline, antibiotics, benzole, carbon monoxide, chinin, cytostatic drugs, saluretics, salycilate.

Infectious:
Herpes, mumps, otitis, sarcoid

Inflammatory/immune mediated:
Paraneoplastic (Anti-Hu associated) (very rare)

Compressive:
Tumors at the cerebellopontine angle

Congenital:
Thalidomide, rubeola embryopathy

Hereditary:
Congenital hearing loss

Hereditary Motor-Sensory Neuropathies: (HMSN or CMT) including:
CMT 1A
CMT 1B
Coffin-Lowry syndrome
Duane's syndrome
Dilated cardiomyopathy with sensorineural hearing loss (CMD1J, CMD1K)
HMSN 6
Neurofibromatosis-2
Neuroaxonal Dystrophy (late infantile)
X-linked, HMSN X (Connexin 32)

Trauma:
Temporal bone fractures

Neoplastic:
Cholesteatoma, metastasis, meningeal carcinomatosis

Tinnitus:
Sensation of noise caused by abnormal excitation of acoustic apparatus (continuous, intermittent, uni- or bilateral). Tinnitus is often associated with sensorineural hearing loss and vertigo. Only 7% of patients with tinnitus have normal hearing.

Causes: conducting apparatus, hemifacial spasm, ischemia, drugs; quinine, salycilates, streptomycin, amyl nitrate, labyrinthitis, arteriosclerosis, otosclerosis, degeneration of cochlea.

Diagnosis

Diagnosis is made by hearing tests and auditory evoked potentials (AEP), genetic testing for known deafness genes, and imaging for traumatic or neoplastic causes.

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Vestibular nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	Posturometry Vestibulometry	+	MRI	

Quality

Special sensory: balance information from the semicircular canals

Anatomy

The vestibular apparatus consists of the saccule, the utricle and the semicircular canals. The semicircular canals perceive angular movement of the head in space. The saccule and utricle perceive the position of the head with respect to gravity.

Hairy cells within the apparatus synapse with peripheral processes of the primary sensory neurons, whose cell bodies constitute the vestibular ganglion. Central processes from the vestibular ganglion cells form the vestibular part of the VIII nerve. The nerve runs with the cochlear division and the VII nerve through the internal acoustic meatus and terminates in the vestibular nuclear complex at the floor of the fourth ventricle. A limited number of axons terminate in the flocculonodular lobe of the cerebellum.

The secondary sensory neurons, whose cell bodies form the vestibular nuclei, send axons mainly to the cerbellum and lower motor neurons of brain stem and spinal cord (modulating muscle activation for keeping balance).

In the lateral vestibular nucleus, axons project ipsilateral and caudal into the spinal cord and vestibulospinal tract (to lower motor neurons for the control of antigravity muscles).

The medial and inferior vestibular nuclei have reciprocal connections with the cerebellum (vestibulocerebellar tract), which allows the cerebellum to coordinate balance during movement. All nuclei in the vestibular complex send fibers into the medial longitudinal fasciculus (MLF), which serves to maintain orientation in space. Connections between CN III, IV, and VI allow the eyes to fixate on an object while the head is moving. Vestibular axons in the descending part of the MLF are referred to as the medial vestibulospinal tract, and influence lower motor neurons in the cervical spinal cord bilaterally.

Symptoms

Patients experience dizziness, falling, vertigo, and nausea/vomiting.

Signs

Lesions result in abnormal eye movements, and problems with stance, gait, and equilibrium.

Pathogenesis

Metabolic:
Diabetes, uremia

Toxic:
Alcohol
Aminoglycosides
Cytostatic drugs: cisplatin, cyclophosphamide, hydroxurea, vinblastine
Heavy metals
Lead
Mercury
Quinine, salicylates

Vascular:
Anterior inferior cerebellar artery (AICA)
Posterior communicating artery aneurysm
Unruptured aneurysms, large vascular loops
Vascular lesions of the spiral ganglion
Vertebrobasilar circulation (history of hypertension, diabetes)

Infection:
Labyrinthitis: specific and unspecific: Suppuration reaches inner ear by either blood, or direct invasion (meningoencephalitis).
Bacterial: streptococcus pneumoniae, hemophilus

Syphilis
Lyme disease
Petrositis

Viral:
Ramsey Hunt syndrome
Herpes zoster oticus
Vestibular neuronitis
HIV may cause sensoneurial hearing loss

Mycotic:
Coccidiomycosis, cryptococcosis

Rickettsial infection

Immunologic disorders:
Hashimoto's thyroiditis
MS, leukodystrophies,
Demyelinating neuropathies
Periarteritis nodosa
Sarcoidosis

Trauma
Blunt-, penetrating-, or barotrauma

Transverse fractures are often associated with CN VII lesion. The less common transverse fractures damage both facial and vestibulocochlear nerves. These fractures involve the otic capsule, passing through the vestibule of the inner ear, tearing the membranous labyrinth, and lacerating both vestibular and cochlear nerves.

Vertigo is the most common neurological sequel to head injury and it is positional.

Neoplastic:
Acoustic nerve neuroma, Schwannoma, metastases, NF

Others:
Hyperviscosity syndromes (polycythemia vera, hypergammaglobulinemia, Waldenstroem's macroglobulinemia)

Vestibular neuropathy

Cupulolithiasis (benign paroxysmal positional nystagmus)

Psychogenic

Congenital and hereditary:
Aplasia

Degeneration after development of the cochlea:
Hereditary, sensorineural deafness

Degeneration with other defects:
Arnold Chiari
Atrophy of CN VIII
Cockayne syndrome
Goiter
Hallgren's syndrome
Kearns Sayre syndrome
Pigmentary Waardenburg syndrome
Refsum's disease
Retinitis pigmentosa

Diagnosis

Diagnosis is based on vestibular testing, laboratory testing (including genetics for hereditary causes), and imaging (for trauma, etc.).

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Glossopharyngeal nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		++	

Quality

Branchial motor: stylopharyngeus muscle.
Visceral motor: otic ganglion, fibers to stimulate the parotid gland.
Visceral sensory sensation: carotid body and sinus.
General sensory: posterior one third of the tongue, skin of the external ear, and the internal surface of the tympanic membrane.
Special sensory: taste, from the posterior third of the tongue.

Anatomy

The nuclei consist of: the nucleus ambiguus, inferior salivatory nucleus, and nucleus solitarius.

The nerve emerges from the medulla oblongata at the dorsal border of the inferior olive. A dural isthmus separates the nerve from the vagus nerve. It leaves the cranial vault through the jugular foramen (jointly with the vagus and accessory nerves), and passes in the upper neck between the carotid artery and jugular vein. Then it passes superficially to the internal carotid artery behind the styloid process. The nerve follows the posterior inferior part of the stylopharyngeus muscle, between the constrictors of the pharynx, and finally reaches the deep hypoglossus muscle. Its extracranial course includes several ganglia (superior and petrous ganglia).

Symptoms

Lesions can cause minor swallowing difficulties, disturbance of taste, glossopharyngeal neuralgia (rare: pain behind the angle of the jaw, deep within the ear and throat).

Abnormal lacrimation ("crocodile tears") may occur, but may also be a complication of Bell's palsy with lesions proximal to the geniculate ganglion.

Signs

Taste on the soft palate, pharynx, fauces, and posterior third of tongue is disturbed.
The gag reflex is reduced or absent. Salivary production of the parotid gland can be reduced.
Acute sectioning bilaterally may cause hypertension.

Pathogenesis

Lesions are rarely isolated, and more often associated with vagus nerve lesions.

Topographical:
Brainstem: vascular brainstem lesions (e.g., Bonnier's syndrome): pons, medulla oblongata. Wallenberg's syndrome, pontine tumors.

Intracranial:
Tumors: Neuroma: cerebellopontine angle, meningeal carcinomatosis, venous thrombosis. Meningitis, "polyneuritis cranialis", AIDP

Exit from the cranial vault: jugular foramen syndrome (with CN X, XI; Vernet's syndrome) caused by: chordoma, fracture of base of skull, neuroma, metastasis.

Neck (iatrogenic): carotid operations, resection of aneurysms, neck dissection ear nose and throat (ENT and neurosurgical procedures). Tonsillectomy is rarely a cause (0.1%), by lesions of the lateral pharynx wall.

Metabolic:
Amyloid-deposition
Porphyria

Toxic:
Nitrofurantoin
Tetanus toxin

Vascular:
Brainstem lesions

Infectious:
Diphtheria
Herpes zoster
Polio

Inflammatory and immune mediated:
AIDP
Cryoglobulinemia
Miller Fisher syndrome
Periarteritis nodosa
Sarcoid
Serum sickness
SLE

Neoplastic:
Leptomeningeal carcinomatosis
Leukemia
Myeloma
Vagal rootlet neuroma

Surgery:
Tonsillectomy (rare)

Trauma:
Basal fracture of skull

Association with neuropathies:
AIDP
Diphtheria
Paraneoplastic

Glossopharyngeal neuralgia is a rare occurrence, much less frequent than trigeminal neuralgia. Several trigger points have been described. Pain radiates into the ear, pharynx, neck and the base of the tongue.

Diagnosis

Diagnosis is made by examination, and subsequent imaging and laboratory tests that may be helpful in identifying suspected causes.

Differential diagnosis

Bulbar muscular disorders
Motor neuron disorders
Myasthenia gravis
Pain: trigeminal neuralgia

Therapy

For neuralgia: amytriptyline, carbamazepine, gabapentin

References

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Vagus nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+	+	MRI	

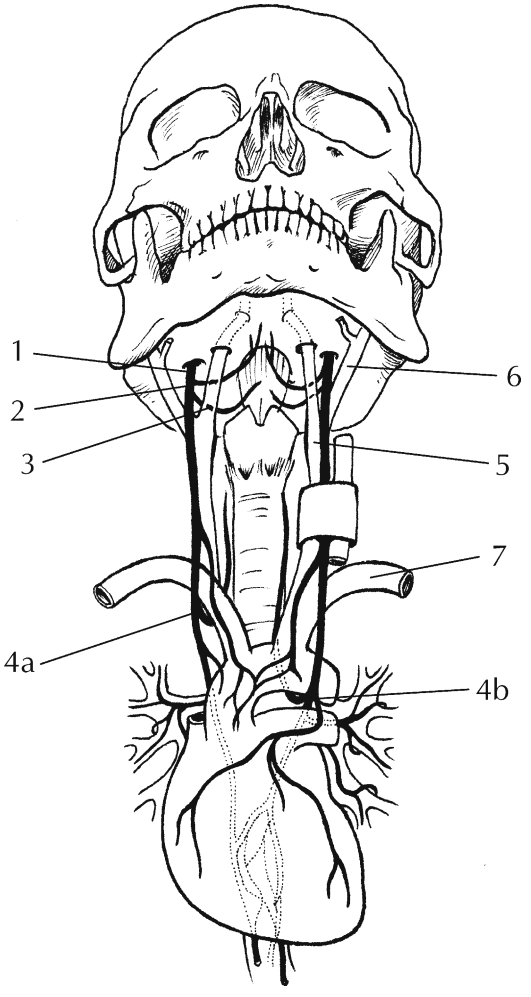

Fig. 12. *1* Vagus nerve, *2* Pharyngeal branch, *3* Internal laryngeal branch, *4a* Right recurrent laryngeal nerve (across the subclarian artery), *4b* Left recurrent laryngeal nerve (across the arch of the aorta), *5* Internal carotid artery, *6* Extemal carotid artery

Qualities

Branchial motor:	pharynx (except stylopharyngeus and tensor veli palatini), larynx, tongue.
General sensory:	auditory meatus, skin on the back of the ear, external tympanic membrane, pharynx.
Visceral sensory:	larynx, trachea, esophagus, thoracic and abdominal viscera, stretch receptors in the wall of the aortic arch, chemoreceptors in the aortic body.
Visceral motor:	smooth muscle and glands of pharnyx, larynx, thoracic and abdominal viscera

Anatomy

The vagus nerve is the longest cranial nerve, with the widest anatomical distribution.

The vagus nuclei consist of a branchial motor component (nucleus ambiguus), a visceral motor component (dorsal motor nucleus of the vagus), a visceral sensory component (nucleus solitarius), and a general sensory component (spinal trigeminal tract).

Intracranial pathway:
The vagus nerve emerges from the medulla with several rootlets, and exits through the jugular foramen (within same dural sleeve as the accessory nerve). Two external ganglia, the superior and inferior vagal ganglia, are found along the nerve's course within the jugular fossa of the petrous temporal bone.

Extracranial pathway:
In the neck region, the nerve branches into pharyngeal rami, and the superior laryngeal nerve (internal and external rami). The pharyngeal rami innervate all the muscles of the pharynx except the stylopharyngeus and the tensor veli palatini muscles. The superior laryngeal nerve divides into the internal and external laryngeal nerves. The external laryngeal branch supplies the inferior constrictor muscles. The vocal cords are innervated by the superior laryngeal nerve, and the external and internal rami of the inferior laryngeal nerve.

The recurrent laryngeal nerve passes under the subclavian artery on the right side and the aortic arch on the left side, then returns to the larynx to innervate all of its muscles, except the cricothyroid muscle (superior laryngeal nerve). Both recurrent nerves are located between the trachea and esophagus, and emit visceral branches. Visceral fibers of the vagus nerve innervate cardiac, pulmonary, esophageal and gastrointestinal structures (see Fig. 12).

Symptoms

Patients with vagus damage experience swallowing difficulties and hoarseness.

Signs

Vagus damage can cause paralysis of the palate, pharynx, and larynx according to the site of the lesion. Bilateral lesions can lead to nasal voice and regurgitation through the nose.

Pathogenesis

Metabolic:
Hypophosphatemia
Hyperpotassemia

Toxic:
Alcoholic polyneuropathy
Thallium

Vascular:
Medullary infarction

Infectious:
Botulism
Diphtheria
Herpes
Meningitis
Poliomyelitis
Tetanus

Inflammatory/immune mediated:
Dermato- and polymyositis

Neoplastic:
Jugular foramen tumor, metastasis (with CN IX involvement)
Meningeal carcinomatosis

Iatrogenic:
Operations of trachea and esophagus, thoracotomy, mediastinoscopy, mediastinal tumors, thyroid surgery (recurrent nerve)

Trauma
Fractures that affect the jugular foramen (uncommon).
Hyperextension neck injuries are also sometimes associated with injury to these nerves at the craniocervical junction.

Other:
Familial hypertrophic polyneuropathy
Idiopathic
Myopathies
Polyneuropathies: amyloid (some types), diphtheria, alcohol

Special segments to be considered

Focal superior and recurrent laryngeal neuropathies:
Peripheral lesions affecting the recurrent laryngeal nerve, with or without involvement of the superior laryngeal nerve, are most common from trauma, surgery, thyroidectomies, carotid endarterectomies, or idiopathic causes.

Clinically, laryngeal neuropathy leads to the inability to cough forcefully and hoarseness of the voice. If the superior laryngeal nerve is affected in addition and the cricothyroid is no longer functional the vocal cords will be in an intermediate position. This causes a breathy and weak voice, and constant clearing of the throat.

Causes of focal damage of the recurrent laryngeal nerve include diseases of the lung, tumors in the thoracic cavity (lung cancer), aneurysm of the aortic arch, lymph nodes, and thyroid surgery. About 25% of cases are idiopathic.

Neuralgia of the laryngeal nerve (rare)
Other entities:
Focal laryngeal dystonia
Spastic dystonia

Idiopathic:
Vocal cord paralysis: other causes must be excluded.

Diagnosis

Diagnosis can be facilitated with ENT examination and vocal cord inspection (with endoscopy), imaging, and video swallowing studies. EMG of the cricothyroid muscle (superior laryngeal nerve) or thyroarytenoid muscle (recurrent nerve) can be done, but is uncommon.

Differential diagnosis

Bulbar disorders, neuromuscular transmission disorders, motor neuron diseases.

Therapy

Treatment depends upon the etiology.

Prognosis

Prognosis depends upon the etiology.

References

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Accessory nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		MRI	

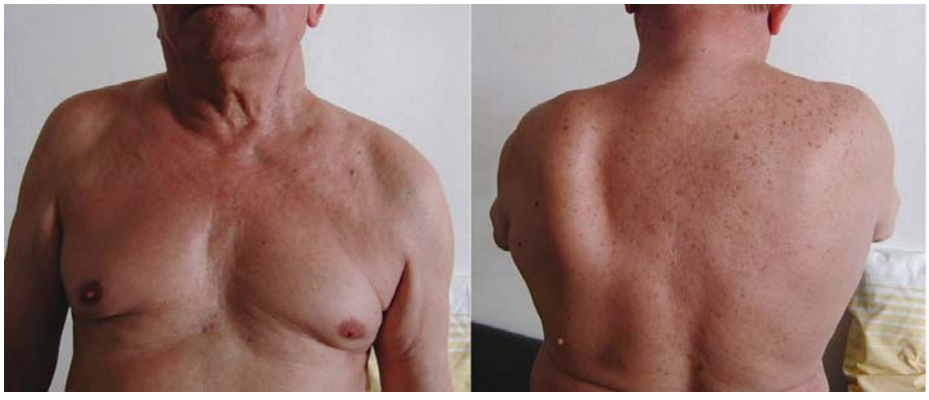

Fig. 13. Left acessory nerve palsy. Note the unilateral loss of the trapezoid muscle (diagnostic clue) and the winging of the scapula with abduction of the medial scapular border

Quality

Branchial motor: innervation of the sternocleidomastoid and trapezius muscles.

Anatomy/distribution

The cell bodies of the motor neurons are located in the spinal cord. Their axons emerge as rootlets anterior to the dorsal roots of the cord (C1-6), and form a trunk that extends rostrally and laterally to the foramen magnum and posterior to the vertebral artery to enter the posterior cranial fossa. The trunk joins with fibers of the vagus nerve, then separates from them within the jugular foramen.

Outside the jugular foramen, the nerve passes posteriorly and medially to the styloid process, then descends obliquely to enter the upper portion of the sternocleidomastoid muscle. The nerve crosses the posterior triangle of the neck, closely associated to lymph nodes. Above the clavicle it passes the deep anterior border of the trapezius to supply this muscle.

Symptoms

Damage to the accessory nerve may cause shoulder pain of variable severity, paresthesias over shoulder and scapula, weakness of the shoulder, and a dropped shoulder.

Signs

Lesion causes weakness of head rotation to the opposite side, and trapezius weakness that results in inability to lift the shoulder and raise the arm above horizontal.

Dropping of the shoulder and moderate winging of the scapula are also observed (see Fig. 13).

Pathogenesis

Topographical lesions

Intracranial part:
Rare, intracranial tumors.

At the jugular foramen:
Lesions occur in association with the glossopharyngeal and vagus nerves – Vernet's syndrome, local tumors, Schwannomas, metastasis.
Sarcoidosis, Siebmann syndrome, Collet Siccard syndrome.

Injury to the neck:
Biting
Blunt trauma
Carotid endarterectomy
Coronary bypass surgery
Radiation
Shoulder blows
Shoulder dislocation
Stretch/hyperextension injury
Variant of neuralgic amyotrophy

Neoplastic:
ENT tumors, metastasis at the base of the skull, Collet Siccard syndrome, spinal tumors.

Iatrogenic:
Surgery in the neck (posterior cervical triangle), deep cervical lymph node extirpation. "Neck dissection procedures", shunt implantation. Fibrosis following radiotherapy. Shoulder support in the Trendelenburg position.

Diagnosis

Sternocleidomastoid muscle:
Difficulty with head rotation.

Trapezius muscle:
Upper, middle and lower parts of the trapezius muscle must be examined separately. Upper and middle part lesions may produce winging of the scapula (Upper part- in contrast to lower part when caused by serratus anterior dysfunction)

Test: Abduct the arm through 180° from its resting position. The trapezius muscle is responsible for the upper 90° of movement above shoulder level.

NCV: Stimulation of the nerve at the posterior aspect of the sternocleidomastoid muscle.

EMG: sternocleidomastoid, trapezoid upper, middle, and lower parts.

Differential diagnosis

Acute idiopathic onset may resemble acute brachial plexopathy.

Therapy

Nerve grafting (bridge).
No operation is effective in long standing scars.
Orthotic devices are not effective.

Prognosis

Uncertain: recovery is slow and often incomplete.

Further expoloration is warranted if no improvement occurs after closed trauma.

References

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Hypoglossal nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

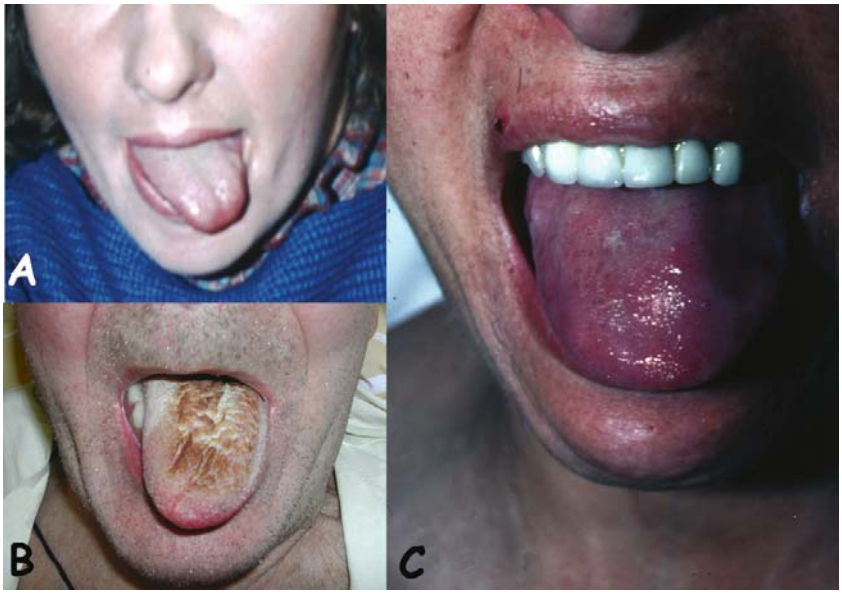

Fig. 14. Hypoglossal nerve lesions. **A** Left hypoglossal peripheral paresis. Note deviation of the tongue to the left. **B** Right sided hypoglossal paresis, in a patient with meningeal carcinomatosis. Midline of the tongue shifted to the right. **C** Amyloid tongue in a patient with multiple myeloma. Patient's subjective impression was, that the tongue was "too big"

Quality

Somatic motor intrinsic and extrinsic muscles of tongue except palatoglossus muscle.

Anatomy

Intracranial:
The nerve originates in the hypoglossal nucleus, beneath the floor of the fourth ventricle, and extends caudally to the lower limit of the medulla. In the brainstem the fibers traverse the reticular formation and medial part of the olive, then exit the medulla in the lateral sulcus.

The nerve emerges in two bundles that pass separately through the dura as it enters the anterior condyloid foramen (hypoglossal canal).

Extracranial:
Some dural fibers leave the nerve at the exit of the foramen. Outside the skull the nerve passes downward, to the level of the angle of the jaw, where it innervates the thyrohyoid muscle, and the extrinsic and intrinsic muscles of the ipsilateral side of the tongue.

The descending portion has anastomoses with the glossophayngeal, vagus and accessory nerves.

Fibers from the first and second cervical nerves join the hypoglossal nerve close to its exit from the skull, but leave the nerve shortly as a descending branch that turns around the occipital artery.

Symptoms

Unilateral loss of hypoglossal function causes mild difficulties with speaking, but swallowing is not impaired.

Bilateral impairment leads to speech difficulties and severe difficulty in swallowing. Tipping of the head is necessary for swallowing.

Headache may occur in hypoglossal lesions due to its connection with the ansa cervicalis.

Signs

Unilateral lesion leads to wasting of the ipsilateral side of the tongue and excessive furrowing. Deviation occurs towards the side of the lesion when the tongue is protruded. Bilateral lesions cause difficulty in tongue protrusion, speech, and the ability to move food in the oral cavity. Patients are hardly able to eat, and have difficulty pronouncing “d” and “t” (see Fig. 14).

Pathogenesis

This cranial nerve is rarely affected, except in disorders of the base of the skull and neck.

Vascular:
Vertebral basilary aneurysm, dissection of internal carotid artery.

Infection:
Basal meningitis, infections: mononucleosis, granulomatous meningitis, post vaccination mononeuropathy.

Inflammatory/immune mediated:
Rheumatoid arthritis: subluxation of odontoid process in rheumatoid arthritis, Paget’s disease.

Iatrogenic:
Surgery of the oral cavity and neck, carotid endarterctomy. Radiotherapy, in association with other cranial nerves. Compression of lateral part of tongue (with lingual nerve).

Neoplastic:
Schwannoma, primary nerve tumors (neurofibroma, neuroma).
Metastasis to the base of the skull, meningeal carcinomatosis. Affection of hypoglossal canal by glomus jugulare tumors, meningioma, chordoma (sometimes in association with other cranial nerves). Tongue carcinoma may infiltrate the nerve.
Lymph node enlargement with Hodgkin’s disease and Burkitt’s lymphoma.
Amyloid deposition in myeloma.

Trauma:
Head injury, penetrating head wound (often with other CN injuries), or dental extraction. Hyperextension of the neck. Hypoglossal tubercle or occipital condyle.

Idiopathic:
Isolated unexplained pathogenesis, usually reversible.

Malformation:
Chiari malformation

Glossodynia:
Burning pain in tongue and also oral mucosa, usually occuring in middle aged or elderly persons.

Differential diagnosis

Motor neuron disease
Pseudobulbar involvement

Therapy

Treatment is based on the underlying cause.

References

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Cranial nerves and painful conditions – a checklist

CN	Base of the skull lesions	Sinus cavernosus lesions	Neuralgic pain	Other
Optic nerve	+			Temporal arteritis, headache
Oculomotor nerves	Metastases, meningeal carcinomatosis	+	Tolosa Hunt syndrome	Diabetes, giant cell arteritis, metastatic tumor, lymphoma, leukemia, mucormycosis Orbital disease: pseudotumor, sinusitis, ophthalmoplegic migraine Posterior fossa aneurysm: posterior cerebellar artery (PCA), basilar
Trigeminal nerve	Metastasis, meningioma, ganglion gasseri syndrome	V 1	+ Trigeminal neuralgia	V 1 Tolosa Hunt syndrome, jaw mastication
Glosso-pharyngeal nerve	+		+	Neck pain
Accessory nerve				Shoulder pain
Hypoglossal nerve	+			Pain, connection via cervical plexus
Parasellar syndrome				Trauma Neoplastic: adenoma, craniopharyngioma, epidermoid, ganglion Gasseri meningioma, neurofibroma, pituitary sarcoma Vascular: carotid artery aneurysm, PCA, carotid cavernous fistula, thrombosis, intracerebral venous occlusion Primary tumors: chordoma, chondroma, giant cell tumor Metastases: nasopharyngeal, squamous cell carcinoma, lymphoma, multiple myeloma Inflammatory: Fungal: mucormycosis mucocele, periostitis, sinusitis Viral: herpes zoster, spirchochetal Bacterial: mycobacterial Others: eosinophilic granuloma, sarcoid, Tolosa Hunt syndrome, Wegener's
Cervical plexus	+			Cervical operations, surgery

References

Kline LB, Hoyt WF (2001) The Tolosa Hunt syndrome. J Neurol Neurosurg Psychiatry 71: 577–582

Stewart JD (2000) Peripheral neuropathic pain. In: Stewart JD (ed) Focal peripheral neuropathies. Lippincott Williams Wilkins, Philadelphia, pp 531–550

Cranial nerve examination in coma

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	Blink and Jaw Reflex Brainstem evoked potentials Motor evoked potentials (Magnetic stimulation) Somatosensory evoked potentials	+ Endocrine Metabolic Toxic	+ Structural Edema	

CN examination in coma	
Pupil	Metabolic and toxic causes often spare the light reflex. Lids must be passively held open: anisocoria, examine consensual light reaction Early manifestation of herniation syndrome-decline of pupil, usually on the side of the mass. Followed by an ipsilateral mydriatic pupil. Differential diagnosis: Miotic eye drops, organophosphates
Oculovestibular reflexes are dependent on functions of CN VIII, III, IV, and VI	Extraocular movements are more sensitive to toxic and metabolic influences. Quick and saccadic eye movements are absent. Clinical test: oculocephalic manuever, caloric testing. Deviation of eyes to one side. Bobbing, inverse ocular bobbing (dipping) nystagmus retractorius, convergence nystagmus. Lesions of the MLF.
Palatal and gag reflex	Relatively well preserved reflex: absent gag is a severe sign. Imminent danger of aspiration.
Corneal reflex	Needs localizing if unilaterally absent. Bilateral absence is not a sign of a structural lesion, but of metabolic or toxic encephalopathy.
Pain	Pain can be elicited in the trigeminal nerve distribution. More complex is the "Ciliospinal" reflex. Pain in the limbs and body may induce mimic changes and ipsilateral dilatation of the pupil.
Trismus	Biting down, lesion above midpons.
Acoustic startle reflex	The acoustic startle reflex is usually present in superficial coma. Exaggerated acoustic startle reflex can be a sign of disinhibition, as observed in hypoxic brain damage.

References

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Pupil

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy	Pharmacologic testing
			+		

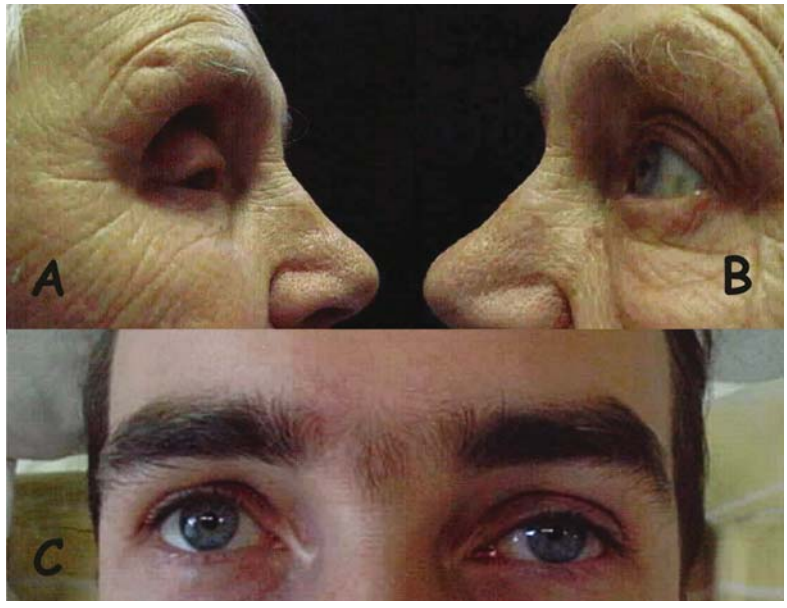

Fig. 15. Horner's syndrome: **A** Shows a Horner syndrome of l0 years duration, characterized by mild ptosis and enophthalmos, compared to normal side **B**. **C** Shows a Horner syndrome with mild ptosis, and miosis (cause: carotid artery dissection)

Innervation:
2 antagonistic muscles: circular muscle of iris (cervical sympathetic) and pupillary sphincter (CN III)

Paralysis of sphincter pupillae:
Between Edinger-Westphal nucleus and the eye: widens due to unantagonized action of sympathetic iris dilator muscle.

Paralysis of dilatator pupillae:
Ocular sympathetic paralysis, as in Horner's syndrome

Paralysis of accommodation:
Drugs: pilocarbin, eserin
Atropine, homatropine, psychotropics and antidepressants
Cocaine causes dilatation by stimulating sympathetic nerve endings

Pupillary size and equality:
Anisocoria indicates an inequality in pupil size between the right and left pupils.

Light reflex = direct/indirect

Horner's syndrome: see Horner's syndrome

Ciliospinal reflex: see CN and Coma

Pinpoint pupils:
May be a sign of opioid intoxication or a structural lesion of the pons (pontine hemorrhage).

Botulism:
Foodborne: Cranial nerve duction appears first, then dilated fixed pupils (not always present)

Reflex iridioplegia:
Argyll Robertson pupils

Optic nerve lesions: (swinging flashlight test) – MS

Adie tonic pupils

Unilateral dilatation: Raised intracranial pressure

References

Chadwick D (1993) The cranial nerves and special senses. In: Walton J (ed) Brain's diseases of the nervous system. Oxford University Press, Oxford, pp 76–126
Shintani RS, Tsuruoka S, Shiigai T (2000) Carotid cavernous fistula with brainstem congestion mimicking tumor on MRI. Neurology 55: 1229–1931

Multiple and combined oculomotor nerve palsies

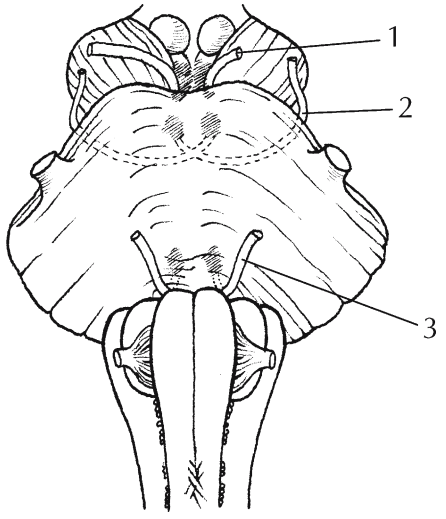

Fig. 16. The optomotor nerves: *1* Oculomotor nerve, *2* Trochlear nerve, *3* Abducens nerve

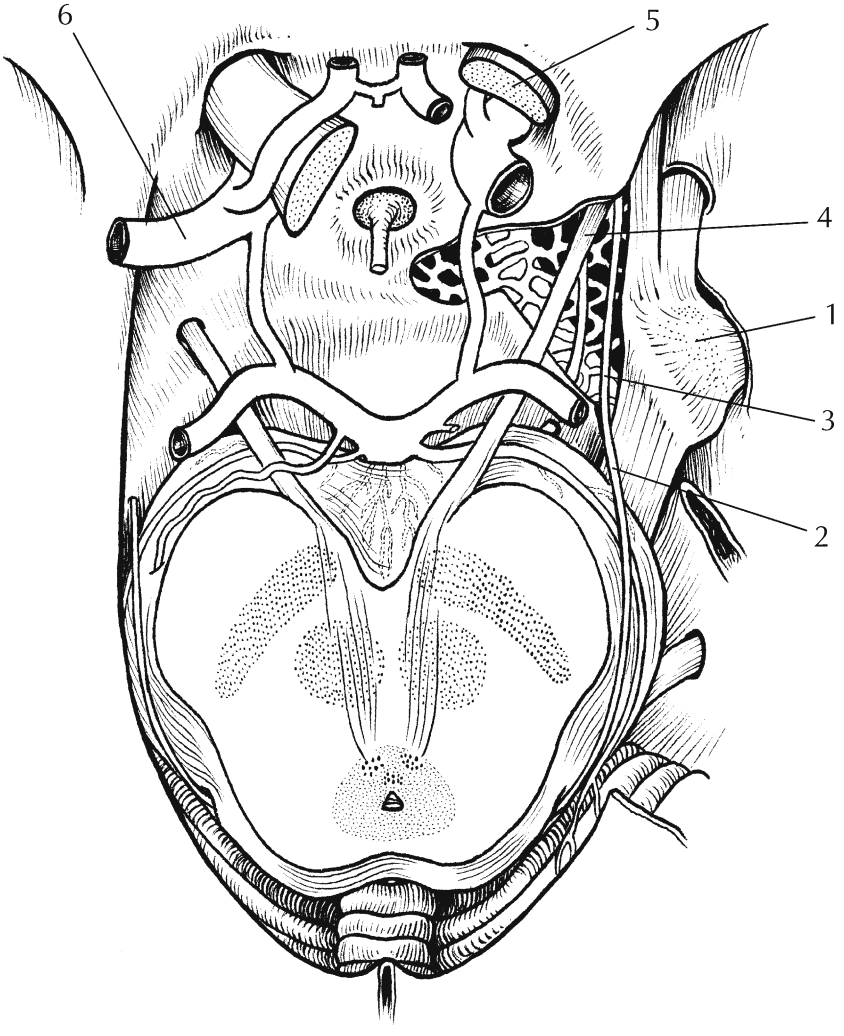

Fig. 17. Optomotor nerves and relation to vessels and brainstem: *1* Trigeminal ganglion, *2* Trochlear nerve, *3* Abducens nerve, *4* Oculomotor nerve, *5* Optic nerve, *6* Internal carotid artery

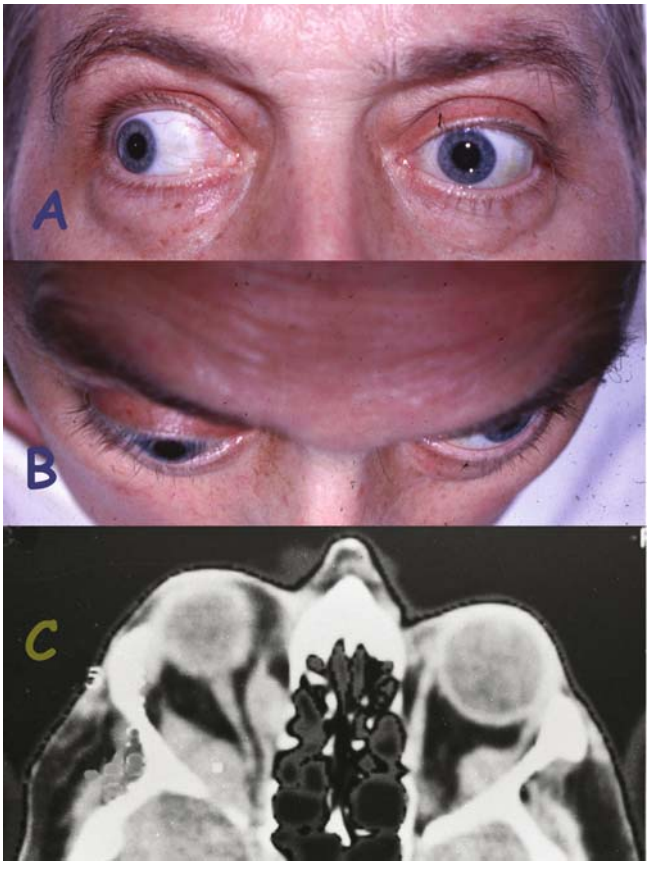

Fig. 18. Orbital metastasis: **A** Atypical optomotor function; **B** Exophthalmos, best seen from above; **C** CT scan of orbital metastases

III, IV, VI

Site of lesion	Cause	Associated findings
Brainstem:	Infarction Leigh syndrome Tumor Wernicke's disease	Associated brainstem signs
Subarachnoid space	Aneurysm Clivus tumor Meningeal carcinomatosis Meningitis Trauma	Other cranial nerve palsies
Cavernous sinus	Aneurysm Carotid-cavernous Fistula Herpes zoster Infection Mucormycosis Mucocele Nasopharyngeal Carcinoma Pituitary apoplexy Tolosa Hunt syndrome Tumor: meningeoma	Ophthalmic division of trigeminal nerve involved, orbital swelling pain
Orbital	Thyroid eye disease Orbital cellulitis Pseudotumor Trauma Tumor	Proptosis
Uncertain	Cranial arteritis Miller Fisher syndrome Diabetes Toxic	Pain, polymyalgia Ataxia Vincristine

Differential diagnosis: orbital muscle disease including thyroid disease, MG, rare ocular myopathies

Reference

Garcia-Rivera CA, Zhou D, Allahyari P, et al (2001) Miller Fisher syndrome: MRI findings. Neurology 57: 1755–1769

Plexopathies

Cervical plexus and cervical spinal nerves

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

Anatomy

The ventral rami of the upper cervical nerves (C1–4) form the cervical plexus. The plexus lies close to the upper four vertebrae. The dorsal rami of C1–4 innervate the paraspinal muscles and the skin at the back of neck.

Cutaneous nerves

Greater auricular
Greater occipital
Lesser occipital
Supraclavicular
Transversus colli
Transverse cutaneous nerve of the neck

Muscle branches

Intertransversarii cervicis (C2–C7)
Rectus capitis anterior (C1–3)
Rectus capitis lateralis (C1)
Rectus capitis longus (C1–3)
M. longus colli (C2–6)
Major motor nerve: phrenic nerve
Fibers from C2–C4 also contribute to the innervation of the sternocleidomastoid and trapezius muscles

The ansa cervicalis connects with the hypoglossal nerve.

Other communicating branches exist with caudal cranial nerves and autonomic fibers, cervical vertebrae and joints, and nerve roots/spinal nerves (C1/C2 and C3–8).

Clinical picture

Complete cervical plexus injury:
Sensory loss in the upper cervical dermatomes. Clinical or radiological evidence of diaphragmatic paralysis.

High cervical radiculopathies:
Less common, affected by facet joint. C3/4 foramen most often involved.
C2/3: site for Herpes Zoster, with post-herpetic neuralgia possible.
C2 dorsal ramus spinal nerve (or greater occipital nerve) irritation is better labeled “occipital neuropathy”.

Cervical plexopathies:
Rarely affected in traction injuries, and usually in conjunction with the upper trunk of the brachial plexus. Findings include sensory loss in the upper cervical

dermatomes and radiologic evidence of diaphragmatic paralysis (phrenic nerve).

Symptoms

Cervicogenic headache (controversial):
Although often cited, the evidence for this condition is unconvincing.

Lesser occipital nerve:
Damaged in the posterior triangle of the neck (e.g., lymph node biopsy). Causes numbness behind the ear.

Neck tongue syndrome:
Damage to the C2 ventral ramus causes occipital numbness and paraesthesias of the tongue when turning the head. Presumably there are connections between the trigeminal and hypoglossal nerve.

Nervus auricularis magnus (greater):
Traverses the sternocleidomatoid and the angle of the jaw. Injury causes transient numbness and unpleasant paraesthesias in and around the ear.

Injury can occur during face-lift surgery, carotid endarterectomy, and parotid gland surgery (injury to the terminal branches).

Occipital neuralgia/neuropathy:
Accidents, whiplash, fracture dislocation, subluxation in RA, spondylitic changes, neurofibroma at C2.

Pathogenesis

Iatrogenic:
Operations, ENT procedures, lymph node biopsy

Trauma:
Traction injuries

Diagnosis

History of operation. Imaging of spinal vertebral column. There are few reliable NCV studies, except for the phrenic nerve.

Differential diagnosis

Cervical radiculopathies.

Therapy

Pain management, anti-inflammatory drugs, physical therapy.

References

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Brachial plexus

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
(+)	+	+	+	

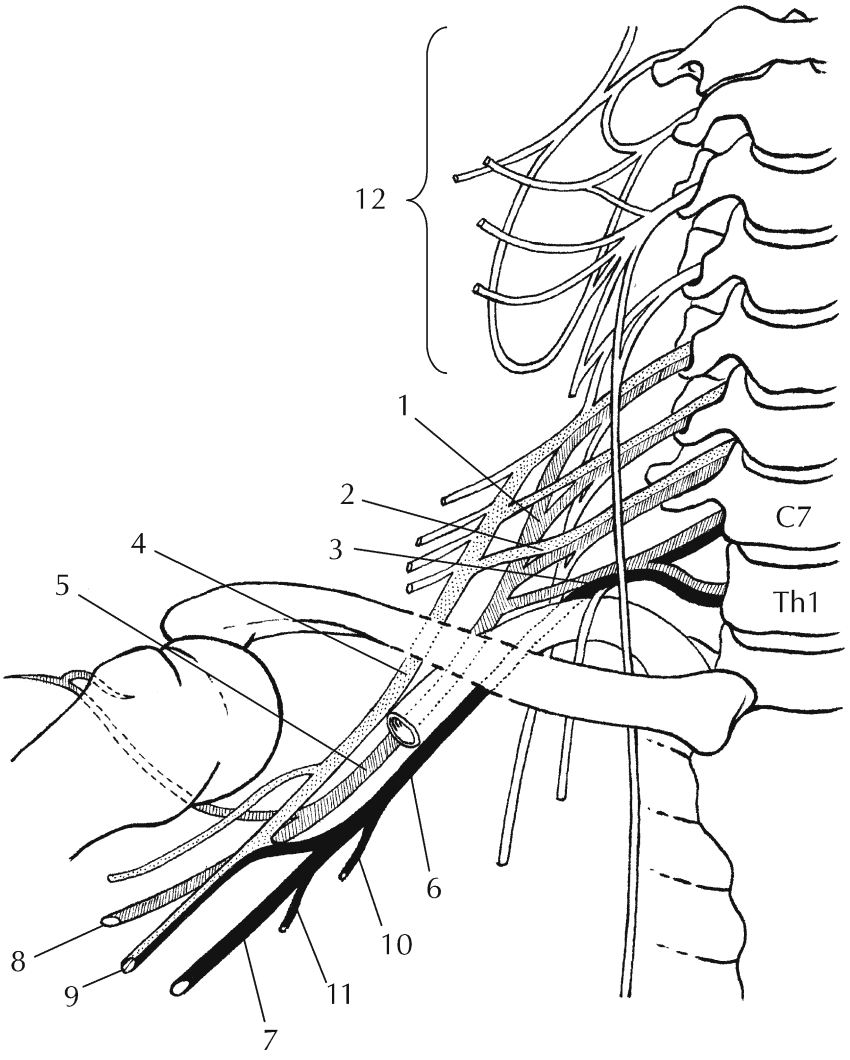

Fig. 1. *1* Upper trunk, *2* Middle trunk, *3* Lower trunk, *4* Lateral cord, *5* Posterior cord, *6* Medial cord, *7* Ulnar nerve, *8* Radial nerve, *9* Median nerve, *10* Medial brachial cutaneus nerve, *11* Medial antebrachial cutaneus nerve, *12* Cervical plexus

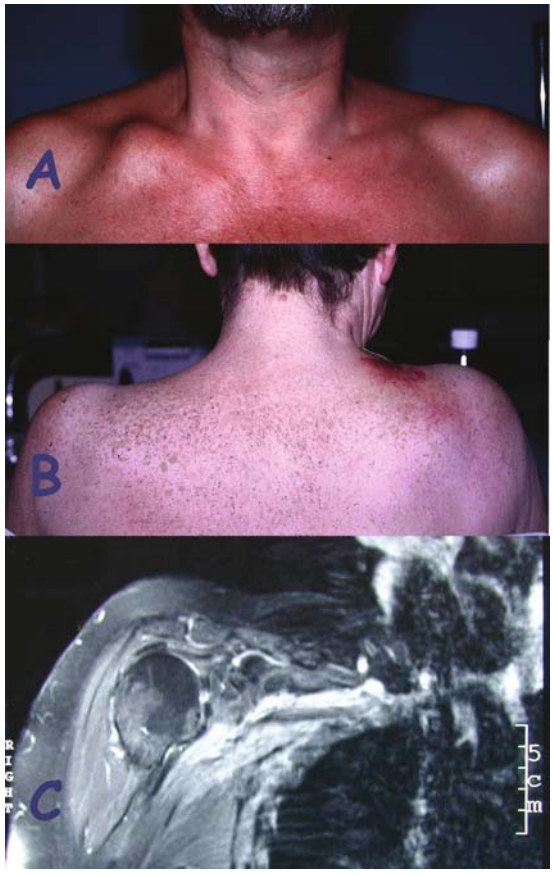

Fig. 2. Various types of mechanical pressure exerted on the brachial plexus: **A** Clavicular fracture with a pseudoarthrotic joint. In some positions electric sensations were elicited due to pressure on the brachial plexus. **B** A patient with arm pain and brachial plexus lesion. Note the mass over her right shoulder. The biopsy showed lymphoma. **C** MRI scan of a brachial plexus of a 70 year old woman, who was treated for breast carcinoma 10 years earlier. Infiltration and tumor mass in the lower brachial plexus

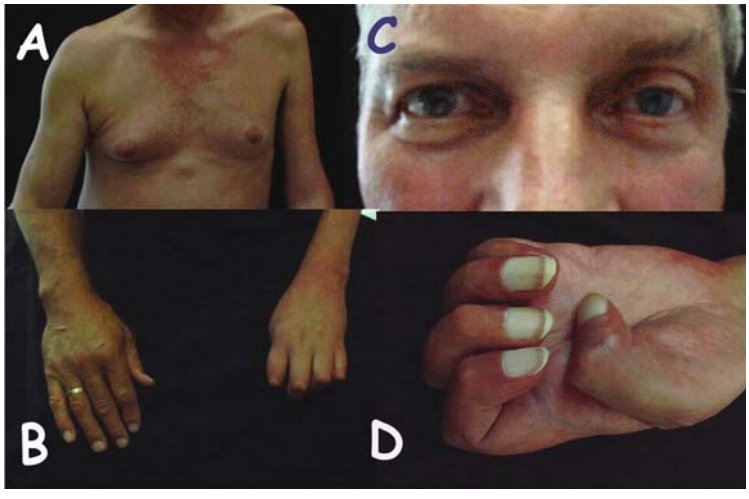

Fig. 3. Features of a long standing complete brachial plexus lesion: **A** Atrophy of the left shoulder and deltoid. **B** The left hand is atrophic and less voluminous than the right hand. **C** Left sided Horner's syndrome. **D** Trophic changes of the left hand, glossy skin and nail and nailbed changes

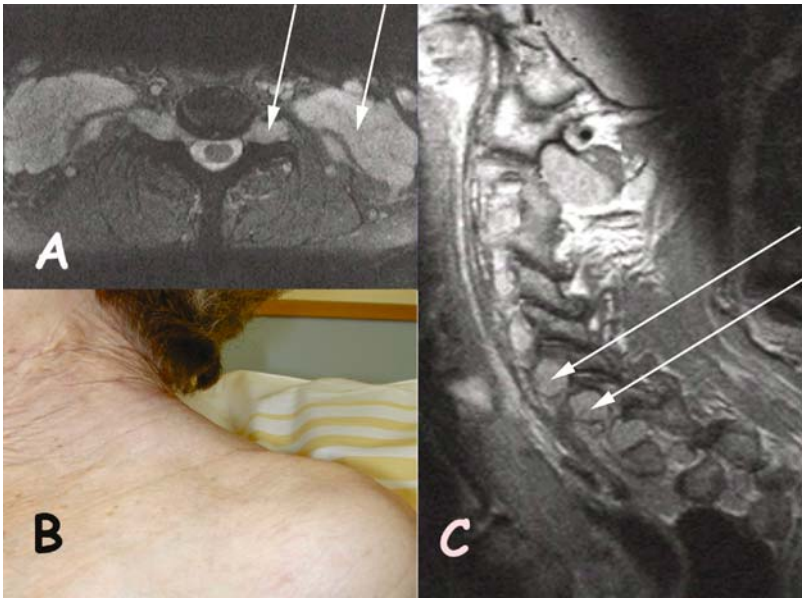

Fig. 4. Neurofibromatosis and the brachial plexus. **A** MRI of the nerve roots and brachial plexus. Note tumorous enlargement of nerve roots and **C** brachial plexus. **B** Note the palpable supraclavicular mass

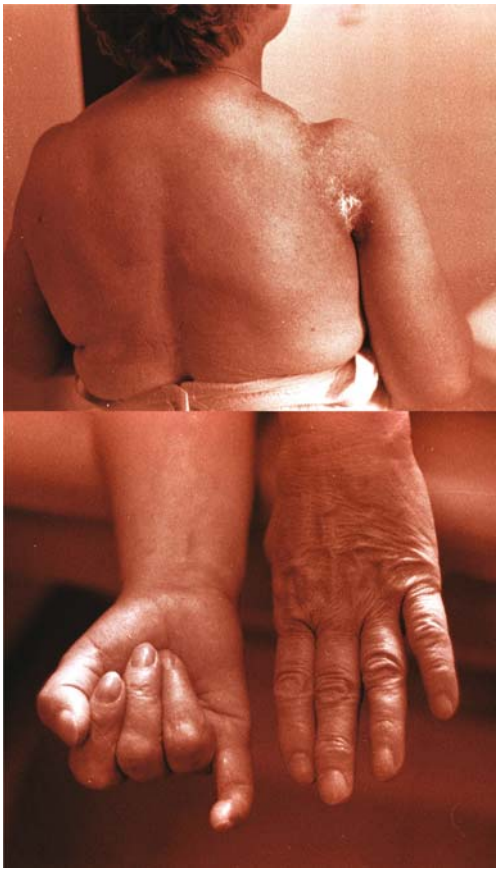

Fig. 5. Radiation injury of the brachial plexus: the upper picture shows the damaged skin after radiation therapy. The right hand is atrophic and has trophic skin changes. The finger movements were spontaneous and due to continuous muscle fiber activity after radiation of the brachial plexus

Anatomy

The trunks of the brachial plexus are formed by the union of the ventral rami of spinal nerves C5 to C8. The three trunks bifurcate into anterior and posterior divisions. The ventral rami from C5 and C6 fuse to form the upper trunk, those from C8 and T1 the lower trunk and the continuation of the ventral C7 fibers form the middle trunk. The trunks branch and reassemble to form the anterior, medial, and posterior cords (see Fig. 1).

The three major nerves of the brachial plexus:

a) The radial nerve is a continuation of the posterior cord and receives contributions from C5–8.
b) The ulnar nerve's fibers stem from C8 and T1 via the lower trunk and the medial cord.
c) The median nerve has two components:
The lateral part, which is mainly sensory, is derived from C5/6 (via the upper trunk and lateral cord) and some C7 fibers.
The medial part (all motor) is from C8 and T1 ventral rami, via the lower trunk and the medial cord (median nerve muscles can be divided into two segmental categories: some are innervated by C5–7, but most are by C8/T1).

Posterior rami of the brachial plexus:
Leave the spinal nerves and innervate paraspinal muscles.

Some nerves stem directly from the plexus:
Phrenic nerve (see also cervical plexus and mononeuropathies)
Dorsal scapular nerve (rhomboid muscles)
Long thoracic nerve (serratus anterior muscle)
Suprascapular nerve (supra and infraspinatus muscles)

Composition of cords

Lateral cord:
Lateral pectoral nerve: upper pectoral
Musculocutaneous nerve: elbow flexors
Median nerve (C5/6)

Posterior cord:
Thoracodorsal nerve: latissimus dorsi
Axillary nerve: deltoid
Radial nerve

Medial cord:
Medial pectoral nerve: lower part of the pectoral muscle
Medial cutaneous nerve: supplying arm and forearm
Ulnar nerve
Median nerve (C8/T1)

Anatomically related structures

Neck:
The interscalene triangle consists of the anterior scalene, medial scalene, and first rib. The plexus emerges from behind the lower part of the sternocleidomastoid muscles, passes under the clavicle, and under the tendon of the pectoral muscle to reach the axilla.

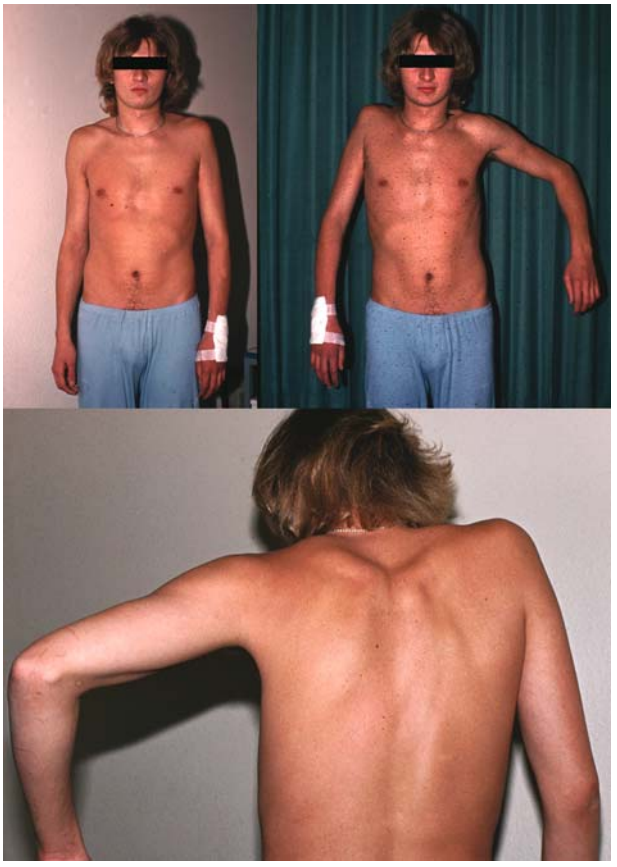

Fig. 6. Traumatic lesion of the left brachial plexus. Note the deltoid muscle and muscles fixing the scapula are intact. Atrophy of the lower arm and hand muscles. Note the inward rotation of the left hand while standing

T 1:
Lung apex and first part of the lower trunk. The lower trunk curves over the first rib.
Subclavian vessels (artery, vein).

Various classifications of brachial plexus divisions:

a) Interscalene triangle
b) Clavicle
c) First rib

Supraclavicular
Infraclavicular

Supraclavicular:
Preganglionic and postganglionic

Supraclavicular:
Upper plexus: incomplete traction, obstetric palsy, brachial plexus neuropathy
Lower plexus: metastatic tumors (e.g., pancoast), poststernotomy, thoracic outlet syndrome (TOS), surgery for TOS

Lesions of the brachial plexus

Infraclavicular:
Cords/branches: radiation, gunshot, humeral fracture, dislocation, orthopedic, axillary angiography, axillary (anesthetic) plexus block, neurovascular trauma, aneurysm

Panplexopathy:
Trauma, severe traction, postanesthetic paralysis, late metastastic disease, late radiation-induced plexopathy

Different classification:
Upper brachial plexus lesion
Lower brachial plexus paralysis
Isolated C7 paralysis
Fascicular lesions (medial, lateral and dorsal)
Complete brachial plexus lesions
Plexus lesion with or without root avulsion

Symptoms

Symptoms depend on the site of the lesion (supraclavicular/infraclavicular), on the cause (traumatic versus inflammatory or neoplastic) or association with pain, sensory, or autonomic symptoms.

Signs

Lateral cord:
Weakness of elbow flexion, forearm pronation.
Sensory loss in the anterolateral forearm. Absent or diminished biceps brachii reflex.

Medial cord:
Weakness of finger flexion, extension and abduction, and of ulnar wrist flexion.
Sensory loss: medial arm, forearm and hand.

Posterior cord:
Weakness of arm abduction, anterior elevation and extension.
Weakness with extension of the forearm, wrist and fingers.
The sensory loss varies over the deltoid to the base of the thumb.

Complete brachial plexus lesion (see Fig. 3 through 5):
Weakness of proximal and distal muscles, including levator scapulae and serratus anterior.
Sensory: complete loss in affected areas, often with pain.

Root avulsion:
Clinically: Functional loss may affect the entire limb. Sweating is intact, with severe burning, paralysis of serratus anterior, rhomboid and paraspinal muscles. Associated with Horner's syndrome (if appropriate root is damaged). Tinel's sign can be elicited in the supraclavicular region.
The neurologic examination may show signs of an associated myelopathy.
Radiographs may show fracture of transverse process, elevated hemidiaphragm.
CT: spinal cord displacement, altered root sleeves, contrast media enhancement.
MRI: traumatic meningoceles, root sleeves are not filled.

Electrophysiology:
NCV: Motor responses are unobtainable. Despite clinical sensory loss, sensory NCVs are obtainable (preserved dorsal rootganglion).
F Waves are absent.
EMG: fibrillations in cervical and high thoracic paraspinal muscles.

Pathogenesis

Metabolic:
Diabetic ketoacidosis

Toxic:
Alcohol, heroin, high dose cytosine arabinoside

Vascular:
Hematoma, transcutaneous transaxillary angiograms, puncture of axillary artery, aneurysm.
Pseudoaneurysms: May result from trauma or injuries. Slow onset and development.

Infectious:
Botulinus
CMV
EBV
Herpes zoster
HIV
Lyme disease
Parvovirus
Yersiniosis

Inflammatory-immune mediated:
Immunotherapy: interferons, IL-2 therapy
Immunization, serum sickness

– Neuralgic amyotrophy (Parsonage-Turner syndrome, acute brachial neuritis):
Clinically: sudden onset and pain located in the shoulder, persisting up to 2 weeks. Weakness appears often when pain is subsiding. The distribution is in the proximal arm with involvement of the deltoid, serratus anterior, supra/infraspinatus muscles. Other muscles that may be involved include those innervated by the anterior interosseus nerve, pronator teres muscle, muscles innervated by the musculocutaneous nerve and diaphragm. Bilateral involvement occurs in 20%. Prominent atrophy develops, but sensory loss is minor. Antecedent illness in 30% of cases: upper respiratory infection, immunization, surgery, or childbirth.
Lab: CSF normal
EMG: Neurogenic lesion in affected muscles. Abnormal lateral antebrachial cutaneous nerve in 50% of cases. Other nerves often unremarkable.
Other nerves that may be affected include the phrenic, spinal accessory, and laryngeal nerve.
Prognosis: improvement begins after one or more months. Ninety percent recovery is achieved in 2–4 years.
Treatment: pain control, physiotherapy.

Childhood variant: onset at 3 years, after respiratory infection, with full recovery.

Table 5. Lesions in neuralgic amyotrophy. A review by Cruz-Martinez, et al (2002) showed the following distribution in 40 patients

Nerve	Number of lesions	Percentage
Suprascapular	25	30.9
Axillary	21	25.9
Musculocutaneous	11	13.6
Long thoracic	7	8.6
Radial	5	6.2
CN XI	4	4.9
CN VII	4	4.9
Dorsal interosseus	1	1.2
Anterior interosseus	1	1.2
Phrenic	1	1.2
Lateral antebrachial cutaneous nerve	1	1.2
Total nerves	81	

Modified from: Cruz-Martinez A, Barrio M, Arpa J (2002) Neuralgic amyotrophy: variable expression in 40 patients. J Peripheral Nervous System 7: 198–204.

Differential diagnosis: Hereditary neuralgic amyotrophy, hereditary neuropathy with liability to pressure palsies (HNPP)

– Multifocal motor neuropathy:
Rare type of polyneuropathy, immune mediated with two or more lesions and with characteristic conduction block in motor NCV. Occasionally, the brachial plexus is affected.
Clinically: progressive muscle weakness and wasting, sometimes with fasciculations and cramps. Pain and sensory complaints are absent.
Electrophysiology: distantly intact NCVs. Motor NCV with supraclavicular stimulation is difficult. Sensory NCVs are unimpaired.
MRI may show diffuse swelling of the plexus.

– Monoclonal gammopathy and CIDP:
MRI investigation of the brachial plexus in patients with these disorders have shown involvement of the plexus.

Compressive:
– Rucksack paralysis:
Caused by carrying of backbags in recreational and military setting.
Clinically: Lesion of the upper and middle trunks, occasionally individual nerves.
Pain is uncommon, parasthesias may occur.
Affected muscles include deltoid, supra/infraspinatus, serratus anterior, triceps, biceps and wrist extensors.
Electrophysiology: conduction block, axonal loss in 25%.
Prognosis: recovery in 2–3 months.

Genetic conditions:
Ehlers Danlos Syndrome
HNPP
Neuralgic amyotrophy

– Hereditary neuropathy with liability to pressure palsies (HNPP)
Chromosome 17p11.2-p12; dominant.
Clinically: recurrent painless brachial neuropathy. May be the only involvement.
Electrodiagnostic: Demyelination
Prognosis: Recovery is common

– Neuralgic amyotrophy (HNA1)
Chromosome 17q24-q25; dominant, distinct from HNPP.
Onset: first (occasionally congenital) to third decade.
Neurological: recurrent episodes occur over periods of years. Several years may pass between episodes. Precipitating factors include surgery, stress, pregnancy, puerperium.
Clinically: weakness and pain.
The maximum weakness develops within several days, and symptoms may be bilateral.
The long thoracic nerve can be involved and result in scapular winging. Cranial nerves may also be associated: VII, X, VIII and associated Horner's syndrome. Sensory symptoms are less prominent.
Additional signs: hypotelorism, small face and palpebral fissure, syndactyly, short stature.
Prognosis: complete recovery common after each attack.

– Chronic neuralgic amyotrophy (HNA2)
Autosomal dominant form.
A preceding event occurs in 25% of cases.
Onset is with painful muscles. May occur gradually (6 weeks to 2 years) leading up to first attack
Persistent pain and weakness may occur between episodes.

Neoplastic involvement of the brachial plexus:
Extension of lymphoma
Metastatic breast cancer
Pancoast tumor (usually lung cancer)

Neoplastic plexus metastases have predominant involvement of C8–T1 roots or of the lower trunk. Some patients have diffuse metastatic plexopathy or epidural tumor extension accounting for the "upper trunk" deficits.

Tumorous brachial plexopathy is an early sign in lung cancer, and a late sign in breast cancer. Extension of the tumor mass into the epidural space may occur and cause additional spinal signs.

Radiation brachial plexopathy may show paresthesias of the first two digits as the earliest symptom, and the majority of patients have weakness restricted to muscles innervated by the C5–C6 roots.

The distinction between neoplastic involvement and radiation induced plexopathy is not always clear on clinical grounds. Many patients with radiation brachial plexopathy have weakness involving mainly the muscles innervated by the C8–T1 roots or lower trunk. Conversely, "diffuse" involvement of the

plexus in some studies was equally common among patients with metastases and patients with radiation damage (see Fig. 5).

Contrary to prior classifications, acute plexopathies may occur during radiation, as an early delayed plexopathy (4 months after radiotherapy), or late ("late delayed plexopathy") – see above.

Also an acute ischemic plexopathy due to thrombosis of the subclavian artery has been described. Possibly concomitant chemotherapy may enhance the radiation toxicity.

Primary tumors of the brachial plexus:
Rare: Neurofibromas associated with NF-1 or intraneural perineuroma (localized hypertrophic neuropathy) (see Fig. 4).

Hemangiopericytoma
Neural sheath tumors
Neurofibromas about 30% NF 1, dumbbell tumors
Lipoma, ganglioneuroma, myeloblastoma, lymphangioma, dermoids
Malignant neurogenic sarcomas and fibrosarcoma
Schwannoma

Iatrogenic:
Radiotherapy: most common type. Usually painless, upper plexus preferred (see Table 6).
Surgery: Neck dissection, carotid endarterectomy. Median sternotomy: e.g., coronary bypass surgery (2–7%). Unilateral lower trunk/medial cord damage (C8), sometimes bilateral. Differential diagnosis: ulnar nerve compression at the elbow.
Orthopedic and other surgeries: shoulder dislocations (axillary nerve), crutch use, shoulder joint replacement, shoulder arthroscopy, radical mastectomy, upper dorsal sympathectomy, humeral neck fractures.

General anesthesia: malpositioning, hyperabduction, stretch. Head rotation and lateral flexion to opposite side. Lower shoulder and arm under the rib cage with poor padding. Upper arm abducted and forearm pronated.
Upper trunk damage: head tilted downward, shoulder supports – less common.
Regional anesthesia: Postoperative paralysis is characterized by weakness, paresthesias. Pain is not prominent. The recovery is usually good (after 3–4 weeks).

Injection paralysis: injection, plexus anesthesia, punctures of the axillary, subclavian artery and jugular vein.

Traumatic:
Can be divided into closed and open plexus lesions.

The brachial plexus is vulnerable to injury, due to its superficial location and the mobility of the adjacent structures (the shoulder girdle and neck).

A frequent cause of brachial plexus lesions are motorcycle accidents, which may cause traction injuries or compress the plexus. Additionally, bone fragments and hematoma can be sources of damage.

In traumatic brachial plexus lesions the additional hazard of root avulsion (in addition to traction injuries) must be considered. The lower roots are often

Table 6. Brachial plexopathy: metastasis versus radiation therapy (RT)

Metastatic	Post-radiation
Onset: Pain in shoulder and hand (C8/T1) Palpable supraclavicular mass Less than three months after RT	Onset: Paresthesia, median nerve innervated hand. Slowly progressive, with or without pain
Lower supraclavicular lesion	Infraclavicular lesion
Metastases elsewhere	Duration: 2–4 years Onset: 4–41 years
Horner's syndrome "Pancoast" symptomatology	RT: 44–50 Gy
Imaging: mass	
Electrodiagnosis: Denervation	Electrodiagnosis: small sensory NCVs, Conduction block across clavicle Myokymia
Treatment Reradiation? Chemotherapy Pain therapy	Supportive

affected, but the plexus lesion can also be confined to the upper plexus or the whole plexus.

Birth injuries are tractional lesions and may affect upper portion (Erbs type) or lower portion (Klumpkes type).

Open plexus lesions are caused by penetration e.g. gunshot, knife, or glass wounds.

Pain is a frequently associated feature of brachial plexus trauma and is worst with root avulsion, where it may be the source of constant pain.

Phrenic nerve conduction studies should be performed if a C4 root lesion is suspected.

Neonatal brachial plexopathy: Occurs in less than 1% of cases in industrialized countries.

Most commonly affects the upper plexus: C5/6, sometimes with C7.

Less frequent: C8/T1–lower plexus. Rarely affects the whole plexus.

The diaphragm can be involved in 5% of cases, and bilateral lesions occur in 10–20%.

Risks: high birth weight, prolonged labor, shoulder dystocia, difficult forceps delivery.

Associated features: fractures of humerus or clavicle.

Half of the patients show complete or partial improvement within 6 months. Surgery remains controversial.

Aberrant regeneration can occur in any traumatic plexus injury, leading to innervation of other muscle groups either with or without motor function.

Others: "Burner" syndrome

Sudden forceful depression of the shoulder, occurs in US football. Transient sudden dysesthesia occurs in the whole limb, but may remain longer in upper trunk distribution.

Proximal Lower Motor Neuron syndrome
Age: 45 to 76 years, predominantly male.
Clinical: upper extremities, asymmetric, with weakness of the lower motor neuron. Asymmetric distribution with shoulder and elbow focus. Bulbar muscles can be involved. Fasciculations occur. Reflexes reduced in arms, preserved in legs.
Progresses to affect the legs and ventilation.
Differential diagnosis from ALS: slower development (2–6 years).
Laboratory:
Associated with anti-asialo-GM1 antibodies (10% to 20%)
Serum CK: Mildly elevated
Electrodiagnostic: EMG with denervation and reinnervation.
NCV: Normal

Differential diagnosis: Primary muscular atrophy (PMA), ALS, primary lateral sclerosis.

Diagnosis

Upon palpation: mass.
Laboratory, genetic analysis
Imaging: plain bone X ray, CT, MRI, adjacent structures: lung, ribs
Electrophysiology: NCV, EMG, more difficult to establish conduction block over the brachial plexus
Sympathetic function: sweat tests

Table 7. NCV studies

Sensory		
Brachial Plexus Trunk	Cord	Peripheral nerve
Upper	Lateral	Lateral antebrachial cutaneous nerve
Upper	Lateral	Median to first and second digit
Upper	Posterior	Radial to base of the thumb
Middle	Posterior	Posterior antebrachial cutaneous nerve
Middle	Lateral	Median to second digit
Middle	Lateral	Median to third digit
Lower	Medial	Ulnar to fifth digit
Lower	Medial	Dorsal ulnar cutaneous
Lower	Medial	Medial antebrachial cutaneous nerve
Motor		
Upper	Lateral	Musculocutaneous nerve
Upper	Posterior	Axillary nerve
Upper		Suprascapular nerve
Middle	Posterior	Radial nerve
Lower	Medial	Ulnar nerve

Other studies: F waves, spinal nerve root stimulation (electrical or magnetic), needle EMG of distal and paraspinal muscles.

Differential diagnosis

Brachialgias
Cervical radiculopathies
Cervical radiculopathies with root avulsion
Effort thrombosis
Myopathies
Proximal mononeuropathies: Axillary, suprascapular, long thoracic, musculocutaneous

Shoulder injury:
Fracture and dislocation (axillary, suprascapular nerve)
Rotator cuff injury
Shoulder joint contractures
Fractures of the clavicle
Subclavian pseudoaneurysm

Orthopedic and rheumatologic conditions:
Periarthropathia humeroscapularis
"Frozen shoulder"

Therapy

Due to the variety of brachial plexus lesions no general statement can be given. Conservative therapy is aimed at pain management and inclusion of physiotherapy to avoid contractures and ankylosis. If no improvement can be expected, muscle transfer to facilitate function can be considered.

The traumatic brachial plexus lesion is often a matter of controversy. Generally speaking a period of four months is considered appropriate to wait for the recovery of neurapraxia. Then the brachial plexus is explored. Suturing and grafting may lead to innervation of proximal muscles, but rarely reaches distal muscles.

New developments show that avulsed roots can be reimplanted.

Prognosis

The prognosis is highly dependent on the cause.

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Thoracic outlet syndromes (TOS)

Several entities have been described

True neurogenic TOS
Arterial TOS
Venous TOS
Nonspecific (disputed) neurologic TOS
Combinations
Droopy shoulder (see below)

True neurogenic TOS

Involvement of the lower trunk of the brachial plexus; young and middle aged females, often unilateral.

Symptoms:
Paresthesias in the ulnar border of the forearm, palm, and fifth digit. Pain is unusual, but aching of the arm may occur.

Signs:
Insidious wasting and weakness of the hand, with slow onset. Thenar muscles (abductor pollicis brevis) are more involved than other muscles. Only mild weakness of ulnar hand muscles. Sensory abnormalities are in lower brachial plexus trunk distribution (ulnar nerve, medial cutaneous nerve of the forearm and arm). Contrary to ulnar sensory loss, the fourth finger is usually not split. Only in severe cases are intrinsic hand muscles wasted. Weakness may also involve muscles of the flexor compartment of forearm.

Causes:
Compression by the anterior scalene muscle
Elongated transverse process (C7)
Fibrous band that extends from this "rib" to reach the upper surface of the first thoracic rib
Musculotendineous abnormalities
Rudimentary cervical rib

Differential diagnosis

Median and ulnar neuropathies: thenar wasting may be confused with carpal tunnel syndrome (CTS)
Lower trunk or medial cord lesions
C8 and T1 radiculopathies
Syringomyelia

Investigations

Plain radiographs
CT and MRI do not detect fibrous bands, but are good to exclude other causes
Electrophysiology: to exclude CTS
Characteristics: low or absent sensory NCV of ulnar and medial cutaneous nerves.
EMG abnormalities of muscles lower trunk
Paraverterbrals are normal.

Treatment

1. Conservative treatment: posture correction, stretching may relieve problems.

2. Orthosis to elevate shoulder
3. Surgery: resection of the first rib

Thoracic outlet syndromes: Arterial

Due to cervical rib and vascular involvement (subclavian artery compression with poststenotic compression, or subclavian artery aneurysm).
Clinically may present with weakness and pain: resulting in unilateral hand and finger ischemia and pain.
Minor vascular involvement results in reduced arterial pulse during hyper-abduction of the arm.
Occurs in young athletes and swimmers, from throwing, occlusion, stenosis, aneurysm, or pseudoaneurysm. Humeral head may compress axillary artery.
With (or without) cervical rib.

Disputed neurogenic TOS

No rib changes. Symptoms, but no objective changes of TOS.
Symptoms are variable: pain and paresthesias in the lower trunk distribution, supraclavicular tenderness.
Stable and non-progressive.
Treatment: disputed, potentially the removal of the anterior scalene muscle.

Droopy shoulder syndrome

Females with low set shoulders and long necks.
Symptoms: pain and paresthesias in upper neck, shoulder, head, sometimes bilateral.
Reduced by passive shoulder elevation, increased by downward arm traction.
Electrodiagnosis: normal.

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Lumbosacral plexus

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+	+	+	DM (femoral)

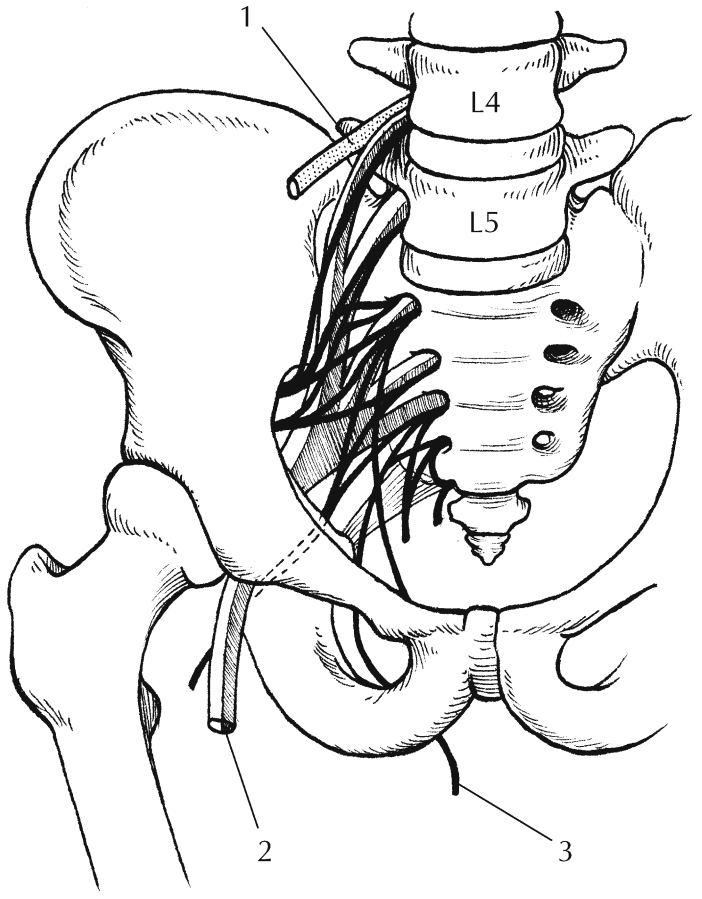

Fig. 7. *1* Branch to lumbar plexus, *2* Greater sciatic nerve, *3* Pudendal nerve

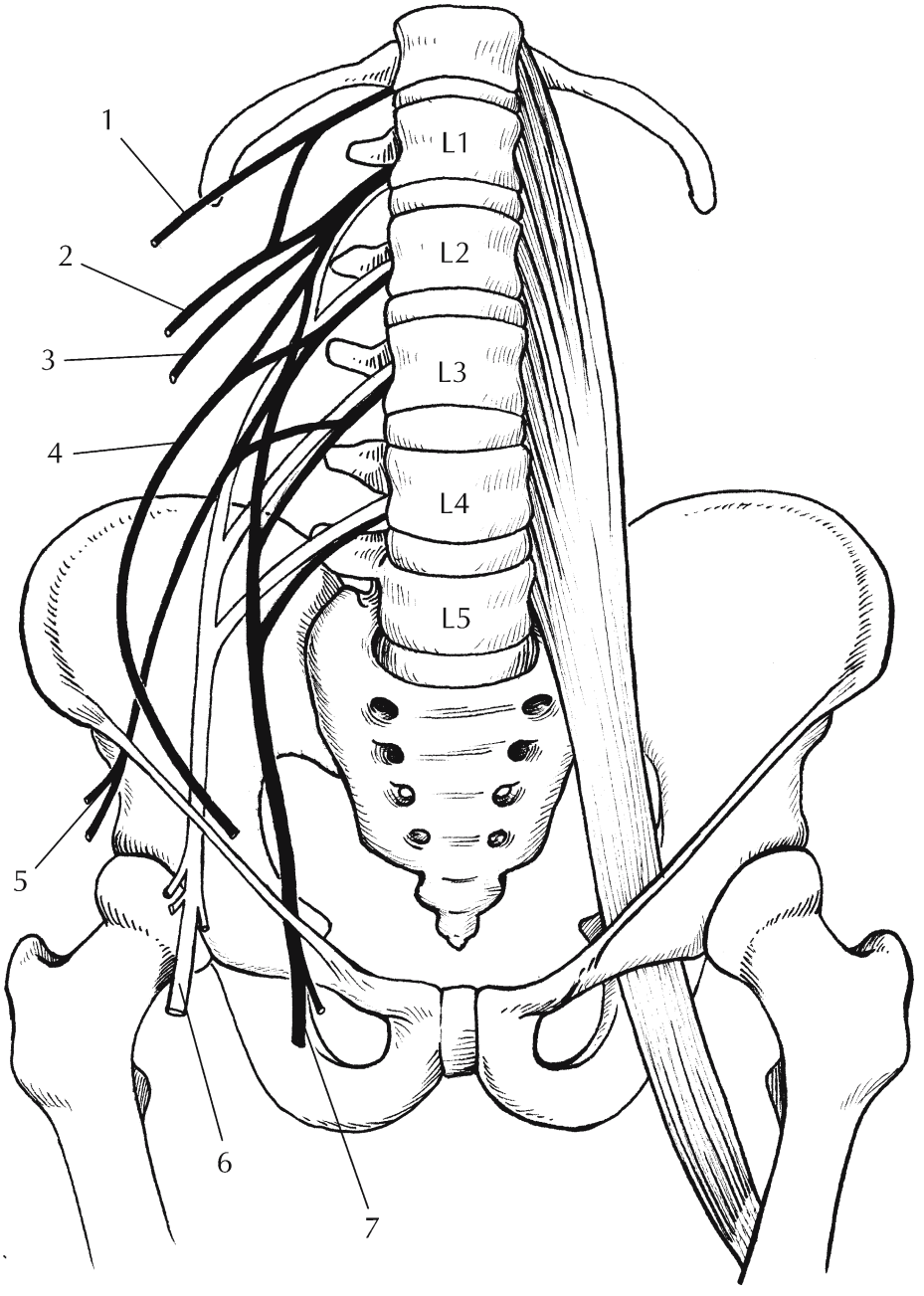

Fig. 8. *1* Subcostal nerve, *2* Iliohypogastric nerve, *3* Ilioinguinal nerve, *4* Genitofemoral nerve, *5* Lateral cutaneous femoris nerve, *6* Femoral nerve, *7* Obturator nerve

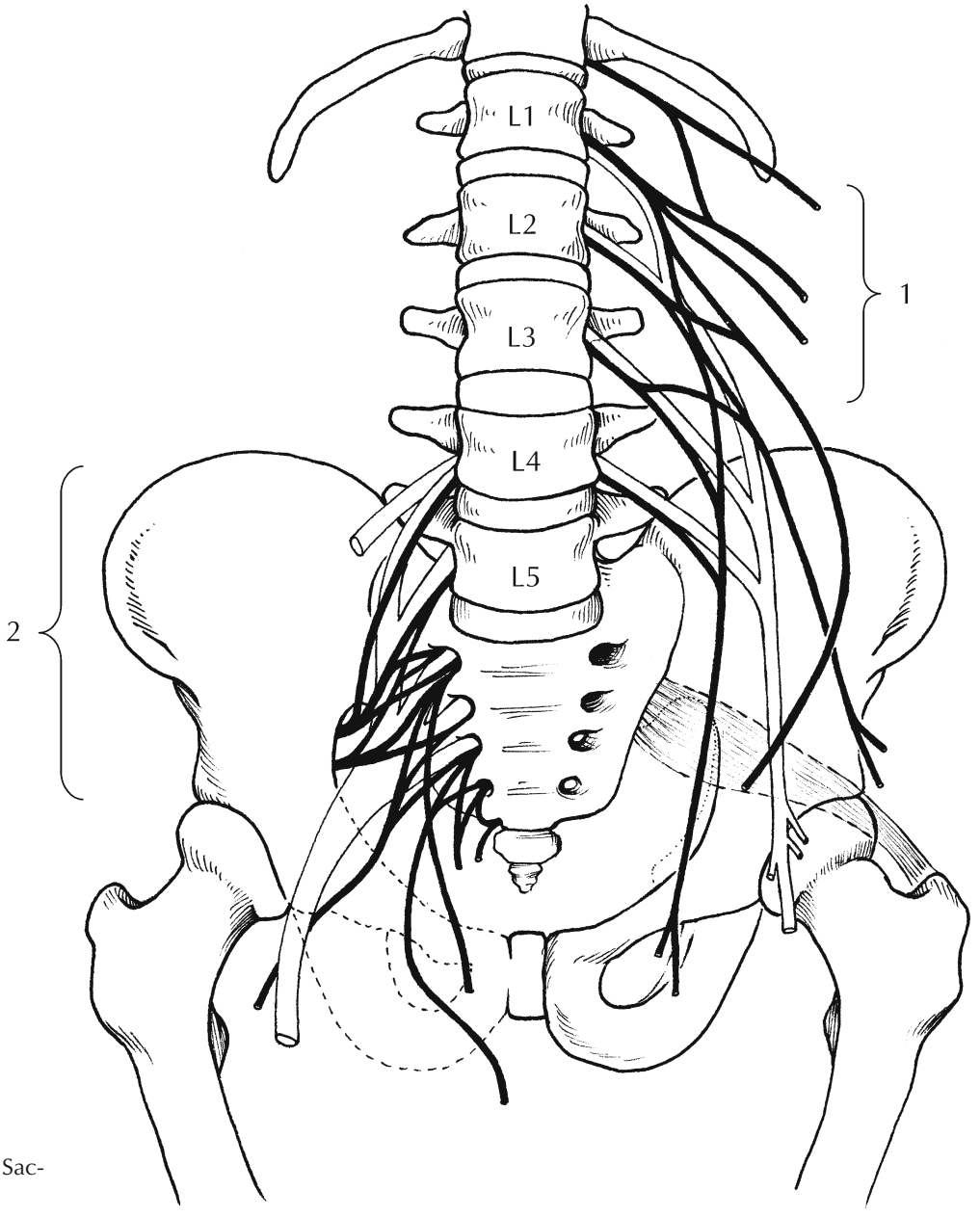

Fig. 9. *1* Lumbar plexus, *2* Sacral plexus

Anatomy

Three nerve plexus are commonly termed the "lumbosacral" plexus: lumbar, sacral and coccygeal plexus (see Fig. 7 through 10).

Lumbar

Formed by the ventral rami of the first to fourth lumbar spinal nerves. Rami pass downward and laterally from the vertebral column within the psoas muscle, where dorsal and ventral branches are formed.

The dorsal branches of L2–4 rami give rise to the femoral nerve, which emerges from the lateral border of the psoas muscle. The femoral nerve passes through the iliacus compartment and the inguinal ligament.

The obturator nerve arises from the ventral branches of L2–4 and emerges from the medial border of the psoas, within the pelvis.

The lumbar plexus also gives rise to the lateral cutaneous nerve of the thigh, the iliohypogastric, ilioinguinal, and genitofemoral nerves, and motor branches for the psoas and iliacus muscles.

Communication with the sacral plexus occurs via the lumbosacral trunk (fibers of L4 and all L5 rami).

The trunk passes over the ala of the sacrum adjacent to the sacroiliac joint.

Sacral

The sacral plexus is formed by the union of the lumbosacral trunk and the ventral rami of S1–S4. The plexus lies on the posterior and posterolateral walls of the pelvis, with its components converging toward the sciatic notch.

Sacral ventral rami divide into ventral and dorsal branches.

The lateral trunk arises from the union of the dorsal branches of the lumbosacral trunk (L4, 5), and the dorsal branches of the S1 and S2 spinal nerves. The lateral trunk forms the peroneal nerve.

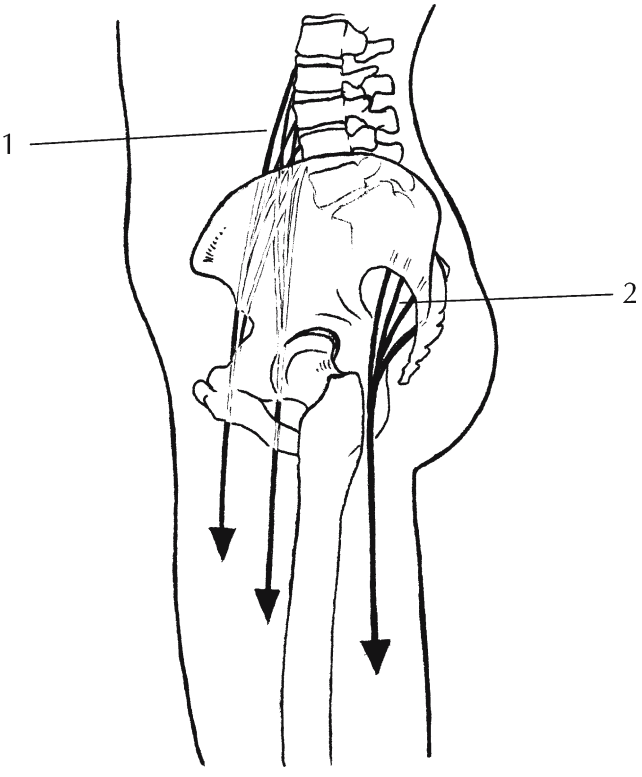

Fig. 10. Topical relations of lumbar (*1*) and sacral (*2*) plexus

The medial trunk of the sciatic nerve forms the tibial nerve, and is derived from the ventral branches of the same ventral rami (L4–S2).

Other nerves originating in the plexus include the superior and inferior gluteal nerves, the pudendal nerve, the posterior cutaneous nerve of the thigh and several small nerves for the pelvis and hip.

Autonomic fibers are found within lumbar and sacral nerves.

Symptoms

Lumbar plexus injury can be mistaken for L2–L4 radiculopathies, or for femoral mononeuropathies. Pain radiates into the thigh, with sensory loss in the ventral thigh, and weakness of hip flexion and knee extension.

In sacral plexus injury sensation is disturbed in the gluteal region and somewhat in the external genitalia. All lower limb muscles display weakness, except those innervated by the femoral and obturator nerves.

Motor loss in some pelvic muscles, gluteus muscles, tensor fasciae latae, hamstrings, and all muscles of the leg and foot can be caused by sacral plexopathies with L5/S1 radiculopathies, or proximal sciatic neuropathies.

Signs

Lumbar plexus lesions may have pain radiating into the hip and thigh. The motor deficit causes either loss of hip flexion, knee extension, or both. Adductors can be clinically spared, but usually show spontaneous activity in EMG. Sensory loss is concentrated at the ventral thigh, but the saphenous nerve can be involved. In acute lesions, patients have the hip and knee flexed.

The sacral plexus pain resembles sciatic nerve injury. Depending on the lesion of the sacral plexus, motor symptoms are concentrated in L5, S1, resulting in weakness of the sciatic nerve muscles. Proximal muscles that exhibit weakness include the gluteus maximus muscle, but the gluteus medius muscle is usually spared. Sensory symptoms may also involve proximal areas, such as the distributions for the pudendal nerve and the posterior cutaneous nerve of the thigh. Sphincter involvement can occur.

Pathogenesis

Metabolic:

Diabetic amyotrophy ("Bruns Garland syndrome"):
This entity has several names, including diabetic femoral neuropathy, although usually more than the femoral nerve is affected.

Diabetic amyotrophy is usually a unilateral (but can be bilateral) proximal plexopathy affecting the hip flexors, femoral nerve, and some adjacent structures. Vasculopathies, metabolic causes, or vasculitic changes have been described.

A paper by Dyck (1999) summarizes the characteristic features: it typically strikes elderly diabetic individuals between 36 and 76 years (median 65 years). The duration of diabetes has a median of 4.1 years (range 0–36 years), HbA1c has a median value of 7.5 (range 5–12). The CSF protein can be moderately elevated and a mild pleocytosis may occur. All except one patient of this series had type II diabetes.

A clinical feature is severe weight loss before the neurologic disease.

Pain is the dominant symptom, radiating into the hip or anterior thigh, and weakness and atrophy occur. Hip flexors, gluteal muscles, and quadriceps showed weakness, and adductors can be involved, demonstrating clearly that

this is not an isolated femoral neuropathy. The pain resolves, and quadriceps atrophy occurs. After stabilization slow recovery can be expected.

Biopsies from the sural and peroneal superficial nerve display vasculitic changes.

Therapy is confined to adequate pain control, as no specific treatment is available.

Toxic:
Heroin

Vascular:
Ischemic plexopathy

Hemorrhage (thrombopenia, anticoagulation therapy) can lead to hematoma in the psoas muscle, which induces weakness in the obturator and femoral nerve territories. The femoral nerve can also be directly compressed. Knee jerk is lost (see Fig. 12).

Arterial injections in the buttock may cause ischemic sciatic nerve and plexus lesions. The onset varies from minutes to hours. Ipsilateral pelvic muscles or blood vessels can be involved.

Injection of cis-platinum or fluoracil into the internal iliac artery may result in plexopathy.

Abdominal aortic aneurysm may result in claudication.

Rarely, **ischemic lumbosacral plexopathy** with uni- or bilateral signs occurs. Signs and symptoms can be expected after exercise, in particular walking uphill or riding a bicycle. At rest patients can be symptom free, and have no signs.

The pain occurs in the gluteal region after exercise, and sensory loss or disturbance is distally accentuated and not dermatomal. Weakness is proximal.

Electrodiagnostic tests are often normal. The causes are bilateral stenoses of the iliac arteries or distal abdominal aorta, common or internal iliac arteries. Treatment: Percutaneous transluminal angioplasty and application of stents.

Hemorrhagic compartment syndromes:
May be caused by anticoagulants or bleeding disorders.
Most frequently the femoral nerve is affected. The proximal iliacus muscle may also be affected by hemorrhage.
Psoas bleeding may cause lumbar plexopathy.
Treatment is not clear: operative versus non operative treatment.

Infectious:
Abscess, Lyme disease, immunizations, EBV, HIV, CMV
Bilateral lumbar and sacral plexopathy can occur in HIV.

Inflammatory-immune mediated:
Injury caused by immune vasculopathy is characterized by advanced age, asymmetric proximal weakness, and variable sensory loss. The course is progressive over weeks and months, sometimes associated with diabetes.

Lab investigations show elevated sedimentation rate. Nerve biopsy demonstrates inflammatory cells around small epineurial blood vessels.

Treatment with corticosteroids induces recovery.

A similar condition can be induced by vaccination and resembles serum sickness.

Hypersensitivity in drug addicts using intravenous heroin can cause limb dysfunction, bladder dysfunction, and rhabdomyolysis.

Compressive:
Lesions by compression are rare, except for tumors (especially retroperitoneal tumors and lymphomas).

Genetic:
Neuralgic amyotrophy, HNPP

Neoplastic (predominantly sacral plexus):
Malignancy: colorectal, breast, cervical carcinomas, sarcomas, lymphomas. Characterized by insidious pelvic or lumbosacral pain, radiation into the leg, paresthesias, variable involvement of bladder and bowl function. Nerve sheath tumors.

Most commonly the result of direct tumor extensions: pelvic, abdominal, and retroperitoneal tumors. Rarely caused by lymphoma and neurolymphomatosis. Metastases are rare.

The presentation is	Lumbar	31%
	Sacral	51%
	Lumbosacral	18%, often unilateral.

Symptoms: pain, either back or buttock.
Sacral: posterolateral thigh, leg, and foot.
Numbness and weakness may not appear for months.
Gait abnormalities, lower limb edema may occur.
Rectal mass and incontinence are uncommon.

Two particular syndromes observed in cancer patients:

Malignant psoas syndrome (para-aortic lymph nodes, with infiltration of the psoas muscle) (see Fig. 11)
Can be caused by bladder, prostate, and cervical tumors. Causes anterior thigh pain. Hip held flexed to relieve pain.

Warm and dry foot syndrome:
Injury to post-ganglionic axons, often by cervical or uterus cancer, and associated with lower limb pain.
Examination: warm and dry foot.

Iatrogenic:
Radiation therapy.
Onset is variable after a latent period of months to decades. Painless weakness of proximal and distal limbs. Mild limb paresthesia, with rare involvement of bowel and bladder.
EMG: myokymia.

Postoperative lumbosacral plexopathy:
Few descriptions, involving renal transplant, iliac artery used for revascularization of the kidney, and after hip surgery.

Trauma:
Uncommon.
Exceptionally violent trauma, road accidents, falls, rarely gunshot wounds.

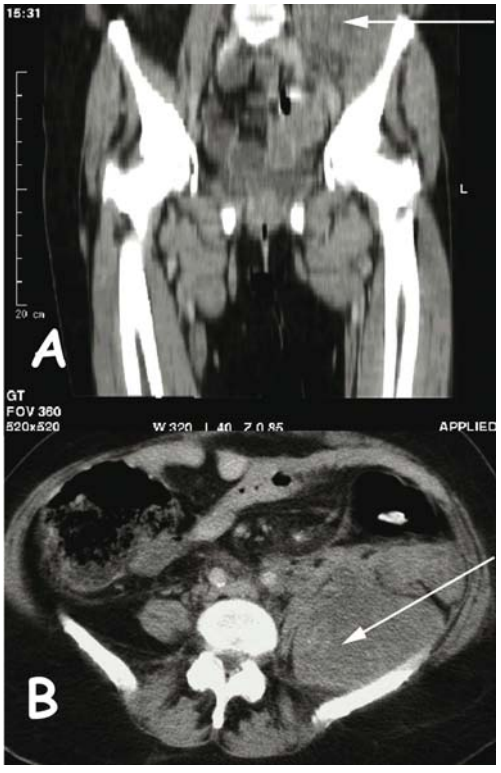

Fig. 11. The malignant psoas syndrome: **A** Shows a CT reconstruction; note the mass infiltrating the psoas (normal on the other side). **B** Also shows the mass infiltrating and destroying the psoas muscle. Clinically, the patient had a gastrointestinal stromal tumor and intractable pain. She was only able to lie in supine position with the hip and knee flexed

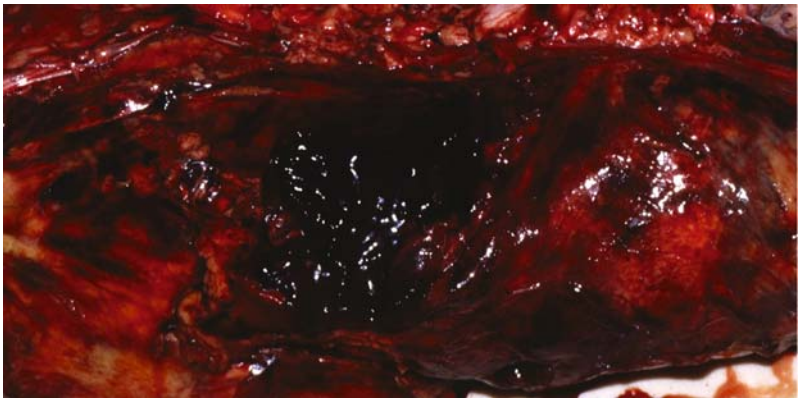

Fig. 12. Autopsy site showing large haematoma in the psoas muscle, in a patient with anticoagulant therapy

Lesions of the plexus are often associated with bony fractures of the pelvic ring or acetabulum, or rupture of the sacroiliac joint.
Gunshot: greater chance of involving the lumbar plexus.
Most commonly, injury is secondary to double vertical fracture dislocations of the pelvis. Resulting symptoms are in the L5 and S1 distribution with poor recovery.

Pelvic fractures:
Classification of pelvic fractures: stable, partially stable and unstable.
Classification of sacral fractures: lateral, foraminal, transforaminal, medial foraminal.

Incidence: Out of 2054 patients with pelvic fractures, 784 had sacral fractures. Neurologically, lumbosacral plexopathy is rare (0.7% of cases).

Maternal lumbosacral plexopathy (maternal paralysis):
The lumbosacral trunk, superior gluteal, and obturator nerves can be compressed by the fetal head pushing against the pelvic rim. May happen intrapartum, but also occurs in the third trimester.
Symptoms: Buttock pain, L5 distribution, foot drop. Sensory loss at the lateral leg and dorsum of the foot.
Motor symptoms: foot drop.
It may also be caused by prolonged labor, cephalopelvic disproportion and midpelvic forceps delivery.
Recovery is frequent.
Femoral nerve and obturator neuropathy may also occur.

Differential diagnosis: neoplastic versus radiation damage of the lumbosacral plexus:

Neoplastic	**Radiotherapy**
Pain	Indolent leg weakness
Unilateral weakness	Bilateral weakness
Short latency	Long latency
Reflexes unilaterally absent	Reflexes bilaterally absent
Mass on imaging	Normal MRI
Palpable mass	Myokymia in EMG
Leg edema	Paraspinal fibrillations
Hydronephrosis	High dose therapy

Episodic weakness of lumbosacral plexus (Table 8)

Diagnosis

Laboratory: exclude diabetes
Imaging: radiograph, CT, MRI
CT or MR angiography for suspected vascular lesions
CSF: when cauda equina lesion or inflammatory lesion is suspected

Electrophysiology: motor and sensory studies:
NCV, late response, needle EMG, evoked potentials
Bulbocavernosus reflex

Table 8. Episodic weakness of the lumbosacral plexus

Episodic weakness of the lumbosacral plexus		
Cauda equina lesion	Exacerbated walking downhill Unaffected by bicycling Pain & Sensory loss: distal	Lumbar vertebrostenosis, improves when bending forward, less symptoms when cycling
Ischemic plexopathy	Pain: distal No progressive sensory-motor loss during exercise Distal pulses: reduced or absent	
Peripheral arterial occlusive disease	Local pain radiating into hip and thigh (exercise dependent)	

(From Wohlgemuth, 2002).

Sensory NCV are crucial in distinguishing plexopathy from radiculopathy.

CMAP: axon loss
SNAP: extraforaminal from canal root therefore are absent in plexopathy

Paraspinal muscles are normal with plexopathies

Lumbar plexus:

Sensory NCV	**EMG**
Saphenous nerve	Femoral quadriceps L2-L4
Lat. cutaneous nerve of the thigh	Peroneal muscles, tibialis anterior muscle L5

Sacral Plexus:

Sensory NCV	EMG
Superficial peroneal nerve L5	Peroneal muscles, extensor digitorum communis L5/S1
Sural nerve S1	Peroneal muscles, tibialis posterior muscle L4/5
	Abductor hallucis S1,2
	Abductor digiti minimi pedis S1,2

Differential diagnosis

Polyradicular involvement (Lyme disease, neoplastic involvement)
Inflammatory asymmetric conditions
Mononeuropathy multiplex

Therapy

Depending on the cause.

Prognosis

Depending on the cause, variable.

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Radiculopathies

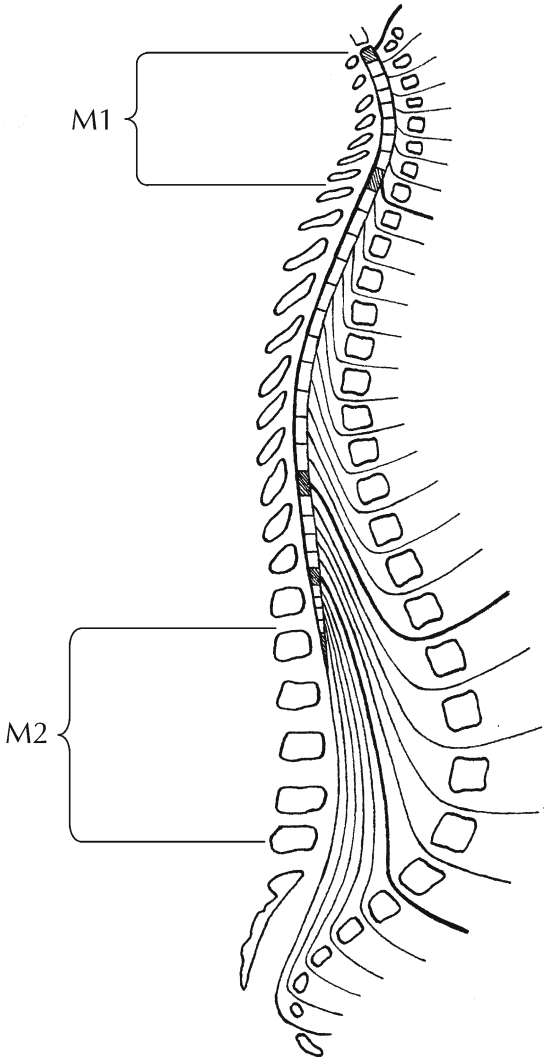

Fig. 1. Vertebral column. M1 + M2: represent the mobile parts

Cervical radiculopathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		++	

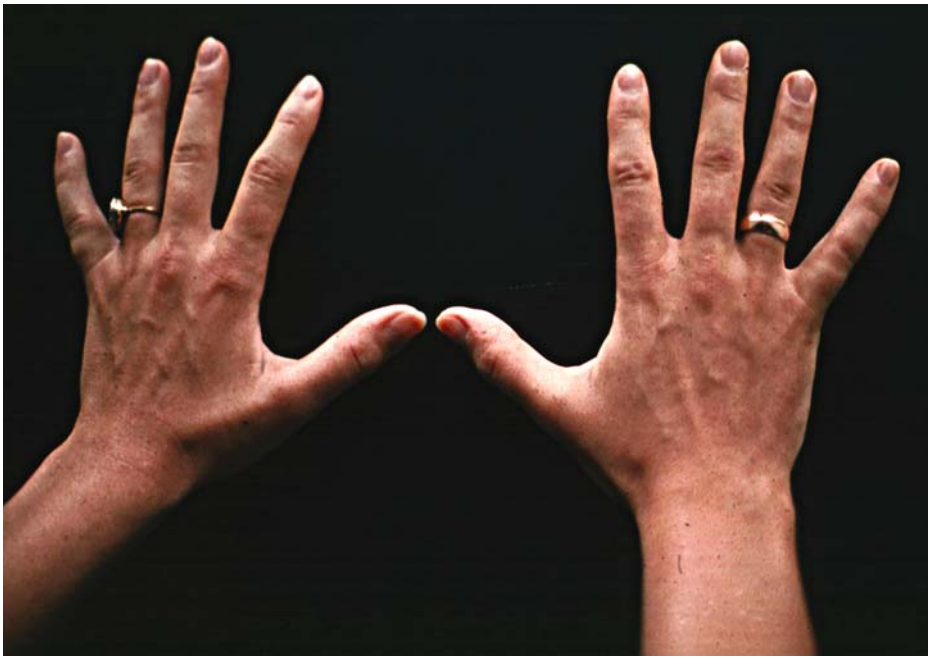

Fig. 2. Left hand: C8 radiculopathy with atrophy in a patient with leukemic infiltration

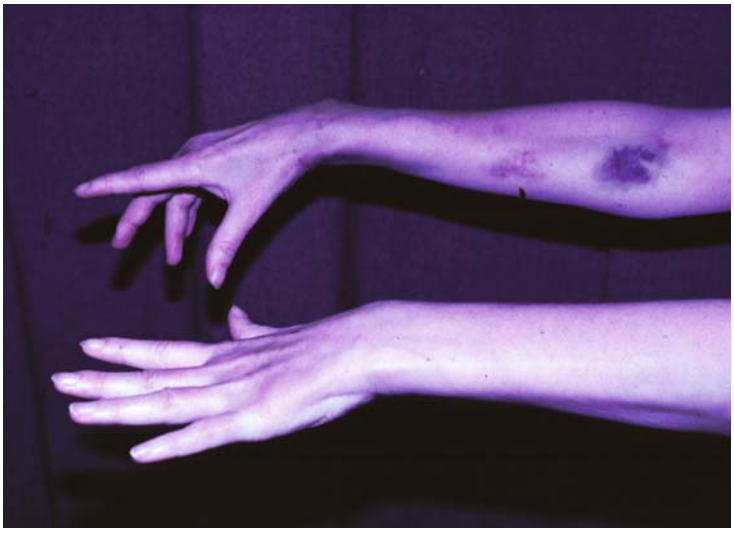

Fig. 3. Meningeal carcinomatosis with neoplastic deposits in C6 and C7. Extensor deficits of fingers 3, 4, 5 mimicks partial radial paralysis

Anatomy

With exception of the upper two, the cervical vertebrae articulate with each other by an intervertrebral disc, plus a pair of smaller joints between articular facets and pedicles.

The intervertebral foramina are formed by the pedicles (above and below), anteriorly by intervertebral discs and joints of Luschka, and posteriorly by the facets and facet joints. The transverse processes are (except in the case of C7) foramina for the vertebral arteries. A deep horizontal groove lies on the upper surface of each transverse process. The scalene muscles are attached to the transverse processes. Two important structures are the longitudinal ligaments and the intervertebral discs. The laminae of the vertebral arches are connected by the ligamentum flavum.

Rootlets of ventral and dorsal origin form roots (fusing in the intervertebral foramen). The dorsal root ganglia (DRG) lie just dorsal to the fusion. Dura and arachnoid extend around nerve roots into the intervertebral foramina as root pouches or sleeves. In the cervical spine, the nerve roots exit over the vertebral body and are numbered by the vertebral body beneath the root (e.g. C6 exits between C5–C6, the C8 root exits between C7 and T1). While the cervical roots exit horizontally, there is about a one segment difference (see Fig. 1).

Symptoms

Classically, the patient with cervical disc rupture complains of neck, shoulder, and arm pain, with or without distally radiating paresthesias.

Neck and arm pain are often combined. Pain is described as radiating into the shoulder, periscapular, or pectoral regions, or the “whole” arm. C5/6 lesions tend to cause more shoulder pain than C7/8 lesions. Upper medial arm pain is characteristic of C7/8 lesions. Pain radiating into the scapula or interscapular regions points to C7/8.

Sensory symptoms (paresthesia, dysesthesia or numbness) may occur in the nerve root distribution. Thumb and index finger are associated with C6; index and middle finger with C7; ring and little finger with C8. Pain may increase with neck movement. Valsalva, sneeze, and coughing enhance pain.

Pain quality:

Lancinating, shooting, or radiating into an extremity, with a narrow spatial distribution (2 inches). Dull aching pain is constantly felt in surrounding structures.

Signs

Weakness, and later atrophy occurs in a myotomal distribution (caveat: pain may impede examination of muscle power). Correspondingly diminished or absent tendon reflexes.

Reproduction of the patient’s pain on extension and ipsilateral rotation of the head (Spurling’s maneuver) is pathognomic for cervical root irritation and analogous to sciatica produced by straight leg raising with herniated lumbar discs.

Neck movement may also produce paresthesias or radiating pain.

Dermatomal sensory changes may occur.

Percussion or pressure on the spinous process of the affected vertebral body may induce segmental, shock like radiating pain (resembling Tinel’s phenomenon).

Patients sit with head tilted away from the affected side and support the head with one hand. This position opens the foramen and alleviates the additional stretch to a compressed root by supporting the arm’s weight.

Multiple cervical radiculopathies:
13–20% are multiple. Bilateral incidence is unknown. Multiple and bilateral lesions are atypical for simple compressive lesions – other causes can be expected:

Polyradicular lesions:

Extradural lesions:
Ankylosing spondylitis
Cervical spinal stenosis
Degenerative spine disease
Herniated disc
Osteomyelitis
Paget's disease
Vertebral column metastasis, lymphoma

Intradural-extra-axial:
Arachnoiditis
Ependymoma
Leptomeningeal carcinomatosis
Neurolemmoma
Sarcoidosis
Trauma

Intraaxial-medullary:
Encephalomyeloradiculomyelitis (postrabies vaccine)
Motor neuron disease
MS – may have radicular symptoms and signs due to focal intramedullary lesions affecting radicular fibers
Olivopontocerebellar atrophy
Posttraumatic anterior horn cell lesion
Postpolio syndrome
Spinal cord ischemia
Spinocerebellar degeneration

Vascular:
Acute and subacute cervical radiculopathy with cervical spinal stenosis

Infectious:
Herpes zoster: occurs less frequently than in the thoracic region. If the cervical segments C2,3 are involved, pain and vesicles may appear. Sensory fibers are predominantly affected, rarely also motor fibers (anterior horn cells). C3–5 herpes may cause diaphragmatic paralysis.

Inflammatory:
Radiculomyelitis of various etiologies
Spondylodiscitis

Immune mediated:
Ankylosing spondylitis
Atlanto-axial joint involvement in rheumatoid arthritis (RA)
Cervical intervertebral discs are often affected by RA: instability, and encroachment of nerve root foramina and spinal canal.

Pathogenesis

Compressive:

Disc herniation: cervical disc protrusion is rarer than with the lumbar disc; C5/6 and C6/7 are predominantly affected (due to vertebral column mobility). Due to the horizontal position of the nerve root, a cervical disc generally affects one root only.

Movements, in particular abrupt movements, may elicit prolapse with pain, sensory and motor radicular symptoms (Table 9).

Rarely, medial large discs can produce myelopathy – with tetraparesis, spasticity, and bladder and bowel dysfunction.

In young patients trauma and sports are the main cause. In older patients, chronic spondylotic changes often prevail, which are worsened by acute disc protrusion – causing myelopathy.

Symptoms: Severe pain and stiffness. Pain and sensory symptoms occur according to the radicular distribution (Table 10).

Table 9. Cervical radiculopathy findings

Clinical symptoms	Highly suggestive	Suggestive
Pain in neck and shoulder only		C5
Scapular, intrascapular pain		C7 or 8
No pain below elbow		C5
Pain posterior upper arm		C7
Pain medial upper arm		C7 or 8
Paresthesias of thumb	C6	
Paresthesias middle and index finger	C7	
Paresthesias ring and small finger	C8	
Whole hand paresthesias		C7
Depressed triceps reflex	C7 or 8	
Depressed biceps and brachioradialis reflex	C5 or 6	
Weakness spinati muscles	C5	
Weakness deltoid muscle	C5 or 6	
Weakness triceps brachii muscle	C7	
Weakness intrinsic hand muscles	C8	
Sensory loss over thumb only		C6 or 7
Sensory loss middle finger	C7	
Sensory loss small finger	C8	

Table 10. High yield muscles for cervical radiculopathy

C5	C6	C7	C8
Infraspinatus 80%	Anconeus 100%	Triceps brachii 90%	Extensor indicis proprius 100%
Deltoid 80%	Flexor carpi radialis 80%	Flexor indicis proprius 90%	First dorsal interosseus 80%
Brachioradialis 80%	Pronator teres 75%	Anconeus 75%	Abductor digiti V 80%
Biceps brachii 70%	Brachioradialis 70%	Pronator teres 60%	Flexor pollicis longus 60%
Cervical paraspinals 60%	Cervical paraspinals 60%	Cervical paraspinals 30%	Cervical paraspinals 80%

Subacute onset is more common, in association with chronic spondylotic changes.

Cervical spondylosis:
Bony changes may produce narrowing of spinal canal and intervertebral formina. This occurs at the disc joints, the facets, and the Luschka joints. The disc of the older patient is flattened, desiccated and degenerated. Bony exostoses and osteophytes occur in aged patients. Symptoms resemble acute herniation but are less intense. C6/7 roots are predominantly affected. Head movement enhances pain.

Pathologically: posterior osteophytes, as well as bony bars projecting from vertrebral bodies into spinal canal. Additionally, the ligamentum flavum (bridges spaces between vertebral lamina) is thick and unelastic; with extension the neck buckles inward to compress the spinal cord from behind.

Radiculomyeloneuropathy:
Nerve and spinal cord compression, in addition to nerve root compression.

This is caused by flattening of the vertebral bodies, hypertrophy of the facet joints, and narrowing of the foramina.

Clinically variable combinations of radicular symptoms and myelopathy (pyramidal signs-spasticity) are observed. Although there is less pain and radicular symptoms, hand atrophy and clumsiness, and weakness, usually in C6/7 segments, are seen. Bilateral radicular symptoms are common.

Long tract signs may result in dysesthetic symptoms in legs, often with "Lhermitte's" sign and gait disorder. Vibration perception is reduced.

Signs: Reflexes: C5–6 are depressed, while triceps, finger, knee and ankle reflexes are hyperactive, and there are pyramidal signs.

MRI: intramedullary signal changes, as a sign of myelopathy.

Bony changes on CT scan.

Trauma:
Fractures and dislocations with associated spinal cord damage. Myelopathy may be the dominant problem. Root avulsions are usually associated with plexus trauma and myelopathy.

Neoplastic:
Most commonly tumors affecting the cervical vertebral column are breast, prostate and lung cancer. Cervical vertebrae are less involved compared with thoracic or lumbovertebral column metastasis. Local pain or a radicular syndrome results. Additionally, the spinal cord may be compressed, by either local extension of tumor, or through nerve root foramina paraspinal malignant deposits (see Figs. 2 and 3).

Nerve root and spinal nerve tumors:
Schwannomas, or neurofibromas, in combination with NF1.

Diagnosis

Neuroimaging:
CT, MRI

CSF in inflammatory disease

EMG:
The EMG sensitivity depends on the motor involvement. It can reach up to 70%. Most commonly, C6 and C7 roots are affected, followed by C5 and C8.

NCV:
NCV studies can help to distinguish between radiculopathies and focal neuropathies, which may produce similar sensory symptoms.

The sensory NCV can be expected to be normal as are the SNAPs of the median nerve (C6), third digit (C7), ulnar nerve/5th digit (C8) and the medial antebrachial cutaneous nerve (T1).

NCV motor:
Injury to motor fibers distal to the cell body results in CMAP amplitude reduction.

Differential diagnosis

Acute cervical radiculopathies:
Neuralgic amyotrophy
Acute traumatic brachial plexopathy (with or without avulsions)

Limitation of shoulder movement can have several causes and may be accompanied by non-radicular pain (bursitis, capsulitis, tendinitis, impingement), muscle trauma from exercise, and frozen shoulder.

Other conditions producing pain in the neck: myocardial infarction, shoulder disease, bursitis, and arthritis.

Brachial plexus lesions:
Upper trunk plexus vs C 5/6
Lower trunk vs C8/T1
Middle trunk vs C7

Other considerations:
Herpes infection
Mononeuropathies
MS (radiculopathies due to spinal cord involvement)
Osteomyelitis, discitis
Pancoast tumor
"Pseudoradicular" symptoms
Referred pain: Cardiac ischemia
Spinal cord lesions
Syrinx
Thalamic ischemia
Thoracic outlet syndrome

Chronic cervical radiculopathies:
ALS
Multifocal motor neuropathy
Mononeuropathies (e.g., pure motor "ulnar")

Treatment

Conservative
Surgery

Conservative:
A herniated disc often diminishes in size by desiccation, neovascularization, and phagocytosis. In a study comparing conservative treatment vs surgery, the results after 12 months were equal.

Treatment may include periradicular and epidural steroids, analgesic and anti-inflammatory drugs, and neck immobilization with a soft collar to prevent recurrent mechanical root irritation.

The impact of neck traction is unclear.

Neck manipulation and chiropractic maneuvers are controversial.

Surgical:

Used in cases of suspected myelopathy, progressive sensorimotor deficit, or failure of conservative measures. Used in particular in association with pain.

- **Anterior discectomy, with or without fusion:** Neurosurgical method most commonly used. Complications: operative risks of root or cord injury, hoarseness from recurrent laryngeal nerve injury, esophageal perforation or vertebral artery injury, graft displacement.
- **Posterior approaches:** Decompression adds instability, as the facet joints, disc, and supporting ligaments are left intact; fusion of the involved segment is generally unnecessary, as is postoperative immobilization. Extensive laminectomies carry the risk of reverse lordosis, or "swan neck deformity". Chronic pain with or without myelopathy may result.

Prognosis

Variable, depending on the cause.

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Thoracic radiculopathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+	+	+++	

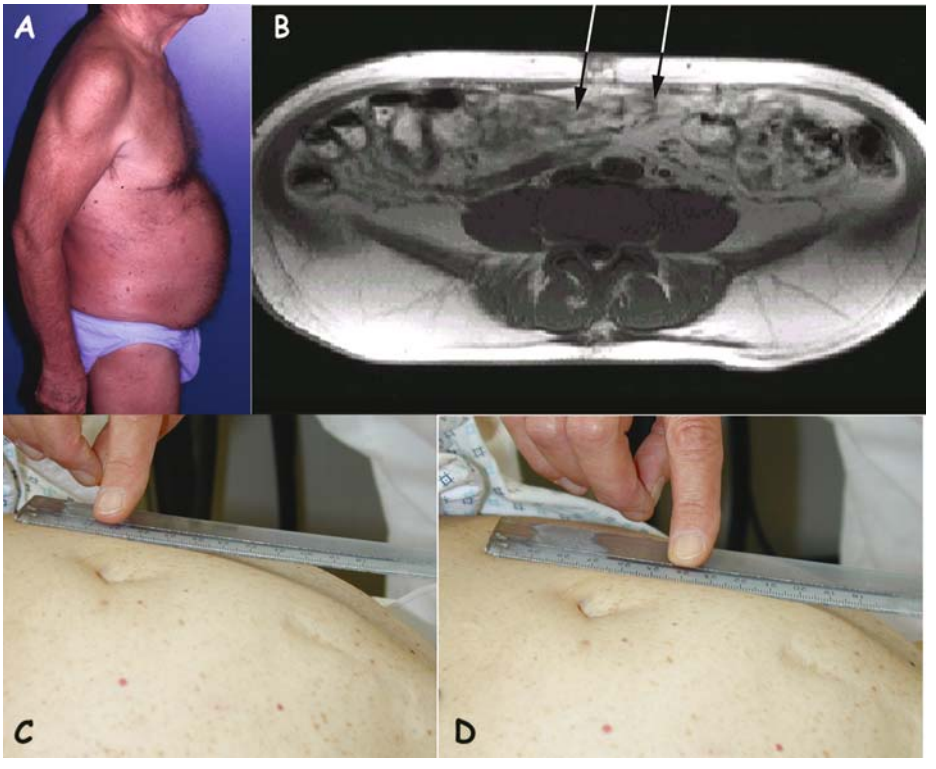

Fig. 4. Abdominal muscle weakness: **A** demonstrates effect of abdominal muscle weakness in a patient with CSF certified borreliosis. His first symptom was a feeling of distension of his abdomen. The MRT scan **B** demonstrates the highly atrophic ventral abdominal muscles. **C** and **D** shows the characteristic Beevor's sign in another patient with abdominal wall involvement of Borreliosis

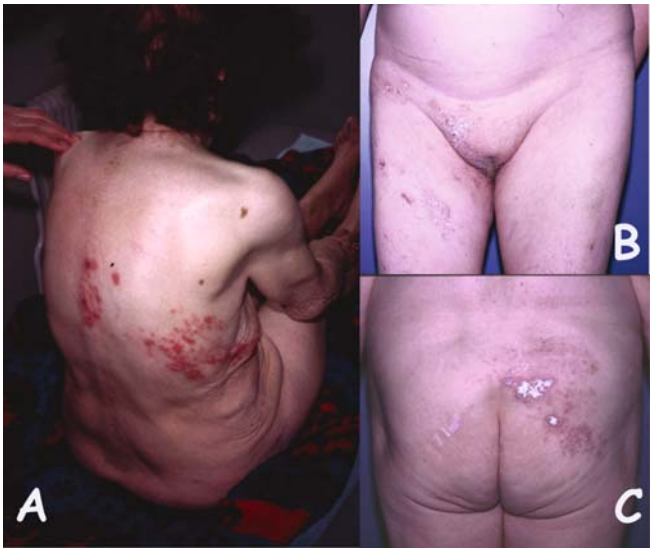

Fig. 5. Herpes zoster: **A** classical herpes with paraspinal-thoracal vesicular lesions and radicular distribution (T8). **B** Herpes zoster in L1 distribution. **C** Sacral herpes zoster

Anatomy

There are twelve pairs of truncal nerves, which innervate all the muscles and skin of the trunk.

The dorsal rami separate immediately after the spinal nerves exit from the nerve root foramina. They pass through the paraspinal muscles, then divide into medial and lateral branches.

T1 ventral ramus consists of a large branch that joins the C8 ventral ramus to form the lower trunk of the brachial plexus, and a smaller branch that becomes the first intercostal nerve.

T2–T6 are intercostal nerves that pass around the chest wall in the intercostal spaces. Half-way around they give off branches to supply the lateral chest. They end by piercing the intercostal muscles near the sternum to form the medial anterior cutaneous nerve of the thorax.

The T2 ventral ramus is unique in size and distribution, and called the intercostobrachial nerve. It supplies the skin of the medial wall and the abdominal floor of the axilla, then crosses to the upper arm and runs together with the posterior and medial nerves of the arm (branches of the radial medial cord).

The second and third intercostobrachial nerves arise from the lateral cutaneous branches of the third and fourth intercostal nerves.

T7–T11 rami form the thoracoabdominal nerves, and continue beyond the intercostal spaces into the muscles of abdominal wall. They give off lateral cutaneous branches and medial anterior cutaneous branches.

The eleventh and twelfth thoracic nerves, below the 12th rib, are called the subcostal nerve.

The roots have a downward slant that increases through the thoracic region, such that there is a two-segment discrepancy with vertebral body and segmental innervation.

Symptoms

Pain and sensory symptoms at various locations (dorsal, ventral nerve). One or more adjacent nerves. Pain is often a feature of truncal neuropathies.

Signs

Muscle weakness only seen if bulging of abdominal muscles can be palpated. Skin lesions may be residual symptoms from Herpes zoster.

Pathogenesis

Disc protrusion:
Uncommon, 0.22–5.3% of disc protrusions.
Surgical intervention may be necessary for symptomatic spinal compression.

Differential diagnosis: postoperative thoracic pain
Drainage in the intercostal space
Injection into the nerve
Postmastectomy pain (spectrum from tingling to causalgia)
Rib retraction

Neoplastic:
Malignant invasion from apical lung tumors
Pleural invasion
Vertebral metastasis: Pain either locally, or in uni- or bilateral radicular distribution. Herpes Zoster may occur in the affected root. Local pain occurs on palpitation.

Leptomeningeal carcinomatosis:
Thoracic roots can be affected.

Inflammatory:
Herpes: preherpetic, herpetic and postherpetic neuralgia. Usually only one nerve, rarely two or more and rarely nerves on opposite sides. Abdominal weakness may be evident (Fig. 5).
Polyradiculopathy is possible with HIV and acquired immunodeficiency syndrome (CMV polyradiculopathy).
Lyme radiculopathy: may affect thoracic roots and cause weakness.

Diabetic truncal neuropathy:
Thoracic spinal nerves; pain and paresthesia

Trauma:
Traumatic disc may cause cord compression.
Herniation of intervertebral disc is uncommon and often caused by trauma.

Thoracic spondylosis:
Rare. Surgical intervention if myelopathy occurs.

Intercostal neuralgia and notalgia paresthetica
T5 paresthesia may mimick angina pectoris.
Other causes: facet joint hypertrophy, arthritis, slipping rib syndrome.
"Chronic intercostal neuralgia" is an ill-defined entity.
Notalgia paresthetica is a sensory neuropathy of second to sixth thoracic rami.
Rectus abdominis syndrome: sharp pain in the anterior wall.

Diagnosis

Laboratory: diabetes, paraproteinemia, Herpes, Lyme
Imaging: plain X ray, CT, MRI
CSF
EMG to assess thoracic paraspinal muscles

Differential diagnosis

Borreliosis (Fig. 4)
Multiplex neuropathy
Multiple sclerosis (root lesions)
Referred pain
Syringomyelia

Therapy

Depending on cause: surgical, conservative

Prognosis

Thoracic disc protrusion with spinal cord compression may have a poor prognosis.

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Lumbar and sacral radiculopathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	+	++	

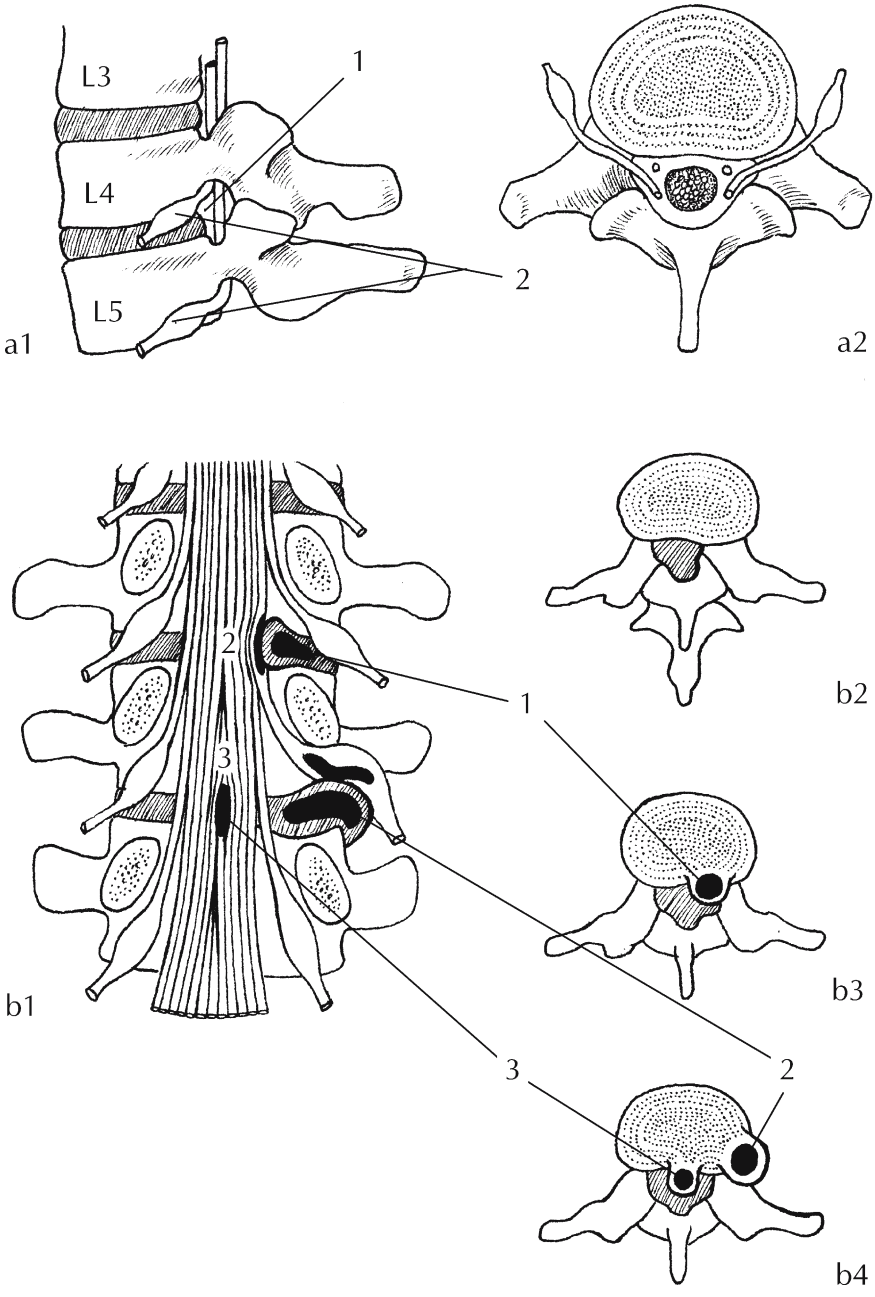

Fig. 6. Lumbar anatomy. **a1** *1.* Intervertebral foramen, *2.* Dorsal root ganglion, **a2** Section at L4-level, **b1** *1.* Mediolateral prolaps, *2.* Lateral prolapse, *3.* Median prolapse, **b2**, **b3** *1.* Mediolateral prolapse, **b4** *2.* Lateral prolapse, *3.* Median prolapse

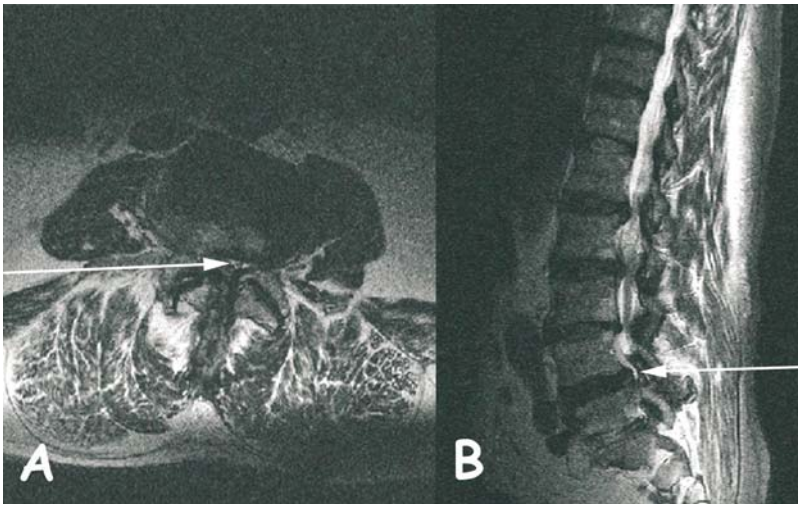

Fig. 7. Lumbar vertebrostenosis. Note the disappearance of the spinal fluid in T2 weighted images **A**. Lateral view shows multiple sites with narrowing **B**

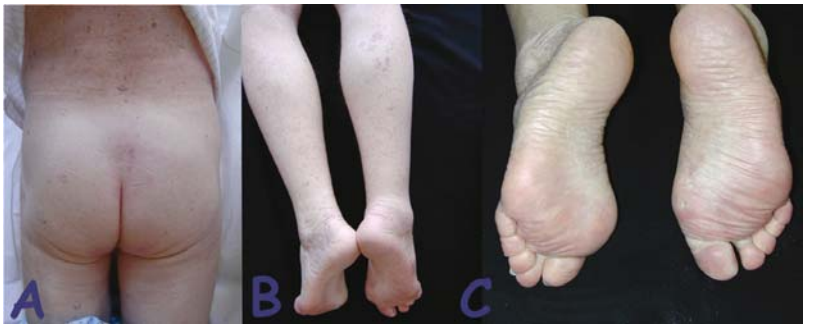

Fig. 8. Motor involvement following sacral herpes S 1 on the right side. The vesicles can no longer be seen. **A** Right sided gluteal weakness with loss of muscle definition on the right compared to the intact left side. **B** Discrete dry skin changes over the right half. **C** Note the skin over the plantar right foot, which appears to be wrinkled compared to left side (atrophy of the small foot muscles)

Anatomy

The nerve root foramina are formed by the pedicles of lumbar vertebrae, which are notched on their upper and lower surfaces. The notches of adjacent pedicles form the upper and lower margins of the nerve root foramina. The anterior borders are the intervertebral discs, and the posterior border is formed by the facet joint and the pedicles.

The spinal cord ends at vertebrum L1. The ventral and dorsal lumbar and sacral roots arise from the conus medullaris and bundle to form the cauda equina.

Lumbar roots run obliquely downward. The dorsal and ventral roots fuse as they enter the foramen. The dorsal root ganglia (DRG) lie within the foramen, although their position may vary. The root divides into ventral and dorsal rami. The lumbar ventral rami form the lumbar plexus (see Fig.).

The sacral spinal nerves divide into rami within the vertebral canal. Each dorsal ramus emerges through a dorsal sacral foramen to supply lower paraspinal muscles and the skin of the sacral and medial gluteal area.

The cauda is enveloped by an arachnoid membrane, from which a sleeve extends to cover each nerve root. As it passes the foramen, the root is covered by a short sleeve of dura (the root pouch).

Autonomic fibers are contained within S2–4 fibers, within the pudendal nerve (which regulates bladder, rectum, anus, sexual function, and regional

blood flow), and pelvic splanchnic nerves. Sympathetic innervation begins with the upper two (sometimes three) lumbar spinal nerves, and then enters the sympathetic chain. Postganglionic fibres are distributed in abdominal and pelvic structures. Patients with the most common radiculopathies (L5/S1) do not have signs of sympathetic dysfunction.

The nerve roots exit in relation to the vertebral column. The cord terminates at vertebral level L1/2; the remaining roots drop vertically downward to exit their respective foramina.

Practical example:
The L5 root arises at vertebral level L1/2 and transverses the interspace of L1/2, L2/3 L3/4 and L4/5. Damage to this root can theoretically occur at several levels: A central disc at L2/3 or L3/4, or a posterolateral disc at L4/5, or a lateral disc stenosis at L5/S1.

The disc protrusions are not uniform. The most common protrusion is in the posterolateral direction. Central or posterior disc protrusions are less common. Also sequestrated tissue from a disc protrusion may protrude and float between segments (see Fig. 6).

In addition to disc protrusions, degenerative spine changes, osteophytic bars and spurs, chronic bulging discs, arthritic and thickened laminae and pedicles, and hypertrophied facets may either compress roots or exert chronic compression in intervertebral foramina.

Symptoms

Virtually all patients suffer from "sciatica": radiating leg pain that increases with sitting, and can be exacerbated with coughing or sneezing. Usually amelioration occurs in the supine position.

Spinal stenosis and neurogenic claudication: pain, weakness, numbness, and dysesthesias occur when walking or standing. In these patients symptoms decrease by bending forward or sitting.

Differental diagnosis: In vascular claudication, it is necessary to sit down for relief. Vascular claudication is characterized by intensely crampy calves when the patient stoops or stands.

Walking uphill increases symptoms of vascular claudication, but relieves neurogenic conditions. Bicycling increases vascular symptoms but improves neurogenic symptoms.

Pain:
Abnormalities of bones, joints and ligaments do not cause pain radiating in the leg, buttock, posterior thigh and below the knee. Bending, sneezing, coughing, and straining with bowel movements are suggestive of neurogenic causes.

Sensory:
Paresthesias are more suggestive of radiculopathy. May be separate from pain, or pain may have a paresthetic component. Mostly, the distal part of the dermatome is affected (e.g., big toe, lateral foot).

Signature areas: dorsum of the foot and big toe – L5. Lateral aspect of the foot and little toe – S1.

Weakness:
Depends on the affected segment. The most commonly observed weakness is foot drop in L5/S1.

Signs

Straight leg raising tests (transmitted between 30° and 70 °). Crossed straight leg raising test suggests extensive lesions.

Reverse straight leg raising test or femoral stretch test suggests higher lumbar levels: L3/4.

The strength of major lower extremity muscle groups is reduced, depending on the affected segment. Muscle atrophy is the rule, very rarely muscles may become hypertrophic.

Monopedal ability to stand on toes or heel is impaired.

Knee and ankle reflexes: no good reflex for L5 (possibly medial hamstring).

Myotomal distribution:

L 1: no motor or reflex changes
L 2: weakness of psoas muscle
L 3: weakness of psoas and quadriceps muscle, knee jerk depressed
L 4: weakness of quadriceps, tibalis anterior and posterior muscles; knee jerk depressed
L 5: weakness in tibialis anterior muscle, toe extensors, peroneal and gluteal muscles; ankle jerk is depressed
S 1: weakness of gastrocnemius muscles, toe flexors, peroneal and gluteal muscles; ankle jerk is depressed
S 2: weakness in gastrocnemius muscle, toe flexors; ankle jerk depressed
S 3: no muscle weakness, no reflex changes; bulbocavernosus and anal wink are abnormal

Radicular sensory findings:

L 1: sensory symptoms in upper groin and trochanter
L 2: sensory symptoms in anterior ventral thigh
L 3: sensory symptoms in anterior thigh and medial knee region, and anterior (saphenal) medial lower leg (over the shin)
L 4: sensory symptoms over medial lower leg and ankle
L 5: sensory symptoms over anterolateral lower leg and dorsum of foot
S 1: sole and lateral border of foot, ankle
S 2: posterior leg sensory loss or paresthesias
S 3: upper medial thigh, medial buttock (without muscle weakness or reflex changes)

It is important to keep in mind that two or more roots can be affected in lumbar disc protrusions, due to how the nerve roots exit (see above).

Pathogenesis

Most frequent lesion: disc herniation

Acute disc herniation
Subacute disc herniation
Bony root entrapment

Vascular:

Epidural hematoma due to anticoagulation therapy
AV malformation, spinal claudication

Infectious:

Epidural abscess
Herpes with rare motor involvement
HIV (CMV)-polyradiculopathy

Lyme disease
Spinal arachnoiditis
Spondylodiscitis

Inflammatory immune mediated:
Ankylosing spondylitis
Sarcoidosis

Compressive:
Disc protrusion

Congenital:
Tethered cord

Trauma:
Fractures of sacrum
Spinal trauma
Vertebral fractures

Neoplastic:
Chondroma
Leptomeningeal carcinomatosis
Ligamentum flavum cysts
Metastases
Neurofibroma
Schwannoma

Bony changes:
Degenerative osseous changes
Fluorosis of the spine
Iatrogenic: operations, punctures
Paget's disease (bony entrapment)
Sequelae from radiotherapy (cauda equina)
Spondylolisthesis
Degenerative spondylolisthesis (Pseudospondylolisthesis)

Lumbosacral spinal stenosis syndrome:
Chronic degenerative disease with narrowing of the spinal canal and nerve foramina.

Symptoms: radicular symptoms, claudication of the cauda equina, and associated weakness.

Pain in the lower back, radiating to both legs. Cauda equina claudication is characterized by pseudoclaudication and intermittent claudication.

Symptoms: pain, paresthesias when walking and standing, resting and bending forward improves symptoms. Some patients also have weakness during the height of symptoms.

Signs: often normal, or signs which are attributable to one or more roots.

Muscle wasting may mimic chronic polyneuropathy.

Due to the fact that a slightly bent forward posture gives the spinal space a maximum extension, patients try to achieve this position as much as possible.

Anatomically, a narrowing of the spinal canal due to abnormal structure, narrowing of the foramina, and degenerative changes of spondylosis can be found.

"Pseudoradicular":
The term "pseudoradicular" is often applied in the German speaking neurologic nomenclature. It implies that the symptoms of the patients resemble a radicular distribution. However, definite radicular symptoms (dermatomal and myotomal symptoms) are often incomplete, and signs are absent or obscured by local pain or reduced mobility due to pain.

The origin of pseudoradicular symptoms is variable and ranges from degenerative vertebral column disease, to osseous disease and pathologic conditions involving the hip.

Far lateral disc protrusion (with MRI diagnosed 10%, previously diagnosed in 2%):
Comprise approximately 10% of all lumbar disc protrusions. They result in foraminal and extraforaminal nerve root compression. The caudal displacement causes displacement of the inferior root. The far lateral herniation causes the rostral displacement of the superior root. Severe pain is characteristic and may be the result of compression near the DRG. The outcome of surgeries to repair this injury is generally good.

Lumbar stenosis:
Acquired lumbar stenosis tends to present at an age later than 50 or 60 years. With surgical treatment about 60% improvement is achieved, with only 30% relief achieved in the conservatively treated group. However no significant deterioration was seen in the untreated group in the following 3 years, whereas 25% of the surgically treated patients felt worse.

Complete laminectomies may result in instability. Multiple lesions are treated with multilevel lumbar laminectomies. Single level disease is most common in L4/5 and surgery is successful in up to 80%. Re-operations have only a 50% success rate.

Spondylolisthesis:
Treatment is by stabilization and neural decompression. Iatrogenic spondylolisthesis results from wide decompression for lumbar stenosis. Overall, there is a 10% rate of spondylolisthesis at 6 years. Degenerative spondylolisthesis results from facet arthropathy with an intact neuronal arch. This most commonly occurs at the L4/5 level. Segmental stenosis and neurogenic claudication accompany the symptoms.

In all individuals, a period of conservative care is warranted: bedrest, diminished activities, and non-steroidal antiinflammatory agents are indicated prior to surgery. The best surgical results occur for patients with preoperative neurogenic claudication, showing symptoms for 4 years or less. Approximately 10% have recurrence and improve with decompression.

Diagnosis

Imaging: plain X ray, CT, MRI

EMG:
High yield muscles are suggested for identification of lumbosacral radiculopathy. Most lesions occur at the L4/5 or L5/ S1 level. Five limb muscles have been suggested for a reasonable screening: the rectus femoris or adductor longus, tibialis anterior, gastrocnemius, gluteus maximus, and tibialis posterior or peroneus longus muscles.

The examination of the paraspinal muscles is useful, but must be handled with caution in patients who have had a laminectomy and in older patients. Diabetics may have fibrillations. Two practical points have to be considered: the relaxation of patients with low back pain for paravertebral EMG may be difficult, and the paravertebral muscles are not ideally innervated in a monosegmental fashion.

Sensory nerve conductions in radicular disease should be normal, despite the patient's sensory symptoms. This is based on the fact that the DRG is spared from compromised disc or bony protrusion. Occasionally true DRG lesions may occur, if the DRG is situated slightly more proximally within the canal or in the foramen.

Despite this consideration, the sensory NCV of the superficial peroneal (L 5), sural nerve (S1), saphenal nerve (L4), and lateral cutaneous nerve of the thigh (L2/3) can be used.

Differential diagnosis

Borreliosis: multiradicular lesions
Diabetic proximal amyotrophy ("Bruns Garland" syndrome)
Facet arthropathy
Leptomeningeal carcinomatosis
Lumbar and sacral plexopathies
Nerve sheath tumors
Spondylosis
Spondylolisthesis
Tethered cord syndrome (rarely in adults)

Therapy

Conservative therapy:
Traditionally bed rest, but also early return to regular activities (early mobilization) is suggested. Excercise for the back and trunk muscles is often helpful.

Medications: non-steroidal anti-inflammatory agents, and opioids only in severe pain for limited periods of time.

Oral steroids, injected steroids, and local anesthetics are also used.

Epidural injections provide short-term pain relief.

Others:
Corsets, TENS, acupuncture, and trigger point injection. There is little evidence for these methods in the literature.

About 80% recover without surgery.

Surgical techniques:
Conventional laminectomy, microdiscectomy, percutaneous discectomy, arthroscopic disc excison, spinal fusion. The success of surgery with modern techniques is favorable.

Urgent surgical interventions are mandated in:
Acute cauda equina symptoms
Marked or progressive weakness
Loss of sphincter control

Relative surgical indications:
Uncontrollable pain
Functionally limiting symptoms and pain after an appropriate trial of conservative therapy (6 weeks)

Table 11. Prognostic factors in lumbar pain

Favorable	Poor
Age < 40	Age > 40
Associated with non-industrial accident	Industrial accident
No prior surgery	Workers compensation litigation
Self employed	
No premorbid medical conditions	Multiple other medical problems

Lumbar fusion:
Required to maintain stability. Three main techniques are used: posterior, posterolateral, and anterior. The development of adjacent level disease following a lumbar fusion is a significant problem, and occurs in 11– 41% of all fusions.

Prognosis

Bed rest and analgesics: resolution in 30%
Prolonged physiotherapy: resolution in 40%
Incapacitating pain or profound neurologic deficit warrant surgical intervention in up to 20%.

In an overview and analysis of lumbar disc protrusions treated conservatively and surgically within a ten year period, remaining sensory and motor deficits were evenly distributed. Better results are seen from surgical treatment after one year. The only significant changes were noted in those with persistent symptoms treated with surgery in the first year following diagnosis. In both the conservatively and surgically treated groups the recurrence rate was approximately equal (20%) over the 10 year period.

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Cauda equina

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		++	

Anatomy

The conus medullaris terminates at vertebrum L1. The lower segmental ventral and dorsal lumbar and sacral nerve roots form the cauda equina.

The lumbar nerve roots run obliquely downwards and laterally. The sacral spinal nerves divide into rami within the spinal canal. Each ramus passes through a pelvic sacral foramen to join the sacral plexus; each dorsal ramus emerges through a dorsal sacral foramen to supply paraspinal muscles and the skin over the sacral and medial gluteal areas.

The cauda equina is loosely enveloped by arachnoid membrane, from which a sleeve extends to cover each nerve root. As a nerve passes into the nerve foramen it is invested in a short sleeve of dura.

Symptoms

Acute central (disc) herniation:
Pain bilaterally in the buttock, sacral, perineal, and posterior leg regions, and sphincter dysfunction.

Chronic:
Back pain, perineal pain, paresthesias. Urinary and erectile dysfunction may occur in men.

Signs

Acute:
Weakness of S1 and S2 muscles, sensory loss from soles to perineal region with saddle anesthesia. Loss of anal wink.

Roots positioned most laterally (lower lumbar and upper sacral) are most often affected, while the central roots can be spared (S3–S5). Thus, the bladder is often spared.

Chronic:
Similar signs as acute injury.
Muscle wasting in chronic conditions may resemble chronic polyneuropathy.

Pathogenesis

Toxic:
Anesthesia (spinal and epidural anesthesia)
Contrast media
Cytotoxic drugs (intrathecal methotrexate)
Radiation: TRI (transient radicular irritation)
Spinal arachnoiditis

Vascular:
AV fistulas (spinal/dural) may mimic spinal stenosis
Cauda equina claudication
Spinal subarachnoid hemorrhage

Infectious:
AIDS: CMV infections
Herpes simplex infection
Others: cryptococcal, syphillis, tuberculosis

Inflammatory/Immune:
Bechterew's disease

Neoplastic:
Ependymoma
Neurofibroma

Rare: dermoid, hemangioblastoma, lipoma, meningioma, paragangliomas, schwannoma

Malignant disease: astrocytoma, bone tumors, leptomeningeal carcinomatosis, metastases, multiple myeloma

Acute central disc protrusion:
A large acute central disc may cause acute and dramatic bilateral sciatic pain. Also pain in the buttock and perineal regions, numbness and weakness of the legs, and sphincter dysfunction. "Saddle anesthesia".

Chronic central disc:
Mimics tumors of the conus medullaris and is associated with perineal pain, paresthesias and urinary dysfunction.

Trauma:
Fractures of the sacrum
Spinal surgery
Vertebral injury

Genetic:
Tethered cord

Diagnosis

Imaging of bony structures and MRI.
CSF in inflammatory conditions

Electrophysiology:
EMG of S1–S3 muscles
Sensory conductions
Reflex techniques (F waves, H reflex)
Spincter EMG including bulbocavernosus reflex
Magnetic stimulation

Differential diagnosis

Spinal cord (epiconus- medullary lesions)
Rapidly ascending polyneuropathy
Sensorimotor neuropathies with autonomic involvement

Therapy

Depends on the cause

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Mononeuropathies

Introduction

Mononeuropathies are an essential part of clinical neurology. The clinical diagnosis depends on the knowledge of anatomy, the presentation of clinical syndromes and numerous etiologies.

The individual mononeuropathies of the upper extremity, the trunk and the lower extremities are discussed by the anatomic course of the nerve , anomalies and their symptoms and signs. The most likely causes of damage are discussed and differential diagnosis is considered. Therapeutic aspects and if available prognosis are mentioned.

The references are limited to a few key references. Most of our artist's illustrations are devoted to this section. The clinical photography should help the reader to identify the patient's abnormalities.

The concept is an accurate and brief description of the most important clinical features. The trunk nerves which are often neglected are summarized in a separate subsection.

Mononeuropathies: upper extremities

Axillary nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

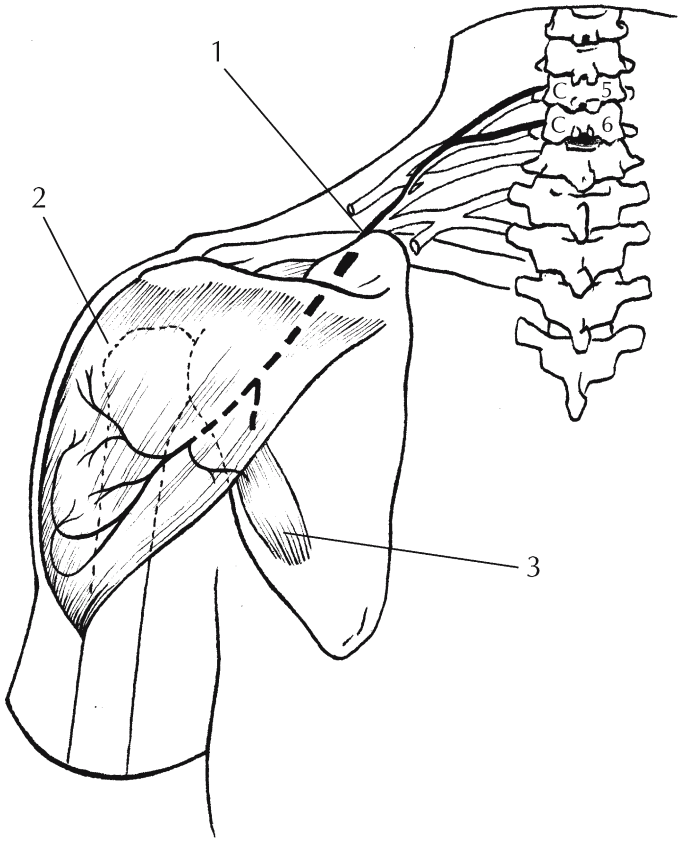

Fig. 1. *1* Axillary nerve. *2* Deltoid muscle. *3* Teres minor muscle

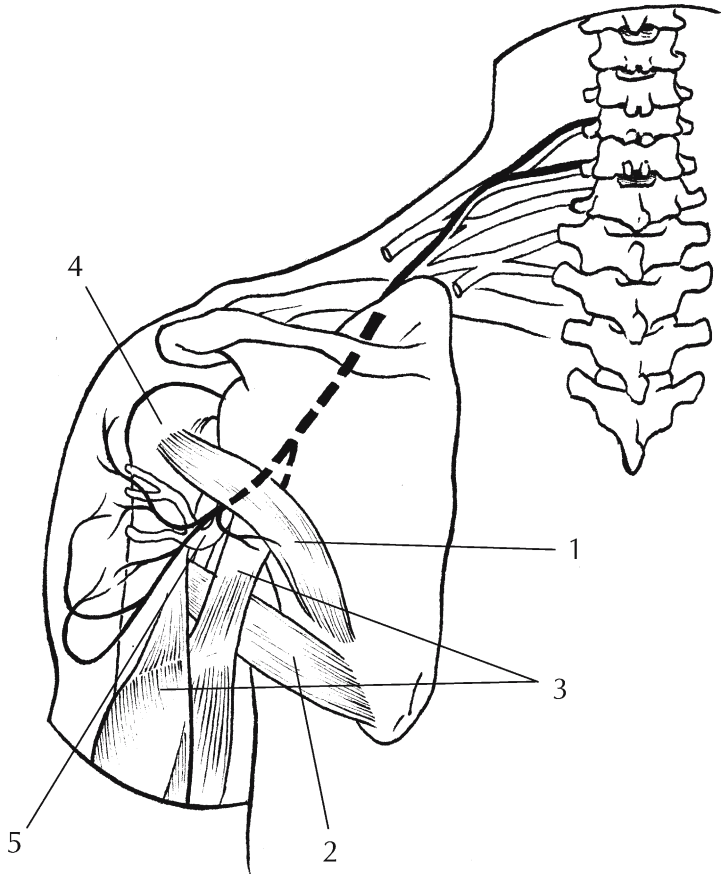

Fig. 2. Quadrilateral space. *1* Teres minor. *2* Teres major. *3* Medial and lateral-caput longum of triceps muscle. *4* Neck of humerus. *5* Circumflexor humeri posterior artery

Anatomy

Fibers originate from roots of C5-C6, and travel through the upper trunk and posterior cord of the plexus.

The nerve continues through the axilla (quadrilateral space), with a motor branch to the teres minor and two further divisions. The posterior division innervates the posterior head of the deltoid muscle and gives off the superior lateral cutaneous nerve. The anterior division innervates the lateral and anterior heads of the deltoid muscle (see Figs. 1 and 2).

Symptoms

Weakness in elevation of the upper arm.

Signs:
Atrophy, and flattening of the lateral shoulder.
Reduction of external rotation and shoulder adduction (teres minor muscle).
Deficits of shoulder abduction, flexion, and extension (deltoid muscle).
Shoulder abduction is the most clinically relevant deficit, as the other muscles are well compensated.

Sensory:
Deficits are variable (and may be absent), involving lateral shoulder and upper arm.

Causes

Acute trauma:
Anterior dislocation of the humeral head, fractures of the proximal humerus or scapula.
Prognostic factors are the time between dislocation and reposition, presence of hematoma, and age.

Blunt trauma:
Heavy objects striking shoulder, contact sports, falls on shoulder

Open injury:
Gunshot, arthroscopy, intramuscular injection

Burner syndrome:
Anterior nerve lesion in association with other nerve structures due to blows to superior shoulder

Neuralgic amyotrophy:
Mainly in association with other nerves, particularly with the suprascapular nerve, and rarely isolated

Malpositioning:
Sleep, anesthesia

Tumors:
Benign nerve sheath tumors, osteochondroma

Quadrilateral space syndrome:
Neurovascular compression syndrome, with pain, paresthesias (non-anatomic distribution throughout the limb), and shoulder tenderness

Birth trauma

Infectious:
Measles

Diagnosis

Electrophysiology:
Axillary nerve latency CMAP most relevant
Disadvantages: No sensory conduction studies. The only stimulation site is proximal to common entrapment locations. Hence, conduction block is hard to differentiate from axonal lesion in the early stage of nerve injury.
EMG: teres minor and all three heads of the deltoid muscle.

Imaging:
Traumatic lesions, quadrilateral space syndrome, space occupying structures
X-ray and CT: all traumatic lesions
MRI: teres minor atrophy often seen in quadrilateral space syndrome
Subclavian arteriography: to demonstrate posterior humeral artery occlusion with shoulder abduction and external rotation.
Axillary arteriogram, duplex scan: pseudoaneurysm

Differential diagnosis

Radicular C5 lesion
Brachial plexus posterior cord lesion

Musculoskeletal:
Multiple steroid injections in the deltoid muscle
Periarthropathia
Rotator cuff rupture
Rupture of the deltoid muscle

Multifocal motor neuropathy

Chronic inflammatory demyelinating polyneuropathy

Therapy

Conservative:
Trauma: neurapraxia, partial lesion (mild axonotmesis)
Blunt trauma
Neuralgic amyotrophy
Malpositioning
± Quadrilateral space syndrome

Operative:
Trauma: severe axonotmesis, neurotmesis
Extrinsic space occupying lesions

Prognosis

Good

References

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Musculocutaneous nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+			

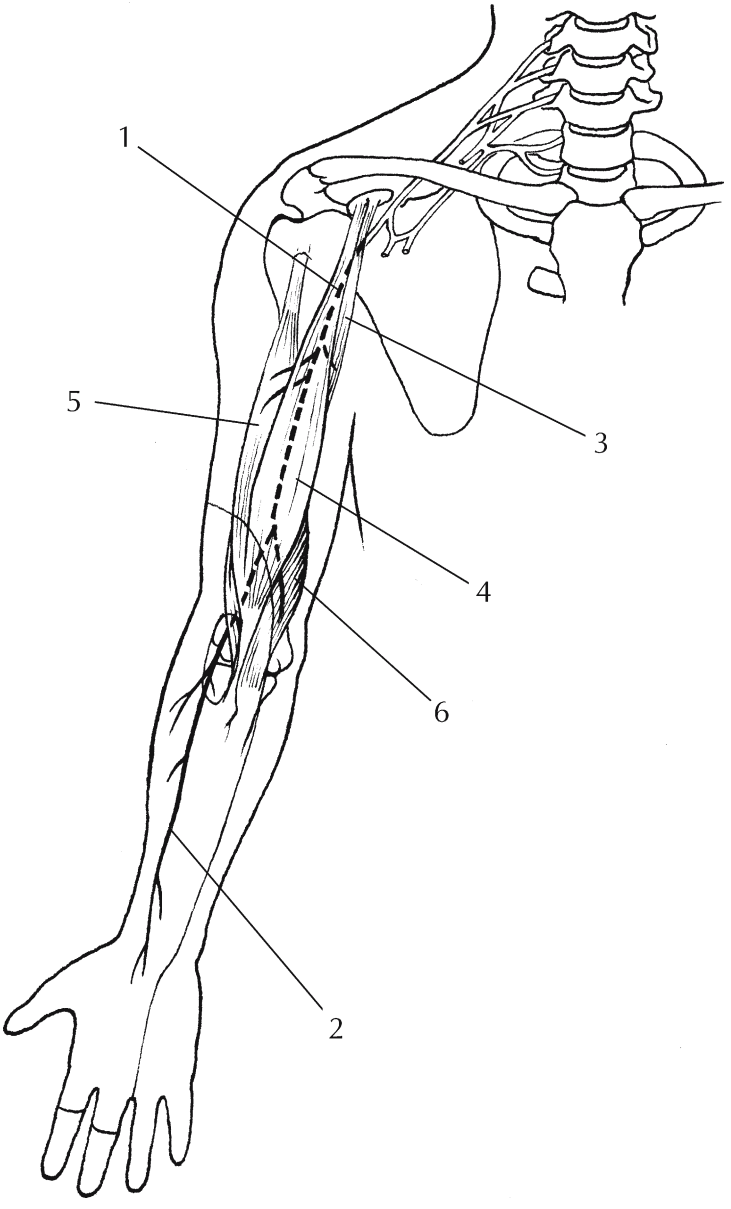

Fig. 3. *1* Musculocutaneous nerve. *2* Cutaneus antebrachii lateralis nerve. *3* Coracobrachialis muscle. *4* Short head of biceps muscle. *5* Long head of biceps muscle. *6* Brachialis muscle

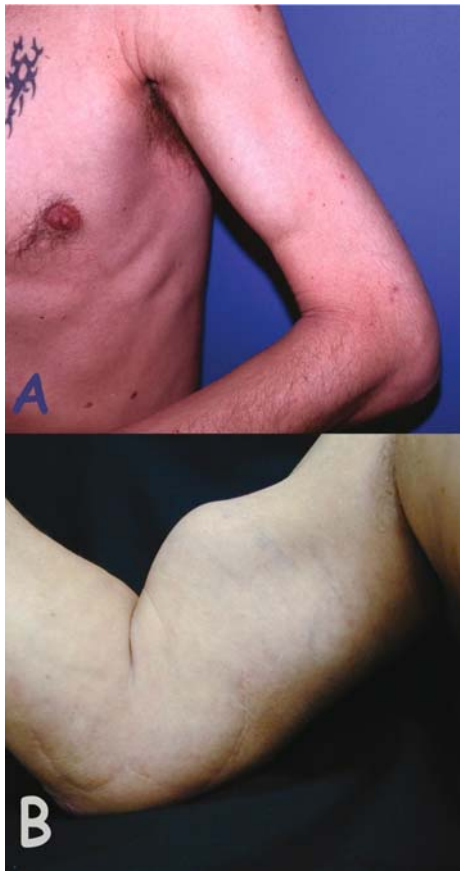

Fig. 4. Biceps pathology. **A** Atrophy of the biceps brachii in a patient with neuralgic shoulder amyotrophy. Note the absent relief of the muscle. **B** Biceps tendon rupture. Typical clinical manifestation with flexion of the elbow

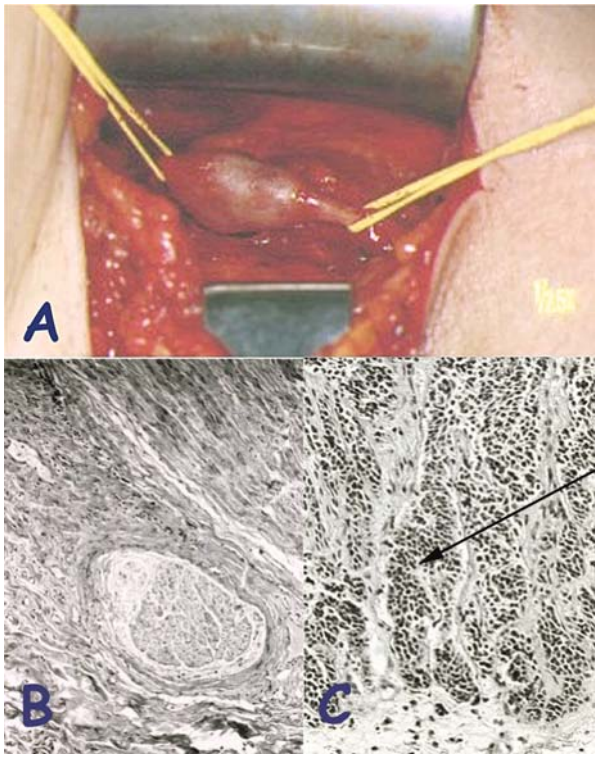

Fig. 5. Nerve metastasis of a carcinoid tumor in the musculocutaneous nerve. **A** Intraoperative site. **B** The nerve fascicles are in close connection with the tumor tissue. **C** Tumor strands within the nerve (arrow)

Anatomy

Fibers from C5–7.
Brachial plexus, lateral cord.
Innervation: coracobrachialis, biceps, brachialis muscles.
Sensory: lateral antebrachial cutaneous nerve – radial aspect of forearm (see Fig. 3).

Symptoms

Wasting of biceps muscle may be noted, difficulties to flex and supinate (rotate outward) the elbow, reduced sensation along radial border of forearm, paresthesia/causalgia (chronic compression or after veinpuncture common), local forearm pain (chronic compression).

Signs

Wasting of biceps muscle. Weakness of elbow supination more prominent than elbow flexion (compensated by brachioradialis and pronator teres muscle). Hypesthesia along radial border of forearm – sensation becomes normal at wrist. Absent biceps tendon reflex (see Fig. 4).

Causes

Rarely isolated.
Abnormal strenuous exercise (carpet carrier, weight lifting)
Entrapment: strap of a bag carried across the antecubital fossa
Iatrogenic: malpositioning during anesthesia, veinpuncture (lateral antebrachial cutaneous nerve), tight bandage
Neuralgic amyotrophy (isolated and in combination)
Proximal humeral osteochondroma, nerve tumors, false aneurysm
Trauma: anterior dislocation of shoulder (frequently associated with axillary nerve), traumatic arm extension, missiles.

Diagnosis

NCV: CMAP and SNAP (compared to unaffected side), EMG, Imaging

Differential diagnosis

C6 radiculopathy
Ruptured biceps tendon

Therapy

Isolated complete trauma: operative, otherwise conservative

Prognosis

Usually good

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Median nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	+ –	?	

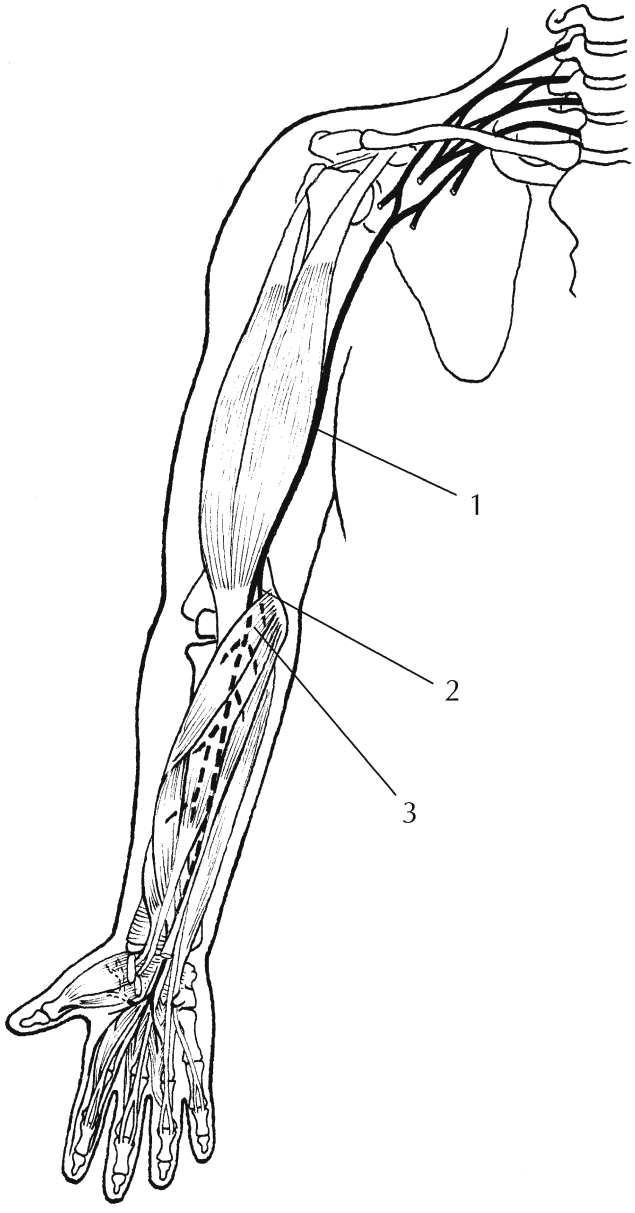

Fig. 6. *1* Median nerve. *2* Interosseus anterior nerve. *3* Pronator teres muscle

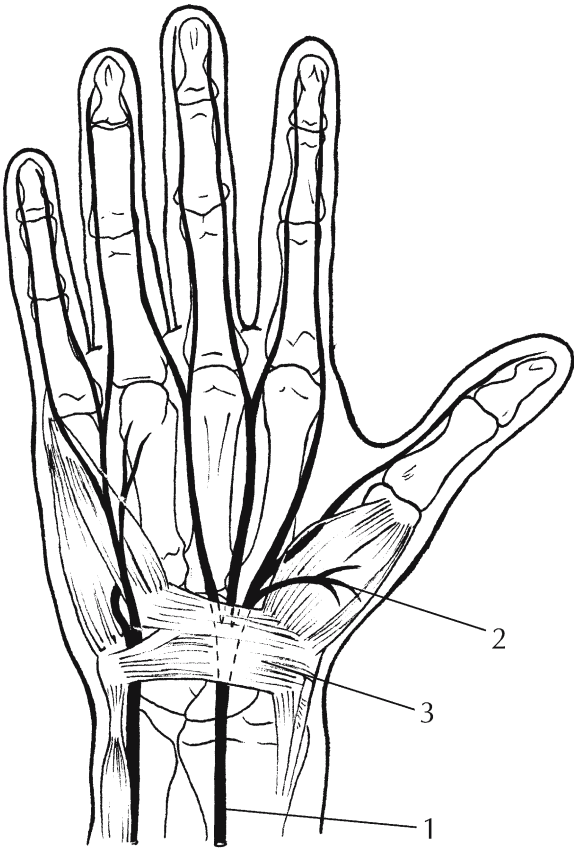

Fig. 7. *1* Median nerve. *2* Thenar branch. *3* Transversal carpal ligament

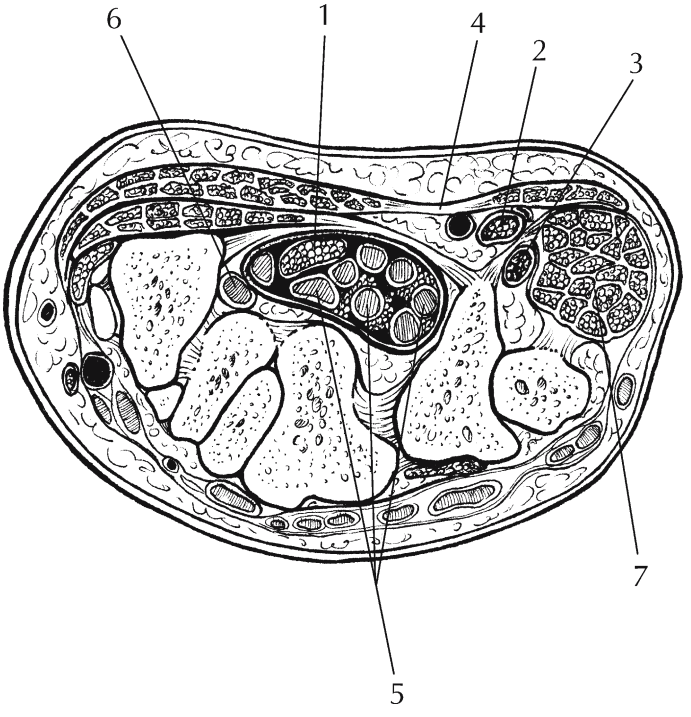

Fig. 8. Section at the distal end of the carpal tunnel. *1* Median nerve. *2* Ulnar nerve. *3* Deep ulnar nerve. *4* Flexor retinaculum. *5* Flexor tendons. *6* Flexor pollicis longus. *7* Abductor digiti minim) muscle

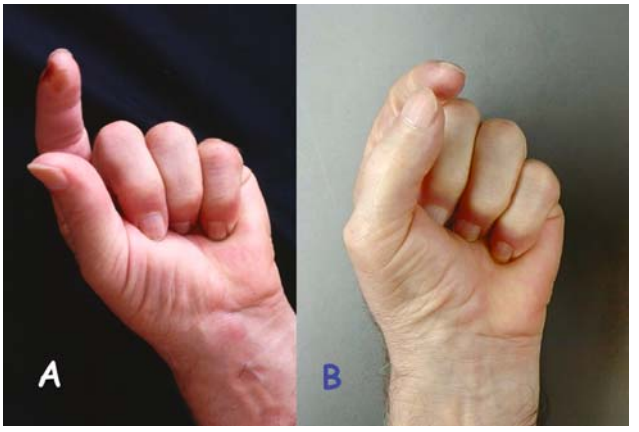

Fig. 9. Transsection of the median nerve and sural nerve interplantate in a 24 month follow up. **A** Orators hand prior to operation, **B** after 24 months the long flexors of the thumb and particularily the index finger show increased mobility

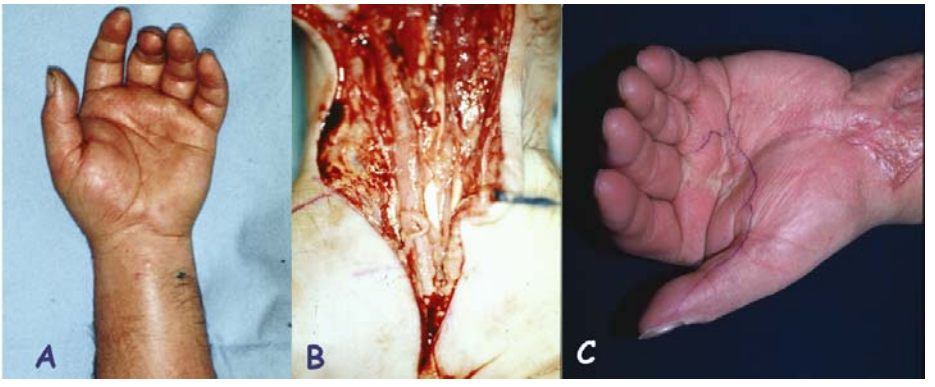

Fig. 10. Acute carpal tunnel syndrome. **A** Local painful swelling of the left volar wrist, sensory loss in median nerve distribution. **B** After confirmation with ultrasound the median nerve was released. **C** Residual deficits were a sensory loss of the volar sides of the fingers (marked with a ball pen)

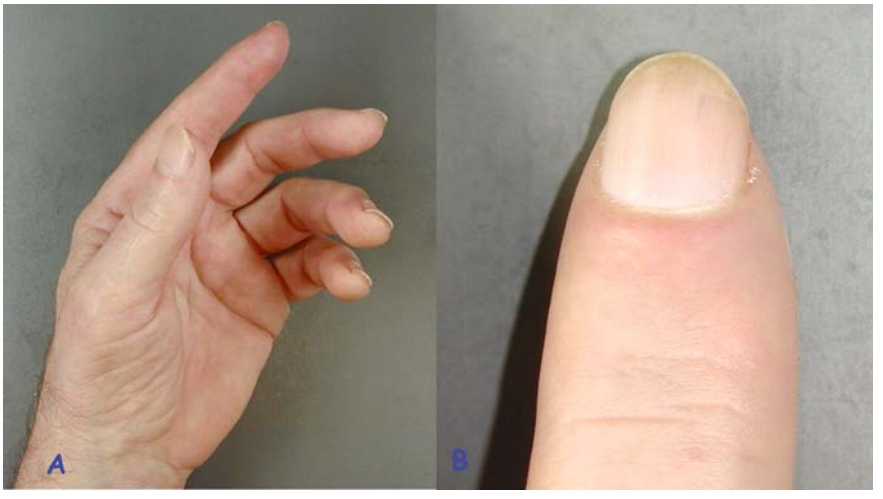

Fig. 11. Trophic changes after a median nerve transsection and nerve implantation. **A** Shows "orators hand", with thenar atrophy. **B** Shows glossy skin over index finger, and trophic changes of the nailbed

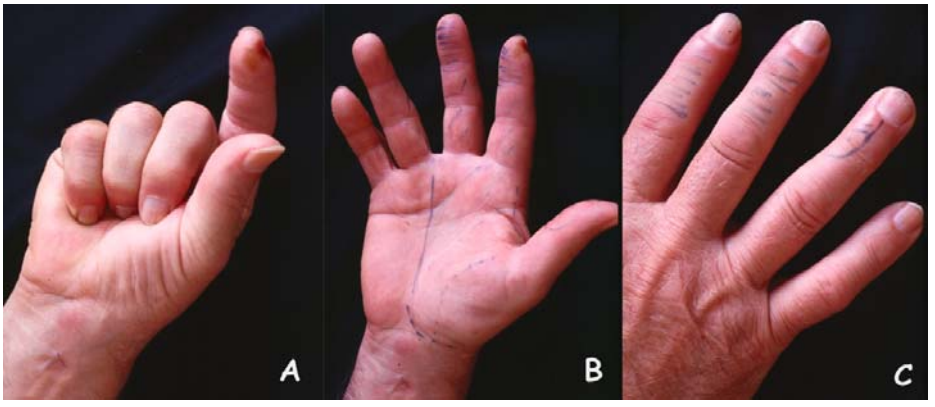

Fig. 12. Complete transsection of the median nerve at the upper arm. **A** Handposition trying to make a fist. Inability to flex index finger and thumb. Ulcer due to sensory loss at the tip of the index finger. **B** Sensory loss is accentuated at the tip of the fingers, but also palm is involved. **C** Dorsal view of the hand, delineating the sensory impairment

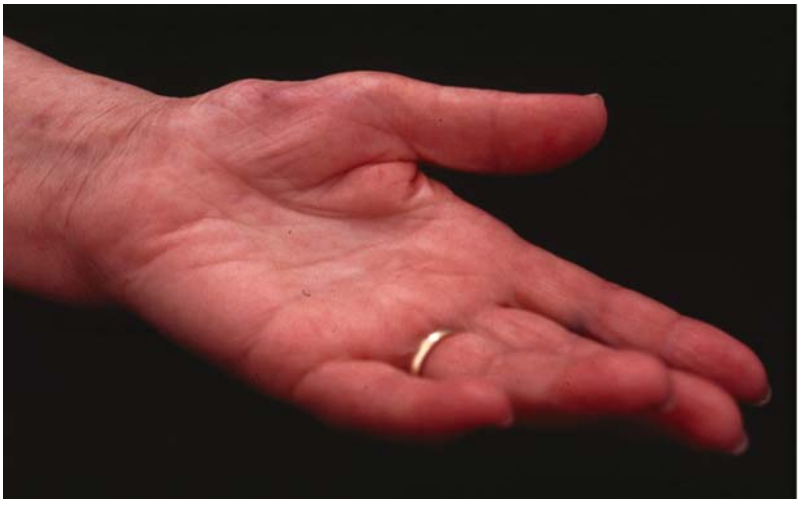

Fig. 13. Carpal tunnel syndrome. Typical atrophy of the thenar eminence

Fig. 14. Neuropathic pain. This patient suffered from a complete median nerve transsection at the upper arm. 2 years later his hand felt uncomfortably and painfully cold. Touch could elicit neuropathic pain. The patient wears a glove to avoid these sensations

Anatomy

Fibers for the median nerve are found in the lateral and medial cord of the brachial plexus, C5–T1. The nerve runs along the lateral wall of the axilla, adjacent to the axillary artery, continuing through the upper arm close to the brachial artery, and then medial to the biceps tendon. In the forearm, it is found between the superficial and deep heads of the pronator teres muscle, which it supplies. The nerve sends branches to the flexor carpi radialis, palmaris longus, and flexor digitorum superficialis muscles, then divides into a pure motor branch, the anterior interosseus nerve, innervating the flexor pollicis longus, pronator quadratus, and the flexor digitorum profundus I and II. The main branch enters the hand through the carpal tunnel and innervates the abductor pollicis brevis, opponens pollicis, the lateral half of the flexor pollicis brevis, and the first and second lumbrical muscles. There are also sensory palmar digital branches (see Figs. 7 and 8).

Anomalies

Martin Gruber anastomosis:
Nerve fibers cross from the median nerve to the ulnar nerve in the forearm. Variations include:

a) Median fibers crossing to the ulnar, then travel to the hand and supply muscles which are normally supplied by the median nerve
b) Similar to a), but the motor fibers supply both median and ulnar muscles
c) Ulnar nerve motor fibers enter the median nerve from the brachial plexus, travel to the forearm, then travel to the hand and innervate muscles supplied by the ulnar nerve

Rare: ulnar-median anastomosis
Richie Cannieu anastomosis

Rare: sensory crossover
Recurrent motor branch of median nerve
Palmar cutaneous branch

Clinical Syndrome

(Topographical order)

Lesions in shoulder, axilla, upper arm:
Weakness in pronation (compensated partially by the brachioradialis muscle), wrist flexion (associated with ulnar deviation), and loss of hand function (weak abduction and opposition of thumb, inability to flex distal interphalangeal joints of dig I–III, and of proximal joints of dig I and II) (see Fig. 12).

Elbow:
Pronator teres syndrome:
Pain over the pronator teres muscle, weakness of flexor pollicis muscle, preservation of pronation, and sensory changes over the thenar eminence

Anterior interosseus syndrome:
Synonymous with Kiloh and Nevin syndrome. Pain in the forearm, but normal sensation. Pinch sign: inability to form a circle with fingers I and II.

Wrist: carpal tunnel syndrome (CTS) (see Figs. 9 through 11, 13 and 14):
Nocturnal paresthesias in the hand, may radiate up to shoulder.
Paresthesias during daytime, particularly during the use of the hand with forced flexion or extension at the wrist.

Local pain at the wrist.
Sensory symptoms of the first three digits and the radial half of the fourth digit.
Most commonly, hypesthesia is restricted to the volar tip of the second and third finger.
Weakness of thumb abduction and opposition.
Sensory loss may result in clumsiness.
Motor sign: Thenar atrophy
Clinical testing:
Tinel's sign – about 70% sensitivity
Phalen's sign – about 80% sensitivity

Fingers:
Digital nerve entrapment: Dysesthesia in local distribution

	Causes
Crutches	Axilla
False aneurysm	
Missile	
Shoulder dislocation	
Sleep palsy	
Stabbing	
AV fistula	Upper arm
Compartment syndrome	
Fracture of the humerus	
Sleep	
Stabbing	
Tourniquets	
Angiography	Elbow
Compression:	
Anomalous fibrous bands	
Bicipital aponeurosis	
Pronator teres syndrome	
Adjacent structures	
Elbow dislocations	
Humerus supracondylar fracture	
Medial epicondyle	
Supracondylar spurs	
Tumors & masses	
Pronator teres syndrome:	Proximal forearm
Anterior interosseus neuropathy	
Chronic compression	
Direct injury	
Excessive muscular exercise	
Midshaft radius fractures	
CTS	Wrist
Space reduction in carpal tunnel:	
Exostoses	

Ganglia
Gout
Osteophytes
Rheumatoid arthritis (RA)
Tendons
Vascular

Increased susceptibility:
Diabetes
Hereditary neuropathies
Leprosy
Uremic neuropathy

Others:
Acromegaly
Amyloidosis
A-V shunt
Familial disposition
Hypo- and hyperthyroidism
Infections
Idiopathic
Mucopolysacharidosis
Pregnancy, lactation
Work related

Acute CTS (rare)
Hematoma
Infection
RA exacerbation
Wrist fracture and dislocation

Digital nerves

Digital nerve entrapment:
Inflammation
Trauma
Tumor

Diagnosis

Electrophysiology (NCV, EMG)
Imaging
Laboratory

Differential diagnosis

Radicular lesions C6 and C7
Thoracic outlet syndrome
Thalamic infarcts

Therapy

Depends on the etiology and electrophysiology.
CTS: forearm splint at nighttime, ultrasound at wrist.
In acute CTS, CTS with motor impairment, or persistent entrapment despite conservative therapy: operative split of carpi transversum, either via endoscopic or open technique. Prognosis for both techniques is good (85% success).

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Ulnar nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy	Neurosurg. exploration
	+		+		

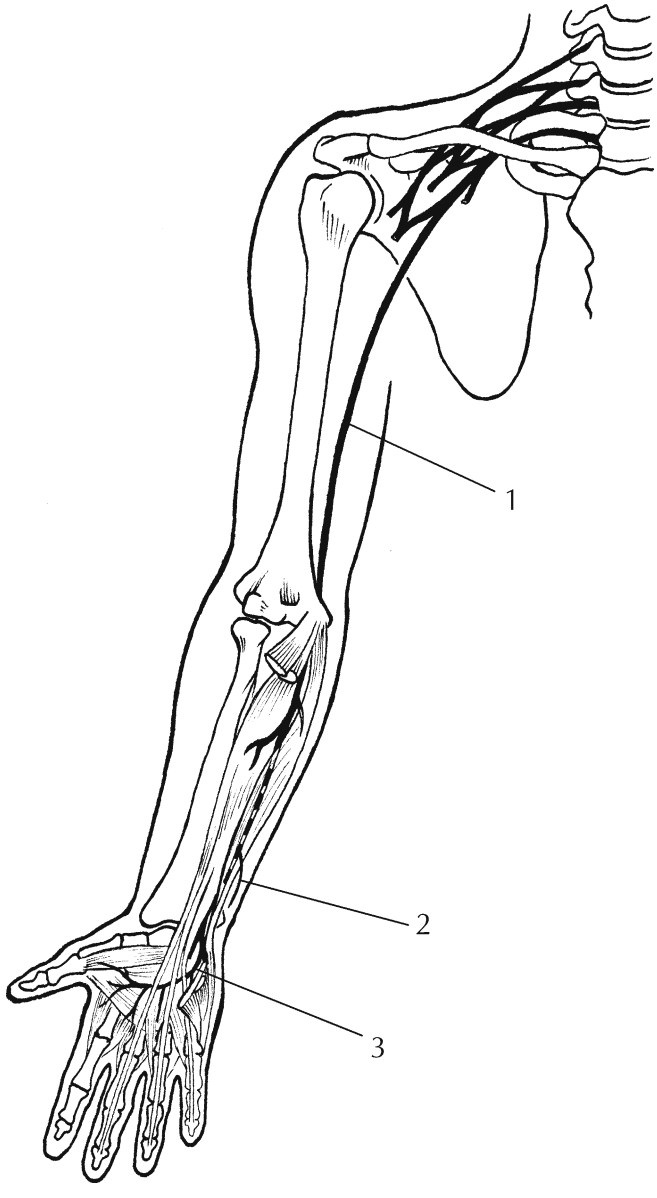

Fig. 15. *1* Ulnar nerve. *2* Dorsal cutaneus branch. *3* Deep motor branch

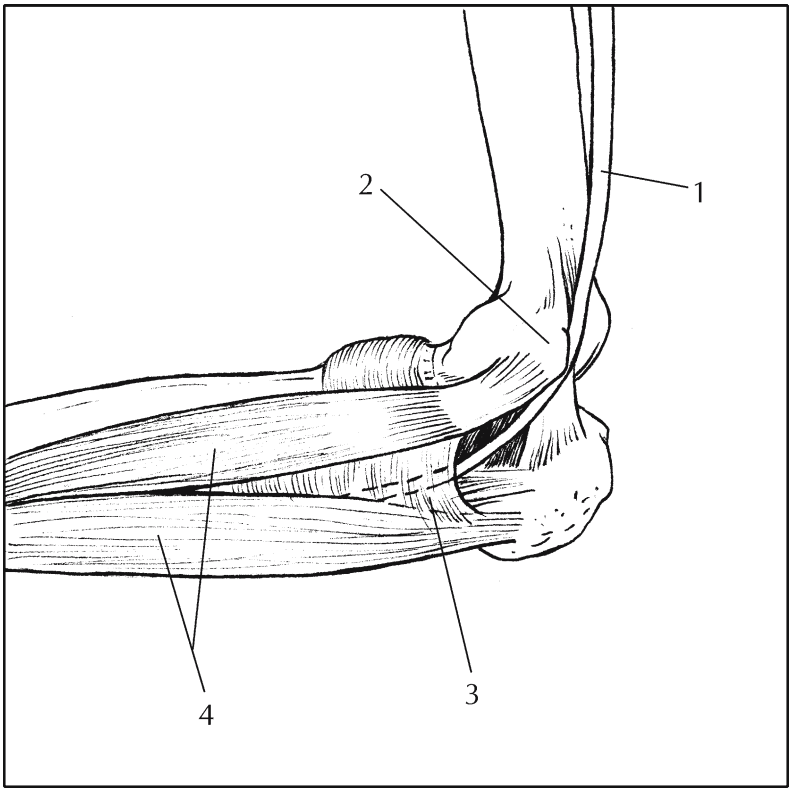

Fig. 16. Medial epicondyle and cubital tunnel. *1* Right ulnar nerve. *2* Medial epicondyle. *3* Aponeurosis. *4* Flexor carpi ulnaris

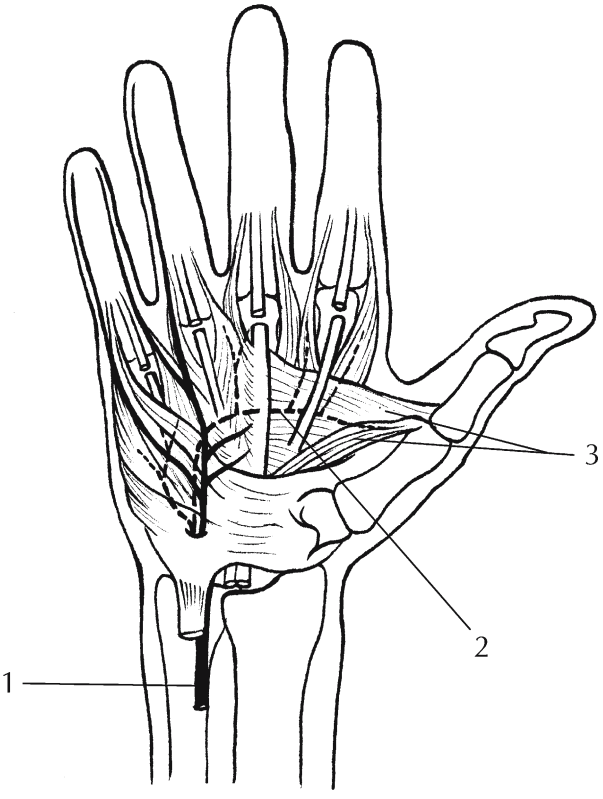

Fig. 17. *1* Ulnar nerve. *2* Deep terminal branch. *3* Thenar muscles

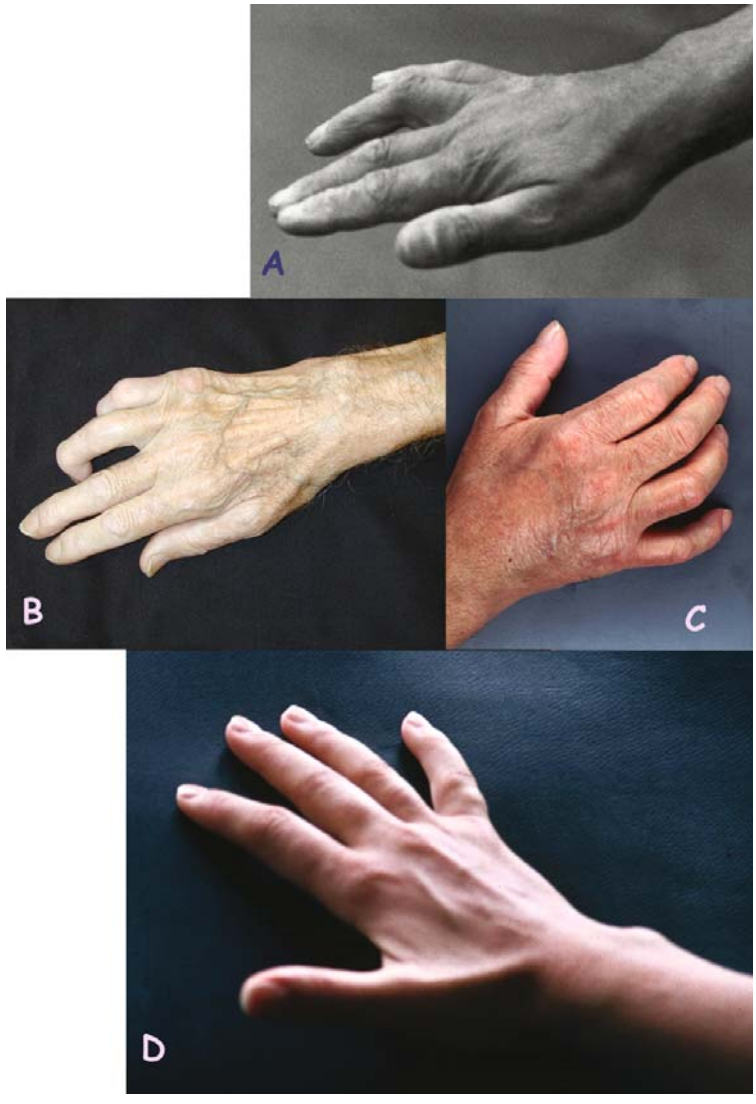

Fig. 18. Ulnar nerve lesion. **A** Complete transsection at lower arm level by a glass pane. Note the typically flexed finger 4 and 5. **B** Distal ulnar nerve lesion with a 50 year duration. **C** Distal ulnar lesion, after the exit of the branch to the hypothenar. Note the atrophy of the interosseus I. **D** Long lasting ulnar nerve palsy. Atrophy of interosseus I and other interossei

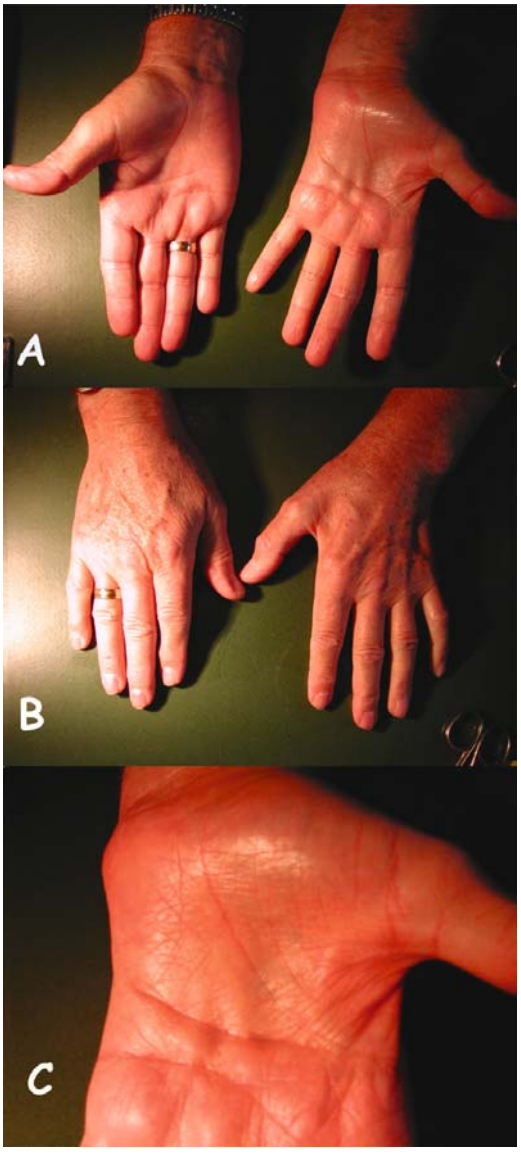

Fig. 19. Traumatic ulnar nerve lesion at the elbow, during intensive care treatment and malpositioning. **A** Atrophy of the small hand muscles with protruding flexor tendons and preserved thenar, and atrophied opponens muscles. **B** Dorsal view with interosseus atrophy. **C** Unusual atrophy of the opponens muscles, leaving a groove over hypothenar

Anatomy

The nerve fibers arise from C8 and T1, and pass through the lower trunk and medial cord of the brachial plexus. The nerve continues along the humerus and the ulnar condylar groove (the humeroulnar arcade).

Motor branches innervate the flexor carpi ulnaris, flexor digitorum profundus, most of the hand muscles (abductor digiti minimi, flexor digiti minimi, interossei I–IV, lumbricals III, IV, adductor pollicis, flexor pollicis brevis).

Sensory branches (superficial terminal, palmar cutaneous, dorsal cutaneous nerves) innervate the hand (see Fig. 15 through 17).

Symptoms

Numbness and tingling (exacerbated by arm use). Pain is restricted to the hypothenar region of palm. Also, loss of dexterity and loss of control of the small finger.

Signs

Sensory distribution of the ulnar nerve: ulnar aspect of the palm, volar surface of the fifth digit, and ulnar half of the fourth digit.

Sensory distribution of the dorsal sensory branch: ulnar aspect of dorsum of hand, and fourth and fifth digit.

Motor disability: weakness of pinch between thumb and adjacent digits (Froment's sign- weakness of first dorsal interosseus muscle). Weakness of the flexor pollicis brevis muscle and adductor pollicis muscle. Weak digital flexion during grasp (digits 4 and 5) (see Figs. 18 and 19).

Full blown ulnar lesion results in claw deformity (see Fig. 18).

Tinel's sign may be elicited by palpation of the ulnar nerve at the elbow.

Causes

Axilla and upper arm

Entrapment at the arcade of Struthers
External pressure: crutch palsy

Elbow

Deformities of joint
Elbow deformity with chronic stretch
External pressure
Fibrous band
Fractures
Mass: gangloid, sesamoid bone
Recurrent subluxation
Repetitive flexion
Supracondylar spurs
Trauma

Forearm

Hypertrophic flexor carpi ulnaris

Wrist and hand

Forced use**:** Bicycle (Loge de Guyon)
Injuries
Lacerations
Pressure: Ganglion, pisohamate ligament

Diagnosis

Nerve conduction studies:
Motor
Sensory
Dorsal sensory ramus
EMG
MRI, Ultrasound

Differential diagnosis

ALS/MND
Brachial plexus- lower trunk
Monomelic atrophy
Multifocal motor neuropathy
Radicular: C8 lesion
Syringomyelia

Therapy

Conservative therapy is indicated if there is no detectable structure and mild abnormality (clumsiness, no atrophy), or moderate abnormality (intermittent or constant paresthesias, mild atrophy, mild weakness).

Surgery is indicated for severe abnormality (constant paresthesias, atrophy, moderate weakness).

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Radial nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

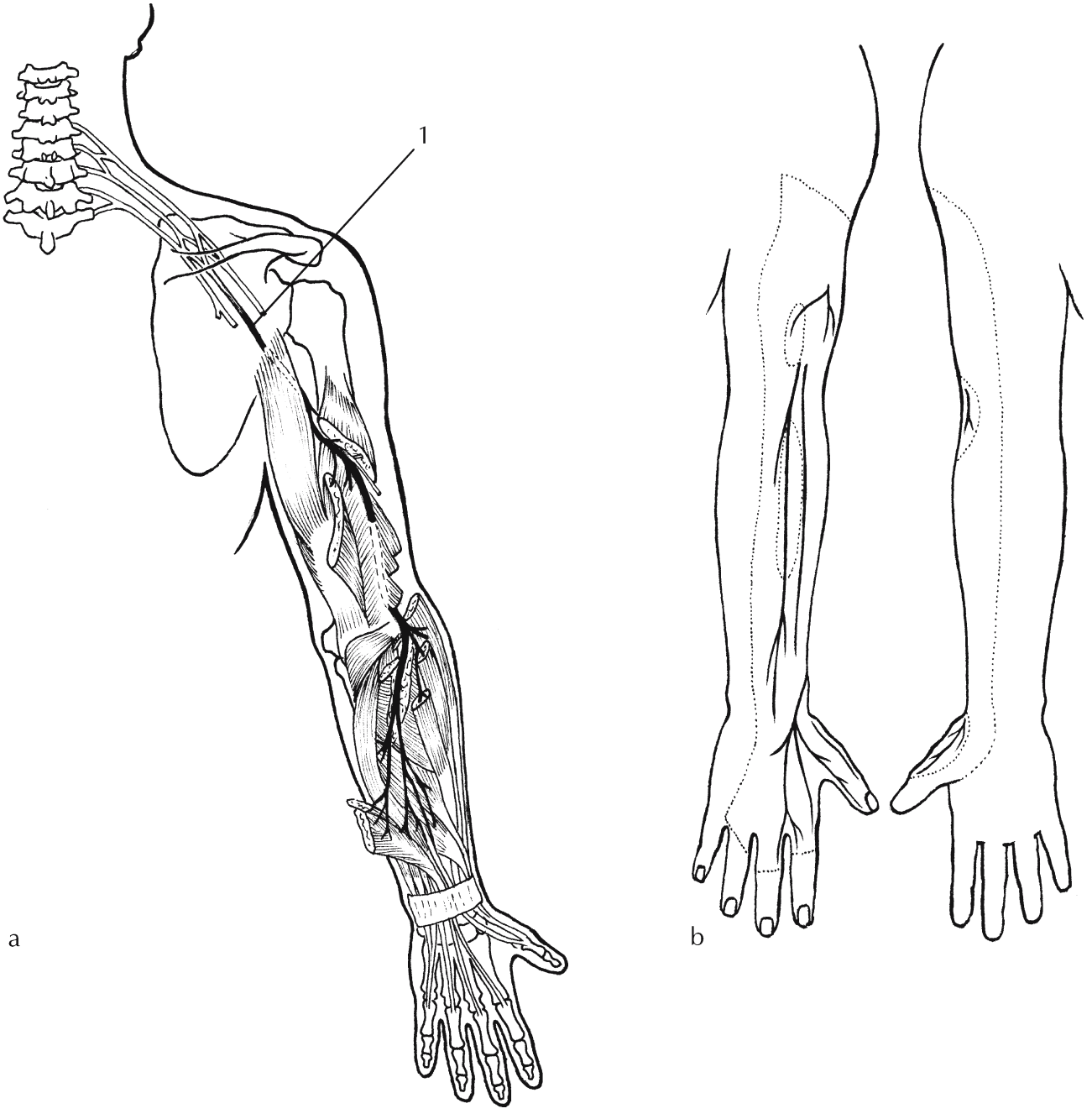

Fig. 20. a *1* Radial nerve. **b** Sensory area of the posterior cutaneous and the superficial radial nerve

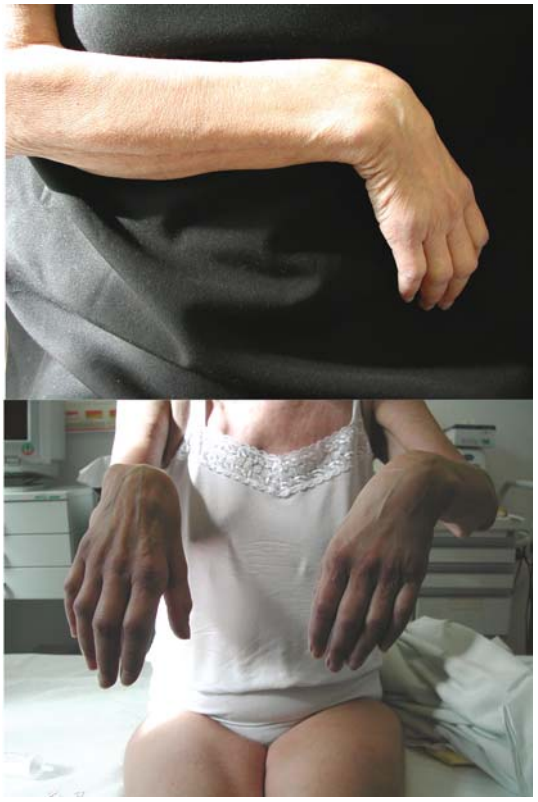

Fig. 21. Radial nerve injury. Hand drop and wrist drop

Anatomy

Fibers from C5-T1 spinal cord contribute to the radial nerve.

The nerve travels through the brachioaxillary angle, then along the spiral groove of the humerus, continuing in the anterior compartment of arm. At the elbow joint, it gives two branches: the posterior interosseus nerve, which travels along the radius and innervates the supinator muscle and the extensor muscles of the digits and the extensor carpi ulnaris; and the superficial radial nerve, which travels under the brachioradialis muscle, then passes through the dorsal forearm and wrist, giving off multiple terminal branches.

The sensory branches of the radial nerve are the posterior cutaneous and superficial radial nerves (see Fig. 20).

Clinical symptoms and causes

Axilla

Motor:
Axillary lesions cause problems with elbow extension, wrist drop and finger extension.

Sensory:
Sensory deficits occur in the dorsal upper arm and distal radial nerve distribution. Triceps tendon and radioperiosteal reflexes are absent.

Causes:
Compression by a fibrous arch of the triceps – slowly progressive, painful, sometimes bilateral
Crutch (occasionally bilateral)
Hyperabduction in surgery
Shoulder dislocation
Strenuous muscular effort – acute onset, painless
Missile wounds

Upper arm

Motor:
Impairments include flexion of the elbow (brachioradialis muscle) in middle position of pronation and supination, and hand/finger extension.

Sensory:
Impairments in the distribution of the superficial radial nerve: medial dorsal aspect of the hand
Absent radioperiosteal reflex

Causes:
Humerus fracture (quite frequent – about 11% of cases). Onset is acute, and often from a traction injury. "Delayed" onset is rare, but can result from entrapment of the nerve in fracture, callus or scar tissue.

Compression at the spiral groove: common. During unconsciousness (coma, head injury, substance abuse, sleep paralysis (Saturday night palsy), unusually long pressure to the upper arm (military personnel – shooting, training), tourniquet, neonates (compression by umbilical band, amniotic bands or uterine constriction rings).

Injections
Malpositioning
Missile injury
Neoplasms
Trauma: blunt trauma, neurapraxia, partial lesion

Forearm

Posterior interosseus nerve (PIN): Purely motor branch, supplies dorsiflexor muscles of the fingers. Dull pain in the deep extensor muscle mass (occasionally sharp pain), "inability to use the hand", no sensory symptoms.

Radial deviation of the hand, weak wrist extension, weak extension of all digits (in a complete lesion) weak extension of fourth and fifth digits (in a partial lesion, the "pseudoclaw" hand), normal sensory findings.

Causes:
Fracture of radius
Iatrogenic: radial head resection, elbow arthroscopy, hemodialysis shunt
Neuralgic amyotrophy isolated to PIN distribution.
Overuse of musical instrument
Rheumathoid arthritis
Soft tissue mass, tumors, ganglions
Trauma: missiles, laceration, fractures (Monteggia fracture – combination of fracture and dislocation), tardy neuropathy.

Supinator syndrome:
Entrapment/compression of the nerve at the Arcade of Frohse, the tight pathway through the supinator tunnel (also called supinator channel syndrome, radial tunnel syndrome).

Tennis elbow:
Local pain at lateral elbow epicondyle, no direct involvement of the radial nerve.

Radial tunnel syndrome:
Controversial clinical speculation in patients with resistant tennis elbow, no objective data, and no motor or sensory deficits.

Posterior cutaneous nerve of arm and forearm:
Rarely lesioned, injury and surgery

Distal lesions:

Distal posterior interosseus nerve syndrome:
Persistent, dull, aching pain (aggravated by repetitive wrist dorsiflexion) on the dorsum of the wrist.

Causes:
Occupational (repetitive wrist dorsiflexion)
Surgical procedures (e.g. removal of ganglion) on dorsum of wrist

Superficial radial neuropathy:
Sensory loss (wide anatomic variation), occasionally painful dysesthesias.

Causes:
Compression: bracelets, handcuffs, ganglia, scaphoid exostosis
Iatrogenic: Surgical procedures (e.g. tenosynovectomy, plating), vein puncture, tight casts
Nerve infarct: Diabetes
Occupational overuse
Trauma: Lacerations (e.g. glasses, knives)

Diagnosis

Electrophysiology (Motor and sensory NCV, EMG)
Imaging (x-ray, CT, MRI)

Differential diagnosis

Brachial plexus: posterior cord lesion
Central paresis (pseudo-radial nerve paralysis)
Radicular C7 lesion (Fig. 21)

Musculosketal:
Rupture of extensor tendon, tendinitis, ischemic muscle necrosis

Neuromuscular disorders:
HNPP
Lead neuropathy (often bilateral)
Migrant sensory neuritis (Wartenberg's syndrome)

Multifocal motor neuropathy
Myotonic dystrophy
Neuralgic amyotrophy
Spinal muscular atrophy

Therapy

Conservative

Operative:
Warranted for extrinsic space occupying lesions, trauma.

References

Atroshi I, Johnsson R, Ornstein R (1995) Radial tunnel release: unpredictable outcome in 37 consecutive cases with a 1–5 year follow-up. Acta Orthop Scand 66: 255–257
Barnum M, Mastey RD, Weiss AP, et al (1996) Radial tunnel syndrome. Hand Clin 12: 679–689
Carfi J, Ma DM (1985) Posterior interosseus syndrome revisited. Muscle Nerve 8: 499–502
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Linscheid RL (1965) Injuries to radial nerve at the wrist. Arch Surg 91: 942–946
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Spinner M, Freundlich BD (1968) Posterior interosseus nerve palsy as a complication of Monteggia fractures in children. Clin Orthop 58: 141–145
Sturzenegger M (1991) Die Radialisparesen. Ursachen, Lokalisation und Diagnostik. Nervenarzt 62: 722–729
Wartenberg R (1932) Cheiralgia paresthetica: Neuritis des Ramus superficialis Nervi radialis. Z Neurol Psychiatr 141: 145–155

Digital nerves of the hand

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	(+)	+ –		

Symptoms

Sensory loss in the fingers

Signs

Tinel's sign, callus, local swelling

Causes

Trauma

Joint abnormalities: mucous cyst from arthritis, osteophytes

Mechanical trauma: scissors, bowlers thumb, "mouse neuropathy", nylon shopping bags

Miscellaneous:
Diabetes
Leprosy
Rheumatoid arthritis
Vasculitis

Musicians: instrument, bow

Nerve tumors, Schwannoma

Tendon sheath pathology:
Cysts
Giant cell tumors
Rheumatoid tenosynovitis

Trauma:
Blunt trauma digit and palm
Chronic external compression
Fractures
Lacerations

Diagnosis

NCV
MRI

Therapy

Conservative treatment
Surgical procedures rarely necessary

Reference

Dawson DM, Hallet M, Wilbourn AJ (1999) Digital nerve entrapment in the hand. In: Dawson DM, Hallet M, Wilbourn AJ (eds) Entrapment neuropathies. Lippincott Raven, Philadelphia, pp 251–263

Mononeuropathies: trunk

Phrenic nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy	Pulmonary function tests
	+ NCV EMG of the diaphragm	+ –	+ X ray Ultrasound of diaphragm		

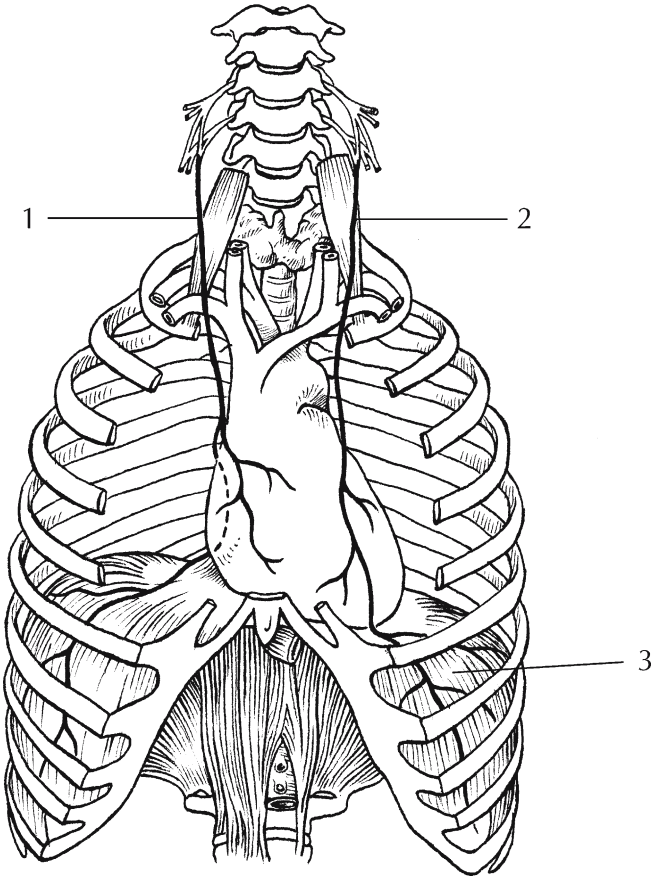

Fig. 22. Phrenic nerve is in the vicinity of the pericardium. *1* Right. Phrenic nerve. *2* Left. Phrenic nerve. *3* Anterior portion of Diaphragm

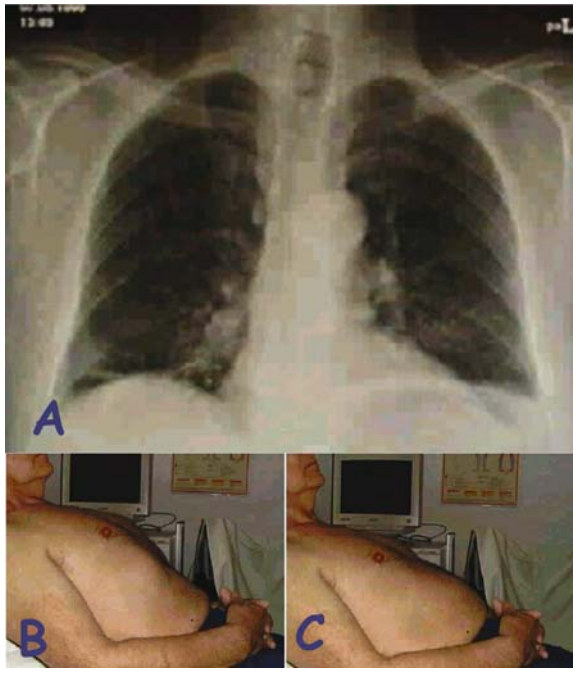

Fig. 23. Diaphragmatic injury. **A** Diaphragmatic paralysis. **B** Inspiration. **C** Expiration

Anatomy

The phrenic nerve fibers are from C3, 4, and 5. The connection with C3 may be via the inferior ansa cervicalis (cervical plexus). The nerve travels over the anterior scalenus muscle, dorsal to the internal jugular vein, and crosses the dome of the pleura to reach the anterior mediastinum. On the right side, it is positioned next to the superior vena cava and near the right atrium. Sensory branches innervate the pericardium. After transversing the diaphragm, the phrenicoabdominal branches supply the peritoneum of the diaphragm, liver, gall bladder and pancreas. Terminal branches end in the celiac plexus (Fig. 22).

Symptoms

Unilateral lesion: mild dyspnea, or asymptomatic.

Bilateral lesions: age dependent, with babies and small children developing respiratory problems. Newborns with bilateral lesions require ventilation.

Adults are easily dyspneic, particularly upon exertion, and unable to lie in a supine position.

Causes

Birth trauma (with or without associated brachial plexus lesions)
Idiopathic
Polyneuropathies (AIDP, critical illness, multifocal neuropathy with conduction block)
Neuralgic amyotrophy

Frequent sites of lesion

Chest:
Intrathoracic malignant tumors
Chest operations (intraoperative mechanical or local cooling)
Neck wounds
Traction, with upper trunk of brachial plexus damage
Chest radiograph

Diagnosis

Clinically: respiration, ability to recline supine (Fig. 23)
Electrophysiology: NCV, EMG of diaphragm
Pulmonary function tests
Transdiaphragmatic pressure

Differential diagnosis

Adult onset maltase deficiency
Herpes zoster with motor involvement
Motor neuron disease
Myotonic dystrophy
Poliomyelitis (spinal)
Polymyositis/Dermatomyositis

Therapy

Newborn and young children with bilateral lesions need ventilatory support.

Trauma cases can be considered for surgical repair (re-innervation may reach related muscles of the upper extremity, such that breathing discharges can be seen in EMG).

Adults: unilateral lesions may be compensated, but bilateral lesions may require nighttime respiratory support.

References

Bolton CF, Chen R, Wijdicks EFM, Zifko UA (2004) Neurology of breathing. Butterworth Heinemann, Elsevier Inc (USA)
Cavaletti G (1998) Rapidly progressive multifocal motor neuropathy with phrenic nerve paralysis; effect of nocturnal assisted ventilation. J Neurol 245: 613–616
Chen ZY, Xu JG, Shen LY, et al (2001) Phrenic nerve conduction study in patients with traumatic brachial plexus palsy. Muscle Nerve 24: 1388–1390

Dorsal scapular nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+ –			

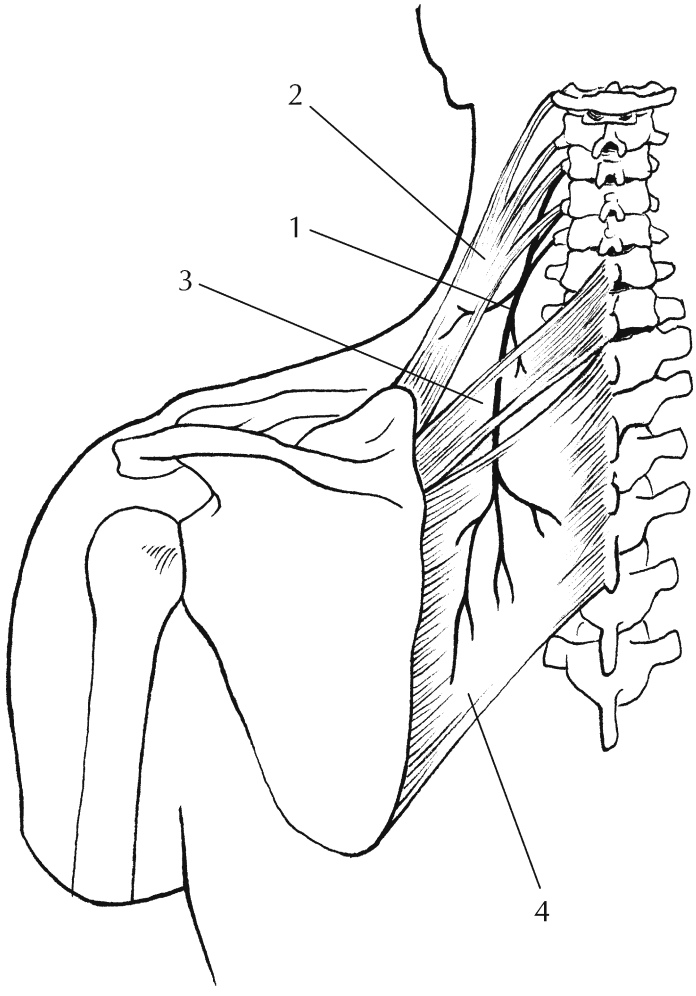

Fig. 24. Dorsal scapular nerve anatomy. *1* Dorsal scapular nerve. *2* Levator scapular muscle. *3* Minor rhomboid muscle. *4* Major rhomboid muscle

Anatomy

The dorsal scapular nerve arises from fibers of C4, 5 and travels through the medial scalene muscle and along the medial border of the scapula. This nerve is purely motor, and innervates the levator scapulae and rhomboid muscles (Fig. 24).

Function:
To elevate and adduct the medial border of the shoulder blade (together with the rhomboid muscles).

Symptoms

Almost no symptoms are reported, and usually only with powerful arm movements.

Signs

Atrophy of muscles cannot be seen. The scapula becomes slightly abducted from the thorax wall, with outward rotation of the inferior angle.

Pathogenesis

Neuralgic shoulder amyotrophy
Iatrogenic: operations
Nerve is sometimes used as a graft for nerve transplantations.

Diagnosis

EMG

Therapy

None

Reference

Mumenthaler M, Schliack M, Stöhr M (1998) Läsionen einzelner Nerven im Schulter-Arm-Bereich. In: Mumenthaler M (ed) Läsionen peripherer Nerven und radikuläre Syndrome. Thieme, Stuttgart, pp 296–311

Suprascapular nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		MRI, US	

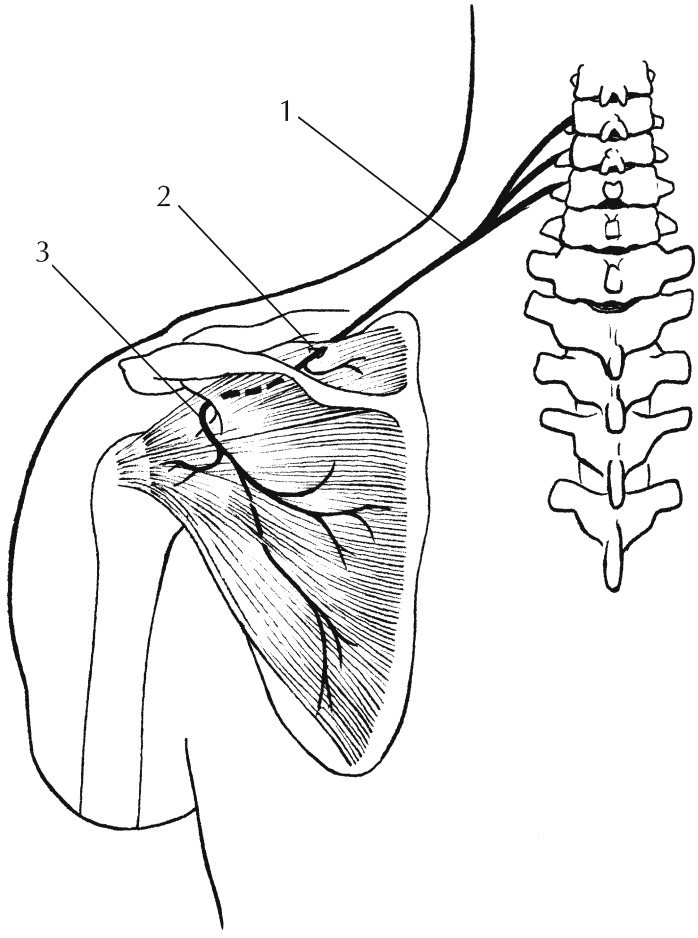

Fig. 25. Suprascapular nerve anatomy. *1* Suprascapular nerve. *2* Suprascapular notch/foramen. *3* Spinoglenoid notch

Anatomy

Fibers mainly come from C5 and C6, and travel through the upper trunk of the brachial plexus to innervate the supra- and infraspinatus muscles. The nerve has no cutaneous sensory distribution (Fig. 25).

Symptoms

Dull, aching pain in the posterior aspect of shoulder, which is aggravated by arm use. The patient is unable to lie on his shoulder due to pain. Shoulder elevation and external rotation are weak. Also, slight atrophy of the muscles may be noted.

Signs

Muscle wasting.
Lesion at the suprascapular notch: involvement of both muscles.
Lesion at the spinoglenoid notch: only infraspinatus muscle impairment.

Causes

Abnormal transverse scapular ligaments (occasionally bilateral)
Arthroscopic shoulder surgery
Closed trauma: the most common cause
Entrapment by the transverse superior or inferior ligaments
Neuralgic amyotrophy
Open trauma
Overuse: athletic activities (basketball, volleyball, boxing) or construction trades (e.g. carpentry)
Soft tissue masses: ganglion cysts
Surgery: arthroscopy
Systemic lupus erythematosus
Trauma: hematoma and fracture
Tumors: ganglion, cyst, metastasis

Diagnosis

NCV of supraspinatus nerve
Needle EMG of muscles
MRI, ultrasound

Differential diagnosis

C5 (C6) radicular lesion
"Frozen shoulder"
Rotator cuff tears
Tendinitis of the supraspinatus muscle
Upper trunk brachial plexus
Upper trunk brachial plexopathy

Therapy

Depends on the etiology and severity.
Conservative: rest the limb, analgesics, activity modification, nerve block.
Operative: nerve decompression at entrapment sites.
Replacement surgery: if the lesion appears to be permanent, a transfer from the horizontal part of the trapezoid muscle can be considered.

Prognosis

Depends on the etiology

References

McCluskey L, Feinberg D, Dolinskas C (1999) Suprascapular neuropathy related to a glenohumeral joint cyst. Muscle Nerve 22: 772–777
Mumenthaler M, Schliack H, Stöhr M (1998) Läsionen einzelner Nerven im Schulter-Arm-Bereich. In: Mumenthaler M, Schliack H, Stöhr M (eds) Läsionen peripherer Nerven und radikuläre Syndrome. Thieme, Stuttgart, pp 261–368
Staal A, van Gijn J, Spaans F (1999) The suprascapular nerve. In: Staal A, van Gijn J, Spaans F (eds) Mononeuropathies. Saunders, London, pp 23–25
Stewart J (2000) Nerves arising from the brachial plexus. In: Stewart JD (ed) Focal peripheral neuropathies. Lippincott, Williams & Wilkins, Philadelphia, pp 157–181

Subscapular nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		?	

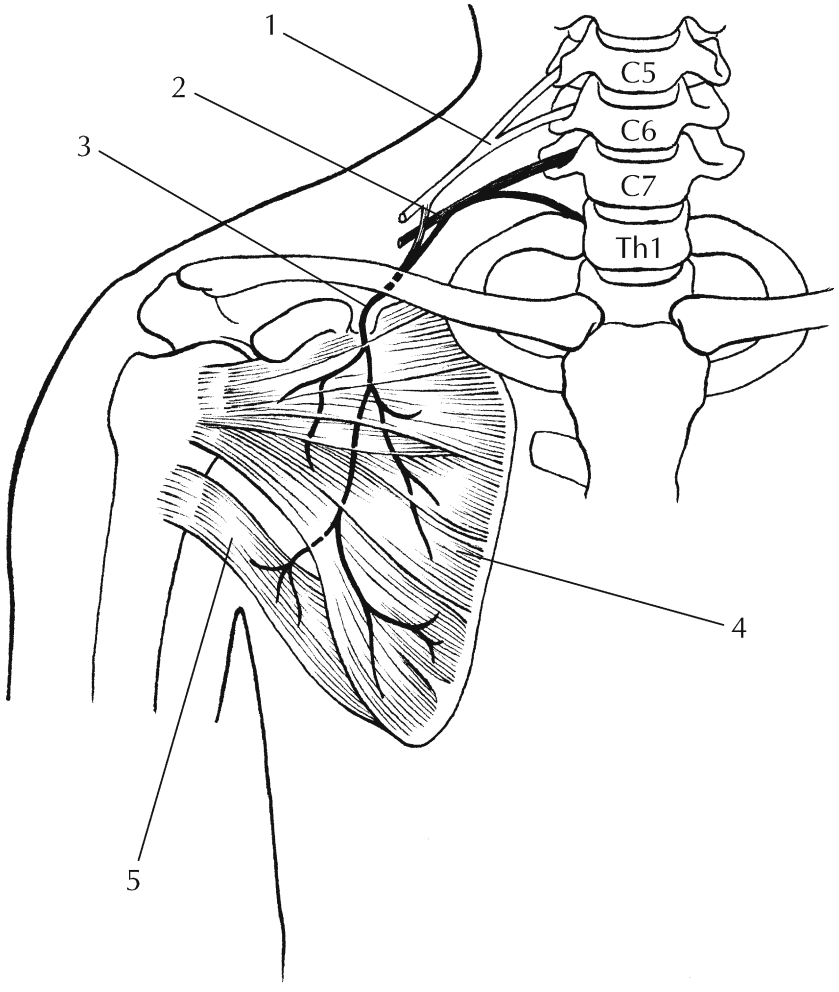

Fig. 26. Subscapular nerve anatomy. *1* Upper trunk. *2* Posterior cord. *3* Subscapular nerve. *4* Subscapular muscle. *5* Teres major muscle

Anatomy

Nerve fibers arise from C5 and C6, and travel through the upper trunk and posterior cord of the brachial plexus. The nerve innervates the subscapularis and teres major muscle, to secure the shoulder joint and provide inward rotation of the shoulder (Fig. 26).

Symptoms

Compensation for the function of both muscles is provided by the pectoralis major, latissimus dorsi, and anterior deltoid muscle.

Signs

Upon securing shoulder joint, an outward rotation of the upper arm.
Atrophy is not visible, and there are no sensory findings.

Pathogenesis

Involvement either in association with radiculopathies or with posterior cord brachial plexus injury. There are no entrapment lesions.

Diagnosis

EMG of the teres major muscle

Differential diagnosis

C5/C6 radiculopathy, posterior cord lesion of the brachial plexus

Therapy

Conservative

Long thoracic nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++		+	

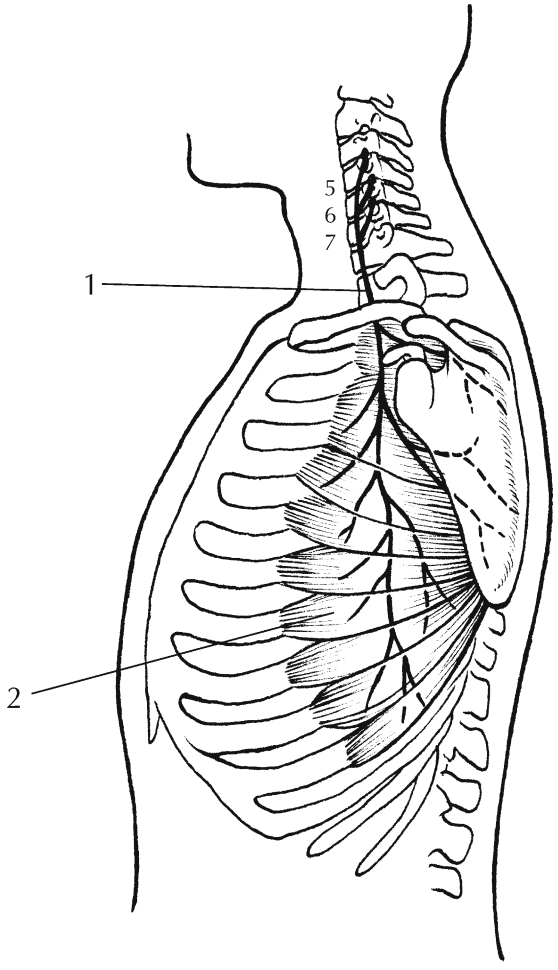

Fig. 27. Long thoracic nerve anatomy. *1* Long thoracic nerve. *2* Serratus anterior muscle

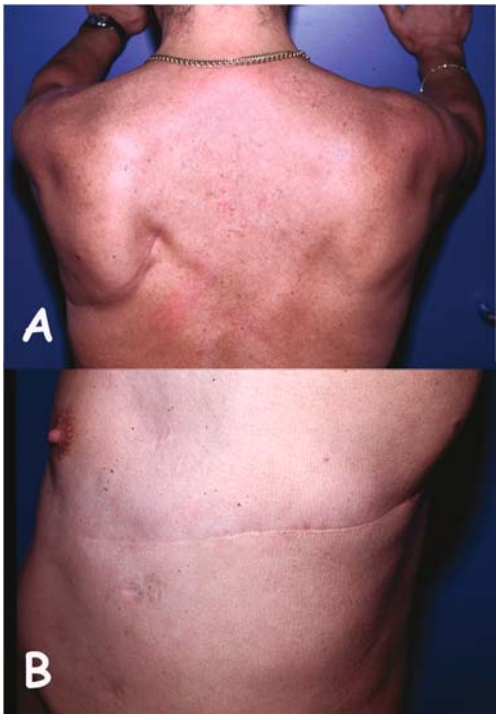

Fig. 28. Long thoracic nerve palsy after thoracic surgery. **A** Note winging of caudal edge of the scapula. **B** Scar after thoracic surgery

Anatomy

Fibers stem from the ventral rami of C5–7, and travel through the dorsal part of the plexus. The nerve traverses the middle scalene muscle, and then passes below the brachial plexus on the thoracic wall. The nerve contains motor fibers exclusively for the serratus anterior muscle (Fig. 27).

Symptoms

Dull ache in the shoulder, affected shoulder seems lower, weakness of arm abduction, no sensory abnormalities.

Signs

Atrophy with scapular winging (Fig. 28)
Restriction of abduction and flexion of the arm above shoulder level.

Pathogenesis

Infection:
Lyme disease, typhoid fever

Inflammatory-immune mediated:
Neuralgic amyotrophy: seen mainly in association with other shoulder nerves, particularly with suprascapular nerve. Rarely isolated.

Compressive:
Pressure – part of Rucksack paralysis

Iatrogenic:
Intraoperative: thoracotomy, mastectomy, resection of the first rib, lymph node extirpation. Intraoperative positioning.

Trauma:
Acute trauma
Birth trauma
Blunt trauma
Motor vehicle accidents
Open injury
Sports: falls, football, wrestling (traction forces), carrying weights, backpacks, plaster casting, extreme shoulder movements (hitting, punching)

Idiopathic:
No apparent reason

Diagnosis

NCV: recording either with needle or surface electrodes
EMG
X-ray and CT: for all traumatic lesions

Differential diagnosis

Acute brachial neuropathy
Multifocal motor neuropathy
Muscular dystrophy
Root lesions C5–C7
"Sprengel" syndrome (hereditary shoulder elevation)
Upper limb predominant, multifocal chronic inflammatory demyelinating polyneuropathy
Winging of scapula is encountered in several conditions

Therapy

Conservative:
Trauma: neurapraxia, partial lesion (mild axonal lesion)
Blunt trauma
Neuralgic amyotrophy
Malpositioning

Operative:
Trauma: severe axonal lesion, neurotmesis

Prognosis

Generally good-partial lesions are common.

References

Gorson KC, Ropper AH, Weinberg DH (1999) Upper limb predominant, multifocal chronic inflammatory demyelinating polyneuropathy. Muscle Nerve 22: 758–765
Kim KK (1996) Acute brachial neuropathy – electrophysiologic study and clinical profile. J Korean Med Sci 11: 158–164
Monteyne P, Dupuis MJ, Sindic CJ (1994) Neuritis of the serratus anterior muscle associated with Borrelia burgdorferi infection. Rev Neurol (Paris) 150: 75–77
Phillips MF (1986) Familial long thoracic nerve palsy: a manifestation of brachial plexus neuropathy. Neurology 36: 1251–1253

Thoracodorsal nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+			

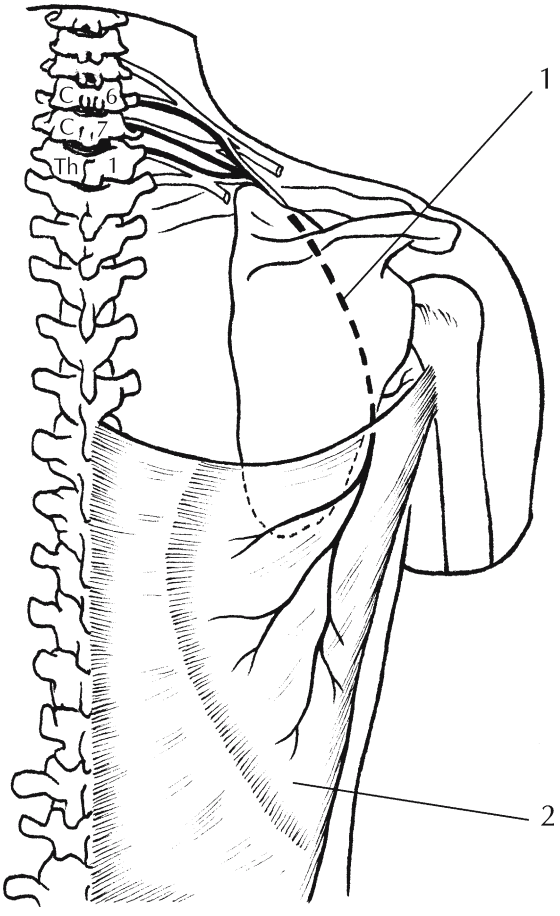

Fig. 29. Thoracodorsal nerve anatomy. *1* Thoracodorsal nerve. *2* Latissimus dorsi muscle

Anatomy

Fibers stem from C5–C7 roots. (Only 50% of cases have fibers from C7.) The fibers pass through the upper and middle trunks and the posterior cord, and continues with the lower subscapular nerve.

Occasionally this nerve is a branch of the axillary and radial nerves.

A motor branch goes to the latissimus dorsi muscle, and may also innervate the teres major muscle.

Both muscles are adductors and inward rotators of the scapulohumeral joint and help to bring down the elevated arm (see Fig. 29).

Symptoms

Few clinical symptoms, weakness compensated in part by pectoralis major and teres major muscles.

Signs:
Atrophy, and slight winging of the inferior margin of the scapula
Motor: Latissimus dorsi: weakness in adduction and medial rotation of shoulder and arm.

Causes

Isolated lesion is very uncommon.
Neuralgic amyotrophy (rarely)
Plexus lesions: injury in association with posterior cord or more proximal brachial plexus lesions.

Diagnosis

EMG

Differential diagnosis

Plexus: posterior cord lesions, upper/middle trunk lesions
Radicular: C5–C7 lesion

Therapy

Conservative. Surgical interventions are not necessary because of the minor dysfunction.

Due to this fact, this muscle can be used for grafting to the biceps brachii and outward rotators of humeroscapular joint.

Prognosis

Good

Pectoral nerve

Symptoms

Patients note painless atrophy.

Signs

Weakness and atrophy of the pectoral muscle. Compensatory hypertrophy of other chest muscles.

Anatomy

Lateral pectoral nerve:
Receives fibers from C5–7 (lateral cord of plexus) and supplies upper part of pectoral muscle.

Medial pectoral nerve:
Receives fibers from C8/T1 and supplies lower part of pectoral muscle.

Causes

Aplasia
Entrapment in hypertrophies of minor pectoral muscle
Neck dissection
Weight lifting

Reference

Bird SJ (1996) Acute focal neuropathy in male weight lifters. Muscle Nerve 19: 897–899

Thoracic spinal nerves

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	(+)	+	+	

Anatomy

The twelve pairs of thoracic spinal nerves innervate all the muscles of the trunk and surrounding skin, except the lumbar paraspinal muscles and overlying skin. Dorsal and ventral rami can be affected.

Three groups: T1, T2–T6, T7–T12.

a) T1 and C8: first intercostal nerve
b) T2–T6: innervation of the chest wall
   T2 is the intercostobrachial nerve (see also brachial plexus)
c) T7–11: Thoracoabdominal nerves
   T12 is the subcostal nerve

Symptoms

Pain, sensory symptoms, depending on whether dorsal or ventral rami are affected.

Signs

Muscle weakness may be difficult to assess, except in the case of abdominal muscles, where bulging occurs during coughing or pressure elevation.

Pathogenesis

Metabolic:
Diabetic truncal neuropathy

Infectious:
Herpes: Pre-herpetic neuralgia (1–20 days before onset)
Herpetic neuralgia
Post-herpetic neuralgia
Lyme disease

Compressive:
Abdominal cutaneous nerve entrapment
Notalgia paresthetica: involvement of dorsal radicular branches
Thoracic disc disease (rare)

Neoplastic:
Invasion at the apex of the lung
Schwannoma
Vertebral metastases

Traumatic:
Trauma

Iatrogenic:
Postoperative (abdominal surgery, post mastectomy, and thoracotomy)

Diagnosis

Laboratory: Fasting glucose, serology (herpes, borreliosis)
CSF examination (e.g., pleocytosis and antibodies in Lyme disease)
Imaging: vertebral column: plain X-ray, CT, MRI
Electrophysiology: NCV of intercostal nerves is difficult and not routinely done.
EMG: paraspinal muscles, intercostals, abdominal wall muscles

Differential diagnosis

Local painful conditions of the vertebral column (disc herniation, spondylodiscitis, metastasis)
"Intercostal neuralgia"
Muscle disease with abdominal weakness
Slipping rib/Cyriax syndrome

Therapy

Depends on the etiology

References

Daffner KR, Saver JL, Biber MP (2001) Lyme polyradiculoneuropathy presenting as increasing abdominal girth. Neurology 40: 373–375
Gilbert RW, Kim JH, Posner JB (1978) Epidural spinal cord compression from metastatic tumor; diagnosis and treatment. Ann Neurol 3: 40–51
Love JJ, Schorn VG (1965) Thoracic disc protrusions. JAMA 191: 627–631
Stewart JD (1999) Thoracic spinal nerves. In: Stewart JD (ed) Focal peripheral neuropathies. Lippincott, Philadelphia, pp 499–508
Vial C, Petiot P, Latombe D, et al (1993) Paralysie des muscles larges de l àbdomen due a une maladie de Lyme. Rev Neurol (Paris) 149: 810–812

Intercostal nerves

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	(+)	+ –	Osseous structures of vertebral column and ribs	

Anatomy

The intercostal nerves are the ventral rami of the thoracic spinal nerves. They innervate the intercostal (first 6) and abdominal muscles (lower 6), as well as skin (via anterior and lateral branches). The first ventral ramus is part of the brachial plexus.

Intercostobrachial nerve:
Originates from the lateral cutaneous nerve of the second and third intercostal nerves to innervate the posterior part of the axilla.
Often anastomizes with the medial cutaneous nerve of the upper arm (stemming from medial cord of brachial plexus).
The 7–11th ventral rami are called the thoracoabdominal nerves.
The 12th thoracic nerve is the subcostal nerve.

Symptoms

Radicular pain (beltlike)

Signs

Over the thorax cavity, no muscle weakness can be detected. However, bulging of abdominal muscles may be apparent.

Pathogenesis

Abdominal cutaneous nerve entrapment
Diabetic truncal neuropathy
Herpes zoster
Notalgia paresthetica
Post-operatively: abdominal, retroperitoneal, and renal surgery.
Traumatic lesions
Thoracic disc trauma (rarely)
Vertebral metastasis

Diagnosis

Laboratory: fasting glucose
Serology (herpes, Lyme disease)
Imaging: vertebral column, MRI
Electrophysiology is difficult in trunk nerves and muscles

Differential diagnosis

Pain may be of intra-thoracic, intra-abdominal, or spinal origin.
Compartment syndrome of the rectus abdominis muscle

Costochondritis
Head zones (referred pain)
Hernia
"Intercostal neuralgia"
Pseudoradicular pain
Rupture of the rectus abdominis muscle
Slipping rib
Thoraconeuralgia gravidarum

Therapy

Depending on etiology

References

Krishnamurthy KB, Liu GT, Logigian EL (1993) Acute Lyme neuropathy presenting with polyradicular pain, abdominal protrusion, and cranial neuropathy. Muscle Nerve 16: 1261–1264
Mumenthaler M, Schliack H, Stöhr M (1998) Läsionen der Rumpfnerven. In: Mumenthaler M, Schliack H, Stöhr M (eds) Läsionen peripherer Nerven und radikuläre Syndrome. Thieme, Stuttgart, pp 368–374
Staal A, van Gijn J, Spaans F (1999) The intercostal nerves. In: Staal A, van Gijn J, Spaans F (eds) Mononeuropathies. Saunders, Londons, pp 84–86
Stewart J (2000) Thoracic spinal nerves. In: Stewart J (ed) Focal peripheral neuropathies. Lippincott, Williams & Wilkins, Philadelphia, pp 499–508
Thomas JE (1972) Segmental zoster paresis: a disease profile. Neurology 22: 459–466

Intercostobrachial nerve

Anatomy

Originates from lateral cutaneous nerve of second and third intercostal nerves to innervate the posterior part of the axilla. This nerve often anastomizes with the medial cutaneous nerve of the upper arm (from the medial cord of the brachial plexus).

Symptoms

Pain in the axilla, chest wall, or thorax. Often occurs one or two months after mastectomy. Reduced movement of the shoulder enhances pain.

Signs

Sensation is impaired in the axilla, chest wall, and proximal upper arm.

Differential diagnosis

Operations in the axilla (removal of lymph nodes)
Following surgery for thoracic outlet syndrome
Lung tumors

Reference

Assa J (1974) The intercostobrachial nerve in radical mastectomy. J Surg Oncol 6: 123–126

Iliohypogastric nerve

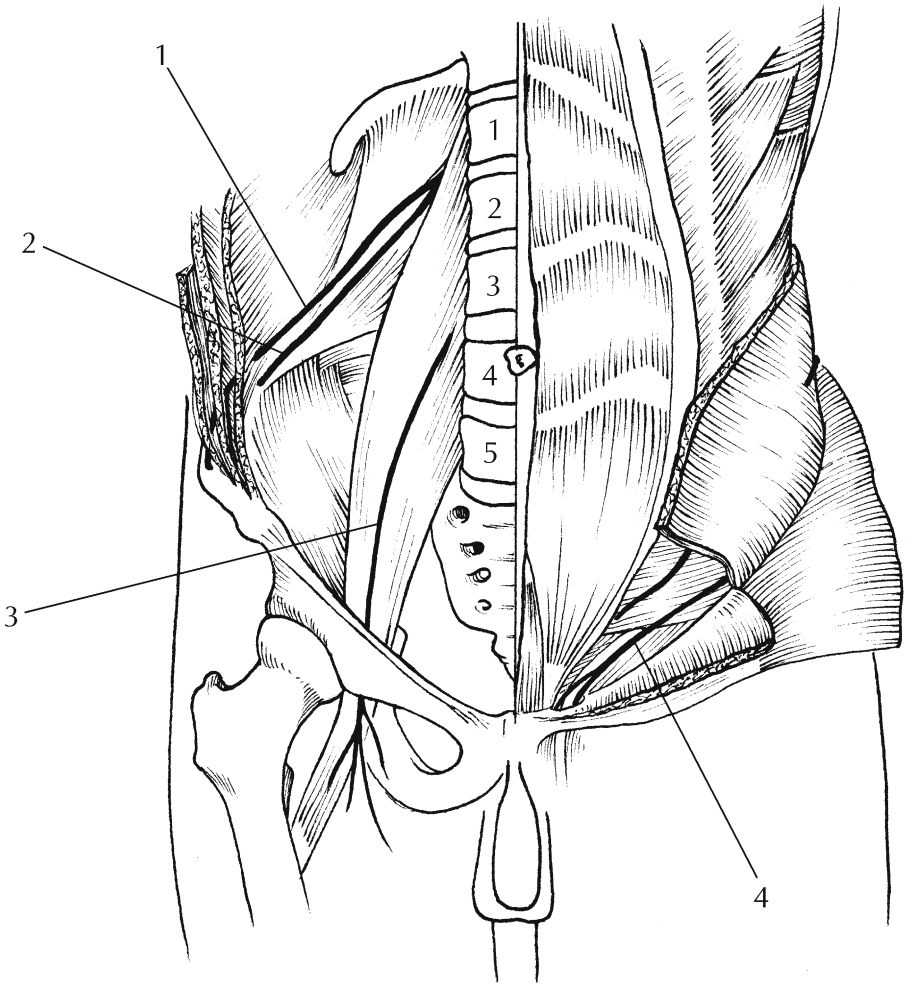

Fig. 30. Iliohypogastric nerve anatomy. *1* Iliohypogastric nerve. *2* Ilioinguinal nerve. *3* Obturator nerve. *4* Genitofemoral nerve

Anatomy

Fibers originate at L1, then emerge from the lateral border of the psoas, crossing the lower border of the kidney, then the lateral abdominal wall. Then the nerve crosses the transverse abdominal muscle above iliac crest and passes between the transverse and oblique internal abdominal muscles. Finally two branches are given off: the lateral anterior and anterior cutaneous nerves.

Symptoms

Burning and stabbing pain in the ilioinguinal region, which may radiate towards the genital area or hip. Symptoms increase when walking.

Signs

Difficult to examine. Spontaneous bulging of abdominal wall. Sensory deficit may be present. Tinel's sign over a surgical scar may be observed. Slight flexion of hip while standing.

Diagnosis Electrophysiology is not routinely available. Clinical distribution.

Differential diagnosis Spontaneous entrapment in abdominal wall, surgery, herniorraphy, appendectomy, abdominoplasty, nephrectomy, endometriosis.

Therapy Steroids locally, scar removal, neurolysis.

Ilioinguinal nerve

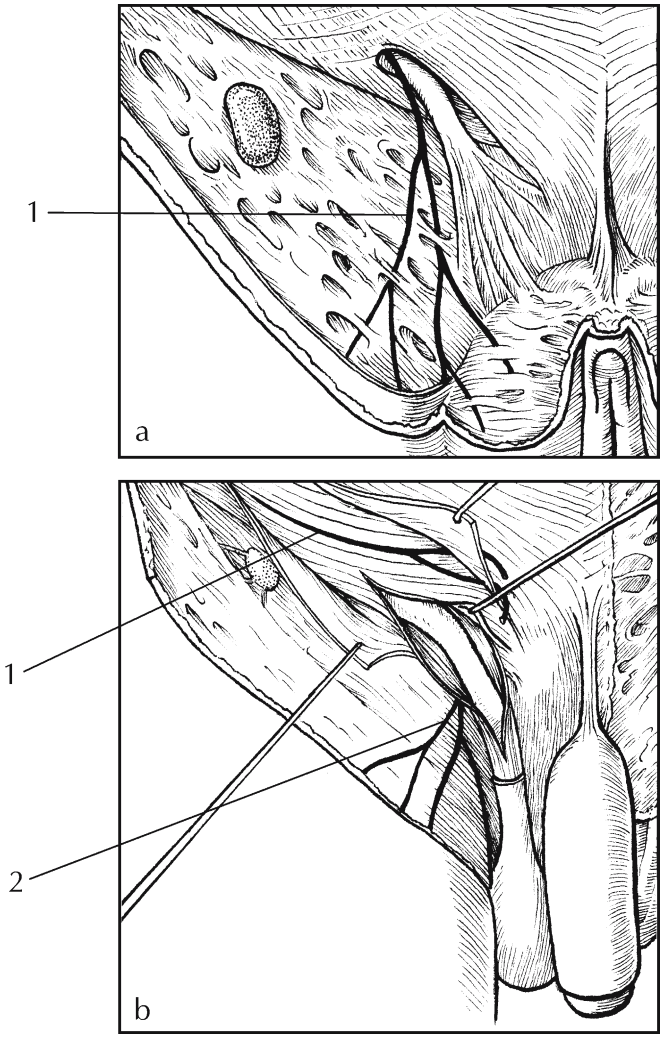

Fig. 31. Ilioinguinal nerve anatomy. **a** A-female. *1* Ilioinguinal nerve. **b** B-male. *1* Iliohypogastric nerve. *2* Ilioinguinal nerve

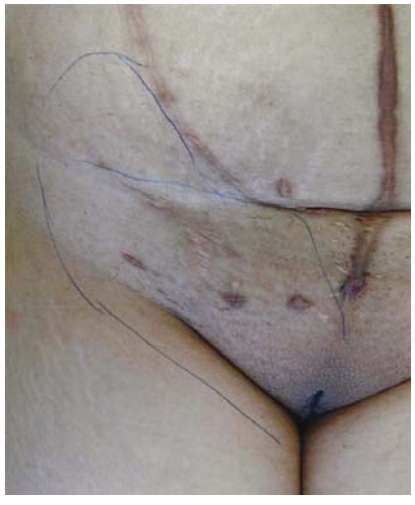

Fig. 32. Ilioinguinal nerve lesion after gynecologic surgery. The sensory loss (marked with a ball pen) reached almost the labia

Anatomy

The ilioinguinal nerve originates with fibers from T12 and L1. The motor component innervates the internal and external oblique muscles, and the transverse abdominal muscle.
The sensory component covers the skin overlying the pubic symphysis, the superomedial aspect of the femoral triangle, the anterior scrotal surface, and the root of the penis/labia majora and mons pubis (Fig. 31).

Clinical syndrome

Hyperesthesia, sometimes with significant pain over the lower abdominal quadrant and the inguinal region and genitalia (Fig. 32).

Signs

Weakness of lower abdominal muscles, hernia.

Causes

Abdominal operations with a laterally placed incision
Biopsy
Endometriosis, leiomyoma, lipoma
Herniotomy
Iliac bone harvesting
Pregnancy, child birth
Spontaneous entrapment – “inguinal neuralgia“

Diagnosis

Studies: no standard electrophysiologic techniques are available

Therapy

Local anesthetic infiltration
Surgical exploration and resection of the nerve

Differential diagnosis

Genitofemoral neuropathy
Inguinal pain syndrome
Iliohypogastric neuropathy
L1 radiculopathy (very rare)

References

Dawson DM (1990) Miscellaneous uncommon syndromes. In: Dawson DM (ed) Entrapment neuropathies. Little Brown, Boston, pp 307–323
Komar J (1971) Das Ilioinguinalis Syndrom. Nervenarzt 42: 637–640
Mumenthaler M (1998) Läsionen einzelner Nerven im Beckenbereich und an den unteren Extremitäten, 7. Aufl. G. Thieme Verlag, Stuttgart, pp 393–464
Purves JK, Miller JD (1986) Inguinal neuralgia; a review of 50 patients. Can J Surg 29: 585–587
Stulz P, Pfeiffer KM (1982) Peripheral nerve injuries resulting from common surgical procedures in the lower portion of the abdomen. Arch Surg 117: 324–327

Genitofemoral nerve

Anatomy

The nerve originates from the ventral primary rami of L1 and L2, then runs along the psoas muscle to the inguinal ligament. In the inguinal canal the genital branch runs with the ilioinguinal nerve, to supply the skin of the mons pubis and labium majus. The genital branch also innervates the cremaster muscle, while the femoral branch innervates the proximal anterior thigh.

Symptoms

May give rise to continuous pain, sometimes called “spermatic neuralgia”.
Can present as a post-operative inguinal neuralgia.
Paresthesias (may be painful) of the medial inguinal region, upper thigh, side of scrotum, and labia majora.

Signs

Tenderness in the inguinal canal. Cremaster reflex unreliable.

Causes

Appendectomy
Bone graft removal
Hernioraphy
Nephrectomy
Trauma
Tumors (uncommon)
Tuberculosis
Varicocele testis

Diagnosis

No electrophysiologic studies are available
Diagnostic anesthetic blockade

Differential diagnosis

L1, 2 radiculopathy
Iliohypogastric neuropathy
Ilioinguinal neuropathy

Therapy

Anesthetic blockade
Operative neurolysis

Prognosis

Good

References

Magee RK (1942) Genitofemoral causalgia (a new syndrome). Can Med Assoc J 46: 326–329
Staal A, van Gijn J, Spaans F (1999) The genitofemoral nerve. In: Staal A, van Gijn J, Spaans F (eds) Mononeuropathies. Saunders, London, pp 95–96

Superior and inferior gluteal nerves

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

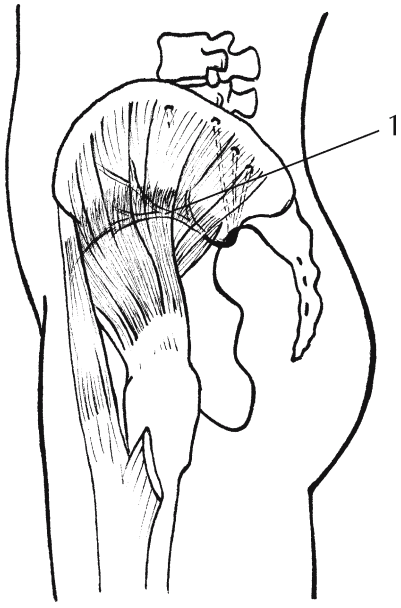

Fig. 33. Superior gluteal nerve anatomy. *1* Superior gluteal nerve

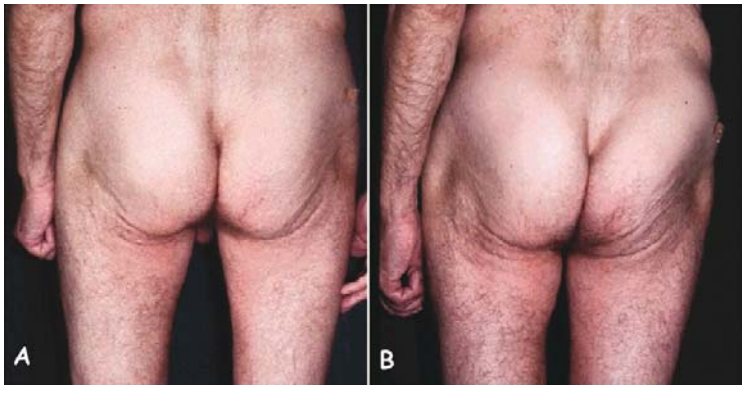

Fig. 34. Trendelenburg's sign, indicating weakness of the hip abductors (gluteus medius muscle). **A** Standing on both feet the pelvis remains in horizontal position. **B** When the patient stands on his left leg, his pelvis tilts to the right side. This patient had a left gluteus medius nerve lesion, caused by an iliac aneurysm. Note that the greater gluteal muscles are not affected

Anatomy

Superior gluteal nerve:
Originates with the posterior branches from ventral rami of L4–S1, to innervate the gluteus medius and minimus muscles.

Inferior gluteal nerve:
Originates with the posterior portions of L5 and S1, and ventral primary rami of S2. It innervates the piriformis and gluteus maximus muscles.

Symptoms and Signs

Superior:
Causes Trendelenburg's gait. Excessive drop of the non-weight-bearing limb and a steppage gait on the unaffected side. Hip abduction is weak, sensation is normal.

Inferior:
Causes buttock pain and weak hip extension (weakness getting up).

Pathogenesis

Superior:
Misplaced injection, trauma, hemorrhage, arthroplasty, aneurysm.

Inferior:
Rarely isolated, often associated with the sciatic nerve, occasionally with pudendal nerve. Colorectal carcinoma, injections, trauma.

Diagnosis

EMG, imaging

Differential diagnosis

Sacral plexus lesion
Hip and pelvic pathology

References

Grisold W, Karnel F, Kumpan W, et al (1999) Iliac artery aneurysm causing isolated superior gluteal nerve lesion. Muscle Nerve 22: 1717–1720
Rask MR (1980) Superior gluteal nerve entrapment syndrome. Muscle Nerve 3: 304–307
Wilbourn AJ, Lesser M (1983) Gluteal compartment syndrome producing sciatic and gluteal mononeuropathies: a report of two cases. Electrencephal Clin Neurophysiol 55: 45–46

Pudendal nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+ –		+	

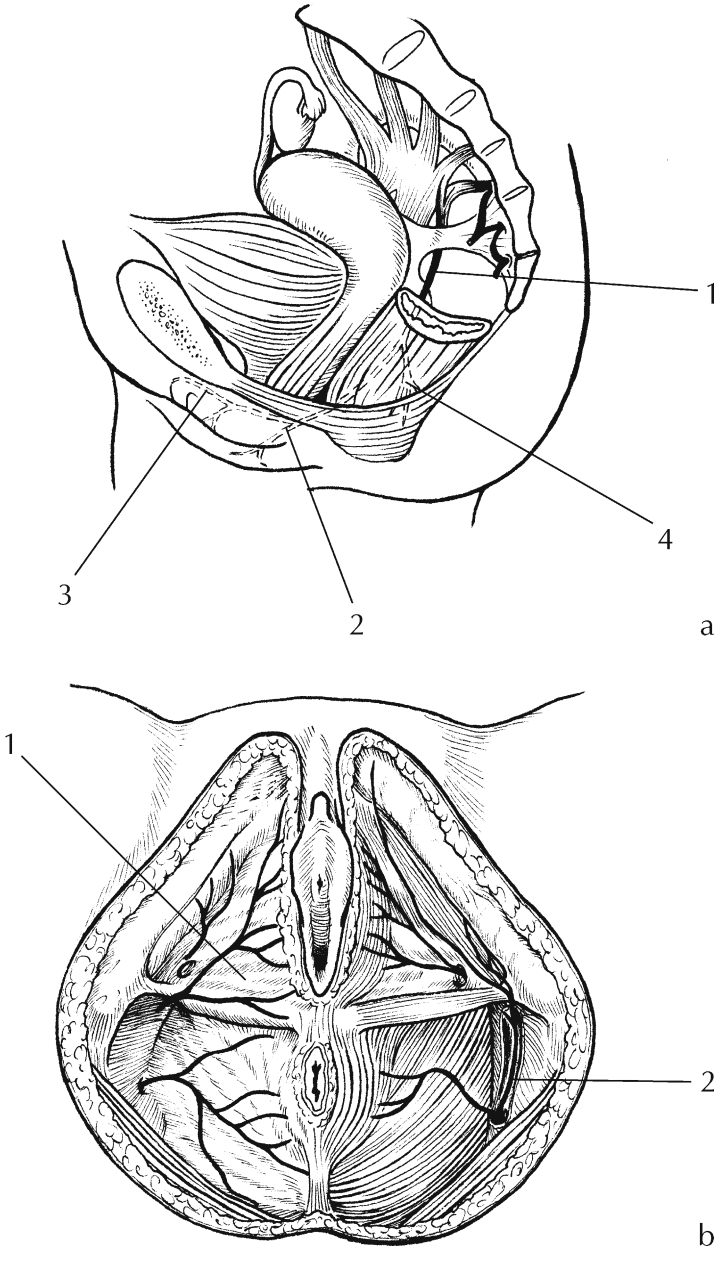

Fig. 35. Pudendal nerve anatomy. **a** *1* Pudendal nerve. *2* Perineal nerves. *3* Dorsal nerve of clitoris. *4* Inferior rectal nerves. **b** *1* Perineal nerves. *2* Pudendal nerves

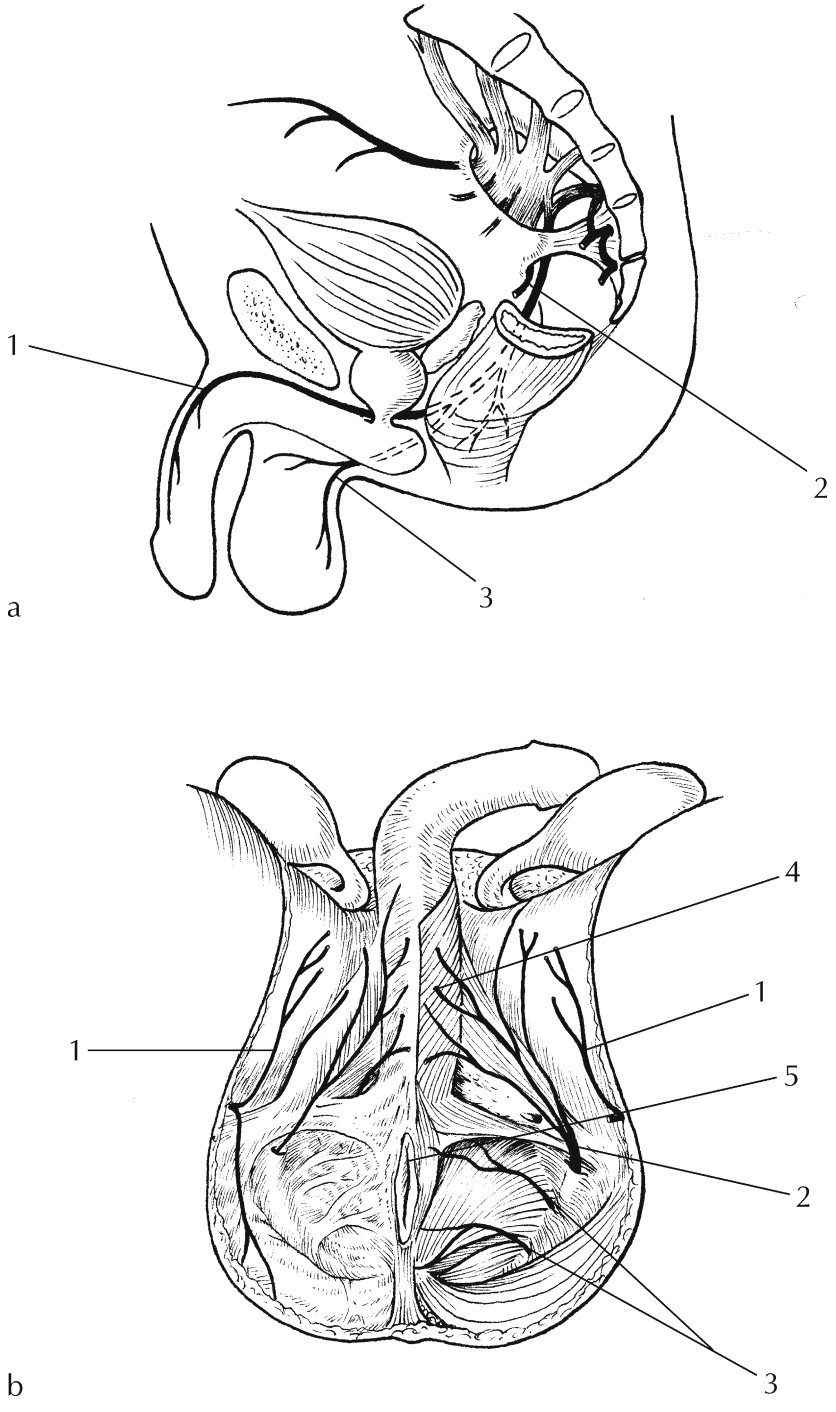

Fig. 36. Pudendal nerve anatomy. **a** *1* Dorsal nerve of penis. *2* Pudendal nerve. *3* Perineal nerves. **b** *1* Perineal branch of cutaneous femoral posterior nerve. *2* Pudendal nerve. *3* Rectal inferior nerves. *4* Bulbo spongiosus muscle. *5* External anal sphincter muscle

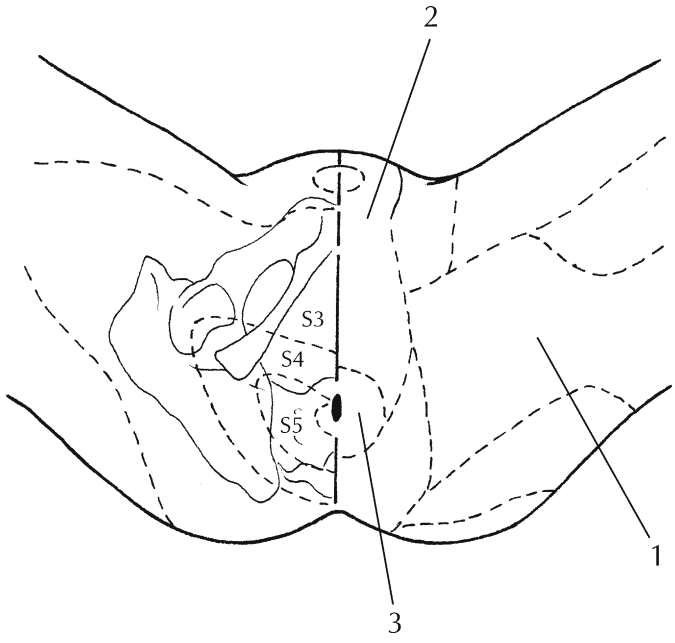

Fig. 37. Pudendal nerve anatomy. *1* Cutaneous femoris posterior nerve. *2* Labial/scrotal nerves. *3* Anococcygeal nerve

Anatomy

The nerve originates from S2–S4, and passes through the sciatic foramen and pudendal canal. Its terminal branches are the inferior rectal nerve (innervating the levator ani, external anal sphincter muscles, and skin around the anus), the perineal nerve (innervating the external urethral sphincter muscles, bulbocavernosus, perineum, and dorsal aspect of scrotum/labia), and the terminal branch of the pudendal nerve (providing sensation to the clitoris, glans penis, dorsal region of the penis) (see Fig. 35 through 37).

Clinical picture

Perineal sensory symptoms, sexual dysfunction.
Bilateral lesions may cause urinary or fecal incontinence, impotence/anorgasmy, and sensory disturbances.

Signs

Sphincter reflexes (anal, bulbocavernosus reflex absent)

Causes

Selective injury is rare

External compression:
Perineal, post-operative of hip fractures
Long bicycle rides
Suturing through sacrospinal ligament during colonoscopy

Stretch:
Straining during defecation
Childbirth

Pelvic fracture
Pelvic surgery

Hip dislocation
Intraarticular foreign body

Differential diagnosis

Polyneuropathy
Radicular lesion (S2–S4)
Sacral plexus
Structural abnormalities of the pelvic floor or viscera

Diagnosis

EMG of external anal sphincter
Bulbocavernosus reflex
Pudendal SEP
Anorectal manometry, urodynamic examinations
Imaging

References

Amarenco G, Ismael SS, Bayle B, et al (2001) Electrophysiological analysis of pudendal neuropathy following traction. Muscle Nerve 24: 116–119
Podnar S, Vodusek DB (2001) Standardization of anal sphincter electromyography: utilty of motor unit potential parameters. Muscle Nerve 24: 946–951

Mononeuropathies: lower extremities

Obturator nerve

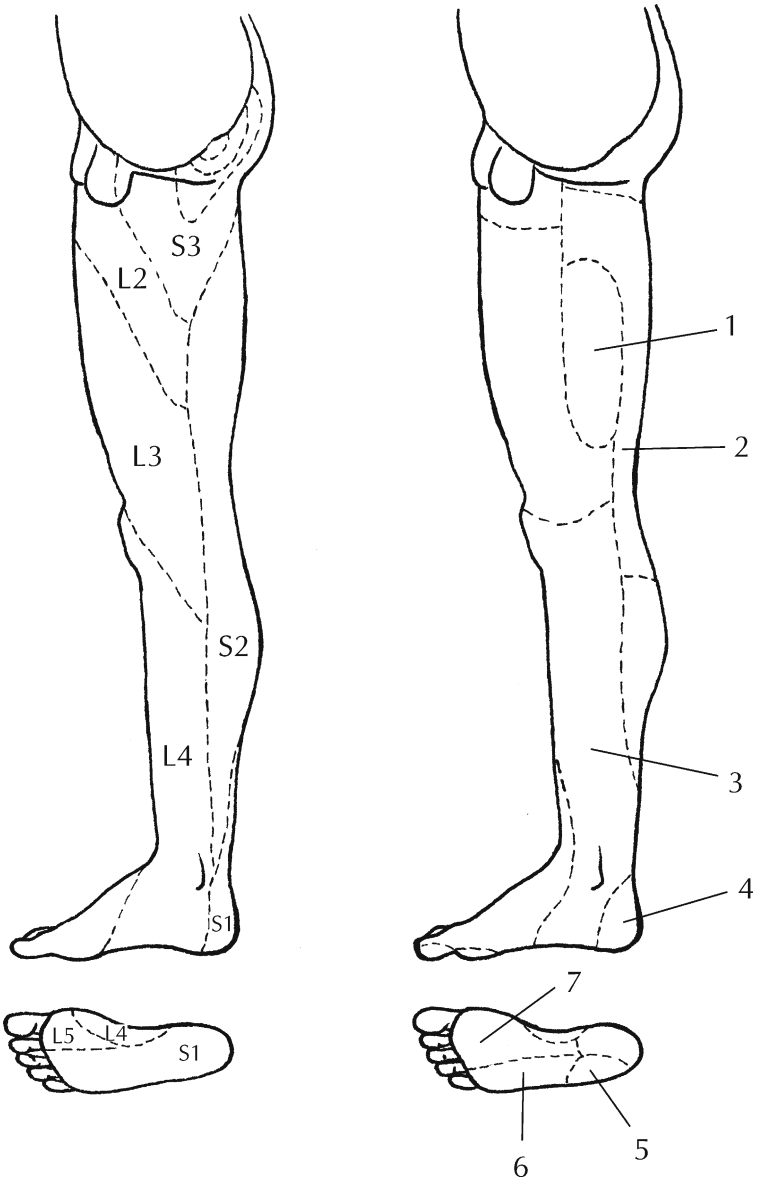

Fig. 38. Obturator nerve anatomy. *1* Obturator nerve. *2* Cutaneous femoris posterior nerve. *3* Sapheneous nerve. *4* Calcaneal nerve. *5* Sural nerve. *6* Lateral plantar nerve. *7* Medial plantar nerve

Anatomy

The obturator nerve fibers stem from L2–4, and course within the belly of the psoas muscle, emerging on the medial side of the psoas, then passing over the sacroiliac joint, and continuing along the wall of pelvis to the obturator canal.

Symptoms

Sensory loss, paresthesias, or radiating pain in the medial thigh. Disability in walking due to impaired stabilization of the hip joint. The leg is held in an

abducted position, leading to a wide-based gait. The adductor tendon reflex may be absent.
Neuralgic pain may be confused with osteitis.

Signs

Adductor weakness, with or without sensory deficits.

Causes

Compression: Obturator hernia, scar in thigh, labor, endometriosis, retroperitoneal Schwannoma
Iatrogenic: Hip surgery, fixation of acetabular fracture, intrapelvic surgery Laparoscopic dissection of pelvic nodes, gracilis flap, prostatectomy
Hypogastric artery aneursym
Metastatic cancer
Trauma: pelvic fracture, gunshot, retroperitoneal hematoma

Obturator nerve injury occurs commonly with a femoral nerve lesion. Causes include retroperitoneal hematoma, cancer, hip arthroplasty, lymphoma.

Diagnosis

EMG
Imaging

Differential diagnosis

L2–L4 radiculopathy

Therapy

Depends on etiology and type of nerve injury

Prognosis

Depends on etiology and type of nerve injury

References

Roger LR, Borkowski GP, Albers JW, et al (1993) Obturator mononeuropathy caused by pelvic cancer: six cases. Neurology 43: 1489–1492
Sorenson EJ, Chen JJ, Daube JR (2002) Obturator neuropathy: causes and outcome. Muscle Nerve 25: 605–607
Staal A, van Gijn J, Spaans F (1999) The obturator nerve. In: Staal A, van Gijn J, Spaans F (eds) Mononeuropathies; examination, diagnosis and treatment. Saunders, London, pp 109–111

Femoral nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+	+ –	+	

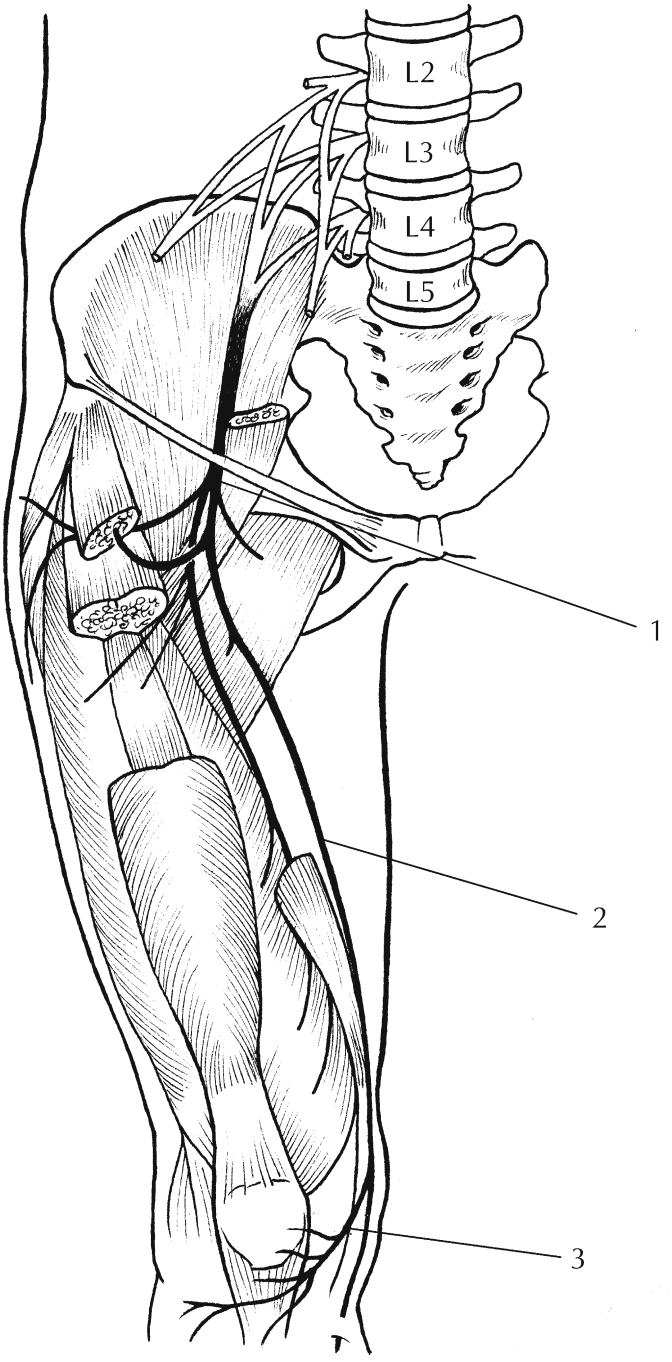

Fig. 39. Femoral nerve anatomy. *1* Femoral nerve. *2* Saphenous nerve. *3* Patellar branch

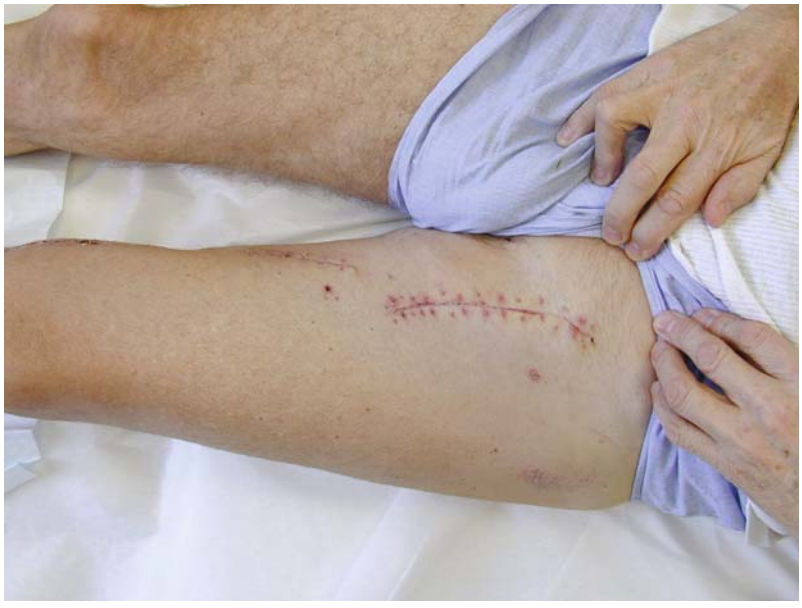

Fig. 40. Femoral nerve lesion after vascular surgery

Anatomy

The femoral nerve is derived from the lumbar plexus (originating from the ventral roots of L2–L4). Proximal (intrapelvic) branches go to the psoas major and iliacus muscles, passing through the inguinal ligament. Motor branches go to the pectineus, sartorius and quadriceps muscles. Sensory branches to the medial aspect of the thigh, anterior medial knee, and lower leg (saphenous nerve) (see Fig. 39).

Symptoms

Sensory loss on the ventral thigh, perhaps with saphenal involvement (over the tibial bone).

Buckling of the knee (on uneven surfaces) and falls (leg "collapses"). Sensory symptoms may be mild or absent.

Pain is variable, depending on the cause of the neuropathy. Often felt in the inguinal region or iliac fossa. Nerve trunk pain with or without sensory symptoms (e.g., in diabetes).

Clinical syndrome

Atrophy and weakness of quadriceps muscles. Weakness of the psoas and quadriceps muscles only occurs with proximal lesions. Decreased or absent knee jerk. Sensory loss over anterior aspect of thigh and medial side of lower leg.

Causes

Compressive:

Compression or stretch during surgery or obstetrical procedures: hip arthroplasty, pseudoaneurysm in the groin, retraction in abdominal surgery, vaginal hysterectomy in lithotomy position, laproscopic hernia repair, kidney transplantation, abdominal hysterectomy, vaginal delivery (see Fig. 40).

Synovial cyst of hip.

Iatrogenic:
Femoral arterial puncture, femoral catheterization, inadvertent suturing, local infusions of chemotherapeutic agents, local anesthetic injections
Prolonged pressure: marked extension or flexion of hip in unconscious patients, pregnancy (bilateral)

Idiopathic:

Inflammatory: heterotopic ossification, bursitis of iliopsoas muscle, lymph nodes in ilioinguinal region, hip abscess

Metabolic: Diabetic femoral neuropathy is a misnomer; it should be called diabetic lumbosacral plexopathy or diabetic polyradiculopathy.

Neoplastic: local tumors, perineuroma, malignant invasion

Traumatic: Penetrating injury

Vascular:
Anticoagulant therapy
Hematoma in psoas or iliacus muscle from rupture of an abdominal aortic aneurysm
Trauma

Saphenous nerve lesions:
Bursitis of pes anserinus
Entrapment, medial side of knee
Entrapment by a branch of the femoral artery
Meniscectomy, arthroscopy
Neurolemmoma

Diagnosis

EMG: quadriceps and iliac muscles, include paraspinal, iliopsoas, hip adductor
NCV: femoral nerve latencies and CMAPs
Sensory nerve conduction of the main trunk difficult
Sensory nerve conduction of saphenal nerve
Saphenous SEP (stimulation inferomedial to patella) is more reliable.
Neuroimaging: CT scan for psoas hematoma (has to be done acutely if hematoma is suspected) or tumor infiltration of psoas muscle
MRI-femoral nerve tumors
Laboratory tests: fasting glucose, vasculitis serologies

Differential diagnosis

Aneurysm of iliac artery
Irradiation of the inguinal area
L2–L4 radiculopathy
Mononeuropathy multiplex

Therapy

Depends on the etiology.
Complete, postoperative lesions require surgical approach. Surgery is also indicated for hematoma, depending upon the location and size. Otherwise, conservative management.

Prognosis

Generally good, depending on the cause of the lesion.

References

Biemond A (1970) Femoral neuropathy. In: Vinken PJ, Bruyn GW (eds) Handbook of clinical neurology. American Elsevier, New York, pp 303–310
Busis NA (1999) Femoral and obturator neuropathies. Neurol Clin 17: 633–653
Kim DH, Kline DG (1995) Surgical outcome for intra- and extrapelvic femoral nerve lesions. J Neurosurg 83: 783–790
Kuntzer T, Van Melle G, Regli F (1997) Clinical and prognostic features of femoral neuropathies. Muscle Nerve 20: 205–211
Mark MD, Kwasnik EM, Wright SC (1990) Combined femoral neuropathy and psoas sign: an unusual presentation of iliac artery aneurysm. Am J Med 88: 435–436
Simmons Z, Mahadeen ZI, Kothari MJ, et al (1999) Localized hypertrophic neuropathy; magnetic resonance imaging findings and long term follow up. Muscle Nerve 22: 28–36

Saphenous nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+			

Anatomy

The saphenous nerve is one of three sensory branches of the femoral nerve. (The others being the medial and intermediate femoral cutaneous nerves.) It has a long course through the adductor canal, penetrating the fascia above the knee and supplying the medial calf, medial malleolus, a small portion of the medial arch of the foot, and great toe.

Symptoms

Numbness, but also severe neuropathic pain may occur.

Signs

Sensory loss. Tinel's sign. Loss of sudomotor function.

Anatomical sites

Entrapment at Hunter's canal causes pain in the lower thigh and leg. Diagnosis is made by application of local anesthetics.
Infrapatellar branch: Lesion of the infrapatellar branch may cause a small sensory loss below the knee.
Entrapment above the medial ankle (nerve anterior to the prominence of medial malleolus) causes saphenous neuritic pain.

Causes

Arthroscopy
Bursitis of pes anserinus
Compression in the subsartorial canal
Hunter's canal operations, vascular disease, venous stripping
Gonyalgia paresthetica
Knee surgery (infrapatellar branch): meniscectomy
Neurolemmoma
Neuropathia patellae: distal terminal branch of infrapatellar ramus.
Phlebitis of the saphenous vein
Postures: straddling surfboard, playing "viola da gamba"
Surgery: arterial reconstruction, venous grafting, varicose vein operations
Transplantation: this nerve is often used for nerve transplantation

Diagnosis

Sensory NCV
EMG (for differentiation from L4)

Differential diagnosis

L4, partial femoral neuropathy

References

Dawson DM, Hallet M, Wilbourn AJ (1999) Entrapment neuropathies of the foot and ankle. In: Dawson DM, Hallet M, Wilbourn AJ (eds) Entrapment neuropathies. Lippincott-Raven, Philadelphia, pp 297–334

Mumenthaler M, Schliack H, Stöhr M (1998) Isolierte N. saphenus-Läsionen. In: Mumenthaler M, Schliack H, Stöhr M (eds) Läsionen peripherer Nerven und radikuläre Syndrome. Thieme, Stuttgart, pp 393–464

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Stewart JD (2000) Femoral and saphenous nerve. In: Stewart JD (ed) Focal peripheral neuropathies. Lippincott, Philadelphia, pp 457–473

Cutaneous femoris lateral nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+ –			

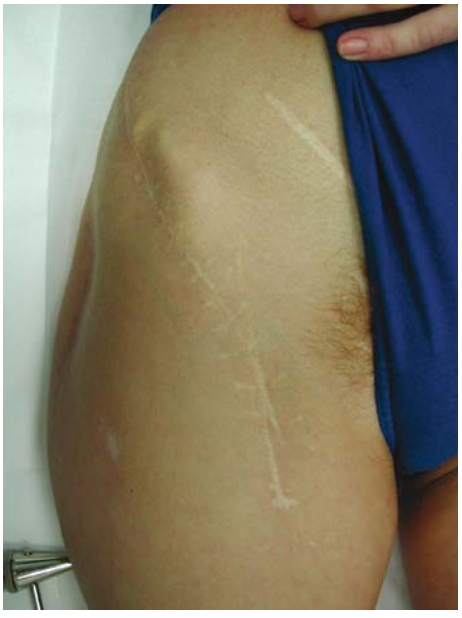

Fig. 41. Iatrogenic lesion of the lateral cutaneous femoris nerve. Several scars near anterior superior iliac spine

Anatomy

Sensory nerve, with fibers from L2 and L3. Exits the pelvis medial to the anterior superior iliac spine. It is enclosed between two folds of the lateral attachment of the inguinal ligament, with various paths to exit the pelvis.
The nerve changes course from a horizontal to a vertical position.

Symptoms

Pain, tingling or burning, or numbness of the anterolateral and the lateral aspects of the thigh. Symptoms do not extend to the knee. Sometimes highly irritable (can be irritated by clothes). Standing or walking can also aggravate, whereas hip flexion provides relief.
Infrequently bilateral. Allodynia ("Fear of putting hand in pocket").

Signs

Deficits of superficial sensory sensation in the center of the lateral cutaneous nerve's distribution, known as meralgia paresthetica. May be precipitated by hip extension, or pressure on an entrapment point (Tinel's sign).

Pathogenesis

Exercise or postural
Extension of hip
External compression
Flaccid belly due to adiposity
Iatrogenic
Pregnancy, (protuberant abdomen, with improvement after childbirth)
Psoas muscle, iliacus compartment of pelvis, inguinal ligament
Seat belts – motor vehicle accidents
Surgery: Renal transplant, lower abdominal surgery, iliac bone for grafting, Laparoscopic hernioraphias
Trauma
Tumors and mass, retroperitoneal malignancies

Upper thigh:
Blunt trauma, lacerations, misplaced injections
Diabetes

Diagnosis

EMG: differential diagnosis radiculopathy
NCV
SEP
MRI

Differential diagnosis

Coxarthrosis
Neurinoma
Pelvic neoplasm
Radiculopathy L2
Wartenberg syndrome – “migrant sensory neuritis”

Therapy

Anesthetics, local infiltration, steroids
Local novocain infiltration
Spontaneous recovery
Surgical intervention: only if pain persists

Prognosis

Short term: depending on etiology
Long term: good

References

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Cutaneous femoris posterior nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+			

Anatomy

Fibers come from the lower part of the lumbosacral plexus, roots S1–3. The fibers descend together with the inferior gluteal nerve through the greater sciatic notch, below the piriformis muscle. A branch leaves to the perineum and scrotum. The sensory area includes the lower buttock, parts of the labia or scrotum, dorsal side of the thigh and proximal third of the calf.
The autonomic field is a small area above the popliteal fossa.

Symptoms

Paresthesias and numbness over the lower part of the buttock and posterior thigh.

Signs

Sensory deficit

Pathogenesis

Bicycle riding
Colorectal tumors
Fall on the buttocks
Gymnastic exercises on buttocks
Hemangiopericytoma
Iatrogenic injection in buttock
Ischemia of lower extremity
Sedentary occupation
Venous malformation
Wounds of the dorsal thigh

Diagnosis

NCV – difficult technique
EMG: may distinguish from sacral lesion
Need to differentiate from sacral plexus lesions

Differential diagnosis

Sciatic nerve lesion
Sacral plexus or radicular lesion S2, S3

References

Arnoldussen WJ, Korten JJ (1980) Pressure neuropathy of the posterior femoral cutaneous nerve. Clin Neuro Neurosurg 82: 57–60
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Sciatic nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy	Surgical revision
	+		+		

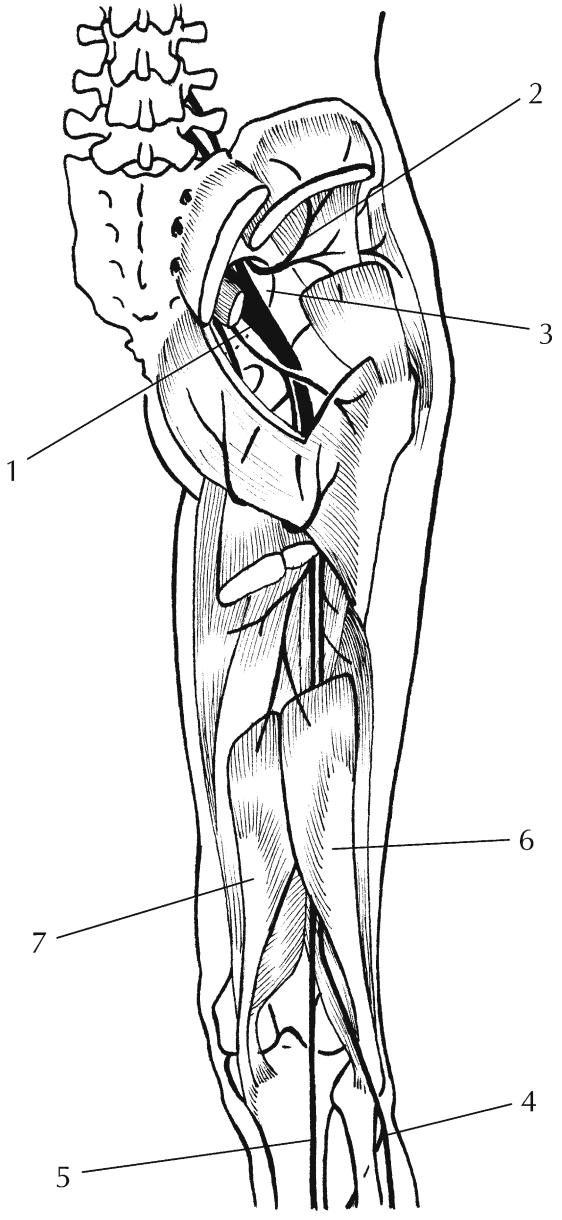

Fig. 42. Sciatic nerve anatomy. Greater sciatic nerve. *1* Great sciatic nerve. *2* Gluteal superior nerve. *3* Infrapiriform foramen. *4* Peroneal nerve. *5* Tibial nerve. *6* Semitendinosus muscle. *7* Semimembranosus muscle

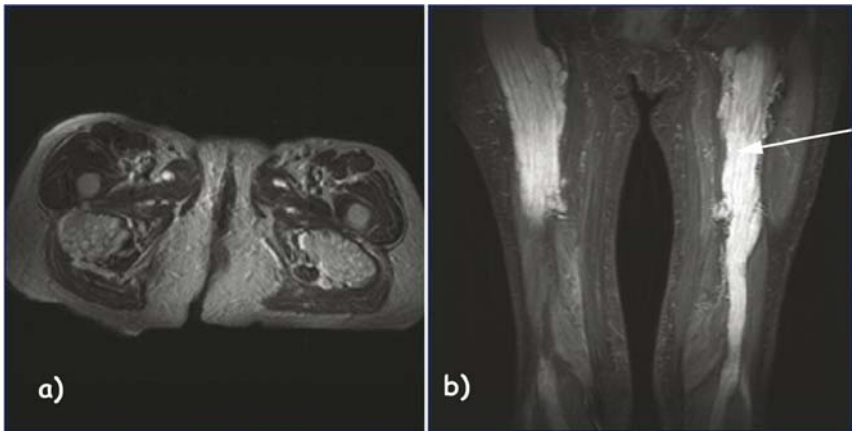

Fig. 43. Neurofibromatosis. Bilateral enlargement of the sciatic nerve in transverse **a** and longitudinal section **b**

Anatomy

Fibers from L3 to S3 und S4 leave the pelvis through the sciatic foramen. The nerve passes below the piriform muscle (or pierces it), into the gluteal region and moves first laterally, then caudally. It continues between the greater trochanter and the ischial tuberosity through the inferior buttock, where it is embedded in fatty tissue in the subgluteal space.

It is positioned on the dorsal side of the femoral bone, between the flexor muscles of the knee. The location of the division into the tibial and peroneal nerves varies, but usually occurs in the upper thigh. Fibers from the lateral and medial divisions of the sciatic nerve become the peroneal and tibial nerves. Fibers from the lateral division (peroneal nerve) are more prone to compression. The peroneal and tibial nerves include motor, sensory and autonomic fibers.

The nerve provides motor innervation to the following muscles: the semitendinosus, the long head of the biceps femoris, the semimembranosus, part of the adductor magnus (medial trunk), the short head of the biceps femoris (lateral trunk) and all muscles innervated by the peroneal and tibial nerves (see Fig. 42).

Symptoms

Complete proximal transsection produces a paralysis of hamstring muscles and all the muscles innervated by the peroneal and tibial nerves. Sensory loss occurs in all cutaneous areas supplied by both nerves, with the exception of a small medial zone that is innervated by the saphenous nerve.

Many sciatic lesions are partial and tend to resemble peroneal nerve lesions, due to the increased susceptibility of the peroneal nerve fibers.

Painful neuropathic syndromes can result from sciatic nerve lesions.

Signs

Inspection and palpation along the sciatic nerve (the sciatic notch in the thigh). Tenderness in the notch is a non-specific sign. Muscle testing should include hip muscles (gluteal), which should be spared. Hamstring muscles and knee flexors will be weak. Complete lesions will lead to involvement of all muscles in the lower leg, as well as loss of sensation in all regions except the region supplied by the saphenous nerve. Severe trophic changes may be present in the tibial nerve distribution. Absent (or at least diminished) ankle jerk and gait difficulties will also occur.

Pathogenesis

Causes of lesions in the pelvis:
Aneurysm (hypogastric artery)
AV malformation
Carcinoma
Childbirth (by caesarean section)
Common iliac artery aneurysm
Endometriosis
Lipoma

Causes of lesions in the thigh:
Aneurysm (persistent sciatic artery, popliteal artery)
Lipoma
Neurofibroma (Fig. 43)
Schwannoma
Trauma (gunshot, stabwound, laceration)

Common causes:
Acute compression (coma, drug overdose, intensive care unit, prolonged sitting, falls, hematoma)
Gluteal contusion or rhabdomyolysis with a gluteal compartment syndrome
Gunshot or knife wound
Hip replacement, hip fracture or dislocation, or femur fracture
Infarction (vasculitis, iliac artery occlusion, arterial bypass surgery)
Intramuscular gluteal injection

Less common causes:
Tumor: carcinoma, lipoma, lymphoma, neurofibroma, Schwannoma, endometriosis
AV malformations, ruptured aneurysm, false aneurysm of the aorta, child birth, infection, vasculitis, myositis ossificans

Piriformis syndrome:
Compression of the sciatic nerve at the pelvic outlet

Diagnosis

NCV including F-wave, H-reflex
EMG: distinguish from radiculopathy (paraspinals), outside supply areas: plexus
Neuroimaging: MRI, ultrasound, CT

Differential diagnosis

Cauda equina syndrome
Lyme disease
Meningeal carcinomatosis
Plexopathy (sacral)
Polyneuropathy: inflammatory, vasculitic
Radiculopathies

Therapy/prognosis

Depending on etiology: Traumatic sciatic nerve lesion may have a good prognosis, however in a follow up only 13% experienced complete recovery, while 34% had mild deficits, 28% had moderate deficits, and 24% had severe deficits.
Surgical approach: end-end neuroraphy, nerve transplants.

References

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Peroneal nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
CMT	++	(DM, vasculitis)	+	+

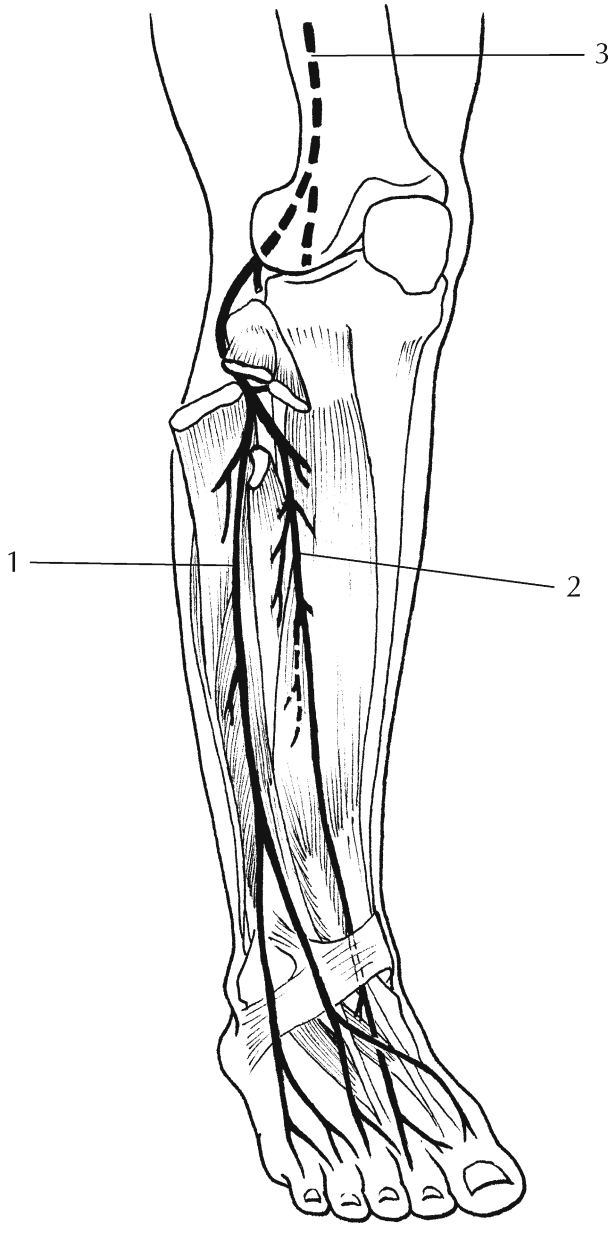

Fig. 44. Peroneal nerve anatomy. *1* Superficial peroneal nerve. *2* Deep peroneal nerve. *3* Sciatic nerve

Anatomy

The peroneal nerve is the lateral trunk of the sciatic nerve, separating from the sciatic nerve frequently in the upper popliteal fossa. The nerve originates from the posterior divisions of the ventral rami of L4, L5, S1, and S2.

The nerve pierces the head of the superficial peroneal muscle (which forms a tendinous arch over the nerve) to reach the anterior compartment of the lower leg. The nerve splits into superficial and deep branches.

The superficial branch innervates the shaft of the fibula and the peroneal muscles.

The deep branch runs between the tibialis anterior and extensor hallucis longus muscles, to innervate these muscles as well as the extensor digitorum longus. The terminal portion of the deep branch reaches the foot, to innervate the extensor digitorum brevis (see Fig. 44).

Sensory distribution

The superficial peroneal nerve provides sensory innervation to the anterolateral lower leg and the dorsum of the foot (except for the skin between toes 1 and 2, which is innervated by the deep peroneal nerves).

Symptoms

Most frequent mononeuropathy of the lower extremity. Acute, or insidiously developing foot drop (depending on the cause) and extension of toes.

Rarely the extensor hallucis longus may be disproportionately affected.

Pain is usually not a feature, sensory symptoms are minor. Incomplete weakness may only manifest itself in tripping over toes and also lead to falls. Eversion deficit may cause sprain or fracture of ankle.

Signs

Foot drop or deficit of ankle dorsiflexion weakness is the hallmark of common peroneal nerve dysfunction.

Varying degree of foot dorsiflexion deficit, maximally complete foot drop and toe weakness.

In common peroneal nerve lesions eversion (long peroneal muscles) is also absent.

Incomplete weakness may only manifest itself in tripping and falling. Eversion deficit may cause sprain or fracture of ankle.

For the assessment of eversion (and inversion-tibial nerve), the foot needs to be passively dorsiflexed (90 °).

Sensory loss may occur on the dorsum of the foot, and may extend to the knee. Tinel's sign may be elicited at the fibular head.

Isolated deep peroneal nerve lesions have sensory loss confined to a small (coin like) area between first and second toes. Eversion remains intact.

Superficial peroneal nerve lesions depend on the site of the lesion: pain and paresthesias over the dorsum of the foot.

Bilateral lesions are rare, and usually the sign of polyneuropathy.

Causes

External compression:
Anesthesia
Coma, sleep, bed rest
Habitual leg crossing
Plaster cast
Prolonged squatting

Compartment syndrome:
Affects the deep peroneal
Cuff or swelling of lower extremity (coagulation disorders)

Direct trauma:
Adduction injury-knee dislocation
Fibular fracture
Injury, laceration
Knee surgery, arthroscopy

Traction injury:
Acute ankle injury

Masses:
Baker cyst of gastrocnemius or semimembranosus muscle
Callus
Fabella
Hematomas (anticoagulant therapy, hemophiliacs)
Lipoma
Nerve sheath
Nerve sheath ganglia
Osteomas
Most common ganglia from the tibio-fibular joint. Benign, but may invade popliteal fossa and peroneus longus muscle and then invade or compress the nerve.
Schwannomas, neurofibromas

Entrapment:
Fibular tunnel

Others:
Vasculitis
Leprosy
Idiopathic

Associations with polyneuropathies:
Diabetes
HNNP
Multiplex neuropathy
Leprosy

Deep peroneal lesions:
Anterior compartment syndrome
External compression at the ankle

Superficial peroneal nerve lesions:
Compression of sensory branch when traversing deep fascia of lower leg
Peroneal (lateral compartment)
Trauma

Accessory deep peroneal nerve:
Is a branch of the superficial peroneal nerve (22%).

Lateral cutaneous nerve of the calf lesions:
Hyperesthesia in the lateral aspect of the leg, worsened by sitting, relieved by extending the knee

Diagnosis

NCV
Inching technique over capitulum fibulae
Sensory NCV
EMG
Ultrasound
CT
MRI

Differential diagnosis

Lesion of L5, lumbosacral trunk, or plexus
Sciatic nerve lateral trunk lesion

Postpartum – L5 lesions

Therapy

Acute trauma/transsection: nerve repair
Incomplete/blunt trauma: wait for spontaneous repair
Compressive episode: decrease pressure.

Prognosis

Depending on the cause, and on the site of the lesion.

References

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Muckart RD (1976) Compression of common peroneal nerve by intramuscular ganglion from the superior tibio-fibular joint. J Bone Joint Surg Am 58: 241–244
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Sarrafian SK (1993) Anatomy of the foot and ankle: descriptive, topographic, functional. Lippincott, Philadelphia
Staal A, van Gijn J, Spaans F (1999) The peroneal nerves. In: Staal A, van Gijn J, Spaans F (eds) Mononeuropathies. Saunders, London Edinburg New York, pp 133–141

Tibial nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

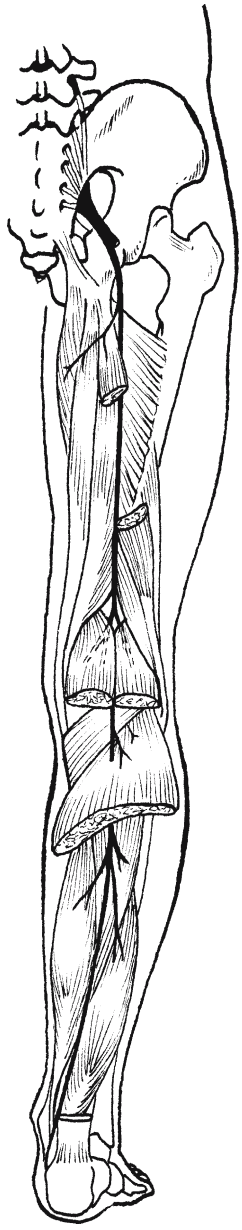

Fig. 45. Tibial nerve anatomy. Tibial nerve originates from sciatic nerve above the knee at variable sites

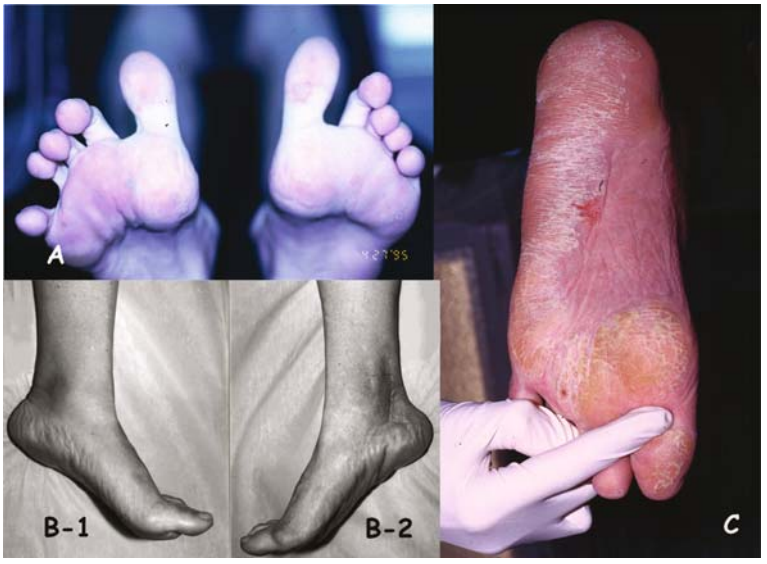

Fig. 46. Tibial nerve lesions. **A** Tibial nerve injury to the left leg. Note, that the patient is unable to spread the toes. **B** Distal tibial nerve lesion: **B-1** Normal, **B-2** Atrophy and wrinkling of the skin of the plantar pedis. **C** Complete tibial nerve lesion, note the discoloration of the skin and hyperkeratosis

Anatomy

Fibers for the tibial nerve come from L3–S4. The nerve originates from the medial part of the sciatic nerve. It has a protected position in the thigh and popliteal fossa. In the lower leg, the tibial nerve innervates the gastrocnemius, posterior tibial, flexor digitorum longus, and flexor hallucis muscles. It passes through the tarsal tunnel (behind the medial malleolus), along with the tibial posterior artery and tendons of the posterior tibial and short flexor digitorum muscles. Here the nerve branches into the medial and lateral plantar nerves. The medial plantar nerve innervates the abductor hallucis and the short flexor digitorum brevis. The lateral plantar nerve innervates the flexor and abductor digiti minimi, the adductor hallucis and the interosseous muscles. The sensory fibers from both plantar nerves innervate the sole of the foot. Branches include the medial plantar proper digital nerve (to the great toe) and the lateral plantar proper digital nerve (to the little toe). Four terminal branches are called interdigital nerves (divide into two digital nerves after the distal ends of metatarsal bone.

In the popliteal fossa, the medial cutaneous nerve arises from the tibial nerve. This nerve unites with the lateral sural cutaneous nerve (from the peroneal nerve) to form the sural nerve. A sensory branch in the foot, the calcaneal nerve, innervates the medial part of the heel (see tarsal tunnel syndrome) (see Fig. 45).

Symptoms

Proximal tibial nerve lesions

Patients present with weakness of the plantar flexors and foot invertors, long toe flexors, and intrinsic foot muscles. Sensory loss usually involves the sole of the foot (see Fig. 46).

Distal tibial and plantar nerves

The terminal branches of the tibial nerve, the medial and lateral plantar and medial calcaneal nerves can be compressed within the tarsal tunnel. Clinical manifestations include foot and ankle pain along with paresthesias on various areas on the sole of the foot, depending on the particular terminal nerve involved.

Tibial nerve injury affecting foot intrinsic muscles can also result in clawing of the toes.

Signs

Proximal lesions result in weakness of plantar flexion, absent inversion (supination), and reduced or absent flexion of the toes. Sensory disturbances occur at the sole of the foot (with or without sural nerve inclusion). Absent ankle jerk.

Autonomic:
Autonomic fibers travel with the tibial nerve. Lesion of the tibial nerve produces trophic skin changes and hyperkeratosis (Fig. 46c).

Pathogenesis

Baker cysts
Blunt injury
Hematoma in the popliteal fossa
Morton's neuralgia
Nerve sheath tumor
Rupture of the popliteus muscle
Stretch from ankle sprain
Superior tibiofibular joint injury
Synovial cyst
Tendinous arch between soleus muscle
Tarsal tunnel syndrome: see below

Diagnosis

Laboratory tests
Electrophysiology: NCV, EMG
Imaging

Differential diagnosis

Sciatic nerve lesion, radicular lesion.
Fasciitis. Burning feet in neuropathies, such as diabetes.

Therapy

Conservative: Pain therapy: carbamazepine, gabapentin, amitryptiline and others.
Physical therapy. Orthotic devices.
Surgical: Baker cysts, nerve sheath tumors.

Prognosis

Depends upon the etiology.

References

Mastaglia FL (2000) Tibial nerve entrapment in the popliteal fossa. Muscle Nerve 23: 1883–1886
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Tarsal tunnel syndrome (posterior and anterior)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy	Hematology
	+		+		

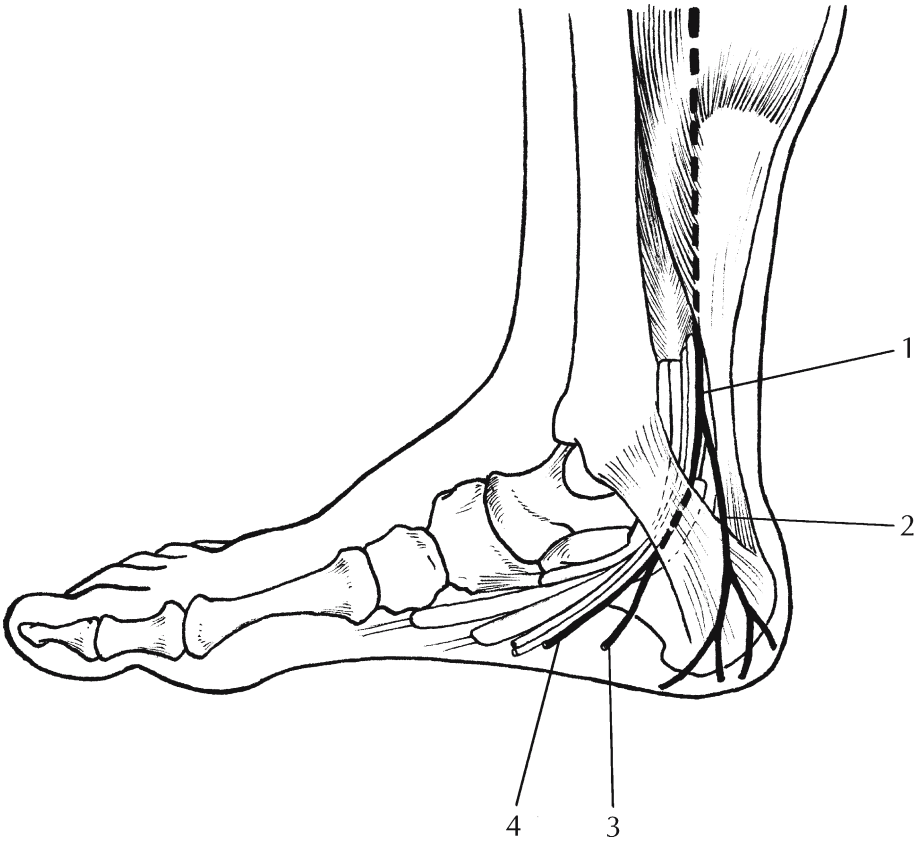

Fig. 47. Tarsal tunnel. *1* Tibial nerve. *2* Calcanea branch. *3* Lateral branch. *4* Medial branch

Anatomy/distribution

See tibial nerve.

The tunnel consists of the tendons of the tibialis posterior muscle and the flexor hallucis longus muscle, the tibial posterior artery, the areas behind the medial malleolus and below the retinaculum flexorum.

Lesions may involve the complete nerve, or in a more distal lesion either the medial or lateral plantar nerves.

At the point of the tarsal tunnel, where the lateral and medial plantar nerves separate, the calcaneal nerve also separates, which is purely sensory and innervates the heel. The calcaneal nerve may also be involved in tarsal tunnel syndrome.

Symptoms

Local pain at the medial malleous, sensory symptoms at the medial or plantar aspect of the foot.

Signs

Tinel's sign, weakness of small foot muscles (difficult to assess).

Pathogenesis

Entrapment:
Footwear
Idiopathic

Inflammatory:
Leprosy
Non-specific tenosynovitis
Rheumatoid arthritis

Trauma
Fibrous scarring
Fracture and soft tissue injury
Hypermobility of the ankle
Stress fracture

Tumor:
Cyst of the nerve sheath
Ganglia: may involve the nerve
Ganglion from flexor hallucis longus tendon
Intraneural ganglion
Lipoma
Neurilemmoma

Others:
Dilated veins, varicosity
Hypertrophy of abductor hallucis muscle
Hypothyroid disease
Lipoid exposition

Differential diagnosis

Arthritis
"Burning feet"
Bursitis
Circulation disorders
Compression of plantar nerve against tuberosities of the navicular bone

Foot pain of other causes
Orthopedic
Plantar fasciitis
Plantar callus
Polyneuropathy

Diagnosis

NCV: medial and lateral branchs of tibial nerve
EMG-small feet muscles
Neuroimaging

Therapy

Anti-inflammatory drugs
Arch support, orthosis
Neurolysis of the tibial nerve
Neurovascular decompression
Steroids

Anterior tarsal tunnel syndrome

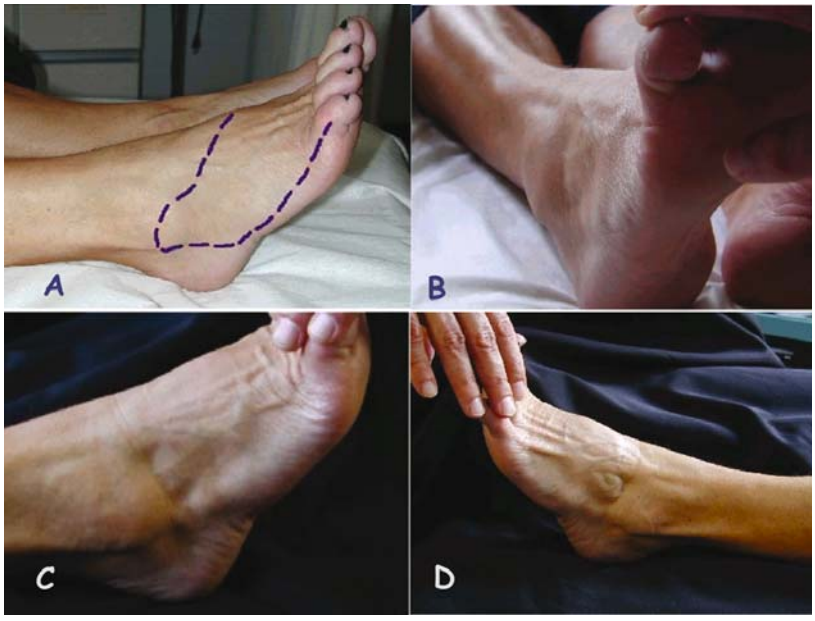

Fig. 48. Anterior tarsal tunnel syndrome. **A** and **B** Sensory loss in a case of anterior tarsal tunnel syndrome, atrophy of extensor digitorum brevis muscle. **C** Atrophy of the the extensor digitorum brevis muscle. **D** Opposite foot with a normal muscle

Terminal branch of the deep peroneal nerve. Passes under the pars cruciforme vaginae fibrosae.

Symptoms

Pain at the dorsum of the foot. Sensory loss over the first interosseus space.

Signs

Atrophy of the extensor digitorum brevis muscle (Fig. 48). Tinel's is sign positive.

Therapy

Splint, comfortable foot position, orthosis, local steroids, surgery.

Electrophysiology

NCV
EMG

Differential diagnosis

Local arthritis, osseous changes.

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Sural nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	used

Anatomy

The sural nerve is formed from two branches: the medial cutaneous nerve of the calf (tibial nerve) and the lateral cutaneous nerve of the calf (common peroneal nerve). In general, the sural nerve contains only sensory fibers. It runs along the middle of the calf region, lateral to the Achilles tendon and lateral malleolus. The nerve innervates the lateral ankle and lateral aspect of the sole, to the base of the 5th toe. The sural nerve gives rise to the lateral calcaneal nerves posterior and proximal to the tip of the lateral malleolus. At the proximal fifth metatarsal tuberosity the nerve divides into a lateral branch (the dorsolateral cutaneous nerve of the fifth toe) and a medial branch, providing sensation to the dorsomedial fifth toe and dorsolateral fourth toe.

Symptoms

Numbness, pain, and paresthesias at the lateral side of the foot.

Symptoms after excision:
Dysesthesias occur in 40–50% of cases. Neuroma formation may also occur. Postoperative scarring may result in dysesthesias. There is no difference in outcome between whole nerve biopsy or fascicular biopsy.

Signs

Tinel's sign may indicate the site of the lesion.

Pathogenesis

Popliteal fossa

Baker's Cyst
Arthroscopy, operation for varicose veins

Calf

Calf muscle biopsies
Elastic socks
Footwear
Tight lacing

Ankle

Acute or chronic ankle sprain
Avulsion fracture of base of 5th metatarsal bone
Adhesion after soft tissue injury
Fractured sesamoid bone in peroneus longus tendon
Ganglion
Idiopathic neuroma
Osteochondroma
Sitting with crossed ankles
Shoes

Surgery:
Ankle fractures, talus, calcaneus, base of fifth metatarsal, Achilles tendon rupture

Diagnosis

Laboratory (include genetics), electrophysiology, imaging, biopsy, sensory NCV

Diagnosis of neuroma:
Tinel's sign, pain and paresthesias below distal fibula or along the lateral or dorsolateral border of the foot.

Differential diagnosis

Asymmetric neuropathy
Herpes zoster (rare)
S1 irritation

Therapy

Padding of shoewear, steroids, excision and transposition of the nerve stump

Prognosis

Depends upon the etiology

References

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Mononeuropathy: interdigital neuroma and neuritis

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

Anatomy

Terminal branch of tibial nerve at the head of III and IV metatarsal bone, and toes.

Symptoms

Pain in the forefoot, localized to the second and third interdigital space. Numbness and paresthesias of adjacent toes may be present. Aggravated by shoes (e.g., high heels).
Worsened by standing and walking.
Sometimes sensory loss at opposing side of affected toes.
Pain may be provoked by compression of metatarsal 3,4 or 3,5.

Clinical syndrome

Interdigital tenderness.
Pain might be elicited by adduction of metatarsals and metatarsal compression.
Pain and paresthesias of adjacent toes may be present.
Forefoot pain and numbness may also occur.

Causes

Mechanical irritation of the nerve may cause neuroma and neuritis**.**
Lateral pressure from adjacent metatarsal heads result in neuritis and neuroma formation.

Diagnosis

NCV (SNAP reduction) – difficult to assess.
Ultrasound
MRI
Local injection: lidocaine

Studies:
Electrophysiology, imaging

Differential diagnosis

Freiberg's infarction
Metatarsophalangeal pathology (instability, synovitis)
Metatarsal stress fracture
Plantar keratosis

Therapy

Avoidance of high heeled shoes
Anti-inflammatory drugs and pain therapy
Steroid or local anesthetic agent injection
Surgery

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Nerves of the foot

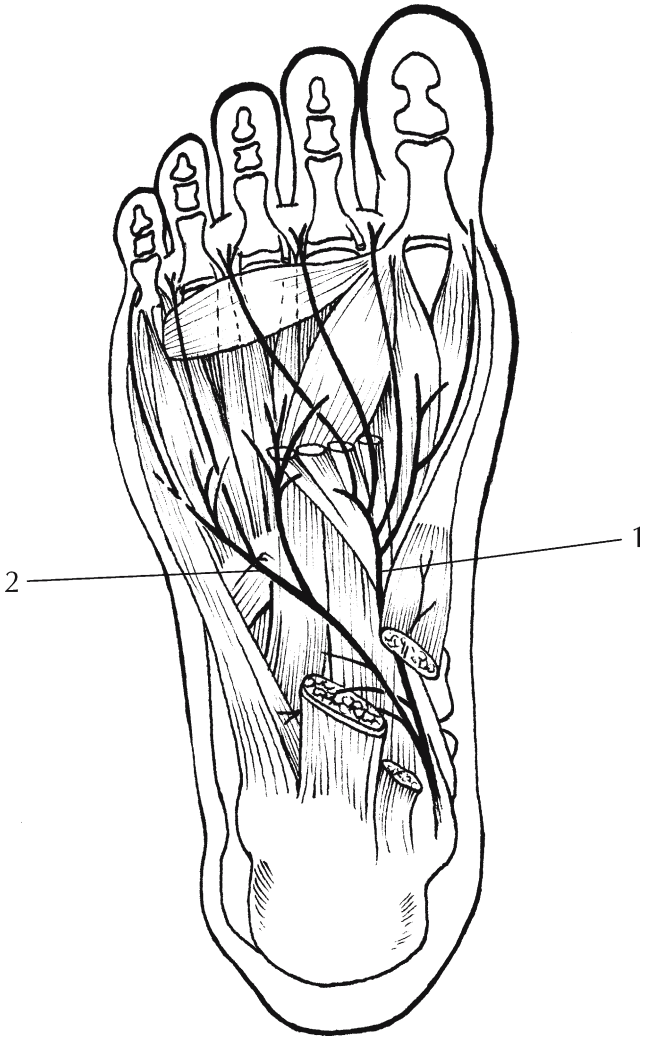

Fig. 49. Foot nerves. *1* Medial plantar branch. *2* Lateral plantar branch

Calcaneal nerve

May be involved in tarsal tunnel. Also, ganglion in tarsal tunnel may involve the nerve.

The calcaneal nerve (pure sensory) originates at the point of the tarsal tunnel, to innervate the medial part of the heel.

Plantar nerves (medial and lateral)

Both nerves pass through the tarsal tunnel, though the arch and sole of the foot.

Causes: trauma, tendon sheath cysts, Schwannomas, hypertrophy or fibrosis of abductor hallucis muscle, sometimes from a discernible cause.

Isolated lateral plantar nerve lesion: occurs less frequently, from a foot fracture or ankle sprain.

Entrapment of the first branch of the lateral plantar nerve has been described. (Affects intrinsic foot muscles, and periosteum of calcaneus. Occurs in athletes with heel pain).

Interdigital nerves (Morton's metatarsalgia)

Occurs at adjacent metatarsal bones before the division into two digital nerves.

Symptoms:
Radiating pain into one or two toes. Worse while standing and walking.
Sitting and removing shoes improves symptoms.
Often from fibrous nodules that are called "neuromas".

Therapy:
Carbamazepine or other drugs used in neuropathic pain.
Electrocoagulation
Injections
Local anesthetic block
Pads
Shoes
Surgery

Diagnosis:
NCV, CT, MRI

Medial plantar proper digital nerve (Joplin's neuroma)

This nerve crosses the first metatarsophalangeal joint on the medial side of the big toe. Damage to the medial plantar proper digital nerve occurs where it crosses the first metatarsophalangeal joint, or on the medial side of the big toe.

Symptoms:
Pain or paresthesias on the medial side of the big toe, especially when walking.
Often mild, but may also be disabling.

Sign:
Tinel's at base of big toe.

Causes:
Acute blunt blows, lacerations,
Blunt trauma
Poor fitting shoes
Scars

Medial plantar proper digital nerve syndrome (Joplin's neuroma)
Differential diagnosis: arthritis of big toe.

References

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Peripheral nerve tumors

Clinical development

Peripheral nerve tumors usually present with a slowly progressive mononeuropathy. Initially paresthesia, pain, followed by motor or sensory loss, or both occur. The tumors may be seen, palpated or detected in imaging.
Mechanical factors (e.g. sitting , stretching the sciatic nerve, walking if tumor is on the foot) can exacerbate pain or paresthesias. Patient's often experience anemia and weight loss.

Signs

Tumor can be palpated or a mass can be seen (e.g. supraclavicular fossa).

Diagnosis

MRI can give a precise location. NCV and EMG can be used to assess the functional impairment of the nerve lesion.

Metastasis

Metastasis of solid tumors into peripheral nerves are rare, but have been described in lymphoma (particularly in neurolymphomatosis) and metastatic cancer. Local involvement of peripheral nerves with either compression or infiltration can be seen more frequently at the brachial plexus and sacral plexus, also at a radicular level in association with metastatic vertebral column disease.

Classification of peripheral nerve tumors: adapted from Birch 1993

Nerve sheath tumors	**Schwannoma** (neurolemmomas, neurinomas): (cellular, plexiform and melanotic)	Malignant Schwannoma
	Neurofibroma: Solitary neurofibroma Plexiform neurofibroma, fascicular spread through peripheral nerve tissue	Neurofibrosarcoma (4–29% as a manifestation of NF1)
	Fibrolipoma	Neuroepithelioma
Neuronal tumors	Ganglioneuroma	Ganglioneuroblastoma Neuroblastoma

Schwannomas

Schwannomas are the commonest benign nerve sheath tumors. They are encapsulated and displace adjacent nerve fascicles. Schwannomas can present as a painless, palpable mass on upper or lower extremities. A Tinel's sign can usually be elicited.

Neurofibroma

They can be divided into a) with association with Recklinghausen's disease and b) without association with Recklingshausen disease.

a) Neurinomas and van Recklinghausen's disease: Neurofibromas occur in cutaneous nerves and in larger nerves. The neurinomas in this patient group have a 15% risk of malignant transformation.

b) Neurinomas occur on extremities. These are more likely to arise from the motor portion of the nerve than from the sensory. They can occur as a localized mass or involve longer nerve segments. Histologically they involve the entire cross section of the nerve.

Other benign nonneuronal nerve sheath tumors are: desmoids, myoblastomas and lymphangiomas, lipomas, lipohamartomas, hemangiomas, hemangiopericytomas , arteriovenous fistulae, ganglions, end epidermoid cysts.

Localized hypertrophic mononeuropathy: is a slowly progressive mononeuropathy with little pain or numbness (may occur with NF1, or isolated). Any nerve can be affected as well as nerve roots.

Malignant neural sheath tumors:
Consist of malignant Schwannomas, neurofibromas, usually termed as "sarcoma". Malignant transformation of a benign nerve sheath cell tumor is more likely in patients with von Recklinghausen's disease. The tumors occur in long nerves of the extremities and in the nerve plexus.

Other tumors of the neural crest:
Neuroblastoma
Ganglioneuroblastoma
Ganglioneuroma
Paraganglioma
Pheochromocytoma

Peripheral nerve involvement in cancer patients

Cranial nerves, nerve roots, the nerve plexus and single nerves can be affected in cancer patients. The table gives an overview over the most frequently affected nerves (Table 12).

Table 12. Involvement of peripheral nerves in cancer patients

Nerve	Neoplastic	Therapy-related	Other causes
CN	Base of skull metastasis Leptomeningeal carcinomatosis Head and neck tumors	Toxicity of chemo- and radiotherapy	
Axillary nerve		Surgery, mastectomy, neck dissection	
Long thoracic nerve		Mastectomy Radiotherapy	Inflammatory neuropathy
Phrenic nerve	Lung cancer, lymphoma, thymoma	Thoracic surgery thymectomy	Critical illness neuropathy in intesive care patients and sepsis
Pectoral nerves		Neck dissection	
Musculocutaneus nerve	Local metastasis	Perioperative position	

Table 12. Continued

Nerve	Neoplastic	Therapy-related	Other causes
Cutaneous antebrachii medialis nerve		Paravenous injection	
Median nerve	Neurolymphomatosis		Amyloid deposition Paraproteinemia
Ulnar nerve	C8 lesion, Pancoast Tumor	Radiotherapy Malpostioning	
Radial nerve		Malpositioning, chemotherapy (vincristine)	
Truncal nerves	Metastasis, local metastasis into vertebral column, collapse of vertebral column	Operations Longterm steroid treatment with osteoporotic bone lesions	Herpes Zoster
Iliohypogastric nerve		Renal operations	
Ilioinguinal nerve		Abdominal surgery	
Genitofemoral nerve		Renal surgery	
Cutaneus femoris lateral nerve		Surgery radiotherapy	
Femoral nerve	Local pelvic tumor, inguinal tumor or lymph nodes	Surgery, anticoagulation, radiotherapy	
Obturator nerve	Metastasis, obturator foramen	Surgery pelvis	
Gluteus medius	Recurrence of local tumor		
Sciatic nerve	Metastasis, Foramen piriforme	Intraarterial cytostatic perfusion, radiotherapy	Injections, malpositioning
Tibial nerve			Rarely affected: cauda equina, sacral plexus lesion
Peroneal nerve	Local destruction of vertebral column, meningeal carcinomatosis Compression of cauda equina Osteolysis of capitulum fibulae	Malpositioning, cytostatic drugs (vincristine)	Paraneoplastic Cachexia Peroneal lesion may be part of sciatic nerve lesion
All local mononeuropathies		Intravenous Intraarterial perfusions	

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Polyneuropathies

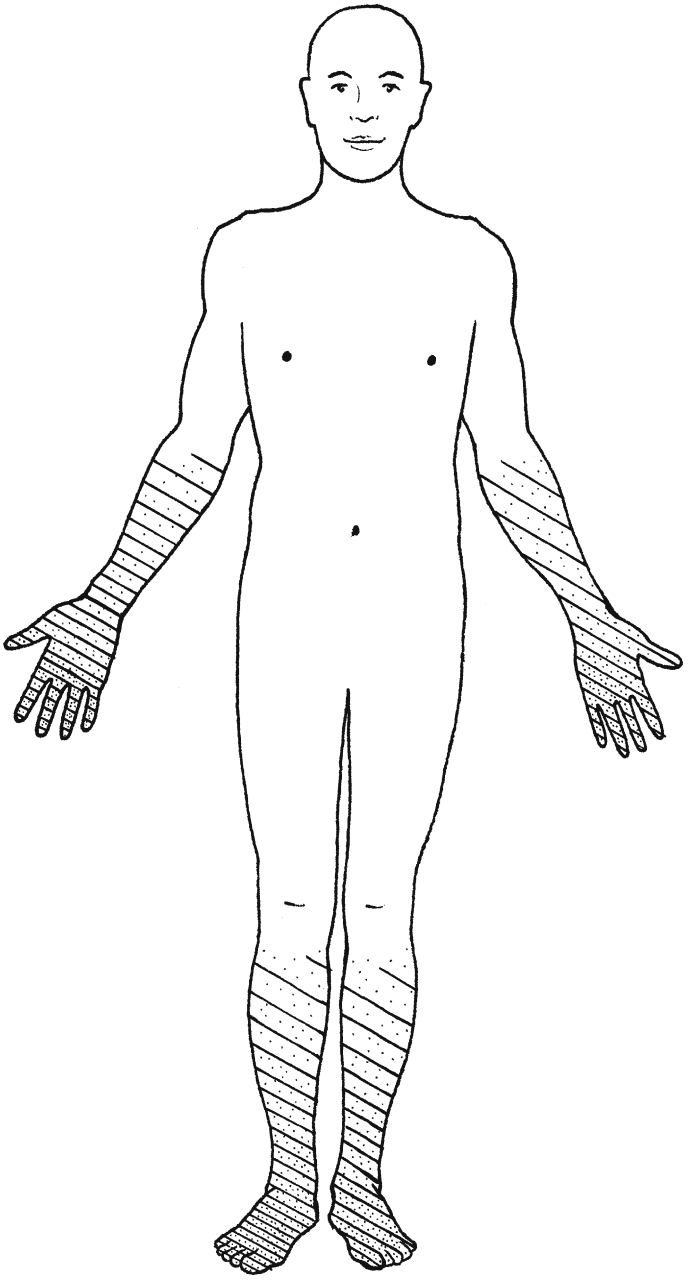

Fig. 1. Common stocking and glove distribution in polyneuropathies

Introduction

The peripheral nervous system (PNS) is defined as cell bodies or axons supported by Schwann cells. The PNS includes the cranial nerves (except the second cranial nerve), the dorsal root ganglia, the spinal nerve roots, the peripheral nerve trunks, and peripheral nerves. The peripheral autonomic system also lies within the PNS.

Peripheral neuropathy in its broadest definition encompasses any injury to the PNS. More precise terminology describes the specific site of PNS injury. Neuronopathies are direct injury to the cell bodies with a secondary axonal loss. Axonopathies represent a primary insult to axons; axonopathies, particularly when severe, can result in a secondary loss of cell bodies. A radiculopathy

is injury to spinal nerve roots while a plexopathy denotes injury in peripheral nerves as they course through a plexus. Polyneuropathy, the main focus of this chapter, refers to bilateral symmetrical injury to the peripheral nerves.

Polyneuropathy is commonly secondary to more generalized disease processes including systemic, metabolic or rheumatological disorders, cancer, vitamin deficiency states, exposure and/or ingestion of toxins and drugs, infections, immune reactions and inherited disorders of Schwann cell function. Table 13 provides a more complete list of disorders that lead to polyneuropathy. Multiple isolated peripheral nerve injuries, known as multiple mononeuropathies or mononeuropathy multiplex, are also usually due to systemic disease. It can be difficulty to distinguish near confluent mononeuropathy multiplex from generalized polyneuropathy. In contrast, isolated peripheral nerve injury is usually due to focal injury and is termed mononeuropathy. The mononeuropathies are discussed in chapter mononeuropathy.

Anatomical distribution

The most common polyneuropathy has a distal distribution with loss of sensory function beginning in the toes. As the sensory loss progresses to mid calf, the patient experiences sensation loss in the fingertips, resulting in the classic stocking-glove distribution of *distal symmetric polyneuropathy* (Fig. 1). Reflex changes parallel sensory disturbances with ankle reflexes being first decreased then absent. Symptomatic distal motor nerve involvement is less common and, when present, suggests specific underlying systemic disease processes, particularly immune mediated and toxic neuropathies. Motor weakness can occur in a proximal distribution, leading to a *proximal symmetric polyneuropathy.* This pattern is also most commonly present in immune or toxic neuropathies. A pure sensory *proximal symmetric polyneuropathy* is very rare but can occur in acute intermittent porphyria. Another less common distribution of symmetric polyneuropathies is with initial motor or sensory loss in the arms. This can occur in immune mediated neuropathies, porphyria and inherited disorders of the PNS.

Clinical syndrome

Patients with polyneuropathy generally fall into two major classes: patients with negative symptoms and patients with positive symptoms. This distinction can be helpful to the clinician in both the diagnosis and care of the patient. As the term suggests, patients with negative symptoms have painless loss of sensory function or motor loss that does not perturb the patient's functional ability. Loss of sensation most commonly reflects loss of both large and small nerve fibers. Patients with negative symptoms develop the insensate foot with loss of vibratory perception and proprioception (large fiber) and light touch, temperature and pain sensation (small fiber). Eighty five percent of patients with diabetic polyneuropathy have no symptomatic complaints (i.e. negative sensory symptoms). This group of patients however is at high risk for ulcer formation because of their lack of pain sensation. In parallel negative motor symptoms, particularly atrophy of distal foot musculature, can lead to foot deformities and can also increase the risk of ulcers. Positive sensory symptoms can occur in patients with polyneuropathy in the absence or presence of external stimuli. At rest patients can experience painful parasthesias and/or frank pain. In response to normal stimuli such as light touch, patients may develop symptoms of hyperalgesia, dysesthesias or allodynia. Positive motor symptoms include cramps, fasciculations and functional weakness.

In summary, this chapter discusses the main polyneuropathies encountered by a physician in daily practice. It is not intended to be inclusive of all

polyneuropathies but the disorders discussed should provide the clinician with the knowledge required to diagnose and treat nearly all patients seen in an outpatient clinic. The neuropathies will be discussed in the order outlined in Table 13. Some key abbreviations used in this discussion include CMAP (compound muscle action potential), SNAP (sensory nerve action potential), and CSF (cerebrospinal fluid).

Table 13. Differential diagnosis of polyneuropathy

- Metabolic Disease
  - Diabetic distal symmetric polyneuropathy
  - Diabetic autonomic neuropathy
  - Diabetic mononeuritis multiplex
  - Diabetic polyradiculopathy
  - Renal Disease
- Systemic Disease
  - Systemic vasculitis
  - Non-systemic vasculitis
  - Paraproteinemia
  - Amyloidosis
  - Cancer
    - Neoplastic disease
    - Paraneoplastic disease
    - Motor neuron disease syndrome
  - Critical Illness
- Infectious
  - Human Immunodeficiency Virus (HIV)
  - Hepatitis B
  - Lyme
  - Diphtheria
  - Leprosy
  - Syphylis
  - Parasites
- Inflammatory
  - Acute motor axonal neuropathy
  - Acute motor and sensory axonal neuropathy
  - Acute inflammatory demyelinating polyradiculoneuropathy
  - Chronic inflammatory demyelinating polyradiculoneuropathy
  - Chronic demyelinating polyradiculoneuropathy with anti-MAG antibodies
  - Miller-Fisher Syndrome
  - Multifocal Motor Neuropathy
- Nutritional
  - Cobalamin
  - Post-gastroplasty
  - Pyridoxine
  - Strachan's syndrome
  - Thiamine
  - Tocopheral
- Industrial Agents, Metals and Drugs
  - Industrial Agents
    - Acrylamide
    - Carbon Disulfide
    - Hexacarbons
    - Organophosphorous Agents

Table 13. Continued

- Drugs
  - Alcohol
  - Amiodarone
  - Chloramphenicol
  - Colchicine
  - Dapsone
  - Disulfiram
  - Vinka alkaloids
  - Platinum
  - Taxol
- Metals
  - Arsenic
  - Mercury
  - Thallium

Hereditary
- Hereditary Autonomic and Sensory Neuropathy
- Hereditary Motor Sensory Neuropathy (Charcot-Marie-Tooth Disease) Types 1, 2
- Hereditary Neuropathy with Pressure Palsies
- Porphyria

Diabetes is the most common cause of neuropathy in the Western World. The 4 main peripheral nervous system complications of diabetes will be discussed: distal symmetric polyneuropathy, autonomic neuropathy, mononeuritis multiplex and the syndrome of plexopathy/polyradiculopathy that is frequently termed amyotrophy.

Diabetic distal symmetric polyneuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+++	+++		+

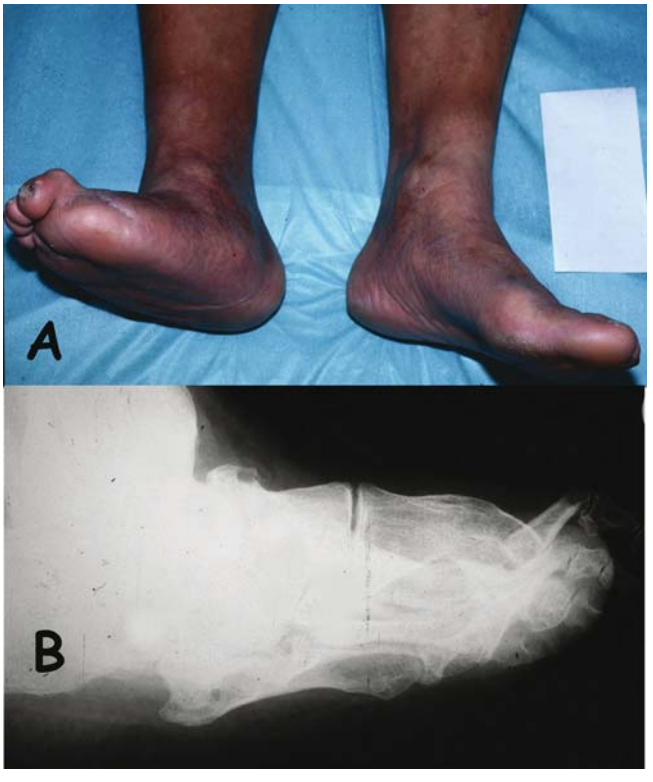

Fig. 2. Diabetic neuropathy. Pes planus **A**, sensory loss may induce osteous changes with collapse of the small foot bones- see X ray **B**

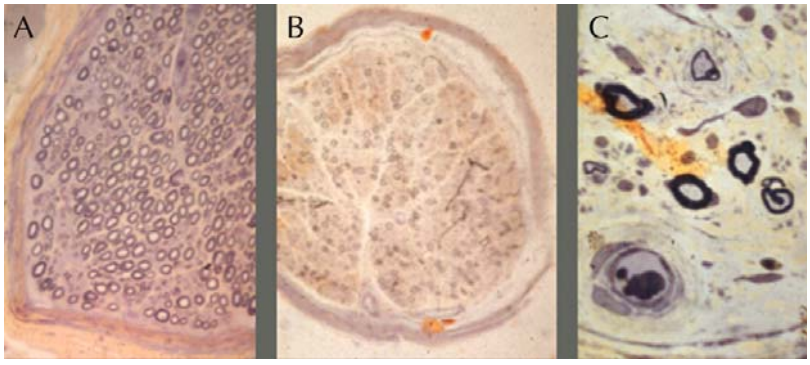

Fig. 3. Sural nerve biopsy from a patient with diabetic neuropathy and an asymptomatic control subject. **A** Normal sural nerve showing an abundant and normal distribution of myelinated fibers. **B** Sural nerve from a patient with diabetes showing severe loss of axons. **C** High magnification view of B showing loss of myelinated fibers, splaying of myelin with early onion bulb form formation

Anatomy/distribution

Both large and small sensory and motor nerves are affected in diabetic distal symmetric polyneuropathy (DPN). DPN is a length dependent neuropathy affecting the feet first.

Symptoms

DPN is most commonly a slowly progressive disorder. A rapid onset can be seen in newly diagnosed type 1 patients when rigorous glycemic control is abruptly instituted. Equally common among men and women, 85% of patients have an insensate foot with negative sensory and motor symptoms. Fifteen percent of patients have positive symptoms with paresthesias, dysesthesias, pain and muscle cramps. Patients with an insensate foot are at risk for foot injury and ulceration.

Clinical syndrome/ signs

DPN occurs in both type 1 and type 2 diabetic patients. The severity of DPN correlates with the degree and duration of diabetes. After 25 years of diabetes, at least 50% if not more of patients have DPN. Examination of the feet reveals atrophic skin changes, callous and fissure formation (Fig. 2). Commonly all sensory modalities are decreased in a stocking-glove pattern with loss of ankle reflexes. Weakness is uncommon and present distally in only the most severe cases. When sensation loss reaches the midcalf, early sensory loss is found in the fingers.

Pathogenesis

The Diabetes Control and Complications Trials (DCCT) confirmed that hyperglycemia underlies the development of DPN. It is likely that the hyperglycemic state disrupts both the normal metabolism and blood flow of peripheral nerves.

Diagnosis

Laboratory:
HbA1C is frequently elevated. Serum proteins, vitamin levels, hepatic function and serological markers of vasculitis should be normal. Frequently patients have serologic evidence of mild renal dysfunction and measurable proteinuria. Unless renal dysfunction is severe, the diabetic state itself, and not the secondary loss of renal function, is the primary cause of neuropathy.

Electrophysiology:
Early in neuropathy NCV reveal low normal or absent sural sensory responses with mild decreases in peroneal motor conduction velocities. As the neuropa-

thy progresses, sensory amplitudes in the hand decline and there is evidence of denervation by EMG in distal foot muscles.

Nerve Biopsy:
There is loss of large and small axons in the absence of inflammation with thickening of blood vessel basement membrane (Fig. 3). Nerve biopsy is usually not required for the diagnosis.

Differential diagnosis

A systematic stepwise elimination of other common causes is required. See Table 13.

Therapy

DPN requires preventative and, in some cases, symptomatic therapy. Preventative therapy consists of optimal glycemic control coupled with daily foot hygiene. The patient should inspect his feet each night and keep his feet clean and dry. Painful DPN can be treated with gabapentin at doses up to 800 mg/QID and amitryptiline or nortryptiline (25 to 150 mg/QHS). Please see the review by Simmons (2002) for a complete approach to the treatment of painful neurpathy.

Prognosis

Fifteen percent of patients with neuropathy develop an ulcer in their lifetime. Prognosis is dependent on daily foot hygiene and care.

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Diabetic autonomic neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
		++	++	

Anatomy/distribution

Both sympathetic and parasympathetic fibers are affected in diabetic autonomic neuropathy (DAN). Like DPN, DAN is a length dependent neuropathy with loss of autonomic function that can vary from mild to severe.

Symptoms

Mild subclinical DAN is common and occurs in patients with DPN. Symptomatic DPN can vary from mild to severe. Cardiac symptoms include fixed tachycardia, orthostatic/postprandial hypotension, arrhythmias, and in severe cases, sudden cardiac death. Gastrointestinal symptoms include constipation, nightime diarrhea and gastroparesis with early satiety, nausea and vomiting. Genitourinary symptoms are common in men, with impotence present in nearly all males after 25 years of diabetes. Urinary retention occurs in men and women. Abnormal pupillary responses and abnormal sweating occurs, with anhydrosis of the feet and hands, and gustatory sweating in more severe cases. Abnormal neuroendocrine responses likely contribute to hypoglycemic unawareness in type 1 patients.

Clinical syndrome/signs

Symptomatic DAN is more common in type 1 patients, although subclinical DAN (diagnosed by cardiovascular testing) is common in type 2 patients. The signs in DAN parallel the symptoms. Patients have an abnormal heart rate, poor cardiac beat to beat variation, orthostasis, weight loss from gastroparesis, urinary tract infections from urinary retention, poor pupillary responses and absent sweating.

Pathogenesis

Like DPN, it is generally held that hyperglycemia underlies the development of DAN. It is likely that the hyperglycemic state disrupts both the normal metabolism and blood flow of autonomic ganglia and nerves.

Diagnosis

Laboratory:
As with DPN.

Electrophysiology:
Standard measures of cardiac autonomic function are required for the diagnosis and include measures of heart rate (R) variability conducted in the supine position with the patient breathing at a fixed rate of 6 breaths per minute during a 6 minute period. The maximum and minimum R-R intervals during each breathing cycle are measured and converted to beats a minute. The 30: 15 ratio

is calculated for patients. The heart rate response is determined on changing from the lying to standing position. The shortest R-R interval around the 15th beat and the longest R-R interval around the 30th beat upon standing is measured to calculate the ratio. Orthostatic hypotension is measured. Patients can also undergo a bladder cystoscopy, gastroesophageal manometry, sweat testing and an eye exam.

Imaging:
Positron emission tomography (PET) quantitates sympathetic cardiac innervation and is an excellent measure of left ventricular function.

Biospy:
None.

Differential diagnosis

It is essential to exclude atherosclerotic heart disease, primary gastrointestinal disease such as peptic ulcer disease or colitis, bladder or urinary tract anatomical abnormalities leading to retention (in males, consider prostatism) and drug induced changes in pupils and sweating.

Therapy

Like DPN, therapy is preventive and symptomatic. Preventive therapy is based on optimal glycemic control. Symptomatic treatment is targeted toward the symptom i.e. hydration and support stockings for orthostasis with extreme cases requiring midodrine 5 mg/TID. Therapy is discussed in detail in Vinik (2002).

Prognosis

Like DPN, DAN usually progresses slowly over years, with a patient becoming more symptomatic. It is estimated that sudden cardiac death due to DAN occurs in 1–2% of all type 1 diabetic patients.

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Diabetic mononeuritis multiplex and diabetic polyradiculopathy (amyotrophy)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	++		++

Anatomy/distribution

Diabetic mononeuritis multiplex (DMM) and diabetic polyradiculopathy (DPR) are due to the loss of motor and sensory axons in one or more named nerves or nerve roots. The term mononeuritis multiplex refers to multiple mononeuropathies in conjunction with polyneuropathy.

Symptoms

Patients experience proximal and distal weakness and sensory loss in specific named peripheral nerves (including cranial or truncal nerves) or nerve roots. The onset is sudden and usually extremely painful in the sensory distribution of the nerve/nerve root. In DMM, the most commonly involved named nerves include the median, radial and femoral nerve and cranial nerve III. In DPR, thoracic and high lumbar nerve roots are frequently affected, initially unilaterally, but frequently with later bilateral involvement.

Clinical syndrome/signs

DMM and DPR are sudden in onset, often self-limited, and occur primarily in older, poorly controlled type 2 patients. In DMM, patients experience sudden pain, weakness and sensory loss in a named peripheral nerve. Patients with DMM of cranial nerve III, present with unilateral pain, diplopia, and ptosis with pupillary sparing. In DPR, involvement of thoracic nerve roots presents as band-like abdominal pain that is often misdiagnosed as an acute intraabdominal emergency. L2-L4 DPR is often confused with a pure femoral neuropathy; the former is common while the later is rare. Patients are weak in hip flexion and knee extension with an absent knee reflex; frequently weakness will spread to involve L5-S1 anterior myotomes.

Pathogenesis

Unlike DPN or DAN, DMM and DPR are due to discreet infarcts in nerves due to vascular occlusions. Epineural vessels are inflamed with IgM and complement deposition.

Diagnosis

Laboratory:
It is essential to exclude vasculitis by appropriate serological screening (see p. 262).

Electrophysiology:
NCV reveals loss of sensory and in advanced cases motor amplitude and mildly slowed conduction velocities in distinct nerves. EMG reveals denervation in myotomes corresponding with the named nerves.

Imaging:
Cranial aneurysm should be excluded in cranial nerve III palsies by cranial MRI. Abdominal and lumbosacral plexus CAT scans are routine to rule out intraabdominal pathology in patients with diabetic thoracic radiculopathy and a mass lesion in the lumbosacral plexus in patients with diabetic lumbar polyradiculopathy.

Biospy:
None.

Therapy

Patients usual require aggressive pain management. Glycemic control is essential to prevent reoccurrence. Physical therapy and supportive care help accelerate recovery. There are reports of using intravenous gammaglobulin (IVIG) in DPR, but efficacy remains unproven.

Prognosis

DMM and DPR improve spontaneously in most cases, but may leave mild residual deficits. It is essential to achieve improved glycemic control in affected patients; if not, it is highly likely that the patient will experience recurrent episodes.

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Distal symmetric polyneuropathy of renal disease

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	++		

Anatomy/distribution

Both large and small sensory and motor nerves are affected in distal symmetric polyneuropathy due to renal disease. Like DPN, this is a length dependent neuropathy.

Symptoms

This is most commonly a slowly progressive disorder. Patients present with pain, dyesthesias, sensory loss, muscle cramps, restless legs and, in more advanced cases, leg weakness.

Clinical syndrome/ signs

This neuropathy commonly occurs in patients with end-stage renal disease on dialysis; 60% of patients on dialysis have some degree of neuropathy. Neuropathy secondary to renal disease is 2 times more common in men. Examination reveals a symmetric stocking-glove loss to all sensory modalities with distal weakness, absent ankle and depressed knee reflexes.

Pathogenesis

While the definitive cause is unknown, the neuropathy may be due to accumulation of metabolites or loss of unknown renal factors.

Diagnosis

Laboratory:
Serum BUN and Cr and 24 hour urine collection all indicate renal failure.

Electrophysiology:
Early in neuropathy there are prolonged distal latencies, slowed motor conduction velocities and prolonged F waves. The relationship between conduction slowing and renal failure is well established. Lowered sensory and motor amplitudes are present, and in severe cases, are absent. There is evidence of denervation by EMG in distal foot muscles.

Imaging:
None.

Nerve Biopsy:
There is evidence of axonal degeneration, with loss of large and small axons in the absence of inflammation. Nerve biopsy is usually not required for the diagnosis.

Differential diagnosis

Diabetes and other drugs, such as colchicine, may mimic or exacerbate the neuropathy.

Therapy

Therapy consists of pain management and physical therapy. Optimizing renal function may improve the neuropathy.

Prognosis

The neuropathy progresses over a period of months and is rarely fulminant. Prognosis is improved following renal transplant, and sometimes with more intensive dialysis.

Reference

Burns DJ, Bate D (1998) Neurology and the kidney. J Neurol Neurosurg Psychiatry 65: 810–821

Systemic disease

Vasculitic neuropathy, systemic

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	++		++

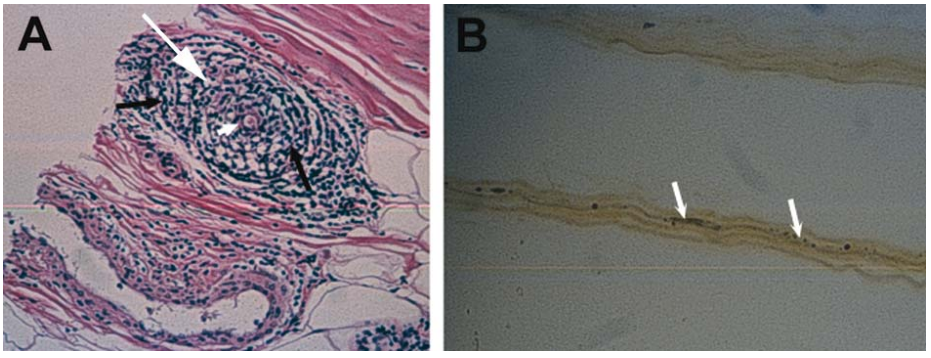

Fig. 4. Sural nerve biopsy from a patient with isolated peripheral nerve vasculitis. **A** Infiltration of a perineurial vessel wall by multiple inflammatory cells including lymphocytes and macrophages (black arrows). There is also evidence of pink fibrin deposits consistent with the presence of fibrinoid necrosis. **B** Teased fiber preparations showing multiple axon balls (white arrows) and evidence of empty strands consistent with axonal degeneration

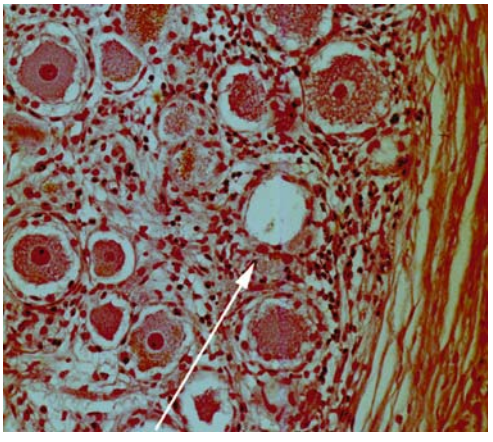

Fig. 5. Dorsal root ganglion biopsy from a patient with severe sensory ataxia due to dorsal root ganglionitis. There are clusters of inflammatory cells (white arrows) surrounding the dorsal root ganglion neurons (black arrows). Many of the neurons show evidence of degeneration

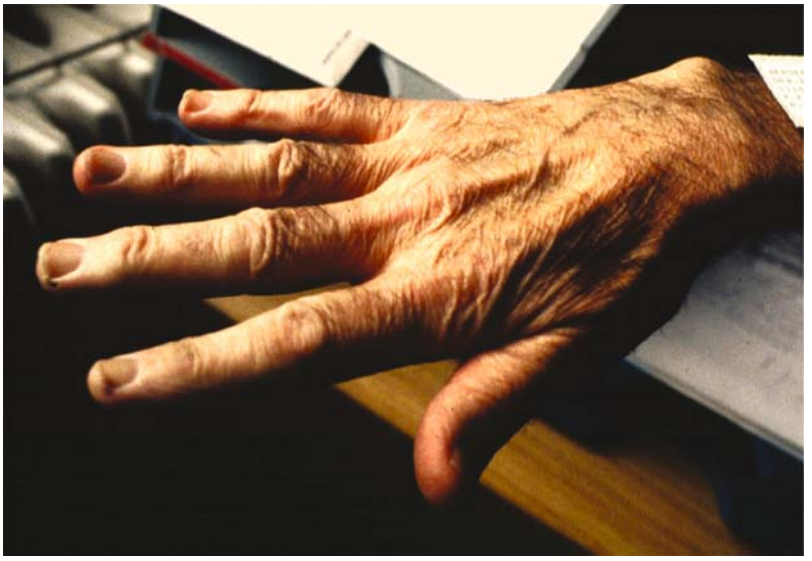

Fig. 6. Hand in a patient with vasculitis. Atrophy of the small hand muscles and vasculitic changes at the nailbed

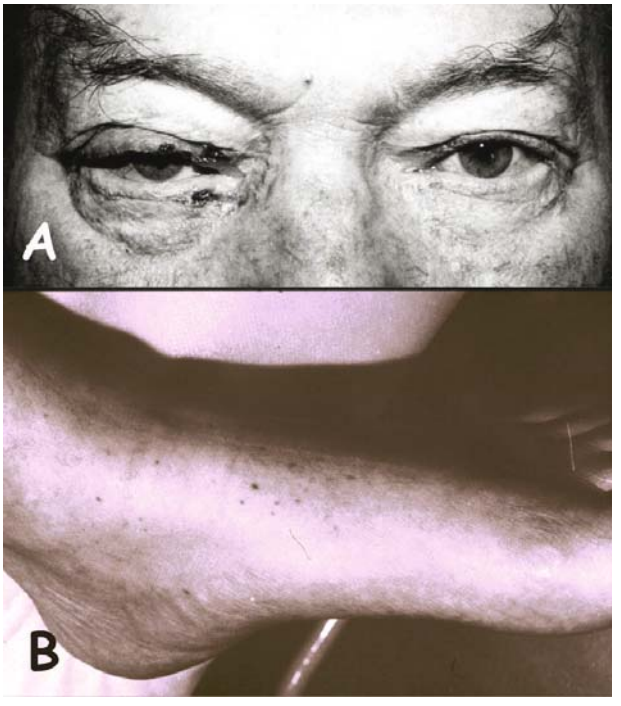

Fig. 7. Wegener's granulomatosis. This patient had right orbital involvement **A**. Vasculitic neuropathy was heralded by vasculitic skin changes **B**

Anatomy/distribution

Nerve and muscle pathology relates to destruction of blood vessels.

Symptoms

Proximal and distal weakness, pain, and sensory loss occur in a multifocal distribution.

Clinical syndrome/signs

May affect isolated nerves (45% of cases), overlapping nerves (40%), or cause symmetric neuropathy (15%). Patients typically present with a mixture of motor and sensory signs. Associated signs of systemic vasculitic disease include: fever, weight loss, anorexia, rash, arthralgia, GI, lung, or renal disease. Usually the

neuropathy presents in patients that have already been diagnosed with a specific vasculitic disease (Fig. 6).

Pathogenesis

Several immune-mediated mechanisms have been identified that lead to destruction of vessel walls. The various mechanisms result in ischemic necrosis of axons (see Figs. 4 and 5).
Systemic disease that can involve vasculitic neuropathy can be divided into the following categories:

Immune/Inflammatory mediated:
Wegener's granulomatosis (Fig. 7), Polyarteritis nodosa, Churg-Strauss syndrome, Hypersensitivity reaction

Paraneoplastic:
Various cancers (rare)

Infectious:
Hepatitis B or C, HIV-1, Lyme disease

Other:
Collagen vascular diseases

Diagnosis

Laboratory:
Findings in conjunction with systemic disease could include elevated ESR, anemia, ANA, ENA, cryoglobulins, P-ANCA, hepatitis B or C antibodies, HIV-1, or Lyme serologies.
EMG and NCV are abnormal, and are important for identifying which nerves are involved. SNAPs and CMAPs are reduced reflecting axonal damage.
Muscle and nerve biopsies should be taken, and show T-cell and macrophage invasion, with necrosis of blood vessels.

Differential diagnosis

Diabetic neuropathy, HNPP, CIDP, multifocal neuropathy with conduction block, plexopathies, porphyria, multiple entrapment neuropathies, Lyme disease, sarcoidosis.

Therapy

The systemic disease should be treated as aggressively as possible. Prednisolone and cyclophosphamide are frequently used in the treatment of systemic vasculitic diseases. Aggressive pain management should be a special concern of the neurologist.

Prognosis

Therapy leads to improvement in most cases, but residual impairments and relapses are possible. Pain symptoms often respond quickly, but this should not be taken as an indication that the vasculitis is under control. Other symptoms may take some time to improve.

References

Davies L (1994) Vasculitic neuropathy. Baillieres Clin Neurol 1: 193–210
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Olney RK (1998) Neuropathies associated with connective tissue disease. Semin Neurol 18: 63–72
Rosenbaum R (2001) Neuromuscular complications of connective tissue diseases. Muscle Nerve 2: 154–169
Said G (1999) Vasculitic neuropathy. Curr Opin Neurol 5: 627–629

Vasculitic neuropathy, non-systemic

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++			++

Anatomy/distribution

Both sensory and motor fibers are affected in individual peripheral and cranial nerves.

Symptoms

The symptoms in vasculitis neuropathy are dependent on which nerve(s) and/or root(s) are affected. As a class, this neuropathy is usually painful and patients experience both sensory loss and weakness in multiple named nerves (85% of cases). 15% of patients present as a symmetric polyneuropathy.

Clinical syndrome/signs

Pure peripheral nervous system vasculitic neuropathies are very rare. Examination reveals sensory loss and weakness in named affected peripheral or cranial nerves (multiple mononeuropathies), and rarely, a stocking-glove pattern of sensory loss and weakness.

Diagnosis

Laboratory:
The serological markers of vasculitis should be normal. Vitamin levels, glucose, hepatic and renal function are normal. There is no monoclonal gammopathy. Cerebrospinal fluid analysis is normal.

Electrophysiology:
Multiple axonal mononeuropathies with low or absent sensory and motor amplitudes and denervation in innervated myotomes are present.

Imaging:
None.

Nerve Biopsy:
There is evidence of epineurial arteriole or venule inflammation and necrosis in multiple sites, producing axonal loss, frequently in a central fascicular pattern.

Differential diagnosis

Disorders that can affect multiple named nerves or nerve roots, such as systemic vasculitis or infectious neuropathies, need to be excluded.

Therapy

Patients may respond to prednisone alone or in conjunction with cyclophosphamide therapy for 6 months.

Prognosis

Prognosis is fair to good, and 80% of patients go on to near full recovery.

Reference

Collins MP, Periquet MI, Mendell JR, et al (2003) Nonsystemic vasculitic neuropathy: insights from a clinical cohort. Neurology 61: 623–630

Neuropathies associated with paraproteinemias

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+	++	Bone	+

Type of paraproteinemia	Type of polyneuropathy	Treatment
Multiple Myeloma	Different types of polyneuropathy Amyloidosis may develop	Treatment of myeloma
MGUS (monoclonal gammopathy of undetermined significance)	Sensorimotor or CIDP like	Immunosuppression, various therapies are described
MGUS – MAG	Distal involvement, predominantly large fibers with ataxia and pseudoathetoid movements	Little beneficial effect of therapy
POEMS Syndrome	CIDP like	Treatment of the myeloma, plasmapheresis
Waldenstrom's macroglobulinemia	Distal sensorimotor neuropathy, predilection for large fibers	Treatment of Waldenstrom's
Amyloidosis (AL type)	Polyneuropathy: autonomic involvement, involvement of skeletal muscle	Colchicine, steroids

Neuropathy in conjunction with multiple myeloma

Anatomy/distribution Axonal neuropathy occurs with amyloid deposits.

Symptoms Patients experience distal symmetric motor and sensory dysfunction.

Clinical syndrome/signs Exam shows proximal and distal weakness and sensory loss, mononeuropathies and autonomic dysfunction.

Diagnosis Nerve conduction velocities are slowed. Serum electrophoresis can show IgA or IgG monoclonal gammopathy. Bone marrow studies reveal myeloma, and examination of the skeletal system can show osteolysis.

Other types of polyneuropathy associated with gammopathies may be responsible for the clinical picture. **Differential diagnosis**

The primary therapeutic goal is treatment of the myeloma and supportive care. **Therapy**

Neuropathies associated with monoclonal gammopathies: monoclonal gammopathy of undetermined significance (MGUS)

Symptoms may be motor, sensory, or sensorimotor depending on IgM antibody specificity. **Symptoms**

Exam shows distal greater than proximal weakness and sensory loss. **Clinical syndrome/signs**

Disease is primarily associated with IgM, IgA and IgG gammopathy. **Pathogenesis**

NCV maybe slowed (see description for CIDP). Serum electrophoresis reveals a monoclonal gammopathy. Bone marrow studies and skeletal examination should be normal, confirming that the gammopathy is of "unknown significance." **Diagnosis**

Other types of polyneuropathy associated with gammopathies may be responsible for the clinical picture. **Differential diagnosis**

Immunosuppression (prednisone) plus plasma exchange is effective in patient's with IgG and IgA gammopathies and a CIDP like picture. Patients who present with an axonal neuropathy are less responsive to treatment. **Therapy**

IgM paraproteinemia with anti-MAG antibodies

Half of patients with MGUS develop antibodies against MAG (myelin associated glycoprotein). Patients have a moderate to severe sensory loss with distal weakness. Nerve conduction velocities are significantly slowed with temporal dispersion and conduction block. These patients do not respond to therapy, but the disorder itself is usually indolent.

Large fiber sensory function is lost, and there may be tremor. **Symptoms**

The disease presents as a sensorimotor neuropathy with predilection of large-fiber dysfunction. It is difficult to distinguish from MGUS, and MGUS may evolve into Waldenstrom's over time. **Clinical syndrome/signs**

There is likely an auto-immune attack against peripheral nerves. **Pathogenesis**

There is no evidence of osseous changes with imaging. **Diagnosis**

Laboratory studies can show IgM monoclonal gammopathy, IgM antibodies to MAG, GMI, sulfatide, GD1a or GD1b. Bone marrow or lymph node biopsy may be abnormal.

Therapy

Chemotherapy, intravenous gammaglobulin or plasmapheresis are usually not effective.

Prognosis

Neuropathy is usually not improved with treatment.

Osteosclerotic myeloma (POEMS syndrome)

POEMS syndrome stands for polyneuropathy, organomegaly, endocrinopathy, M-component and skin lesions. POEMS syndrome is associated with osteosclerotic myeloma, located in the vertebral column and long extremity bones, but not in the skull.

A polyneuropathy resembling CIDP occurs, and papilledema has been described.

Therapeutic efforts are directed against osteomyelosclerotic myeloma.

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Benito-Leon B, et al (1998) Rapidly deteriorating polyneuropathy associated with osteosclerotic myeloma responding to intravenous immunoglobulin and radiotherapy. J Neurol Sci 158: 113–117

Davies LE, Drachman DB (1972) Myeloma neuropathy: successful treatment of two patients and review of cases. Arch Neurol 27: 507–511

Eurelings M, Moons KGM, Notermans NC, et al (2001) Neuropathy and IgM M-proteins. Neurology 56: 228–233

Miralles GD, O'Fallon JR, Talley NJ (1992) Plasma cell dyscrasia with polyneuropathy: the spectrum of POEMS syndrome. N Eng J Med 327: 1919–1923

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Ropper AH, Gorson KC (1998) Neuropathies associated with with paraproteinemia. N Eng J Med 338: 1601–1607

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Amyloidosis (primary)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	+	+	++

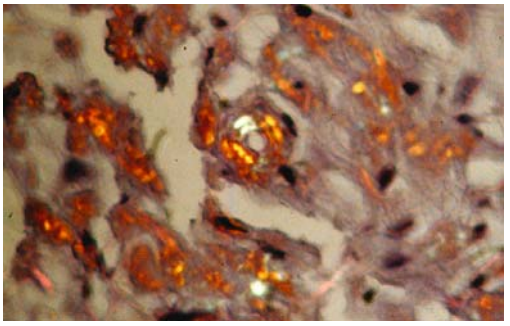

Fig. 8. Peripheral nerve amyloidosis. The biopsy shows a congo red stained section with evidence of apple green birefringence in amyloid deposits within endoneurial vessels

Anatomy/distribution

Primary amyloidosis (AL) is a multi-organ systemic disease affecting the peripheral and autonomic nervous systems. Axonal degeneration, particularly of small myelinated and unmyelinated fibers is present with diffuse amyloid deposits infiltrating epineurial and endoneurial connective tissue.

Symptoms

Initial neuropathic symptoms are most commonly burning pain and loss of sensation in the feet. These symptoms may precede development of multi-organ involvement by 1 year. With disease progression, patients experience distal muscle weakness and in advance cases autonomic symptoms of postural hypotension, syncope and impotence.

Clinical syndrome/signs

AL is a disorder of older men. Approximately 70% of affected patients are men with a median age of 65 who experience weight loss, hepatomegaly, macroglossia, purpura and ankle edema. Early in the disease examination reveals a stocking/glove loss of all sensory modalities and depressed ankle reflexes. Approximately 25% of patients will have signs of a median mononeuropathy with paresthesias in the first 3 fingers with variable weakness of thenar muscles. As AL progresses, distal weakness, absent reflexes and autonomic signs are present, including orthostatic hypotension and abnormal sweating.

Diagnosis

Laboratory:
A serum or urine monoclonal protein is present in 90% of patients with AL. An IgG monoclonal gammopathy occurs in 30% of patients; 20% have free

monoclonal light chains in their sera. 80% have proteinuria and of these patients two-thirds have a urine monoclonal light chain.

Electrophysiology:
Sensory nerve amplitudes are absent, motor amplitudes are decreased or absent but motor latencies and conduction velocities are normal or only mildly decreased. Needle exam reveals fibrillations and positive sharp waves in distal musculature.

Nerve Biopsy:
Congo red positive amyloid deposits are present in the abdominal fat aspirates of 70% of affected patients and in bone marrow aspirates in 50%. If these sites are negative, sural nerve biopsy is indicated and is positive in 85% of AL patients with neuropathy (Fig. 8).

Differential diagnosis

Multiple myeloma, vasculitis and rarely familial amyloidosis.

Therapy

While nephropathy is partially responsive to melphalan and prednisone, anti-inflammatory and alkylating agents (cyclophosphamide) have no affect on the course of neuropathy. Amyloid deposits are permanent.

Prognosis

Neuropathy continues to progress unabated, and most patients die from multi-organ failure within 4 years of diagnosis.

References

Adams D (2001) Hereditary and acquired amyloid neuropathies. J Neurol 248: 647–57
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Kyle RA, Gertz MA, Greipp PR, et al (1997) A trial of three regimens for primary amyloidosis: colchicine alone, melphalan, prednisone, and colchicine. N Eng J Med 336: 1202–1207
Reilly MM, Staunton H (1996) Peripheral nerve amyloidosis. Brain Pathol 2: 163–177
Quattrini A, Nemni R, Sferrazza B, et al (1998) Amyloid neuropathy simulating lower motor neurone disease. Neurology 51: 600–602

Neoplastic neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+	+	+	++

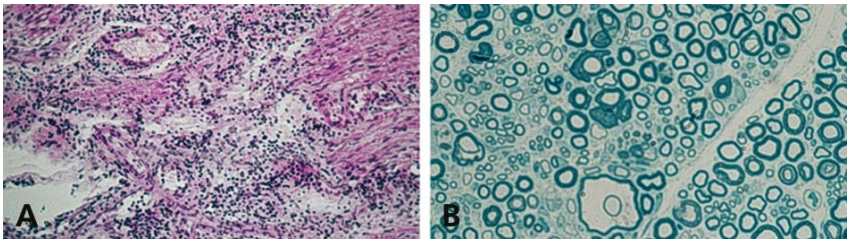

Fig. 9. Sural nerve biopsy from a patient with lymphoma. **A** Infiltration of the peripheral nerve by collections of B cells, with disruption of normal sural nerve architecture. **B** Disruption of myelin, with myelin splaying, and partial loss of axons

Anatomy/distribution

There is diffuse infiltration of peripheral nerves or nerve roots in neoplastic neuropathy.

Symptoms

The symptoms in neoplastic neuropathy are dependent on which nerve(s) and/or root(s) are affected. As a class, neoplastic neuropathy is usually painful and patients experience both sensory loss and weakness.

Clinical syndrome/signs

Neoplastic neuropathies are very rare, and occur almost exclusively in patients with lymphoma, chronic lymphocytic leukemia, and breast and ovarian carcinomas. Infiltration of specific peripheral nerves by lymphoma is known as neurolymphomatosis. Leukemia can affect multiple nerve roots, especially myelomonocytic leukemia. Meningeal carcinomatosis with polyradicular nerve root involvement can occur in leukemia, lymphoma and in both breast and ovarian carcinoma. Carcinomatous invasion of the plexus is discussed separately in chapter brachial and lumbosacral plexus. Examination reveals sensory loss and weakness in named affected nerves (multiple mononeuropathies) or alternatively a polyradiculopathy. Since there is direct nerve and root infiltration, both sensation loss and motor weakness are present in affected patients.

Diagnosis

Laboratory:
There is hematologic and bone marrow evidence of lymphoma and/or leukemia as expected, while vitamin levels, glucose, hepatic function (unless there has been metastatic spread) and serological markers of vasculitis should be normal. Cerebrospinal fluid analysis reveals an elevated protein and neoplastic cells if there is nerve root involvement.

Electrophysiology:
Multiple axonal mononeuropathies with low or absent sensory and motor amplitudes and denervation in innervated myotomes are present. If there is primarily nerve root infiltration, needle examination reveals anterior and posterior myotome denervation.

Imaging:
MRI imaging of the craniospinal axis is required in suspected cases of neoplastic polyradiculopathy. Positron emission tomography (PET) scanning of the plexus and peripheral nerves can reveal areas of tumor deposition.

Nerve Biopsy:
There is direct infiltration of nerve, resulting in axonal loss and the presence of tumor deposits in the nerve (Fig. 9).

Differential diagnosis

Disorders that can affect multiple named nerves or nerve roots, such as vasculitis or infectious neuropathies, need to be excluded.

Therapy

Treatment is of the cancer itself. Rarely, surgery is performed to remove local metastasis or a shunt is placed for chemotherapy directed at meningeal and/or root involvement.

Prognosis

While the prognosis is dependent on the type of cancer, in general, peripheral nervous system involvement is a poor prognostic factor suggesting endstage disease.

References

Grisold W, Piza-Katzer H, Herczeg E (2000) Intraneural nerve metastasis with multiple mononeuropathies. J Periph Nerv Sys 5: 163–167
Krarup C, Crone C (2002) Neurophysiological studies in malignant disease with particular reference to involvement of peripheral nerves. J Neurol 249: 651–661
Odabasi Z, Parrot JH, Reddy VVB, et al (2001) Neurolymphomatosis associated with muscle and cerebral involvement caused by natural killer cell lymphoma: a case report and review of literature. J Periph Nerv Sys 6: 197–203

Paraneoplastic neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy	CSF+
	+	+		+	

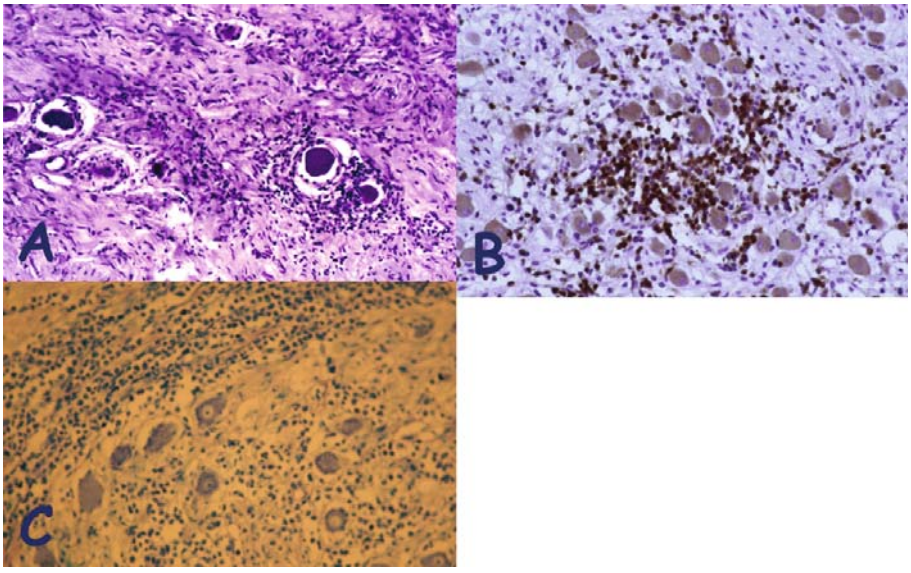

Fig. 10. Dorsal root ganglion pathology: **A** and **B** show an example of an inflammatory paraneoplastic ganglionitis. **B** shows an infiltrate that is immunostained for T cells. **C** is a rare example of neoplastic infiltration of a DRG by lymphoma cells of a Burkitt-like lymphoma. This patient had additional meningeal infiltration

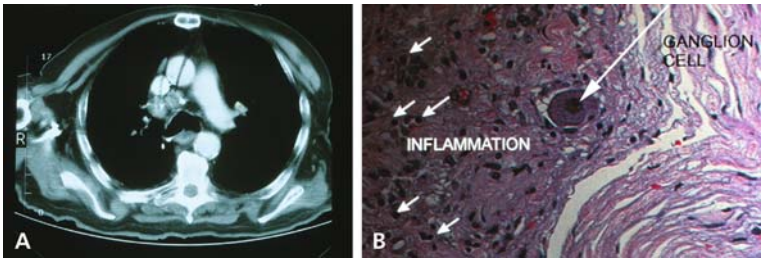

Fig. 11. Paraneoplastic ganglionopathy in a patient with a non-small cell carcinoma of the lung. **A** CT chest showing enlargement of the mediastinal lymph nodes. **B** Single dorsal root ganglion (*DRG*) neuron (large arrow) and evidence of inflammatory cell infiltrates (white arrows). Most of the DRG have degenerated

Paraneoplastic neuropathies are heterogeneous and can affect the peripheral nerve (sensory, sensory/motor), cause ganglionopathies [dorsal root ganglion neuron (DRG) loss], and can be associated with posterior column degeneration. Some are associated with anti-neuronal antibodies. Peripheral neuropathies in cancer patients can also be part of a multifocal paraneoplastic encephalomyelitis (PEM).

Anatomy/distribution

Demyelination and nerve vasculitis are rarely associated with paraneoplastic syndromes. Typically, there is axonal loss of distal sensory and motor nerves.

The ganglionopathy sub-type is secondary to inflammation with DRG loss and possible posterior column degeneration (see Figs. 10 and 11).

Symptoms

- Autonomic neuropathies can cause gastrointestinal symptoms (e.g., pseudo-obstruction), sexual dysfunction and orthostatic hypotension.
- Demyelinating neuropathy like AIDP or CIDP have been described on rare occasions and have no special characteristics.
- Rare cases of vasculitic neuropathy are characterized by painful mono-neuritis multiplex.
- Sensorimotor type: distal symmetric polyneuropathy, sometimes as a sub-clincal finding. Sensory neuropathies can be painful.
- Sensory neuronopathy ("Denny Brown Syndrome") is rare with subacute development of sensory neuropathy, with ataxia, and pseudoathetoid movements of the upper extremities. In the full-blown disease motor force can persist, but deafferentation prevents the patient from coordinated movements.

Clinical syndrome/ signs

- Demyelinating neuropathy cannot be distinguished from AIDP or CIDP.
- Sensorimotor type shows distal symmetric polyneuropathy, glove and stocking distribution, with sensory and motor signs often mild. This is the most common paraneoplastic neuropathy and often occurs late in the disease in patients with severe weight loss.
- Sensory neuronopathy ("Denny Brown syndrome") shows areflexia, dysesthesias, ataxia, pseudoathetoid movements, and is often painful and asymmetric.

Pathogenesis

The pathogenesis of paraneoplastic neuropathies is unclear, but is believed to be the result of numerous auto-antibodies associated with cancer. The sensorimotor type has been associated with anti-CV2 antibodies. Demyelinating forms are more highly associated with lymphoma and Hodgkin's disease. Sensory neuronopathy is related to anti-Hu and other anti-neuronal antibodies, in the context of small cell lung cancer.

Diagnosis

Nerve conduction velocities reveal sensory axonal loss with absent SNAPs.
Anti-Hu antibodies, especially in cases of lung cancer, may be detectable.
Biopsies are rarely indicated, except for presumed vasculitic neuropathy.

Differential diagnosis

Concommitant metabolic diseases, malnourishment, and weight loss have to be considered. Chemotherapeutic neuropathy is a common possibility.
The syndrome of sensory neuronopathy is not exclusively paraneoplastic, but may also be idiopathic or associated with Sjogren's syndrome.

Therapy

No treatments are available for the sensory/motor, demyelinating, and autonomic syndromes.
For sensory neuropathies and neuronopathies immunmodulatory therapies have been suggested and range from steroids to intravenous gammaglobulin, plasmapheresis, and immunosuppression. No definite results are available.

Vasculitic neuropathy can be treated with steroids and immunosuppression (which may be part of the cancer therapy).

Prognosis

The neuropathies may respond to immunotherapy and anti-neoplastic treatments. Subacute sensory neuronopathy usually remains in a plateau phase, responding poorly to therapy.

References

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Krarup C, Crone C (2002) Neurophysiological studies in malignant disease with particular reference to involvement of peripheral nerves. J Neurol 249: 651–661
Storstein A, Vedeler C (2001) Neuropathy and malignancy: a retrospective survey. J Neurol 248: 322–327

Motor neuropathy or motor neuron disease syndrome

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	+		

Anatomy/distribution

Anterior horn cells degenerate, which leads to concomitant degeneration of long tracts.

Symptoms

The degree and course of motor impairment can be variable, but generally there is weakness.

Clinical syndrome/signs

Motor neuron disease syndrome is associated with several cancer conditions and can exhibit different combinations of lower and upper motor neuron signs. One type associated with anti-Hu antibodies is relentlessly progressive and involves mostly lower motor neurons and encephalopathy. Another lower motor neuron syndrome is associated with lymphoma. A syndrome of upper and lower motor neuron signs resembling ALS is linked to numerous tumors (lymphoma, ovarian, uterine, breast, non-small cell lung cancer). Finally, an upper motor neuron syndrome has been reported with breast cancer.

Pathogenesis

The existence of paraneoplastic motor neuron disease is controversial. Some feel that this is an occurrence of two separate common disorders in one patient. Evidence for the existence of paraneoplastic motor neuron disease is based on the presence of antibodies to antigens shared by neurons and tumors, the responsiveness of some motor neuron disease to successful cancer treatment, and occurrence of motor neuron disease in patients exhibiting other well-characterized paraneoplastic syndromes.

Diagnosis

Diagnosis of a paraneoplastic motor neuron disease can be suggested by a lower motor neuron syndrome in association with cancer. Anti-Hu antibodies may be detected.

Differential diagnosis

Polyneuropathy or ALS coinciding with cancer.

Therapy

While some have reported regression of nervous system disease with treatment of cancer and immune therapy, generally treatments are not effective.

Prognosis

The course is progressive and somewhat slower than ALS.

References

Dalmau J, Schold SC Jr (2000) Paraneoplastic diseases of the nervous system. In: Evans RW, Baskin DS, Yatsu FM (eds) Prognosis of neurological disorders. Oxford University Press, New York Oxford, pp 458–469
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Infectious neuropathies

Human immunodeficiency virus-1 neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+	++		+

Peripheral nerve disease in HIV patients can take on numerous manifestations, and may be caused not only by disease-related processes, but by therapies, opportunistic infections, neoplasms, and common causes that affect the general population (i.e., diabetes). Diagnosis can thus become complicated. Some PNS disease syndromes are distinctive of particular HIV disease stages.

HIV-1 AIDP

HIV-1 AIDP occurs early in disease and may be the first manifestation of disease, preceding any other signs and symptoms. HIV AIDP is immune-mediated and resembles AIDP in the general population.

Clinical syndrome/ signs

Distal weakness in two or more limbs that is rapidly progressive, with areflexia. Sensory symptoms may be absent. Respiratory impairment and autonomic dysfunction may pose serious threats.

Diagnosis

Serology is used to detect HIV infection. EMG and NCV results resemble AIDP.

Therapy

IVIG protocol as per AIDP.

Prognosis

AIDP usually lasts for several weeks and then remits, with good prognosis.

HIV-1 CIDP

HIV-1 CIDP usually occurs later in disease and is immune mediated.

Clinical syndrome/ signs

Similar to AIDP, except the course is relapsing-remitting. Disability may become chronic, and sensory complaints are more common than with AIDP.

Diagnosis

CSF analysis shows pleocytosis and elevated protein. EMG and NCV resemble AIDP, but abnormalities are generally more pronounced.

Therapy

Plasmapheresis, IVIG (often transient and needs frequent administration), immunomodulatory agents, ganciclovir, foscarnet, cidofovir.

Good.

Prognosis

MM affects one or more nerves, and causes motor and sensory dysfunction. It usually occurs late in disease and is associated with vasculitis, CMV infection, lymphocytosis or lymphoma.

Mononeuropathy multiplex

Weakness and sensory abnormalities in a nerve or root distribution pattern are typical. Cranial nerve involvement is common.

Clinical syndrome/ signs

Nerve biopsy may show signs of vasculitis. PCR can be used to detect associated CMV infection in the CSF.

Diagnosis

Immunomodulatory agents, anti-HIV and anti-CMV drugs can be used. The efficacy of antivirals in abating peripheral nerve disease is not clear.

Therapy

MM that occurs early in disease is often self-limiting over the course of a year. Otherwise, the prognosis is poor.

Prognosis

Distal sensory or sensorimotor is the most common neuropathy in HIV. Its cause is unknown, but may be the result of cytokine release or treatment toxicity.

Distal sensory or sensorimotor

Pain is the most common feature, in a stocking glove distribution. Foot pain may be so severe that patients cannot walk or tolerate contact with bedding. Often, the only signs are abnormal ankle reflexes. Signs may seem mild to the degree of pain experienced by the patient. Weakness is not common, and distal if present.

Clinical syndrome/ signs

Diminished or absent SNAPs are found with NCV studies. Other treatable causes should be explored, such as vitamin B12 deficiency, alcoholism, and therapy-related toxicity from nucleoside analogues.

Diagnosis

Treatment for neuralgia is selected depending upon the severity of pain: NSAIDs, anti-depressants, anti-convulsants, topical lidocaine or capsaicin, opioids.

Therapy

The pain is chronic and poorly treatable.

Prognosis

Autonomic neuropathy is a late occurrence of unknown cause. It is characterized by orthostatic hypotension and diarrhea. Studies have found decreased intestinal innervation in late-stage HIV.

Autonomic neuropathy

Autonomic testing is not always conclusive, as cardiac dysfunction, anemia, and dehydration may cause signs and symptoms similar to autonomic neuropathy.

Diagnosis

Symptomatic care is all that can be offered.

Therapy

Poor.

Prognosis

References

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Herpes neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
		++		

Anatomy/distribution

Herpes virus remains in a latent state in the dorsal root ganglion or trigeminal ganglion.

Symptoms

Sensory disturbances occur with cutaneous eruptions. Post-herpetic neuralgia can involve three distinct pain situations: lancinating, shock-like pain, a continuous burning or aching pain, or pain caused by innocuous stimuli (allodynia). All of these occur in a dermatomal distribution.

Clinical syndrome/signs

Motor signs are infrequent (herpes zoster), and are caused by radiculopathy. Motor impairment occurs in the corresponding myotome to the sensory distribution. Long standing radicular pain that resembles diabetic neuropathy or infiltrative radiculopathy may be caused by herpes reactivation without the distinctive rash (zoster sine herpete). Cranial nerve palsies are also common, include oculomotor and facial nerve palsies, and optic neuritis or vestibulocochlear impairment (Ramsay-Hunt syndrome).

Pathogenesis

Herpes simplex or Herpes zoster (chicken pox) infection can come out of latency in a sensory ganglion. Herpes zoster occurs frequently in HIV patients and patients recovering from chemotherapy. The virus migrates down the sensory nerve fibers to the skin, causing tissue damage and inflammation. The pain syndromes associated with post-herpetic neuralgia may result from altered CNS pain pathways, aberrant reinnervation following infection, or changes in receptor sensitivity.

Diagnosis

Vesicle smear and PCR may be used to confirm infection.

Therapy

Acyclovir and other antivirals may be used both acutely and prophylactically. Pain can be managed by tricyclic antidepressants or opiates. Nerve block or lidocaine treatment may also be used.

Prognosis

Herpes simplex is recurrent and may be implicated in Bell's palsy. Herpes zoster neuropathy increases in frequency with age and may lead to residual neuralgia, although recovery is generally good.

References

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Fox RJ, Galetta SL, Mahalingam R, et al (2001) Acute, chronic, and recurrent varicella zoster virus neuropathy without zoster rash. Neurology 57: 351–354

Hepatitis B neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	++		++

Anatomy/distribution

There is acute demyelination of peripheral nerves or nerve roots in neuropathy due to Hepatitis B.

Symptoms

The symptoms in Hepatitis B neuropathy are most commonly similar to those of an inflammatory demyelinating polyneuropathy, either acute (AIDP) or chronic (CIDP). Patients experience both sensory loss and weakness, which can be rapid, is usually symmetrical and progressive. Less commonly, patients experience multiple mononeuropathies.

Clinical syndrome/ signs

Hepatitis B neuropathy is very rare and, when present, occurs in the setting of chronic active or chronic persistent Hepatitis B. Examination reveals symmetrical sensory loss and weakness with areflexia. The weakness can be profound affecting all 4 extremities. In rare cases, patients have weakness and sensory loss in multiple named nerves.

Diagnosis

There is hematologic evidence of chronic active or chronic persistent hepatitis B and abnormal liver function tests while vitamin levels, glucose, and serological markers of vasculitis are normal. Cerebrospinal fluid analysis reveals an elevated protein.

Electrophysiology:
Demyelination with prolonged distal motor latencies, slowed motor conduction velocities, prolonged or absent F waves and temporal dispersion and conduction block of motor evoked amplitudes. Sensory responses are usually absent. Needle examination shows decreased recruitment early in the disorder and only later is there evidence of denervation in affected muscles. In rare cases, rather than demyelination, there are multiple mononeuropathies present on nerve conduction studies.

Imaging:
MRI imaging of the abdomen is common but does not directly assist in the diagnosis.

Nerve biopsy:
According to one report, there are deposits of Hepatitis B surface antigen, immunoglobulin and complement in the vasa nervorum.

Differential diagnosis

Disorders that can present as an acute or chronic demyelinating neuropathy must be considered, including AIDP, CIDP, paraproteinemic neuropathy, vasculitis, or porphyria.

Therapy

Treatment is of the Hepatitis B itself (e.g. interferon or ribavirin treatment) and supportive neurological care. Plasma exchange has been suggested, but may be difficult if the patient's coagulation status is impaired due to liver failure.

Prognosis

The prognosis is good in cases of acute viral infection but less certain if the neuropathy is associated with chronic persistent Hepatitis B.

Bacterial and parasitic neuropathies

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
		++		++

Borrelia Burgdorferi (Lyme disease)

Clinical syndrome/ signs

The earliest stage of Lyme disease (stage I) is characterized by the unique skin rash and symptoms of general infection. Neuroborreliosis begins in stage II of the disease.

In stage II disease, the most common occurrence is lymphocytic meningoradiculitis. Motor and sensory symptoms may occur variably and undulate in severity over the course of months. Half of patients have focal or multifocal cranial nerve disease, including the facial, trigeminal, optic, vestibulocochlear, and oculomotor nerves.

Late stage II disease involves distal symmetric sensory neuropathy and encephalomyelitis, lasting for weeks or months. Motor signs are rare.

Asymmetric oligoarthritis, cardiac impairment, and myositis can occur alongside a variety of CNS conditions in stage III disease. Demyelination and subacute encephalitis may be accompanied by ataxia, spastic paraparesis, bladder dysfunction, cognitive problems, and dementia.

Pathogenesis

Lyme disease (sometimes known as Bannwarth's syndrome in Europe) is caused by infection with the *Borrelia Burgdorferi* spirochete. The infection is transmitted by bites from the *Ixodes dammini, scapularis, and pacificus* tick species.

The cause of peripheral neuropathy following infection is unclear, although there is cross reactivity between spirochete antigens and epitopes from Schwann cells and PNS axons.

Diagnosis

Serology commonly leads to false positives. A combination of ELISA and Western blot of CSF and serum is more reliable. PCR of blood and CSF is the most specific method and can be used for difficult cases.

Therapy

Antibiotics are important both for eradication of the infection and quick resolution of painful symptoms. The usefulness of steroids for pain management is not clear at this point.

Prognosis

Antibiotic therapy typically leads to resolution of neurological symptoms in a few weeks to months.

Corynebacterium diphtheriae (Diphtheria)

Cranial neuropathies and peripheral neuropathies with sensory and motor signs occur in 20% of cases, but overall the disease is rare in the U.S. All extremities become weak. Initial infection is characterized by sore throat, dyspnea, and decreased lung function. Neurological symptoms begin with weakness in the diaphragm and pharynx 5–7 weeks later, and progress to trunk and limb weakness at 2–3 months.

Pathogenesis

The bacterial toxin released by *Corynebacterium diphtheriae* causes demyelination, but cannot cross the blood brain barrier, and so damage is restricted.

Diagnosis

Throat culture confirms the presence of bacterium. EMG will show signs of demyelination.

Therapy

Early use of antibiotics can be effective.

Prognosis

Good, if treated early.

Mycobacterium leprae (Leprosy)

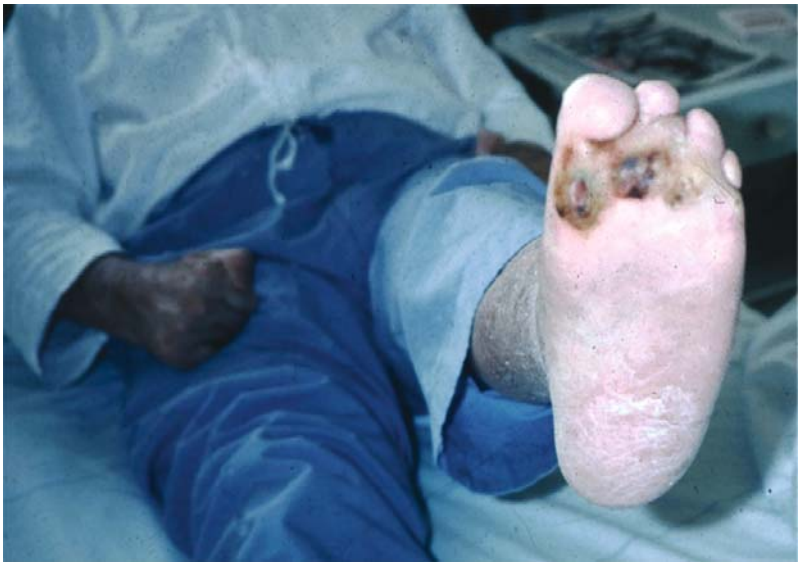

Fig. 12. Leprosy: this patient served with the foreign legion in North Africa. He has mutilated hands and toes and an ulcer

Clinical syndrome/ signs

Leprous neuropathy is characterized by sensory loss in a patchy distribution. "Tuberculoid" leprosy involves only a few skin lesions with accompanying local sensory loss. "Lepromatous" disease is more extensive, with loss of temperature and pain occurring first on the forearms, legs, ears, and dorsum of hands and feet (Fig. 12). Cranial nerve damage can lead to facial damage, including iritis, alopecia, and changes in eyelid and forehead skin. Some patients with intermediate disease may be classified as "borderline". This group is most susceptible to therapy-induced reactions that cause disease to worsen for the first year of treatment.

Pathogenesis

Infection with *Mycobacterium leprae* causes severe disease in patients with an impaired cell-mediated immunity (lepromatous cases) or benign disease in patients with intact immunity (tuberculoid cases). Early lepromatous disease involves infection of Schwann cells with minimal inflammatory response. Later, increased inflammation may lead to axon damage, and scarring and onion bulb formation from episodes of demyelination and remyelination. Nerve damage from tuberculoid and borderline disease results from granuloma formation.

Diagnosis

Patients can be classified as lepromatous or tuberculoid by a skin reaction to injected lepromin antigen. Tuberculoid and borderline cases will have an indurated reaction at the injection site. Skin biopsy can show granulomas. Nerve biopsy is used when other causes need to be excluded. EMG shows segmental demyelination, axon damage, slowed NCV, and low amplitude SNAPs.

Therapy

Lepromatous patients are treated with dapsone for a minimum of 2 years. Tuberculoid and borderline patients are treated with dapsone and rifampin for 6 months. Cases of treatment-induced reactions require quick diagnosis and treatment with high-dose steroids until the reaction subsides. Attention must be given to areas of the body that have lost sensation.

Prognosis

Progression can be arrested by treatment, but outcomes are dependent upon the severity and duration of disease, and the response to treatment.

Other infectious neuropathies

Treponema pallidum (syphilis):

A sexually transmitted disease caused by a spirochete. Peripheral nerve disease may be heralded by lancinating pain, paresthesias, incontinence, and ataxia.

Diagnosis:
Positive VDRL in CSF, pleocytosis.

Therapy:
Penicillin.

Trypanosoma cruzi (Chagas' disease)

Occurs in Central and South American. It is associated with megacolon, cardiomyopathy, and encephalomyopathy.

Diagnosis:
Examination of CSF and blood for parasites.

Therapy:
Nifurtimox, benzidazole.

Prognosis:
Poor.

Tick paralysis

Ascending paralysis occurring after tick bites from *Dermacentor* species, found in North America. May be confused with AIDP. Pathophysiology unknown.

Diagnosis:
Identification of tick bite is important.

Therapy:
Supportive care and removal of the tick are the main interventions.

Prognosis:
May be fatal if bulbar and respiratory paralysis occur.

Mycobacterium tuberculosis

May involve cranial neuropathy, paraparesis, headache, confusion.

Diagnosis:
Infection can be diagnosed by a positive skin test, CSF pleocytosis, and positive culture.

Therapy:
Isoniazid, ethambutol, rifampin.

References

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Inflammatory

Acute motor axonal neuropathy (AMAN)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	++		

Anatomy/distribution

There is specific degeneration of motor axons in this condition, without evidence of demyelination.

Symptoms

Patients present with proximal and distal muscle weakness, sometimes with paralysis of respiratory muscles.

Clinical syndrome/signs

This condition has primarily been described in children from northern regions of China. There may be facial, pharyngeal, and respiratory weakness involved. The condition develops over several weeks. Sensory systems are spared, as are the extraocular muscles.

Pathogenesis

The cause of AMAN is not known, although one theory suggests it may result from *Campylobacter jejuni* infection. Cases almost always occur in the summer months, and are preceded by a gastrointestinal illness. As with AMSAN, axons may be the specific target of autoimmune attack.

Diagnosis

Laboratory:
Protein is increased in the CSF. Sometimes, IgG anti-GMI or anti-GalNac-GD1a ganglioside antibodies are present.

Electrophysiology:
CMAPS are initially low with relative preservation of conduction velocities; amplitudes are then absent. SNAPs remain normal.

Therapy

IVIG and plasma exchange (as outlined for AIDP) and supportive care are the only treatments available.

Prognosis

Younger patients recover better. Recovery is variable overall.

References

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Acute motor and sensory axonal neuropathy (AMSAN)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	++		

Anatomy/distribution

Degeneration occurs in motor and sensory axons.

Symptoms

Both weakness and sensory loss are found, sometimes with respiratory paralysis.

Clinical syndrome/signs

AMSAN is clinically indistinguishable from very acute AIDP. The only major difference is that axons are the specific target of the immune reaction. Most patients become quadriplegic and unable to breathe in a matter of days. There may be changes in blood pressure or pulse.

Pathogenesis

Immune reactions are believed to be directed against axons. Another model suggests that axonal degeneration is secondary to nerve root demyelination. *Campylobacter jejuni* infection is implicated (see AMAN).

Diagnosis

Laboratory:
Protein is increased in the CSF. Sometimes, IgG anti-GMI or anti-GalNac-GD1a ganglioside antibodies are present.

Electrophysiology:
EMG and nerve conductions are abnormal, with reduced SNAPs and CMAPs with relative sparing of conduction velocities. SNAPs and CMAPs usually become unobtainable.

Therapy

IVIG and plasma exchange (as outlined for AIDP) and supportive care are the only treatments available.

Prognosis

Chances for recovery are poor. Residual weakness usually remains, and some require ventilation for long periods of time.

References

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Lindenbaum Y, Kissel JT, Mendell JR (2001) Treatment approaches for Guillain-Barre syndrome and chronic inflammatory demyelinating polyradiculoneuropathy. Neurol Clin 19: 187–204

Acute inflammatory demyelinating polyneuropathy (AIDP, Guillain-Barre syndrome)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+++	+-	+	+

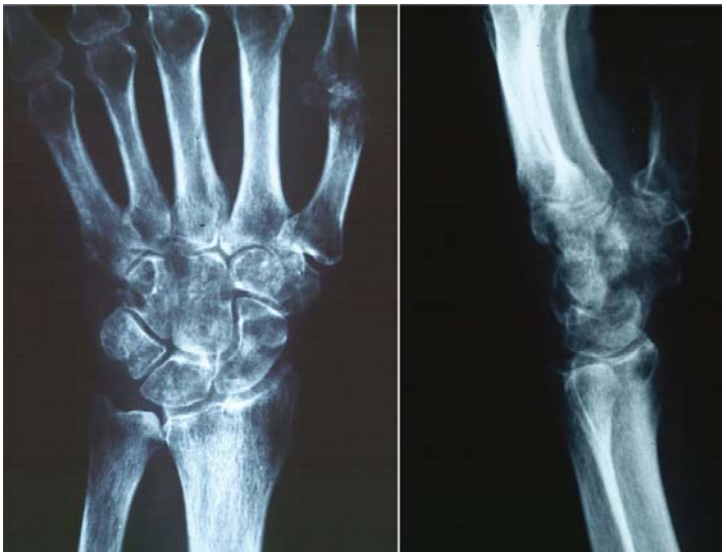

Fig. 13. X ray of the hands of a patient with long standing polyradiculitis. Note the severe osteoporosis

Anatomy/distribution

Inflammatory reactions cause demyelination of peripheral axons.

Symptoms

Classic AIDP presents with rapidly progressing, bilateral (but not necessarily symmetric) weakness. Paresthesias are reported early on, but weakness is the predominant feature. Patients can complain of difficulty with walking or climbing stairs.

Clinical syndrome/ signs

Weakness develops over a course of hours or days. Proximal weakness is more severe. Reflexes are reduced or absent, usually at the time of presentation. Cranial nerve involvement occurs in half of patients. One-third of patients need respiratory support. Numerous types of autonomic dysfunction are possible, but not typical.

Pathogenesis

Eighty percent of patients have an antecedent event (infection, surgery, trauma). Two-thirds of patients have a prior respiratory or GI viral infection (especially

CMV) 1–4 weeks before the onset of symptoms. *Campylobacter jejuni* infection is the most commonly associated bacterial infection. Research suggests a complex interaction of humoral and cell-mediated immunity that leads to complement deposition on myelin.

Diagnosis

Laboratory:
CSF protein is elevated, with no increase in cells, in the majority of cases.

Electrophysiology:
Conduction velocity is less than 75% of the lower limit of normal in 2 or more motor nerves, with distal latency exceeding 130% of the upper limit of normal in 2 or more motor nerves. There is evidence of unequivocal temporal dispersion or conduction block on proximal stimulation, consisting of a proximal-distal amplitude ratio < 0.7 in one or more motor nerves, and an F-response latency exceeding 130% of the upper limit of normal in 1 or more nerves.

Biopsy:
Inflammatory infiltrate with focal myelin loss on teased fiber analysis.

Differential diagnosis

Other causes of polyneuropathy, including HIV infection, hexacarbon abuse, porphyria, diphtheria, arsenic or lead intoxication, uremic polyneuropathy, diabetic polyradiculoneuropathy, and meningeal carcinomatosis need to be explored. Neuromuscular transmission disorders, hypokalemia, hypophosphatemia, and CNS causes also need to be considered.

Therapy

Admission to an ICU to provide ventilatory support maybe required, along with the following treatments:

- Total plasma exchange QOD x 5.
- An alternative to plasma exchange is IVIG is loaded at 2 g/kg I.V. then administered at a rate of 1 g/kg I.V. after 2 weeks, then if needed, monthly.
- General supportive management with initial special attention to autonomic instability. Eventual physical/occupational therapy helps with decreasing long-term disability.

Prognosis

Most patients recover over a course of weeks to months, with the most severely affected patients taking longer to recover. Some patients have a comparatively mild course, and others progress to ventilatory dependence in a matter of days. A small percentage may develop a relapsing course similar to CIDP.

References

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Chronic inflammatory demyelinating polyneuropathy (CIDP)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+++	+–	+	+

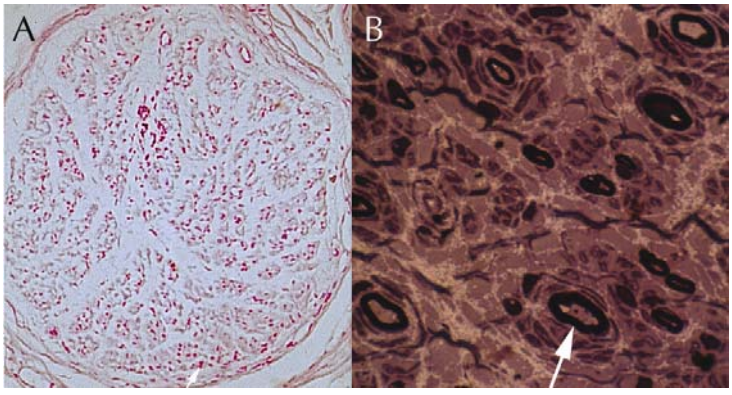

Fig. 14. Sural nerve biopsy from a patient with chronic inflammatory demyelinating polyneuropathy. **A** Multiple inflammatory cells in the endoneurium of the sural nerve (black arrow). **B** Variation in myelin thickness in the presence of multiple onion bulbs (white arrow). This is consistent with chronic demyelination and remyelination

Anatomy/distribution

Demyelination and Wallerian degeneration of peripheral nerves may be features of CIDP, although the spectrum of pathological findings is wide and varied.

Symptoms

CIDP is characterized by progressive weakness and sensory loss. Patients also report muscle pain.

Clinical syndrome/ signs

Exam reveals symmetric, proximal and distal weakness with sensory loss and areflexia. The course may be progressive, monophasic, or relapsing, and usually takes 12–24 months for symptoms to become noticeable. Any age group may be affected. Autonomic and cranial nerve dysfunction is possible but not common.

Pathogenesis

30% of patients have an antecedent event (viral infection, immunization, surgery). CIDP is believed to be an autoimmune disorder, with elements of both cell-mediated and humoral immunity.

Diagnosis

Laboratory:
CSF protein is elevated with < 10 WBC/m^3. Serum and urine protein electrophoresis are used to exclude a monoclonal gammopathy.

Electrophysiology:
Conduction velocity is < 75% of the lower limit of normal in 2 or more motor nerves. Distal latency exceeds 130% of the upper limit of normal in 2 or more motor nerves. There is evidence of unequivocal temporal dispersion or conduction block on proximal stimulation, consisting of a proximal-distal amplitude ratio < 0.7 in one or more motor nerves, and an F-response latency exceeding 130% of the upper limit of normal in 1 or more nerves.

Imaging:
Bone survey or scan is useful to exclude multiple myeloma. Nerve roots can appear enlarged, but imaging of the nervous system is only warranted when concomitant myelopathy is suspected.

Biopsy:
Nerves may on occasion show inflammatory infiltrate, with focal myelin loss on teased fiber analysis (Fig. 14).

Differential diagnosis

Numerous other conditions can appear as a distal sensory motor neuropathy, including HIV neuropathies, hexacarbon abuse, porphyria, diphtheria, arsenic or lead intoxication, uremic polyneuropathy, diabetic polyradiculoneuropathy, and meningeal carcinomatosis. The diagnosis of a patient with idiopathic CIDP will require that numerous other conditions be excluded by examination and laboratory testing.

Therapy

- Prednisone is given 1 mg/kg per day, up to a maximum 100 mg/day.
- Once the patient is stable or improved, the prednisone is tapered to a q.o.d. dosage by approximately 10% at 4 weekly intervals. The dose should be maintained at a steady state if the patient relapses.
- IVIG is given instead of prednisone or as a prednisone sparing agent. Use the dosage schedule outlined for AIDP.
- Azathioprine, at a dose of 2–3 mg/kg per day, is especially indicated for adults over the age of 50 and those who are severely weak.
- In resistant individuals, cyclophosphamide or methotrexate may be required.
- General management includes dietary counseling, twice yearly eye evaluations for cataracts and glaucoma, supplemental calcitriol .5 µg/day, elemental calcium 1,000 mg/day (see Fig. 13), a regular graded exercise program, and regular monitoring of serum electrolytes, liver function tests and glucose.

Prognosis

The chance for recovery is generally good with most patients showing response to therapy. The course may be relapsing, especially when treatment is inadequate. Treatment may be required for years to prevent relapses.

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Demyelinating neuropathy associated with anti-MAG antibodies

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	++		

Anatomy/distribution

Demyelination occurs in sensory, and perhaps motor axons.

Symptoms

Symptoms of ascending numbness and ataxia progress slowly over months to years. Pain is usually minimal.

Clinical syndrome/signs

Gait disorders occur in 50% of patients. Intention tremor may develop late in disease. Weakness is minimal. Sensory loss is symmetric.

Pathogenesis

Anti-MAG IgM antibodies cause complement deposition on myelin sheaths in animal models. Cellular infiltration of nerves is minimal, compared to other inflammatory neuropathies.

Diagnosis

Laboratory:
The availability of anti-MAG IgM antibody testing has made the diagnosis of the disorder much more common in recent times. CSF protein is elevated.

Electrodiagnositic studies:
Nerve conduction velocities are slowed, with no conduction block. CMAPs and SNAPs are reduced. Prolonged distal latencies are present. Signs of motor dysfunction can be much more pronounced in EMG/NCV studies than the clinical picture would suggest.

Therapy

Strong cytotoxic drugs (cyclophosphamide, fludarabine) are medications that may slightly impact the course of the disease. Often, the patients that typically develop this neuropathy are elderly and cannot tolerate these treatments. Steroids, IVIG and plasma exchange are not effective. Recurrent therapy may be necessary, and usually patient response is poor, despite aggressive cytotoxic therapy.

Prognosis

Progression is slow, over many years.

References

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Miller-Fisher syndrome (MFS)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	++		

Anatomy/distribution

Degeneration of axons and demyelination occurs, similar to AIDP.

Symptoms

Patients experience double vision, paresthesias, ataxia, and vertigo. In some cases, there is weakness of other motor cranial nerves and limbs. Symptoms progress over days to weeks.

Clinical syndrome/ signs

MFS is characterized by the triad of extraocular muscle weakness, ataxia, and areflexia. Ptosis and mydriasis can be demonstrated on exam.

Pathogenesis

MFS is considered a variant of AIDP, and cases initially appearing to fall in the classic MFS triad can progress to something more accurately diagnosed as AIDP. This condition is for some reason more common in Japan. It may be associated with *Campylobacter jejuni* (serotypes O–2 or O–10) or *Haemophilus influenzae* infections, but numerous other infections have been implicated.

Diagnosis

Laboratory:
CSF protein may be elevated, but not as often as in classic AIDP. There may be detectable IgG anti-GQ1b antibodies.
Sensory nerve conductions may be abnormal.

Differential diagnosis

Because of the cranial nerve involvement and ataxia, MFS can be confused with brainstem and cerebellar injury. The absence of CNS specific signs, and the presence of abnormal peripheral nerve studies would indicate MFS.

Therapy

IVIG, plasma exchange, supportive care are the only treatments available (protocol as outlined for AIDP)

Prognosis

Most patients will recover.

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Nutritional

Cobalamin neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	+		++

Anatomy/distribution

Vitamin B12 deficiency can cause a mild peripheral axonal degeneration, but it also causes a more pronounced myelopathy (vacuolization of the posterior columns and corticospinal tracts).

Symptoms

The symptoms of neuropathy include paresthesias, with burning in the feet and hands. Weakness may occur later. Symptoms may ascend.

Clinical syndrome/signs

Loss of vibratory and position sense are common sensory signs. Neuropathy is difficult to separate from myelopathy, which involves spasticity, posterior column dysfunction and ataxia. There is also memory loss and confusion. Loss of ankle reflexes may be the most diagnostic sign of neuropathy. Psychosis has also been described.

Pathogenesis

Malabsorption of vitamin B12 is most often a result of an autoimmune-induced deficiency of intrinsic factor (pernicious anemia), but can also be caused by a vegan diet, inflammatory bowel disease, gastric or ileal resection, and nitrous oxide anesthetic. Cobalamin is required for methionine synthase and methylmalonyl CoA reductase, which influence myelin basic protein and sphingomyelin production.

Diagnosis

CMAPs and SNAPs are reduced or absent, with slowed conduction. SEPs and VEPs are often abnormal, but BAERS are usually spared. Laboratory tests can indicate low serum B12, intrinsic factor or parietal cell antibodies, and elevated homocysteine and methylmalonic acid (intermediates in biosynthetic reactions that build up in the absence of B12).

Differential diagnosis

Since myelopathy is usually the most prominent pathology associated with B12 deficiency, other causes of myelopathy should be considered. These can include multiple sclerosis, tumors, compression, vascular abnormalities, and myelitis. Myelopathy and sensorymotor polyneuropathy together should suggest vitamin B12 deficiency.

Therapy

1000 ug crystalline vitamin B12 is injected intramuscularly daily for 5 days, then 500–1000 ug is given IM once a month for life for maintanence. Oral B12

(1000 ug daily) can also be considered for maintenance after the initial 5 day IM load.

Prognosis

Loss of vibratory sensation is the least responsive symptom. Paresthesias may respond if treated early. If treatment begins within 6 months of onset, the prognosis can be very good.

References

Metz J (1992) Cobalamin deficiency and the pathogenesis of nervous system disease. Annu Rev Nutr 12: 59–79
Saperstein DS, Barohn RJ (2002) Peripheral neuropathy due to cobalamin deficiency. Curr Treat Options Neurol 4: 197–201
Saperstein DS, Wolfe GI, Gronseth GS, et al (2003) Challenges in the identification of cobalamin-deficiency polyneuropathy. Arch Neurol 60: 1296–1301
Tefferi A, Pruthi RK (1994) The biochemical basis of cobalamin deficiency. Mayo Clin Proc 2: 181–186

Post-gastroplasty neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
		+		

Biopsy shows a severe axonal sensory and motor neuropathy.

Anatomy/distribution

Patients report distal paresthesias and leg weakness.

Symptoms

Exam can show loss of ankle reflexes, weakness, distal sensory dysfunction, and lumbar plexopathy. Wernicke-Korsakoff syndrome has also been described.

Clinical syndrome/ signs

Thiamine deficiency has been suggested as the cause, but the symptoms are unlike beriberi. RBC transketolase may be elevated.

Pathogenesis

Total parenteral nutrition (TPN) with multivitamins and 100 mg thiamine daily is required for patients experiencing frequent emesis, then oral multivitamins can be given once the patient is able to keep food down.

Therapy

Early recognition and treatment is essential for good long-term prognosis.

Prognosis

Reference

Maryniak O (1984) Severe peripheral neuropathy following gastric bypass surgery for morbid obesity. Can Med Assoc J 131(2): 119–120

Pyridoxine neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	++		

Anatomy/distribution

Pyridoxine deficiency causes injury of motor and sensory axons, whereas an overdose of pyridoxine causes a pure sensory neuropathy.

Symptoms

Distal burning paresthesias in hands and feet.

Clinical syndrome/signs

Pyridoxine is unusual in that both deficiency and overdose cause neuropathies. Deficiency causes a syndrome of motor and sensory neuropathy. Toxicity from high doses causes a sensory neuropathy with prominent sensory ataxia.

Pathogenesis

How pyridoxine deficiency and overdose cause neuropathy is unclear. Deficiency results from polynutritional deficiency, chronic alcoholism, and from treatment with isoniazid and hydralazine. Isoniazid inhibits conversion of pyridoxine to pyridoxal phosphate. Increased pyridoxine can be detected in the urine, but this is not important for diagnosis. Pyridoxine is toxic at doses over 200 mg/day.

Diagnosis

Deficiency can be easily diagnosed by checking blood levels of pyridoxine. EMG shows predominantly sensory abnormality in pyridoxine toxicity, but can show some mild motor involvement as well.

Differential diagnosis

Pyridoxine deficiency looks like other nutritional and metabolic sensory/motor axonal neuropathies.

Therapy

100–1000 mg pyridoxine given daily during isoniazid or hydralazine treatment is effective. Deficiency caused by alcoholism or other states of malnutrition should be treated with pyridoxine and other vitamins, since other deficiencies are likely concurrent.

Prognosis

The deficiency neuropathy may improve with pyridoxine replacement or when INH is stopped. The sensory neuropathy caused by overdose shows little improvement.

References

Bernstein AL (1990) Vitamin B6 in clinical neurology. Ann NY Acad Sci 585: 250–260
Snodgrass SR (1992) Vitamin neurotoxicity. Mol Neurobiol 6: 41–73

Strachan's syndrome

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
				+

Anatomy/distribution

Axonal degeneration with myelin breakdown is seen in the posterior columns of the cervical cord and optic nerves. Sural nerve biopsy shows axonopathy of large diameter fibers.

Symptoms

Patients report symptoms of sensory neuropathy (painful and burning feet).

Clinical syndrome/signs

Strachan's syndrome is defined by painful neuropathy, amblyopia, and orogenital dermatitis. Patients may also exhibit restless legs and ataxia.

Pathogenesis

Strachan's syndrome occurs from a high carbohydrate diet without vitamins (e.g., sugar cane workers, the Cuban optic and peripheral neuropathy epidemic of 1991, POWs). The patients treated with vitamins during the Cuban outbreak responded well, and thus it is thought that the pathology is due to polydeficiency of thiamine, niacin, riboflavin, and pyridoxine.

Therapy

Multivitamin replacement with a nutritious diet is effective. Replacement of riboflavin (B2) quickly affects orogenital dermatitis, but has no effect on neurological symptoms.

Prognosis

The prognosis is good with early treatment.

Reference

Cockerell OC, Ormerod IE (1993) Strachan's syndrome: variation on a theme. J Neurol 240: 315–318

Thiamine neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	+		++

Anatomy/distribution

Thiamine deficiency causes degeneration of sensory and motor nerves, vagus, recurrent laryngeal nerve, and brainstem nuclei. Lactate accumulates in axons due to the absence of thiamine diphosphate and transketolase.

Symptoms

The symptoms indicate a sensory and motor neuropathy: distal paresthesias, aches and pains, and limb weakness.

Clinical syndrome/ signs

"Dry Beriberi" is characterized by painful distal paresthesias, ankle areflexia, and motor weakness. "Wet Beriberi" combines the neuropathy with cardiac failure. "Wernicke-Korsakoff Syndrome", resulting from long-term thiamine deficiency, causes CNS dysfunction that includes confusion, memory loss, oculomotor and gait problems.

Pathogenesis

Beriberi is caused by states of poor nutrition: starvation, alcoholism, excessive and prolonged vomiting, post-gastric stapling, or unbalanced diets of carbohydrates without vitamins, protein, or fat (polished, milled rice or ramen noodles). The importance of thiamine to carbohydrate metabolism may be the cause of the nervous system damage.

Diagnosis

CMAPs and SNAPs are reduced or absent, with distal denervation. RBC transketolase, serum lactate, and pyruvate may elevate after glucose loading.

Differential diagnosis

The sensory motor neuropathy caused by beriberi is similar to other causes of non-specific sensory motor neuropathy. Facial and tongue weakness, and recurrent laryngeal nerve deficiency are uncommon in other causes of sensory motor neuropathy, and should suggest beriberi.

Therapy

For Wernicke-Korsakoff patients: 100 mg thiamine IV and 100 mg IM immediately, plus 100 mg IM or orally for three days. Without Wernicke-Korsakoff, restore a nutritious diet with additional thiamine.

Prognosis

Improvement varies with thiamine replacement. The non-neuronal components respond well, but neuropathic beriberi may result in permanent impairment.

Reference

Kril JJ (1996) Neuropathology of thiamine deficiency disorders. Metab Brain Dis 11: 9–17

Tocopherol neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	++		

Anatomy/distribution

Tocopherol (vitamin E) deficiency causes abnormalities of certain brainstem nuclei, as well as degeneration of the spinocerebellar tracts, posterior columns, and DRG. Neuropathy is related to loss of large sensory fibers.

Symptoms

Symptoms of sensory neuropathy are extremely slow in onset, and are almost always seen along with CNS dysfunction. Adult-onset disease can take 5–10 years to present, but onset latency is shorter in children.

Clinical syndrome/signs

The clinical syndrome is characterized by slowly progressive limb ataxia, and signs of posterior column dysfunction: loss of vibratory and joint position sense, head titubation, absent ankle reflexes, and extensor plantar responses.

Pathogenesis

Vitamin E deficiency results from abetalipoproteinemia (Bassen-Kornzweig Syndrome), fat malabsorption states (cystic fibrosis, biliary atreasia), or a familial defect of the tocopherol transport protein. Tocopherol is a free radical scavenger and probably functions as an antioxidant to maintain nerve membrane integrity.

Diagnosis

EMG shows SNAPs absent or reduced, with CMAPs unaffected. Serum tocopherol is undetectable.

Differential diagnosis

Because of the cerebellar and spinal dysfunction, inherited spinocerebellar ataxias need to be considered. The neuropathy caused by vitamin E deficiency is very nonspecific, and without spinocerebellar disease or evidence of fat malabsorption, it can resemble neuropathies caused by numerous other etiologies.

Therapy

Patients with isolated vitamin E deficiency can be treated by replacement with 1–4 mg vitamin E daily. Patients with cystic fibrosis can be treated with 5–10 IU/kg. Abetalipoproteinemia patients can be treated 100–200 mg/kg per day.

Prognosis

Progression of symptoms can be halted by vitamin E.

Reference

Traber MG, Sokol RJ, Ringel SP, et al (1987) Lack of tocopherol in peripheral nerves of vitamin E-deficient patients with peripheral neuropathy. N Engl J Med 317: 262–265

Industrial agents

Acrylamide neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++			+

Anatomy/distribution

Biopsy shows loss of large diameter fibers. Paranodal axonal swelling, 10–15 nm filament accumulation, dense bodies and axonal degeneration are observed.

Symptoms

Skin irritation (redness of hands and desquamation of palms) and hyperhydrosis of hands are the earliest symptoms of exposure. Mild to moderate exposure leads to numbness of feet and slight paresthesias.

Clinical syndrome/ signs

Mild to moderate exposure can lead to diffuse depressed reflexes, and reduced vibration and touch sensitivity. With more severe exposure, there can be generalized areflexia, sensory ataxia, dysarthria, tremor, weight loss, muscle weakness and atrophy, hallucinations, sleep disturbance, and memory loss.

Pathogenesis

Only monomeric acrylamide is toxic. Harmless polyacrylamide is used widely in industry, including water treatment, paper and textile production, cosmetics, grouting agents, and gel electrophoresis. Workers who handle monomeric acrylamide for production of polyacrylamide are at risk. Absorption is generally through the skin, but may also occur through inhalation or ingestion.

Diagnosis

SNAPs and CMAPs are reduced. Axonal loss on sural nerve biopsy.

Therapy

There is no specific treatment.

Prognosis

Course is variable. Deterioration may continue for 2 wks after cessation of exposure. CNS symptoms often improve early, while motor neuropathies take weeks or months to improve. Residual effects may remain.

References

Mizisin AP, Powell HC (1995) Toxic neuropathies. Curr Opin Neurol 8: 367–371
O'Donoghue JL, Nasr AN, Raleigh RL (1977) Toxic neuropathy – an overview. J Occup Med 19: 379–382

Carbon disulfide neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++			

Anatomy/distribution

In animals, CS2 causes paranodal retraction of myelin and focal axonal accumulation of 10 nm neurofilaments.

Symptoms

Distal paresthesias, painful muscles, sensory loss.

Clinical syndrome/signs

Diminished distal strength, hyporeflexia. Sometimes absent corneal reflexes and optic neuropathy. High levels may cause encephalopathy, extrapyramidal dysfunction, and psychiatric dysfunction. Retinopathy with microaneurysms, hemorrhage, and exudates has been reported.

Pathogenesis

CS2 is used in the manufacturing of viscose rayon and cellophane films, and sometimes in pesticide production and in chemical labs. The main route of intoxication is by inhalation. Strict industrial hygiene has reduced significant clinical problems. Long term low exposure may cause peripheral neuropathy.

Diagnosis

Distal slowing of nerve conductions, especially sensory nerves. Distal denervation on EMG.

Therapy

CS2 may react with pyridoxamine, so vitamin B6 supplement theoretically may help.

Prognosis

Symptoms often worsen after cessation of exposure for a period of months, with slow improvement following.

References

Chu CC, Huang CC, Chu NS, et al (1996) Carbon disulfide induced polyneuropathy: sural nerve pathology, electrophysiology, and clinical correlation. Acta Neurol Scand 94: 258–263

Hageman G, van der Hoek J, van Hout M, et al (1999) Parkinsonism, pyramidal signs, polyneuropathy, and cognitive decline after long-term occupational solvent exposure. J Neurol 246: 198–206

Vasilescu C, Florescu A (1980) Clinical and electrophysiological studies of carbon disulphide polyneuropathy. J Neurol 224: 59–70

Hexacarbon neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++			

Anatomy/distribution

Paranodal demyelination and retraction of myelin and focal axonal accumulation of 10 nm neurofilaments.

Symptoms

Slow onset of distal sensory pain, followed by calf pain and distal weakness.

Clinical syndrome/signs

Variable degrees of atrophy, loss of ankle reflexes. CNS damage may cause delayed spasticity in 15% of cases.

Pathogenesis

Hexacarbons are common in industry and domestic products, but only N-hexane and methyl-n-butyl ketone are known to cause neuropathy. Inhalation is the main route of exposure. Methyl ethyl ketone is not toxic itself, but may potentiate the effects of N-hexane.

Diagnosis

Severe slowing of motor and sensory NCVs. Prolonged BAERS and VERS.

Therapy

There is no effective treatment.

Prognosis

Improvement correlates with severity of exposure. Neuropathy progresses for 2–4 months after cessation of exposure before improvement occurs. Some residual neuropathy and spasticity may remain.

References

Chang YC (1990) Patients with n-hexane induced polyneuropathy: a clinical follow up. Br J Ind Med 47: 485–489
Chang YC (1991) An electrophysiological follow up of patients with n-hexane polyneuropathy. Br J Ind Med 48: 12–17

Organophosphate neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++			

Anatomy/distribution

Dying-back axonal degeneration in both central and peripheral nerve fibers.

Symptoms

Initially, cramping muscle pain in legs. Numbness, burning, and tingling of feet. Progressive weakness, legs more than arms. May be proximal.

Clinical syndrome/signs

Gait ataxia may occur later in the course. Eventually, motor signs predominate with loss of distal reflexes. After weeks and months, hyperreflexia and spasticity may develop.

Pathogenesis

Common in insecticides, anti-parasitic agents, petroleum additives, plastic modifiers. All are AchE inhibitors and cause delayed toxicity by inhibiting neuropathy target esterase. Specific compounds that may cause these effects include tri-ortho-cresyl phosphate (TOCP).

Diagnosis

No specific lab tests. EMG shows axonal neuropathy. Lymphocyte AchE levels may be diminished and predictive of developing delayed neuropathy.

Therapy

Treatment of the acute intoxication has no effect on the delayed neuropathy.

Prognosis

Largely depends on the degree of myelopathy. Without myelopathy, the neuropathy improves over several months.

References

Jamal GA (1997) Neurological syndromes of organophosphorus compounds. Adverse Drug React Toxicol Rev 16: 133–170
Jokanovic M, Stukalov PV, Kosanovic M (2002) Organophosphate induced delayed polyneuropathy. Curr Drug Target CNS Neurol Disord 1: 593–602
Marrs TC (1993) Organophosphate poisoning. Pharmacol Ther 58: 51–66

Drugs

Alcohol polyneuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy	Associated diseases
	+	+			Liver disease, Vitamin deficiency

Anatomy/distribution

Axonal loss of sensory and motor fibers in a distal to proximal distribution, with involvement of autonomic fibers.

Symptoms

Distal sensory loss, paresthesias and burning feet, with leg pain, aching and burning sensations. Stocking glove distribution. Painful calves, cramps, weakness, and sensory ataxia.

Clinical syndrome/ signs

Exam shows sensory loss of all modalities, distal symmetric, weakness: legs > hands, distal areflexia, and orthostatic hypotension, hyperhydrosis from autonomic involvement.
Mononeuropathies due to pressure palsies are common in patients with alcoholic neuropathy and include mononeuropathies of the radial, ulnar, peroneal and sciatic nerves. Brachial plexus neuropathies can also occur.

Pathogenesis

Difficult to separate from nutritional or vitamin deficiency neuropathy. There is axonal degeneration with loss of large and small myelinated fibers in autonomic and sensory and motor nerves. Incidence is 9–30% of hospitalized alcoholics. Occurs after several years of consuming at least 100 mg alcohol daily. Women are more susceptible.

Diagnosis

Laboratory:
Frequently elevated liver function tests due to alcohol consumption. Vitamin levels should be normal.

Electrophysiology:
SNAPs may be absent or reduced, variable involvement of motor nerves; distal degeneration on EMG.

Differential diagnosis

Nutritional and vitamin deficiency neuropathies, toxic neuropathies, other axonal neuropathies

Therapy

Abstinence, multivitamin replacement, pain therapy, management of autonomic orthostatic hypotension.

Prognosis

Depends on duration and severity of symptoms. No regeneration seen in nerve biopsies in 17 patients after 2 years. Autonomic neuropathy reduces life expectancy.

References

Koike H, Mori K, Misu K, et al (2001) Painful alcoholic polyneuropathy with predominant small fiber loss and normal thiamine status. Neurology 56: 1727–1732
Koike H, Iijima M, Sugiura M, et al (2003) Alcoholic neuropathy is clinicopathologically distinct from thiamine-deficiency neuropathy. Ann Neurol 54: 19–29
Monforte R (1995) Autonomic and peripheral neuropathies in patients with chronic alcoholism. Arch Neurol 52: 45–51
Wöhrle JC, Spengos K, Steinke W, et al (1998) Alcohol related acute axonal polyneuropathy. Arch Neurol 55: 1329–1334

Amiodarone neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+			++

Anatomy/distribution

Axonal loss of sensory and motor fibers in a distal to proximal distribution, with involvement of autonomic fibers.

Symptoms

Burning, dyesthesias particularly in the feet with diffuse aching pain in proximal and distal muscles.

Clinical syndrome/signs

Exam shows sensory loss of all modalities, distal symmetric, weakness: legs > hands, distal areflexia, and orthostatic hypotension, hyperhydrosis from autonomic involvement.

Pathogenesis

Class I anti-arrhythmic that is directly toxic to nerves. Neuropathy caused by 400 mg/day for one or more years.

Diagnosis

Electrophysiology:
SNAPs may be reduced or absent, conduction velocities are low normal or slowed with distal degeneration on EMG.
Biopsy shows axonal degeneration, segmental demyelination, lipid lysosomal dense bodies in Schwann cells and perineural cells.

Therapy

Drug withdrawal.

Prognosis

Good with early detection, partial recovery for established neuropathy.

References

Fernando Roth R, Itabashi H, Louie J, et al (1990) Amiodarone toxicity: myopathy and neuropathy. Am Heart J 119: 1223–1225
Hilleman D, Miller MA, Parker R, et al (1998) Optimal management of amiodarone therapy: efficacy and side effects. Pharmacotherapy 18 (6 Pt 2): 138–145

Chloramphenicol neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++			++

Anatomy/distribution

Axonal loss of sensory and motor fibers in a distal to proximal distribution.

Symptoms

Numbness is greater than burning in the feet with accompanying calf tenderness.

Clinical syndrome/signs

Diminished distal pain and touch, loss of ankle reflexes. Rare reports of optic neuropathy. Bone marrow suppression.

Pathogenesis

Occurs in children being treated for cystic fibrosis receiving an average of 255 mg for an average of 10 months. Renal failure may potentiate toxicity, and agranulocytosis is the main dose limiting effect. Thus, neuropathy is very rare today.

Diagnosis

Pathophysiology is unknown but it is likely due to direct toxic effects on axons. Should also consider critical illness neuropathy.

Therapy

Chloramphenicol should be stopped if symptoms cannot be ascribed to another cause. High dose vitamin therapy has been used but there is little data to support it.

Prognosis

Complete recovery can be expected if the drug is stopped soon after the onset of symptoms.

Reference

Shinohara Y, Yamaguchi F, Gotoh F (1977) Toxic neuropathy as a complication of thiophenicol therapy. Eur Neurol 16: 161–164

Colchicine neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++			++

Anatomy/distribution

Widespread degeneration of myelinated and unmyelinated axons in PNS and CNS, changes in DRG.

Symptoms

Mild distal sensory loss and parasthesias. Patients may also experience proximal weakness.

Clinical syndrome/signs

Exam shows sensory loss of all modalities, distal symmetric with decreased or absent tendon reflexes. While there can be mild distal weakness of the lower extremities, the more common presenting sign is proximal weakness due to an accompanying colchicine myopathy.

Pathogenesis

Colchicine blocks microtubular function and impairs axonal transport. Patients with impaired renal function are more likely to develop a colchicine neuromyopathy than a patient on colchicine who has normal renal function.

Diagnosis

Electrophysiology: Decreased SNAPs with near normal NCV.
Biopsy: Mild axonal loss and disruption of myelin with nerve biopsy. Muscle biopsy shows vacuolar and lysosomal changes.

Therapy

Discontinue colchicine.

Prognosis

Neuropathy will improve.

References

Altiparmak MR, Pamuk ON, Pamuk GE, et al (2002) Colchicine neuromyopathy: a report of six cases. Clin Exp Rheumatol 20 [Suppl] 26: S13–S16
Kuncl RW, Cornblath DR, Avila O, et al (1989) Electrodiagnosis of human colchicine myoneuropathy. Muscle Nerve 12: 360–364
Kuncl RW, Duncan G, Watson D, et al (1987) Colchicine myopathy and neuropathy. N Engl J Med 316: 1562–1568

Dapsone neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++			++

Anatomy/distribution

Motor axonal loss with relative sparing of sensory neurons and axons.

Symptoms

Motor neuropathy predominately. Occasionally generalized weakness. Arms greater than legs, especially median nerve. Hand weakness without sensory loss may give impression of motor neuron disease.

Pathogenesis

Dapsone is used for the treatment of leprosy and other dermatologic conditions, and causes neuropathy after long term, high dose use.

Diagnosis

Biopsy:
Non-specific axonal changes on biopsy. Neuropathy from leprosy is predominantly sensory, and should not be confused with this. Mildly slowed motor NCV and minimal signs of denervation.

Therapy

Discontinue usage.

Prognosis

Symptoms may progress after discontinuing use, but will gradually improve.

References

Gutmann L, Martin JD, Welton W (1976) Dapsone motor neuropathy: an axonal disease. Neurology 26: 514–516
Waldinger TP, Siegle RJ, Weber W, et al (1984) Dapsone-induced peripheral neuropathy. Case report and review. Arch Dermatol 120: 356–359

Disulfiram neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++			

Anatomy/distribution

Primary axonal degeneration.

Symptoms

Paresthesias of the feet and unsteady gait. Pain, temperature, and vibration sensation are diminished in the feet. Hand involvement occurs later.

Clinical syndrome/signs

Absent ankle reflexes, dorsiflexor weakness. Optic neuropathy may occur.

Pathogenesis

Used infrequently as an adjunct treatment for chronic alcoholism. Occurs after several months of therapy on standard doses.

Diagnosis

Mild slowing of motor NCV, diminished sensory amplitudes, distal denervation. Biopsy shows loss of all fiber sizes.

Therapy

Drug withdrawal.

Prognosis

Most cases improve after several months.

References

Frisoni GB, Di Monda V (1989) Disulfiram neuropathy: a review (1971–1988) and report of a case. Alcohol Alcohol 24: 429–437
Mokri B, Ohnishi A, Dyck PJ (1981) Disulfiram neuropathy. Neurology 31: 730–735

Polyneuropathy and chemotherapy

Toxic neuropathies caused by chemotherapy are usually dose-dependent, and have a potential reversibility after termination of the drug treatment. Little is known about the influence of preexisting polyneuropathies in the development of a chemotherapeutically induced neuropathy (except vincristine given in patients with hereditary sensorimotor neuropathy), and the toxicity of only a few drug combinations have been described. This is of importance as chemotherapy is not always used as a single agent therapy, but patients often receive drug combinations or second line therapy. Additionally also biological agents such as antibodies, interferons, cytokines and vaccines are used in cancer therapy and also have a risk of inducing polyneuropathies.

Clinical distribution:
Most neuropathies caused by chemotherapeutic agents are symmetric and length dependent, with a stocking glove distribution of sensory loss. Sensory symptoms and distal weakness (lower extremities) occur. The development of distal sensory symptoms (numbness or paresthesias) can be used as a possible sign of neurotoxicity.

Table 14. Overview of the most frequently used chemotherapeutic agents causing polyneuropathy

Cisplatinum and derivatives	• Cumulative dose approximately: 400 mg • Sensory neuro(neurono)pathy, with dysfunction of large fibers, ataxia • Persistence despite discontinuation ("coasting effect"). • Cranial nerves: hearing loss, vestibular dysfunction • Muscle cramps • "Lhermitte's sign"	Frequent
Cytosine arabinside (Ara C)	Polyradiculopathy, resembling AIDP	Very rare
Procarbazin	Mild sensorimotor polyneuropathy	Rare, little clinical relevance
Suramin	Demyelinating polyradicular type of polyneuropathy, resembling AIDP	Rare
Taxane (Docetaxel, Paclitaxel)	Sensory neuropathy, all fiber types involved	Frequent. Combination with cisplatinum increases toxicity
Vinca alkaloids (vincristine and derivatives)	Sensorimotor polyneuropathy, all fibers involved. Distal paresthesias (as initial sign), areflexia, foot drop. Rarely: cranial nerves, or autonomic symptoms	Frequent
VM-26 and VP-16	Mild sensorimotor polyneuropathy	Rare

Vinca alkaloids

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+			

Symptoms

Paresthesias on fingers and toes, sensory loss for pin prick and light touch. Areflexia.

Clinical syndrome/ signs

Dose dependent mixed sensorimotor polyneuropathy. Muscle weakness in distal muscles. Rarely cranial nerves and autonomic dysfunction.

Pathogenesis

Vinca alkaloids bind to microtubules and interfere with their assembly. Structural changes account for abnormal axoplasmic transport and are related to axonal degeneration.

Diagnosis

Electrophysiology: axonal damage with an EMG that shows neurogenic changes.

Differential diagnosis

Paraneoplastic neuropathy, other chemotherapeutic agents.

Therapy

Discontinue drug.

Prognosis

Potentially reversible, sensory symptoms improve within some months.

Platinum-compounds (cisplatin, carboplatin, oxaliplatin)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+			

Symptoms

Predominantly sensory neuropathy with paresthesias in hands and feet followed by numbness. Rapid onset, often with burning pain, with rare weakness. Hearing loss.

Clinical syndrome/ signs

While cisplatin and carboplatin have a similar spectrum of dose dependent neuropathy, oxaliplatin has two types of toxicity.
The acute toxicity of oxaliplatin occurs after infusions. Patients experience dysesthesias and paresthesias, aggravated by cold. The symptoms recur after each chemotherapy cycle with oxaliplatin. Additional symptoms also include eye and jaw pain, leg cramps, and voice changes.
The chronic toxicity is a dose dependent polyneuropathy, resembling cis platinum neuropathy.

Pathogenesis

Proximal and distal weakness and sensory loss, ataxia. Some times Lhermitte's sign.

Large myelinated fiber loss also small fiber loss. Random demyelination may interfere with microtubular transport. Microtubule aggregation in DRG axons.

Diagnosis

Electrophysiology: axon loss changes with small sensory and motor evoked responses, denervation on EMG

Therapy

Drug withdrawal. Symptoms may increase after cessation of therapy ("coasting").
Prophylactic treatment with ACTH analogs, glutathione or amisfostine have not been successful.

Prognosis

Slow reversal of symptoms with variable degrees of residual numbness and reflex changes, motor symptoms if present.
The combination with other cytostatic drugs such as taxanes may potentiate the neurotoxicity.
Clinically the neuropathy can be confused with ganglionopathies, in particular with paraneoplastic subacute sensory neuronopathy. The individual case history and the evaluation of the cumulative dose of previous treatment is necessary.

Reference

Adelsberger H, Lersch C, Quasthoff S, et al (2004) Oxalinplatin-induced neuropathy differs from cisplatin and taxol neuropathy due to acute alteration of voltage-gated sodium channels in sensory neurons. Clin Neurophysiol 111: 143

Taxol

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+			

Taxanes (diterpene alkaloids) are used as cytostatic drugs. Docetaxel induces a mild to moderate neuropathy with loss of deep tendon reflexes, vibration sense. Paresthesias may occcur. Severe neuropathies may occur after high cumulative doses.
Paclitaxel neuropathy results in paresthesias, numbness, sometimes pain in the feet and hands. Fine motor tasks such as buttoning and writing can be impaired. Unsteadiness of walking can occur. Additionally perioral and tongue numbness can appear.
Weakness is mild. Rarely proximal muscle weakness has been observed.

Symptoms

Predominantly sensory neuropathy with paresthesias in hands and feet followed by numbness. Weakness is rare.

Clinical syndrome/ signs

Proximal and distal weakness and sensory loss. Rapid onset, often with burning pain, with rare weakness.

Pathogenesis

Large myelinated fiber loss also small fiber loss. Random demyelination may interfere with microtubular transport. Microtubule aggregation in DRG axons.

Diagnosis

Electrophysiology with small sensory and motor evoked responses, denervation on EMG.

Therapy

Drug withdrawal.

Prognosis

Slow reversal of symptoms with variable degrees of residual numbness and reflex changes, motor symptoms if present.

References

Casey EB, Jellife EM, Le Quesne PM, et al (1973) Vincristine neuropathy. Clinical and electrophysiological observations. Brain 96: 69–86
Delattre JY, Vega F, Chen Q (1995) Neurologic complications of immunotherapy. In: Wiley RG (ed) Neurological complications of cancer. Dekker, New York, pp 267–293
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Walsh RJ, Clark AW, Parhad IM (1982) Neurotoxic effects of cisplatin therapy. Arch Neurol 39: 719–720
Windebank AJ (1999) Chemotherapeutic neuropathy. Curr Opinion Neurol 12: 565–571

Metals

Arsenic neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	++		

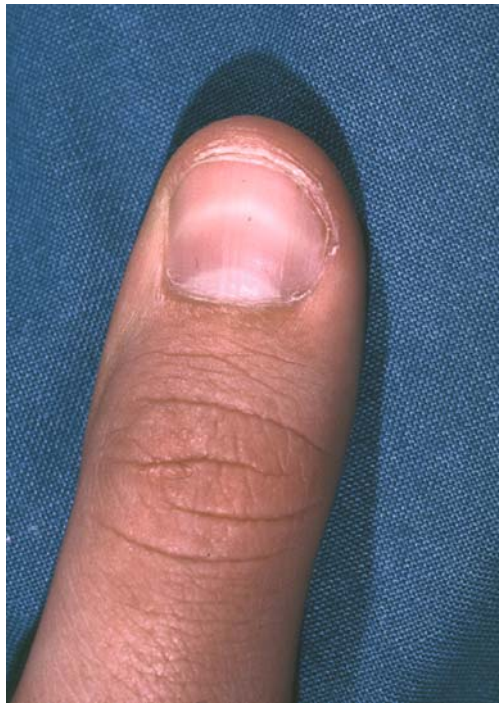

Fig. 15. Meese lines at the nail-bed, in case of arsenic poisoning and polyneuropathy (courtesy Dr. Freymueller, Hermagor, Austria)

Anatomy/distribution

Massive exposure may demonstrate demyelinating polyradiculoneuropathy, distal axonopathy.

Symptoms

Painful stocking-glove sensory neuropathy, motor neuropathy usually mild but can be severe. Malaise, nausea, vomiting, mucous membrane irritation.

Clinical syndrome/signs

Hyperkeratosis, darkened skin, Mee's lines (Fig. 15), pitting edema. Acute massive exposure leads to vasomotor collapse and death. Chronic exposure leads to aplastic anemia.

Pathogenesis

Arsenic can be encountered in copper and lead smelting, wells near mines with arsenic, accidental or intentional poisoning. Arsenic may inhibit conversion of pyruvate to acetyl CoA.

Diagnosis

Signs of demyelination. Absent SNAPs and reduced CMAPs, muscle denervation. Arsenic can be detected in hair, nails, and urine in chronic exposure cases. Urine levels greater than 25 mg/24 hrs, unless recent seafood ingestion.

Therapy

BAL or penicillamine, continued for months if neuropathy is refractory. Neuropathy from less fulminant exposure usually stabilizes over a 2 year period.

Prognosis

Prognosis related to severity and duration of symptoms.

References

Bansal SK, Haldar N, Dhand UK, et al (1991) Phrenic neuropathy in arsenic poisoning. Chest 100: 878–880
Donofrio PD, Wilbourn AJ, Albers JW, et al (1987) Acute arsenic intoxication presenting as Guillain-Barre-like syndrome. Muscle Nerve 10: 114–120
Oh SJ (1991) Electrophysiological profile in arsenic neuropathy. J Neurol Neurosurg Psychiatry 54: 1103–1105

Mercury neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++			+

Anatomy/distribution

Axonal degeneration with relative sparing of sensory fibers.

Symptoms

Mercury metal vapor causes subacute, diffuse, predominantly motor neuropathy that may mimic AIDP. Alkyl mercury causes intense distal limb paresthesias, probably from CNS dysfunction. Elemental mercury may cause sensorimotor neuropathy.

Diagnosis

Biopsy shows axonal degeneration. CMAPs decreased more than SNAPs. Alkyl mercury shows normal EMG.

Therapy

Chelation therapy is of limited benefit.

Prognosis

Degree of CNS recovery determines prognosis.

References

Albers JW, Kallenbach LR, Fine LJ, et al (1988) Neurologic abnormalities associated with remote occupational elemental mercury exposure. Ann Neurol 24: 651–659
Chu CC, Huang CC, Ryu SJ, et al (1998) Chronic inorganic mercury induced peripheral neuropathy. Acta Neurol Scand 98: 461–465
Windebank AJ (1993) Metal neuropathy. In: Dyck PJ, Thomas PK, Griffin JW, Low PA, Poduslo JF (eds) Peripheral neuropathy, 3rd edn. Saunders, p 1549

Thallium neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++	++		

Anatomy/distribution

Distal axonopathy, especially of large diameter fibers.

Symptoms

Three temporal varieties of neuropathy occur. A massive dose causes acute painful neuropathy with GI distress. May resemble AIDP, and proceed to lethargy, coma, and death.
A one week or longer exposure at lesser doses causes neuropathy with alopecia, hyperkeratosis, Mee's lines, ataxia, chorea, CNS palsies, autonomic dysfunction with tachycardia. Mild distal weakness.
Chronic exposure at low levels causes extrapyramidal dysfunction and questionable sensorimotor neuropathy.

Pathogenesis

Thallium is found in rodenticides and insecticides, and may be ingested in situations of homicide and suicide.

Diagnosis

Slight decrease in NCV. Diagnosis made by detection of thallium in urine or organs.

Therapy

Potassium chloride or Prussian blue is used for treatment, but efficacy is questionable.

Prognosis

Recovery begins six months following discontinuation of exposure, and recovery for subacute cases is good.

Reference

Windebank AJ (1993) Metal neuropathy. In: Dyck PJ, Thomas PK, Griffin JW, Low PA, Poduslo JF (eds) Peripheral neuropathy, 3rd edn. Saunders, p 1549–1570

Hereditary neuropathies

Hereditary motor and sensory neuropathy type 1 (Charcot-Marie-Tooth disease type 1, CMT)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
++	++			++

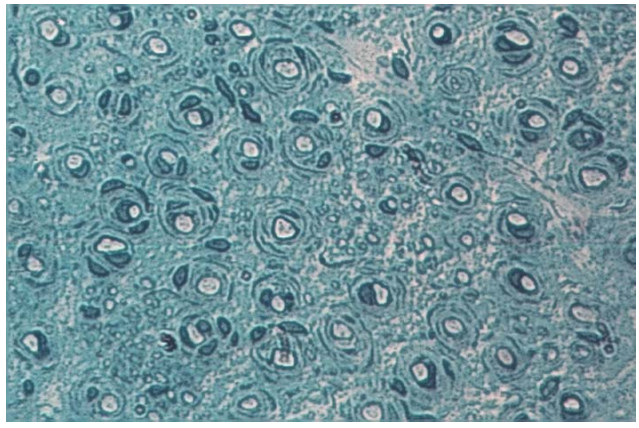

Fig. 16. Sural nerve biopsy from a patient with HMSNIII (Dejerine-Sottas disease). The biopsy shows evidence of severe demyelination with thinly myelinated fibers and formation of multiple onion bulbs (black arrows)

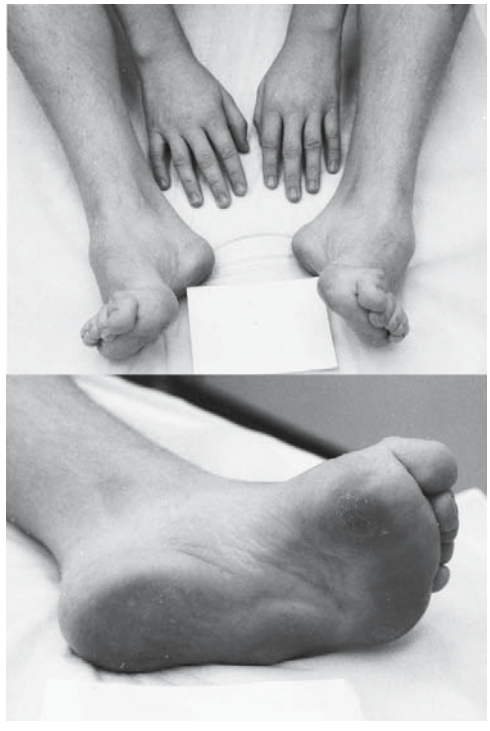

Fig. 17. CMT: Foot deformity and pes cavus

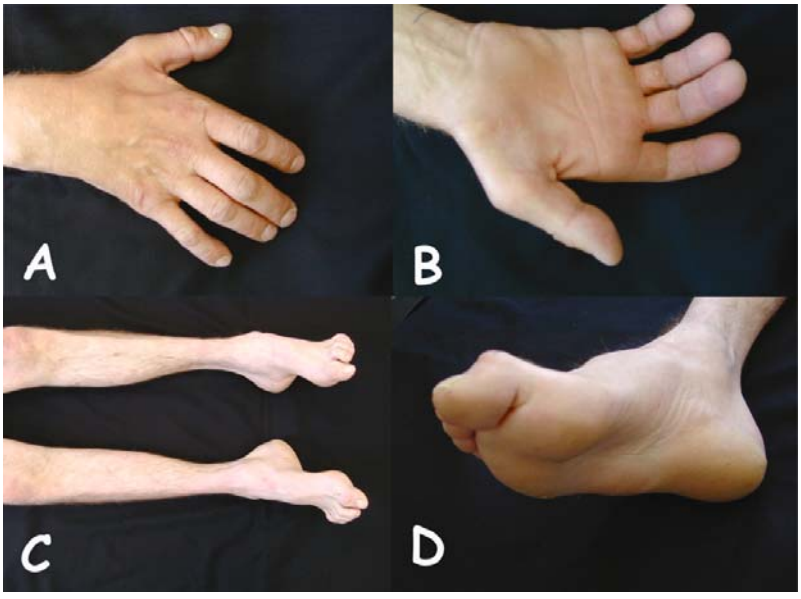

Fig. 18. CMT. **A** and **B** Claw hands. **C** and **D** Atrophic lower legs with foot deformity

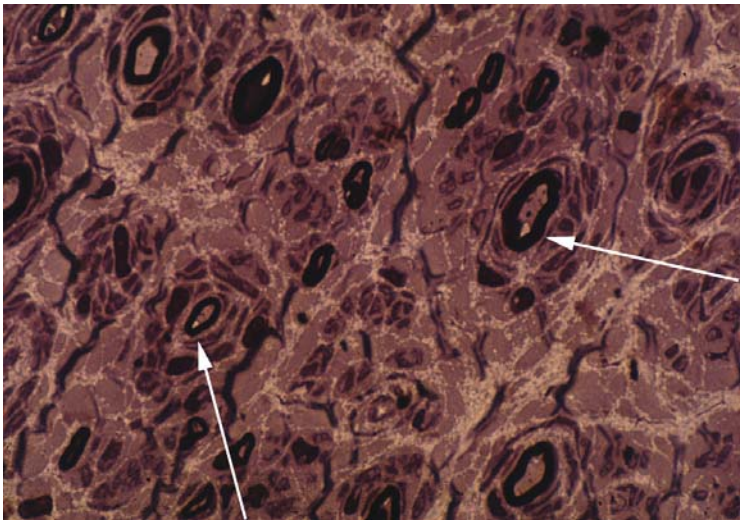

Fig. 19. CMT. Onion bulb formation in a nerve biopsy (arrows)

Anatomy/distribution

CMT type 1 typically results in loss of peripheral nervous system myelin.

Symptoms

Usually within the first or second decade of life, patients experience mild distal sensory loss and more severe distal weakness.

Clinical syndrome/signs

Pes cavus and hammer toes, the characteristic foot deformity of CMT, usually appears in early childhood (Fig. 17). Anterior leg compartment muscles become weak and atrophy over time, leading to foot drop (Fig. 19). Wasting may be seen in the intrinsic hand muscles in severe cases (Fig. 18). Areflexia is more pronounced distally, but may be noted in the upper extremities. Peripheral nerves, especially the greater auricular and brachial plexus, become thick and palpable. Kyphoscoliosis is possible.

Pathogenesis

CMT-1 is further classified by the specific genetic abnormality causing Schwann cell function. All subclassifications are autosomal dominant. CMT-1A is caused by a 1.5 megabase duplication on chromosome 17p11 that is believed to cause a 50% increase in the expression of peripheral myelin protein-22 (PMP-22). Trisomy 17 has been documented in some rare cases, and is accompanied by a spectrum of developmental abnormalities. Point mutations in the genes for the myelin protein Po (CMT-1B) and the transcription factor EGR-2 (CMT-1D) also cause CMT type 1. The locus responsible for CMT-1C is unknown. The various forms of CMT-1 have the same clinical presentation.

Diagnosis

Motor and sensory nerve conduction velocities are uniformly slowed in all four limbs.
Biopsy shows onion bulb formation, suggesting demyelination (Fig. 19).
Genetic testing can be done to identify the responsible mutation. Family members should also be tested to identify carriers.

Differential diagnosis

Other inherited neurologic disorders that present in the early decades of life should be considered. The spinocerebellar ataxias and leukodystrophies can be distinguished by the presence of cranial nerve, cerebellar, and long tract signs that are not found in CMT. HNPP may resemble CMT, but the history of pressure palsies and extremely disproportionate distal latencies, in comparison to almost normal NCVs, will indicate HNPP. Electrodiagnostic studies are usually asymmetric in inflammatory neuropathies. CSF protein is also elevated. Finally, inherited myopathies and spinomuscular atrophy show no impairment of sensory function on examination.

Therapy

The goal of treatment is to manage the physical deformities caused by muscle weakness. Physical therapy will help strengthen and stretch foot muscles. Orthotics and surgery may be helpful in some cases.
Family members should be offered genetic counseling and genetic testing can be used to identify carriers.
Patients with CMT should also be cautioned about the potential worsening of neuropathy that can be precipitated by vincristine.

Prognosis

Most patients have only mild to moderate weakness that can usually be overcome with the help of braces. Some CMT-1 patients may need to use a wheelchair, but this is unusual.

References

Kuhlenbaumer G, Young P, Hunermund G, et al (2002) Clinical features and molecular genetics of hereditary peripheral neuropathies. J Neurol 249 (12): 1629–1650
Reilly MM (2000) Classification of the hereditary motor and sensory neuropathies. Curr Opin Neurol 13 (5): 561–564
Roa BB, Garcia CA, Lupski JR (1991-1992) Charcot-Marie-Tooth disease type 1A: molecular mechanisms of gene dosage and point mutation underlying a common inherited peripheral neuropathy. Int J Neurol 25–26: 97–107
Trobaugh-Lotrario AD, Smith AA, Odom LF (2003) Vincristine neurotoxicity in the presence of hereditary neuropathy. Med Pediatr Oncol 40 (1): 39–43

Hereditary motor and sensory neuropathy type 2 (Charcot-Marie-Tooth disease type 2, CMT)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++			++

Anatomy/distribution

CMT type 2 is due to axonal degeneration, while sparing the myelin sheath.

Symptoms

Patients experience mild distal sensory loss and more severe distal weakness. The age of presentation is later than in CMT-1.

Clinical syndrome/signs

CMT-2 is much rarer than all forms of CMT-1. The clinical picture is very similar, but with notable differences. Nerves do not become palpable, as there is no demyelination/remyelination. Atrophy and areflexia are generally limited to the legs and feet.

Pathogenesis

The genetic pathogenesis of CMT-2 is less well understood than CMT-1. Some families show linkage to sites on chromosome 1p36, and others to 3q. Other sites are likely to be involved. Despite the situation of axonal degeneration with myelin sparing, point mutations in the myelin protein Po have been found in some CMT-2 patients diagnosed by the clinical picture and histology.

Diagnosis

Conduction velocities are only slightly slowed, if at all, in CMT-2. Men typically have somewhat slower NCVs than women. CMAPs are low or absent in the legs, and potentially decreased in the arms. SNAPs are also low in the legs.
Biopsy does not show evidence of demyelination.
At this point, genetic testing is unavailable for CMT-2.

Differential diagnosis

Other inherited neurologic disorders that present in the early decades of life should be considered. The spinocerebellar ataxias and leukodystrophies can be distinguished by the presence of cranial nerve, cerebellar, and long tract signs that are not found in CMT. HNPP may resemble CMT, but the history of pressure palsies and extremely disproportionate distal latencies, in comparison to almost normal NCVs, will indicate HNPP. Electrodiagnostic studies are usually asymmetric in inflammatory neuropathies. CSF protein is also elevated. Finally, inherited myopathies and spinomuscular atrophy show no impairment of sensory functions on examination.

Therapy

The goal of treatment is to manage the physical deformities caused by muscle weakness. Physical therapy will help strengthen and stretch foot muscles. Orthotics and surgery may be helpful in some cases.

Patients with CMT should also be cautioned about the potential worsening of neuropathy that can be precipitated by vincristine.

Prognosis

Most patients have only mild to moderate weakness that can usually be overcome with the help of braces. Diaphragm and vocal cord weakness appears to be more prominent in the CMT-2C subtype, which may lead to respiratory complications that can decrease lifespan.

References

Gemignani F, Marbini A (2001) Charcot-Marie-Tooth disease (CMT): distinctive phenotypic and genotypic features in CMT type 2. J Neurol Sci 184 (1): 1–9
Pareyson D, Sghirlanzoni A, Bolti S, et al (1999) Charcot-Marie-Tooth disease type 2 and P0 gene mutations. Neurology 52 (5): 1110–1111
Vance JM (1999) Charcot-Marie-Tooth disease type 2. Ann NY Acad Sci 883: 42–46

Hereditary neuropathy with liability to pressure palsies (HNPP)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
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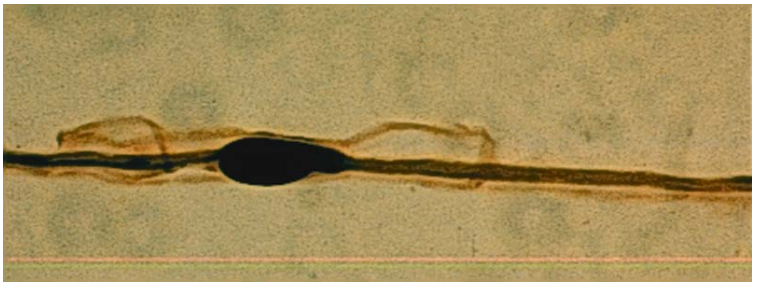

Fig. 20. Teased fibers from a patient with hereditary neuropathy and pressure palsy (*HNPP*) showing a large sausage shaped myelin enlargment (tomacula)

Anatomy/distribution

Peripheral nerves in HNPP exhibit segmental demyelination and tomacula (Fig. 20).

Symptoms

Patients appear to have recurrent mononeuropathies that cause weakness and numbness, often following mild compression or trauma. These neuropathic episodes begin in adolescence.

Clinical syndrome/signs

Men tend to present earlier than women. Some cases present in childhood, while others can be delayed by several decades. Common sites for pressure palsies include the elbow and the neck of the fibula. In some cases, the neuropathies are progressive and can lead to a picture similar to CMT, with pes cavus, absent ankle reflexes, and distal weakness.

Pathogenesis

HNPP is caused by a 1.5 megabase deletion at chromosome 17p11, the same site of duplication in CMT-1A. One copy of the PMP-22 gene is missing, leading to a decrease in expression of this myelin protein. HNPP is inherited as an autosomal dominant event, although sporadic cases thought to arise from mistakes in meiosis can occur.

Diagnosis

EMG shows a demyelinating condition with distal motor latencies very prolonged in comparison to the NCV findings. Entrapment neuropathies can be identified at common sites of pressure palsy (elbow, fibula). SNAPs are reduced or absent. Asymptomatic gene carriers have similar findings.
Genetic testing can be done to identify the chromosomal deletion.

Biopsy is not usually performed, as the EMG and genetic information is decisive.

Differential diagnosis

HNPP may resemble CMT, but the occurrence of pressure palsies and the EMG findings make HNPP distinctive. Inflammatory neuropathies like CIDP and multifocal motor neuropathy (MMN) with conduction block should also be considered. MMN does not usually show signs of sensory impairment with electrodiagnostic studies. The electrodiagnostic findings in CIDP are symmetrical.

Therapy

HNPP is usually treated with support. Surgical intervention for entrapment is controversial, as manipulations frequently cause nerve injury.
Genetic counseling can be provided to family members.

Prognosis

The course of HNPP is usually benign.

References

Andersson PB, Yuen E, Parko K, et al (2000) Electrodiagnostic features of hereditary neuropathy with liability to pressure palsies. Neurology 54: 40–44
Chance PF (1999) Overview of hereditary neuropathy with liability to pressure palsies. Ann NY Acad Sci 883: 14–21
De Jonghe P, Timmerman V, Nelis E, et al (1997) Charcot-Marie-Tooth disease and related peripheral neuropathies. J Peripher Nerv Syst 2: 370–387
Pareyson D, Taroni F (1996) Deletion of the PMP22 gene and hereditary neuropathy with liability to pressure palsies. Curr Opin Neurol 9: 348–354

Porphyria

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
++	++			

Anatomy/distribution

Porphyria causes axonal degeneration with some regions of demyelination.

Symptoms

Patients typically present with debilitating abdominal pain, changes in urine color, constipation, and vomiting. Neuropathy usually follows the abdominal signs by several days, and resembles AIDP, with pain and potentially asymmetric weakness.

Clinical syndrome/signs

CNS disturbances can precede neuropathy, including agitation, psychosis, seizures, and eventually coma. Weakness can involve the face and respiratory muscles. Autonomic dysfunction is common. In some forms of porphyria, skin blisters can accompany an acute attack. Attacks can be precipitated by drugs that stress liver function, fasting, stress, and alcohol.

Pathogenesis

Porphyria is rare and caused by disruption of heme biosynthesis. Subtypes of porphyria result from dysfunction of each of the enzymes in the heme synthetic pathway, but only the subtypes that involve liver enzymes cause neuropathy. These subtypes are aminolevulinic acid dehydrase deficiency, acute intermittent prophyria, hereditary coproporphyria, and variegate porphyria.

Diagnosis

Electrodiagnosis shows predominantly motor impairment.
The primary diagnositic tool for an acute attack is a rapid urine test for porphobilinogen. Genetic testing is useful for exact diagnosis and for family counseling.

Differential diagnosis

AIDP does not involve such intense abdominal pain. Changes in urine color should raise suspicion of porphyria. Poisoning by lead, arsenic, or thallium can appear similar to porphyria, and even cause increases in urine porphobilinogen.

Therapy

The most important treatment for an acute attack is IV heme, with attention to carbohydrate and fluid maintenance. Hyponatremia may occur and needs to be corrected. Any precipitating drugs should be withdrawn. Pain and vomiting should be treated. CNS disturbances can be difficult to treat, although gabapentin may help control seizures.

In the long term, prevention is the best therapy. Drugs that can precipitate attacks should be avoided. Some porphyria can be triggered by hormonal changes during menstruation, and these cases can be very difficult to control.

Prognosis

Heme therapy is very effective at quelling acute attacks, although mortality may still be as high as 10%. Most patients recover on the whole, but severe neuropathy may be resistant because of the axonal degeneration.

References

Kochar DK, Poonia A, Kumawat BL, et al (2000) Study of motor and sensory nerve conduction velocities, late responses (F-wave and H-reflex) and somatosensory evoked potential in latent phase of intermittent acute porphyria. Electromyogr Clin Neurophysiol 40 (2): 73–79

Meyer UA, Schuurmans MM, Lindberg RL (1998) Acute porphyrias: pathogenesis of neurological manifestations. Semin Liver Dis 18 (1): 43–52

Muley SA, Midani HA, Rank JM, et al (1998) Neuropathy in erythropoietic protoporphyrias. Neurology 51 (1): 262–265

Wikberg A, Andersson C, Lithner F (2000) Signs of neuropathy in the lower legs and feet of patients with acute intermittent porphyria. J Intern Med 248 (1): 27–32

Other rare hereditary neuropathies

Many other hereditary neuropathies have been identified, often in just a handful of families in a particular ethnic and geographic region. Several of the more common disorders are summarized in the chart below. X-linked CMT is more common than CMT-2, and Riley-Day syndrome is fairly common in Ashkenazi Jews. All are treated symptomatically and are gradually progressive.

Neuropathy	Genetics	Clinical features
CMT-3 (Dejerine-Sottas disease) see Fig. 16	Autosomal dominant, sporadic, or recessive. Linked to mutations or deletions in PMP22 or Po.	Severe demyelinating neuropathy of childhood. Both motor and sensory involvement. Very slow NCVs.
CMT-4	Autosomal recessive. Several subclassifications have been identified in different families with distinct loci.	Demyelinating motor and sensory neuropathy with slow NCVs.
X-linked CMT	X-linked dominant, more severe in males. Mutation in Connexin 32.	Demyelinating neuropathy with axonal degeneration. Slow or intermediate NCVs. Genetic testing is available.
Hereditary Sensory Neuropathy (HSN)	Autosomal dominant neuropathy identified in several Australian families.	Axonal sensory neuropathy. Normal NCVs.
Riley-Day syndrome (familial dysautonomia)	Autosomal recessive, occurs in 1:50,000 Ashkenazi Jews.	Severe small fiber neuropathy with pulmonary and renal complications. NCV is normal.

Reference

Kuhlenbaumer G, Young P, Hunermund G, et al (2002) Clinical features and molecular genetics of hereditary peripheral neuropathies. J Neurol 249(12): 1629–1650

Neuromuscular transmission disorders and other conditions

Myasthenia gravis

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	Repetitive stimulation Single fiber EMG (SFEMG)	Acetylcholine receptor antibodies (AChR-Ab) Muscle specific tyrosine kinase antibodies (MuSK)	CT: Thymus	

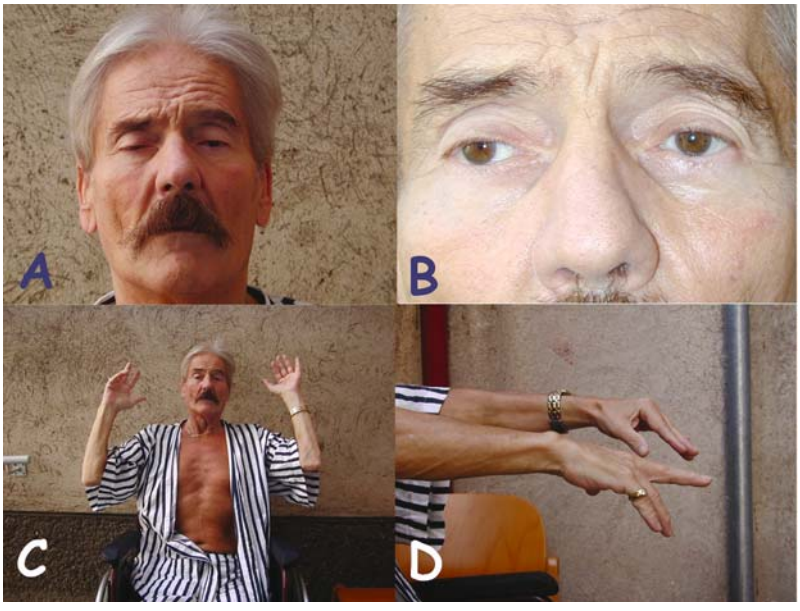

Fig. 1. Generalized myasthenia gravis, key features. **A** Ptosis **B** Attempted gaze to the right. Only right eye abducts incompletely. **C** Demonstrates proximal weakness upon attempt to raise the arms. **D** Holding the arms and fingers extended the extensor muscles weaken and finger drop occurs

Stages of MG	Symptoms
Neonatal	*Transient form acquired from MG mothers*
Juvenile	*– see congenital MG*
Adult group I	Localized, usually ocular
Adult group II	Generalized, bulbar
Adult group III	Acute fulminating, bulbar and generalized, respiration failing
Adult group IV	Late severe developing from I and II
Adult group V	With muscle atrophy from II
Classification (Osserman 1958)	

Prevalence

The incidence in a European study was 7/1,000,000, the prevalence 70/1,000,000. The MG mortality is 0.67/million, and cause of death attributed to MG is only 0.4/1,000,000. The sex prevalence is female to male of 1.4/1.

Anatomical-functional relations

Myasthenia gravis (MG) is an autoimmune disease. Autoantibodies to acetylcholine receptor epitopes block neuromuscular transmission. Long duration badly controlled disease results in a reduced number of acetylcholine receptors (AChR) and damage to the post-synaptic membrane.
Lymphorrhagia in affected muscles has been observed in the past, when immunosuppression was not available.

Types

Congenital myasthenic syndromes
Acquired autoimmune
- Transient neonatal
- Ocular MG
- Generalized MG

Symptoms

Fatigability and weakness are the hallmark (see Fig. 1). Weakness predominantly involves eyelids and extraocular muscles, resulting in diplopia. Ocular, bulbar, truncal, and proximal limb muscles are most commonly affected. Respiration muscles may be involved.
MG is characterized by fluctuations. The symptoms are generally less severe in the morning and worsen over the day. Intensity of the disease can fluctuate over weeks and months. Exacerbations ("myasthenic crisis") and remissions occur.
In clinical terminology the disease is classified into ocular and generalized myasthenia.

Signs

Weakness in the cranial nerves results predominantly in ocular and bulbar weakness, often asymmetrical. Weakness increases with the time of day, depending on muscle activity. Diplopia, dysarthria and dysphagia may result. Speech may become nasal during prolonged talking. Oculobulbar muscles are spared in a few patients.
Weakness in the trunk and extremities tends to be proximal. Also flexors and extensors of the neck may be involved. Subtle weakness may be increased by contractions or outstretched extremities. Ventilation may be involved in generalized forms; occasionally, it can be the presentation of MG.

Pathogenesis

Antibodies against the AChR are present in 80% of generalized cases and 50% of ocular/bulbar cases. 15% of cases are seronegative. Some of these "seronegative" cases harbor a MuSK auto-antibody.

Other associated antibodies

Anti-striatal antibodies

Found in adult onset MG patients. Increases with age, more often with thymoma. Rise in titer may herald a thymoma recurrence.

Anti-titin antibodies

Occurs in MG patients with thymoma (70% to 100%) and occasionally without thymoma.

Other antibodies

Anti-nuclear antibodies in 20% to 40% of cases
Anti-thyroid (microsomal and thyroglobulin; 15% to 40%) and anti-parietal cell (10% to 20%), more common in ocular MG
Smooth muscle antibodies: 5% to 10%
Rheumatoid factor: 10% to 40%
Coomb's antibodies in 10%
Anti-lymphocyte antibodies: 40% to 80%
Anti-platelet antibodies: 5% to 50%

Role of the thymus

MG is often associated with pathology of the thymus. Thymic hyperplasia is found in most young patients. Thymoma is found in approximately 10% of MG patients. MG occasionally appears after removal of a thymoma. MG can also be associated with HLA-B8-DR3 haplotype.

Associated systemic disease

Thyroid disorders:
Thyroid disorders in ~ 15% of MG patients
Hyperthyroidism more common than hypothyroidism
Thyroid testing is always indicated

Increased incidence of other autoimmune disorders:
Rheumatoid arthritis
Lupus erythematosus
Polymyositis
Pernicious anemia

Pregnancy and MG

The course of MG during pregnancy is unpredictable. It tends to worsen at the beginning of pregnancy and the post-partum period. In the long run, there is no influence on prognosis.

Treatment:
Acetylcholinesterase inhibitors, corticosteroids, plasma exchange, intravenous immune globulin (IVIG).

Immunosuppressant use in pregnancy:
Some risk: Cyclosporine A is associated with more spontaneous abortions and preterm deliveries.
Higher risk: Methotrexate should not be used during pregnancy.

Breast feeding:
High doses of acetylcholinesterase inhibitors may produce gastrointestinal disorders in the neonate. Immunosuppressants may also produce immunosuppression in the neonate.

Effect of pregnancy on the child:
May lead to the development of "neonatal MG": general weakness, sucking difficulties. Wears off according to the IgG half-life (several weeks) and does not induce myasthenia in the child.
Congenital arthrogryposis has been described, with antibodies directed towards fetal acetylcholine receptor protein.

Other types of myasthenic syndromes

Presynaptic defects:
Congenital MG and episodic apnea
Paucity of synaptic vesicles and reduced quantal release
Congenital Lambert Eaton myasthenic syndrome (LEMS)

Synaptic defects:
Acetylcholinesterase deficiency at the neuromuscular junction

Postsynaptic defects:
Kinetic abnormalities in AChR junction
Reduced numbers of AChRs
Increased response to AChR: slow AChR syndrome
Delayed channel closure
Repeated channel reopenings
Reduced response to ACh
Fast channel syndrome: epsilon, alpha subunits
gating abnormality: delta subunit
Normal numbers of AChR at the neuromuscular junction:
Reduced response to ACh
Fast channel, low ACh affinity
Reduced channel opening
High conductance and fast closure of AChRs
Slow AChR channel syndrome
Reduced numbers of AChR at neuromuscular junction: AChR mutation, usually epsilon subunit

Other:
Benign and congenital MG
Congenital MG
Familial autoimmune
Limb girdle MG
Plectin deficiency

Diagnosis

Clinical course:
Symptoms fluctuate and worsen as the day progresses.

Strength measurements:
Myometer

Imaging: Imaging of the mediastinum for thymoma

Edrophonium test: Edrophonium (tensilon) is a short-acting acetylcholinesterase inhibitor. The Tensilon test does not distinguish between pre- and postsynaptic transmission disorders.

Antibody testing:
Antibodies against the AChR is the standard immunologic test for MG.
MuSK antibody testing is reserved for seronegative cases.
Other antibodies: Titin, smooth muscle (see above)
Anti-AChR antibody testing is positive in 50% of ocular and 80% of generalized MG cases. The antibody titer does not correlate with disease severity. Test results may vary with different institutions as test sitemaps and antigen preparations vary.

Antibody negative myasthenia

Immune MG: Negative anti-AChR antibody testing by routine assay
- Negative findings are more common with ocular and childhood disease
- AChR abs can be detected by other methods
- Rarely (3%) detected by AChR modulating assay
- Some patients have plasma antibody (IgM) that alters AChR function
- Present in children and adults
- Not present with: Thymoma; Anti-AChR antibodies
- MuSK IgG is often directed against amino terminal (extracellular) sequences
- MuSK IgG may induce some AChR aggregation on myotubes
- In children, rule out congenital and hereditary MG

Electrophysiology

Repetitive stimulation (RNS):
RNS is the most important electrophysiological test. It is positive in generalized MGIR 60–70% and 50% or less in ocular MG. The specificity is around 90%. Warming the affected muscles gives the best results. Five shocks at 3 Hz supramaximal stimulation are given, usually to proximal muscles (deltoid, trapezius muscle).
Errors in RNS: The most common source of error is electrode movement. Fix the electrode with tape and immobilize the stimulated area. Avoid submaximal stimulation. Temperature should be recorded. Stimulation above 10 Hz may produce "pseudo-facilitation" (increase of amplitude and decrease of duration without changing the area under the curve).

RNS abnormalities in other neuromuscular diseases:
Lambert Eaton myasthenic syndrome
Motor neuron disease
Myotonic syndromes
Periodic paralysis
Phosphorylase and phosphofructokinase deficiency
Polymyositis

Needle EMG:
Normal or short MUAPs. Long standing: minimally neurogenic. Spontaneous activity is unusual.

Single fiber EMG (SFEMG):
Variability of NM transmission, such as a discharge to discharge variability in timing of single muscle fibers.
This is a sensitive method for the detection of MG: 85–90% positive in ocular and 90–95% positive in generalized MG. Most commonly, the extensor digitorum communis and frontal muscles are examined. Jitter and blocking usually increase with prolonged muscle activation. Stimulation jitter can be used for evaluation in uncooperative patients.
For both RNS and SFEMG, the concomitant application of acetylcholinesterase inhibitors drugs can induce false negative results.

Differential diagnosis

Brainstem disorders
Cranial nerve compression syndromes
Lambert Eaton myasthenic syndrome (LEMS)
Mitochondrial myopathy
Motor neuron disease (MND)

Myopathies
Oculopharyngeal muscle dystrophy
Psychogenic
Slow channel syndrome
Thyroid eye disesae
Tumors of the tectal plate

MG and operations/other diseases:
Any general illness or febrile condition may aggravate MG.
An operation in a patient with known MG may precipitate an MG crisis.
Failure to wean after general anesthesia can be the first symptom of MG.

Drugs to avoid in a myasthenic person:
See page 346: drug induced myasthenic syndromes
Subclinical MG may become manifest after drug treatment or post-operatively.
Existing MG becomes more severe with some drug treatments.
However, all drugs may be given, if necessary, with thorough monitoring of respiration and swallowing.

Therapy

Acetylcholinesterase inhibitors

Pyridostigmine (mestinon):
Usually the first line treatment. It acts by binding to acetylcholinesterase, raising the concentration of ACh at the junction folds.
Peak concentration occurs after 90–120 min, with a similar half-life.
3–4 h doses are given per day. Higher doses are somewhat more effective but may cause more side effects.
Timespan: preparations 90 to 180 mg at night.
Adverse effects include diarrhea and cramping.
Overdose can lead to a cholinergic crisis.
Other cholinesterase inhibitors as neostigmine (prostigmine) or ambenonium are also used.

Steroids

Steroids play a central role and are effective and reliable.
Prednisone 40–60 mg/daily should be prescribed for 3–6 weeks, then tapered.
Temporary worsening typically occurs with initiation of steroid therapy. Initiation of steroid treatment is recommended for inpatients only, and a standby intensive care unit is mandatory for patients with generalized MG.
Outpatient prednisone treatment: begin at 5 mg *qd*. Increase by 5 mg every week
Maximum dosage: where significant clinical improvement occurs, or 60 to 80 mg *qd*.
The following side effects may be significant and should be avoided: weight gain, hyperglycemia, osteopenia, gastric and duodenal ulcer, cataracts.
MG may recur if prednisone is stopped, without additional immunosuppression.
Monitor weight, blood pressure, blood glucose, electrolytes, and ocular changes during prednisone therapy.
Disadvantages of steroid treatment:

- Transient initial severe exacerbation, usually after 1 to 3 weeks (2% to 5%)
- Many long-term side effects

Plasma exchange and IVIG:
Short-lasting effect, typically used in the treatment of refractive patients or patients in crisis. Both therapies are effective.

Plasma exchange
Indicated in myasthenic crisis where conditions worsen despite high dose therapy.
Several exchanges performed over 9 to 10 days, depending on individual tolerance.

Advantages:
Short onset of action (3 to 10 days).
Probably more effective in treating a crisis than IVIG.

Disadvantages:
Requires specialized equipment not available in all centers.
Increased cardiorespiratory system complications in older patients.

Human immune globulin IVIG
IVIG is used for the management of acute exacerbation crisis, and can be used for a long-term treatment.
Dose (empirically) 2 g/kg over 2–5 days, then 1 g/kg each month.

Easily administered, widely available.
Side effects are rare. Use caution with older patients and renal insufficiency (e.g., diabetes).
High cost.
Short-term action (approximately 4 weeks).

Immunosuppression

Azathioprine (imuran)
Used for frequent relapses, or as a steroid sparing agent.
Imuran is less effective than steroid therapy and has a comparatively long onset of action (6 months).
3–5 mg/kg day, maintenance at 1.5–2.5 mg/kg qd.
Monitor hematocrit, WBC, platelets, and liver function.

Side effects:
Increased risk of malignancy (not demonstrated in MG patients)
Reduced RBC, WBC, platelets (dose-related or idiosyncratic)
Liver dysfunction
Flu-like reaction occurs in 20–30% of patients
Teratogenic
Arthralgia

Other immunosuppressants

Cyclosporin A:
Cyclosporin A was effective in a small trial. A relatively rapid response (1–3 months) can be expected.
Initiate treatment with 150 mg twice daily, and reduce as much as possible for maintenance. Monitoring of therapeutic range can done by specialized laboratories.
Use of cyclosporin is indicated for long-term immunosuppression and steroid sparing.

Side effects include renal insufficiency, hypertension, headache, hirsutism, and increased risk of malignancy.

Mycophenolate mofetil (Cell Cept):
This is a relatively new drug for long term immunosuppression. It acts on B and T cells.
A few studies have been done in MG.
The onset of action is several months.
There are few side effects.
Usual dose: 1g twice daily

Cyclophosphamide:
Standard immunosuppressant that can be used as a maintenance therapy or, in higher doses, to achieve rapid action. Side effects in high doses may cause hemorrhagic cystitis.

Other (anecdotal) reports of immunesuppressants in MG describe: Tacrolimus (FK-506), rituximab (monclonal antibody directed against B cell surface marker CD 20), and methotrexate (MTX).

Thymectomy

Thymectomy is generally suggested for the age group of 10–55 years for patients with generalized MG.
The approach for resection is either trans-sternally or trans-cervically.
Although thymectomy is the standard therapy in many centers, its effectiveness has not been demonstrated in a well-controlled prospective study.
The clinical effectiveness of thymectomy may lag behind.
While there are reported benefits to thymectomy, the efficacy is difficult to judge because of difficulties in comparing the methods of operation and the uncertainty of maximal resection.
Thymectomy is indicated as an initial and primary therapy of patients with generalized limb and bulbar involvement.

Treatment of myasthenic crisis:
Plasmapheresis is used in crisis situations. The beneficial effects of this treatment occur quickly, but are short-lasting (3–6 weeks). Additional immunosuppression must be provided.
However, the main requirement is life-supporting therapy in an ICU setting. This treatment prevents aspiration of mucus and secondary pneumonia that can otherwise lead to life threatening ventilatory failure.

Prognosis

Ocular MG:
When the weakness remains localized in the eyes for more than two years, only 10–20% of these cases progress to general MG. The need to treat these patients with steroids and immunosuppression is controversial.

Generalized MG:
The prognosis has dramatically improved since immunosuppression, thymectomy, and intensive care medicine have been introduced. Grob reports a drop in mortality rate to 7%, improvement in 50%, and no change in 30%. However, a study by Mantegazza et al (1990) demonstrated remission in only 35% of cases followed over 5 years.

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Drug-induced myasthenic syndromes

Neuromuscular transmission and drugs

Neuromuscular transmission (NMT) is a sensitive process in the peripheral nervous system. In general healthy patients have a capacity to overcome the effects of substances and drugs that impair NMT. This capacity is termed the "safety factor" and varies with different species.

In patients with NMT disorders of the MG type, this safety factor is reduced or already absent, resulting in additional weakness if drugs are given. This table gives an overview of drugs that may have an effect on neuromuscular transmission in MG patients.

The physician treating patients with MG must be aware of this fact. These influences must be especially considered in patients receiving several medications.

Analgesics	Morphine does not depress NMT in myasthenic muscles. However, respiratory depression by opiates must be taken into consideration.
Antibiotics	Aminoglycoside antibiotics (amikacin, gentamycin, kanamycin, streptomycin, tobramycin) Ampicillin Fluoroquinolones (ciprofloxacin, ofloxacin, perfloxacin) Lincomycin, Clindamycin Macrolides (erythromycin, azithromycin) Penicillins Polymyxin B, Colistimethate, Colistin Sulfonamides Tetracyclines
Anticonvulsants	Barbiturates Diphenylhydantoin Ethosuximide Carbamazepine Gabapentin
Antimalarial drugs	Chloroquine
Botulinum toxin	In therapeutic applications, the influence on remote sites of NMT demonstrated with single fiber EMG.
General anaesthetics	Potentiation of neuromuscular blocking agents in patients with MG. Majority of patients can tolerate general anesthetics; postoperative waning difficulties are rare.

Local anaesthetics	Intravenous lidocaine, procaine and similar drugs potentiate the effect of neuromuscular blockings agents. Myasthenic crisis after large doses of local anesthetics has been reported.
Cardiovascular drugs	Beta blockers Bretylium Calcium channel blockers Procainamide Quinine and quinidine Trimethaphan (ganglionic blocking agent) Verapamil
Hormones	Estrogen and progesterone Thyroid hormone
Interferon alpha	May develop some months after onset of treatment. Exacerbation of myasthenic weakness
Iodinated contrast agents	Individual reports describe worsening of myasthenic symptoms.
Magnesium	Inhibition of ACh release. Occurs only with parenteral application, almost never with oral use. Drugs containing magnesium: antacids, laxatives Increase of Mg level with renal failure
Miscellaneous conditions	D,L-carnitine Diuretics (potassium wasting) Emetine-ipecac syrup Erythromycin Trihexyphenidyl
Neuromuscular blocking agents	MG and LEMS are more sensitive to competitive, nondepolarizing neuromuscular blocking agents. Depolarizing agents (e.g. succinylcholine) should be handled with caution. Weakness in the intensive care unit may be multi-factorial (blocking agents, disease, critical illness). Steroids may potentiate the neuromuscular blocking effects of muscle relaxants.
Ophthalmic drugs	Beta adrenergic blocking eye drops
Psychotropic drugs	Lithium Phenothiazine Others: amitryptiline, amphetamine, haloperidol, imipramine
Rheumatologic drugs	Chloroquine d-penicillamine

Other toxins affecting NMT

Most toxins enhance the presynaptic release and depletion of ACh

Arthropods		Rare
Heavy metals	Mercurial poison (grain) Gadolinium (MG patients)	
Marine toxins	Conontoxins Dinoflagellates Inimicus (Japan) Stonefish (Synanceja)	
Organophosphate and carbamate poison **War and terrorism**	Agriculture, manufacturing, pharmaceutical industry, weapons, pesticides ("Sarin, tabun, samun, venom X")	Organophosphates Acute cholinergic crisis Myopathy Delayed polyneuropathy
Plant toxins	Conium maculatum (poison hemlock)	Rare
Scorpion bites		
Snake bites	Cobra Rattlesnakes Sea snakes Vipers	Ptosis, ophthalmoparesis, bulbar muscles, limb, diaphragmatic muscles and intercostal weakness follow
Spider bites	Black widow spider Funnel web spider	Muscle rigidity, cramps
Tick paralysis	Dermacentor Ixodes	Resembles GBS

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LEMS (Lambert Eaton myasthenic syndrome)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	++ Repetitive stimulation SFEMG	Antibodies against voltage gated calcium channels (VGCC). In paraneoplastic LEMS: Antineuronal Abs (e.g. anti Hu)	Rule out lung and abdomen carcinoma	

Anatomical and functional situation

Prejunctional disturbance, with reduction of P/Q Ca^{++} channels on presynaptic terminals and reduction of Ca^{++} dependent quantal release. Also associated with N-type Ca channel antibodies (35%). GAD antibodies, thyroid antibodies, parietal cell antibodies, anti-Hu and muscle nicotinic AchR antibodies have been observed.
Voltage-gated calcium channels (VGCC) can be detected in 95% of patients with cancer-associated LEMS and in 90% of patients without cancer.

Symptoms

Patients report proximal weakness of legs and arms as well as autonomic symptoms (dry mouth and eyes). Male patients complain of impotence. Signs of distal sensory neuropathy may occur.
Bulbar and ocular signs are mild and rare. The symptoms may precede the detection of cancer by many years.

Signs

Proximal weakness and areflexia are the most prominent findings upon examination. Brief, sustained exercise of maximum voluntary contraction may improve strength, and reflexes may reappear after repeated tendon percussion ("facilitation" – a well known bedside test).
Ocular muscles are rarely involved. Sensory symptoms may be difficult to evaluate. Dysphagia or ventilatory compromise is rare.

Pathogenesis

50–60% of observed LEMS is related to cancer (small cell lung cancer in particular, rarely other tumors).

Associated neurological conditions:
Anti-Hu syndrome
Ataxia
Encephalopathy
Paraneoplastic cerebellar degeneration
Other autoimmune diseases

Paraneoplastic:
The most frequent cancer association is with small cell lung cancer. Rarely, LEMS has been associated with lymphoma, cancer of the prostate, and thymoma.

Associated autoimmune diseases:
LEMS can be found in association with other autoimmune diseases.

Exacerbations:
Anesthesia, or waning from respiration.
Antibiotics: aminoglycosides, fluoroquinolones
Ca^{++} channel blockers
Iodinated intravenous X-ray contrast agents
Magnesium
Neuromuscular blocking agents

Diagnosis

Antibody testing:
Antibodies against presynaptic voltage-gated calcium channels can be found. These IgG antibodies are heterogeneous, and are directed against several types of calcium channels. There is similarity between presynaptic VGCC and those in tumor cells.

Clinically:
Proximal weakness with areflexia that responds to facilitation (e.g., reflexes may seem absent in rested state, but appear after muscle contraction or repetitive tapping with the reflex hammer on the tendon).
Most patients complain of autonomic signs: dry mouth, dry eyes. In males impotence may be the sign of autonomic involvement.

Tensilon test:
May be weakly positive.

NCV motor:
Low CMAP after first stimulation, increasing with repeated stimulation or after muscle contraction. Sensory conduction velocities are normal.

Repetitive stimulation:
With 20–50 Hz an incremental response up to 400%, with 2–4 Hz a decrement can be found. Post-exercise facilitation and exhaustion can occur.

Needle EMG:
Varying MUAP amplitudes of short duration.

Differential diagnosis

SFEMG:
Abnormal jitter (and blocking) with improvement at rapid discharge rates.

MG
Other NMT disorders
Myopathy
Symmetric polyneuropathy (weakness, reflex loss)

Therapy

3,4 Diaminopyridine (side effects: perioral, acral paresthesias, rarely seizures). 20 mg Tid. (Drug not available in the US).
Pyridostigmine (Mestinon®) may help in some patients.
Immunosuppression with steroids or other immunosuppressants
Plasma exchange and IVIG are reserved for critical interventions.

Prognosis

- Non carcinoma-associated: slow chronic progression without influence on life expectancy- sustained immunosuppression necessary
- Carcinoma-associated: prognosis is related to the neoplasm

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Botulism

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+	+		

Functional anatomy

Botulinum toxin is produced by gram-positive anaerobic bacilli that proliferate in alkaline conditions. 0.05–0.10 µg causes death in humans. Eight immunologically distinct toxins (A, B, C1, C2, D, E, F and G) have been identified. The neurotoxin produces a presynaptic blockade of ACh release at peripheral cholinergic terminals. This results in paralysis and autonomic dysfunction. Although the quantal size is normal, the number of quanta released is below normal.

Symptoms

The incubation period is normally 18–32 hours, but may be as long as a week. Patients have diffuse proximal weakness and bulbar symptoms with dysphagia and dysarthria. Involvement of the extraocular muscles may result in diplopia and ptosis.
Sensory symptoms are not prominent.

Signs

Proximally accentuated weakness with reduced or absent tendon reflexes.
Autonomic signs consist of:
Bradycardia
Gastrointestinal symptoms:
Nausea, constipation, diarrhea
Hypohydrosis
Hypotension
Pupils dilated, blurred vision
Urinary retention

Clinical types

- "Classic botulism" comes from ingestion of contaminated foods (home canned goods, garlic oil). Acidic foods (vinegar) are rarely the source. Symptoms of oculobulbar weakness occur within 2–36 hours. Tongue weakness may be profound. Symptoms occur in a descending pattern, affecting upper limbs and lower limbs. In severe cases, respiratory muscles are impaired. Pupil dilation may be observed in half of the patients. Sympathetic and parasympathetic nerve transmission is also impaired. Intensive care may be necessary, and recovery is often prolonged but complete.
- Infant botulism occurs in children younger than 6 months. *C. Botulinum* spores are ingested and proliferate in the gastrointestinal tract. Ingestion of raw honey may be the cause. Symptoms include weak crying, feeding difficulties, and weak limb muscles. Parasympathetic blockade may be

evident. Differential diagnosis: Other types of hypotonia (myopathy, GBS, familial MG, spinal muscular atrophy, poliomyelitis).

- Wound botulism occurs with infection of traumatic or surgical wounds. Symptoms are similar to classic botulism. Intravenous administration of recreational drugs can cause abscesses that lead to wound botulism.
- Hidden botulism is used to describe cases where no food contamination or wound sources are evident.
- Inadvertent botulism results from patients treated with botulinum toxin that has effects at sites distant from the site of treatment. Prolonged jitter and increased blocking can be observed in SFEMG.

Diagnosis

Laboratory:
C. botulinum found in stool or wound.
Suspected food should be tested for the bacteria and toxin.

Electrodiagnosis:
- Sensory testing is normal.
- Motor conductions are normal; however CMAPs after a single stimulation are reduced. Brief exercise increases this.
- Decrement at 2–3 Hz stimulation is seen frequently.
- Post-tetanic facilitation similar to LEMS can be seen in affected muscles.
- EMG: brief, polyphasic potentials.
- SFEMG: increased jitter, blocking.
- Muscle biopsy: scattered angular fibers.

Differential diagnosis

Diphtheric paralysis
GBS
Miller Fisher syndrome
MG
Tick Paralysis

Descending symptoms are the hallmark, as opposed to ascending symptoms in GBS

Therapy

Supportive care
Antitoxin administration is controversial
Guanidine, 3,4-aminopyridine (Drugs to facilitate the presynaptic release).

Prognosis

Generally the prognosis is good with full recovery.

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Tetanus

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	(+)			

Functional anatomy

Tetanus is caused by the neurotoxin tetrapasmin, which is produced by an anaerobic gram-positive rod, *Clostridium tetani*. Tetanospasmin is transported by axonal transport to the cell bodies in the brain stem and spinal cord. It blocks the release of the inhibitory neurotransmitters glycine and GABA. Spinal reflex arcs are disinhibited resulting in an increase of resting firing rate. Rigidity and tetanospasms result (similar to strychnine poisoning). Also, sympathetic hyperactivity and high levels of circulating catecholamine levels occur.

Symptoms

The incubation period lasts from 3 days to 3 weeks (depending upon the location of the lesion). The onset period is between 3 to 6 days, beginning with infrequent reflex spasms.
In the generalized form, trismus, reflex spasm, neck rigidity, stiffness and dysphagia develop. Fractures due to muscle spasms may occur. Respiration can be impaired.
Autonomic overactivity results in hypertension, dysrhythmia, and urinary retention.

Signs

Sustained muscular rigidity and reflex spasms. Increased sympathetic activity.

Presentations

Localized tetanus:
Localized tetanus is characterized by fixed muscular rigidity confined to a wound-bearing extremity, and may persist for months. Local tetanus may be a forerunner of the generalized form.
Cephalic tetanus is a peculiar form of local tetanus, presenting as trismus plus paralysis of one or more cranial nerves. Facial paresis and dysphagia are common presentations. Abnormal ocular movements including ophthalmoplegic tetanus can appear. Cephalic tetanus is usually associated with infections of paracranial structures, especially chronic otitis media or dental infection.

Generalized tetanus:
Generalized tetanus is characterized by rigidity of the masseter muscles (trismus) and involvement of the facial muscles, causing a smiling appearance (risus sardonicus).
Laryngospasm reduces ventilation and may lead to apnea. This is followed by rigidity of the axial musculature, with predominant involvement of the neck, back muscles (opisthotonus-arched back), and abdominal muscles. Paroxysmal, violent contractions of the involved muscles (reflex spasms) appear repet-

itively only in severe cases. Generalized spasms as well as laryngospasm contribute to ventilatory insufficiency and asphyxia. Tetanospasms may occur, and are painful. They can be elicited by minor stimulation.
Autonomic features are hypertension, tachycardia, arrhythmia, sweating, and vasoconstriction, possibly leading to cardiac arrest.
The alteration of consciousness and true convulsive seizures are the result of severe cerebral hypoxia. The severity continues to increase for 10 to 14 days after onset.
Recovery usually begins after 4 weeks.

Neonatal tetanus:
Neonatal tetanus usually occurs as a generalized form and carries a high mortality. It usually develops during the first 2 weeks in children born to inadequately immunized mothers and frequently follows nonsterile umbilical stump treatment.
Failure to suck, twitching, and spasms are the most frequent symptoms of neonatal tetanus.

Maternal tetanus:
Tetanus occurring during pregnancy or within 6 weeks after any type of pregnancy termination is regarded as maternal tetanus. Approximately 15,000 to 30,000 cases of maternal tetanus occur in developing countries each year.

Cephalic tetanus:
May occur in lesions of the head and neck (e.g., otitis). Symptoms are unilateral facial paralysis, trismus, facial stiffness, nuchal rigidity, and pharyngeal spasms. Caudal cranial nerves and oculomotor nerves may be affected. The incubation period is short, and it may progress to generalized tetanus.

Diagnosis

Diagnosis is based on clinical findings. The absence of a wound does not exclude tetanus, and anaerobic cultures are only positive in a third of cases. CSF is normal. EMG shows continuous discharges resembling forceful voluntary contractions, with shortening or absence of the silent period.

Differential diagnosis

Cephalic tetanus may be mistaken for Bell's palsy or trigeminal pain
Neuroleptic malignant syndrome
Rabies: muscle spasm in deglutition and respiratory muscles
Stiff person syndrome (insidious onset)
Strychnine intoxication (almost identical, except for trismus)
Tetany: accompanied by Chvostek's and Trousseau's
Trismus: peritonsilar abscess, purulent meningitis, encephalitis

Therapy

Therapy begins with elimination of the source of the toxin (if known), administration of human tetanus immunoglobulin (3–6000 units, im), and intensive care. The Ig antitoxin does not cross the blood brain barrier and has no effect on central symptoms. Sedatives and muscle relaxants are used to treat symptoms. Tracheotomy is necessary for severe tetanus. A dimly lit room helps minimize stimulation. Proper nutrition is important to counteract catabolism.

Prognosis

Depends upon the severity of the illness and the available intensive care. Outcome is poor in neonatals and the elderly, and in those with a short incubation from onset of symptoms to spasm. Clinical course extends over 4–6 weeks, but recovery can be complete.

Prevention

Active immunization.

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Muscle and myotonic diseases

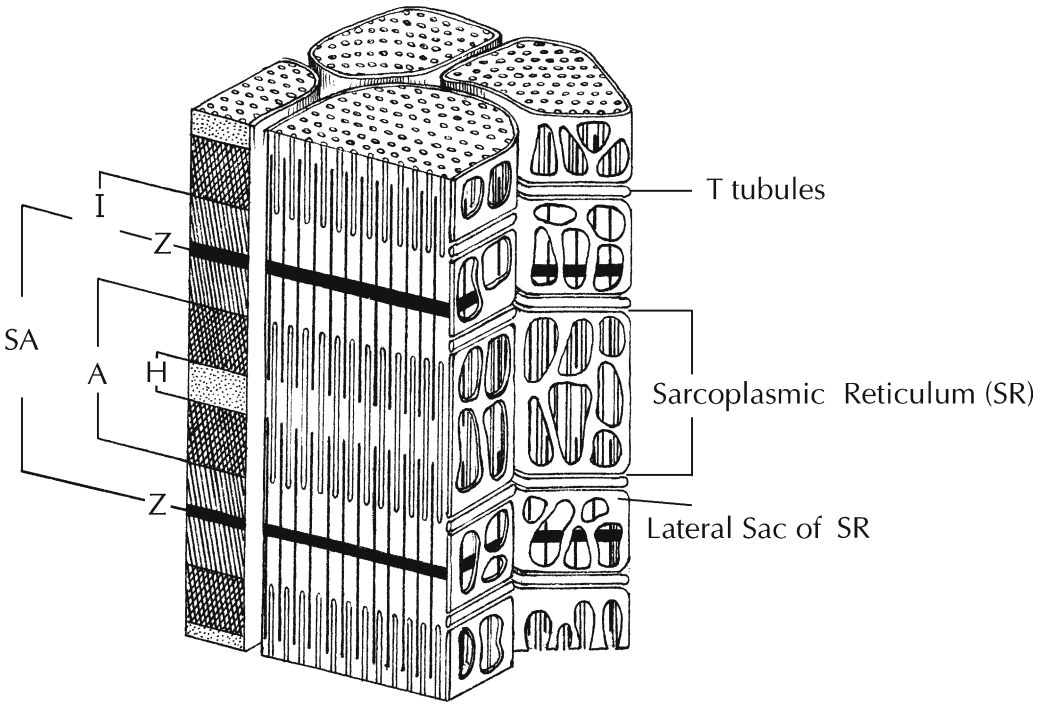

Fig. 1. Human Skeletal Muscle showing the gross and microscopic structure. The sacroplasmic reticulum (*SR*) is an intracellular membrane system. The T tubules are invaginations of the sarcolemma, and communicate with the extracellular space. Ultrastructurally several components of the muscle can be identified. The sarcomere (*SA*) represents the space between the Z discs. The A band comprises thick filaments of myosin, with an overlap of actin at the edges. The H band represents pure myosin, with a thickening in the center called the M line. The I band on either side of the Z line, comprises thin filaments. The Z disc helps to stabilize the actin filaments

Introduction

Although the history and clinical examination remain the most effective way of diagnosing the presence of myopathy, increasingly the clinician has to rely on an understanding of muscle electrophysiology, pathology, and genetics to differentiate between an ever-increasing number of complex disorders of muscle.

Electrophysiology

The basis of the motor system is the motor unit. The motor unit consists of the anterior horn cell, axon, muscle membrane and muscle fiber, and is the final common pathway leading to activation of the muscle. The number of motor units in individual muscles varies depending on size from 10 in extraocular muscles to more than 1000 in lower limb muscles. Electromyography allows us to determine if the abnormality of the motor unit points to a disorder of the axon, muscle membrane, or muscle fiber and allows accurate diagnosis. Activation of the motor unit results in firing of muscle fibers and leads to muscle contraction. Striated muscle is made up of interdigitating thick filaments comprising myosin, and thin filaments comprising actin, and dividing the sarcomere into A and I bands (Fig. 1). Myosin is composed of light and heavy meromyosin and acts as an ATPase, hydrolyzing ATP. Actin filaments comprise actins,

troponins, and tropomyosin. ATPase hydrolysis in the presence of calcium ions activates the troponin-tropomyosin system and permits sliding of actin on myosin filaments as predicted by the "sliding filament theory". The force generated by a muscle is critically depended on its length. The more cross bridges between the filaments, the larger the force generated. In order to induce contraction there is first an increase in calcium ions in the sarcoplasmic reticulum following depolarization of the muscle membrane. The degree of increase in calcium ions equates with increased muscle tension, and is maximal at 10^{-5} to 10^{-4} M. Between contractions calcium is sequestered in the sarcoplasmic reticulum. Electrodiagnosis is useful in diagnosing the myopathies. Firstly, it helps distinguish between primarily myopathic compared to neurogenic disorders, secondly it allows the distribution of the myopathy to be determined, and finally it gives some information about severity and prognosis. Although electromyography can distinguish broad types of myopathic disorders, it cannot diagnose the specific myopathy. This requires analysis of the muscle pathology often coupled with biochemical and genetic analysis. Furthermore, some myopathies show evidence of both myopathic as well as neurogenic types of motor units, for example the inflammatory myopathies and disorders of fatty acid metabolism.

Muscle histology and immunohistochemistry

The second critical diagnostic evaluation in myopathic disorders is the muscle biopsy. Regular histology may diagnose many of the disorders listed in the following sections, and can recognize distinct histological patterns such as those seen in dermatomyositis, or some infective or toxic myopathies. However, increasingly we rely on specific immunohistochemical studies to make an accurate diagnosis. Thus, in the dystrophinopathies antibodies to certain muscle proteins allow us to determine the specific muscle disease, or in mitochondrial myopathies and other metabolic diseases the pathogenic enzyme system can be determined. Increasingly, patients with a metabolic myopathy present with significant symptoms of myalgia or myoglobinuria and have normal or minimally abnormal basic muscle histology, yet biochemical tests reveal significant enzyme abnormalities that would otherwise be missed. However, even the most astute muscle pathologist is dependent on accurate clinical information to decide which of the numerous biochemical studies are most appropriate. Pathological evaluation of muscle should be performed even where genetic analysis is available because it provides information about the severity of the disease, characterizes the presence or absence of a specific protein, and provides a clinical correlate for an available treatment. As discussed below, even the presence of a specific gene mutation may produce widely varying biochemical changes in muscle due to the presence of gene modifying effects.

Regulation of gene defects in muscle

Characterizing the molecular genetics of muscle has become increasingly important in understanding the pathogenesis of myopathy. Most gene defects have been described in the following chapters. The resulting clinical profile is dependent not only on the gene, but also on whether the disorder is autosomal recessive or dominant, the chromosomal localization, size of the gene defect, exon number, the type of gene promoter or enhancer, transcription characteristics, and the number and extent of deletions. A further important effect is that of compensatory or modifying alleles e.g. the utrophin gene can modify the

severity of some dystrophinopathies. A mutation of the same gene can cause widely differing clinical phenotypes. For example, the same mutation of the dysferlin gene may cause either type 2B limb-girdle dystrophy or Miyoshi's distal myopathy. In the mitochondrial myopathies, or disorders of β-oxidation, combinations of gene defects coding for specific enzymes can significantly modify the clinical phenotype. Unfortunately, the exponential increase in knowledge of genetic defects in specific muscle disorders has not been matched by the diagnostic availability of these tests. Furthermore, the cost of genetic studies has made it imperative that the clinician use consummate diagnostic skills to define the type and extent of testing. Thus, clinical judgement still remains the yardstick for diagnosis of a specific myopathy. As effective treatments become aligned with specific genetic and post-translational peptide or protein abnormalities, it will become even more important for the physician to develop a superb diagnostic acumen.

Polymyositis (PM)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
–	+++	+	+	+++

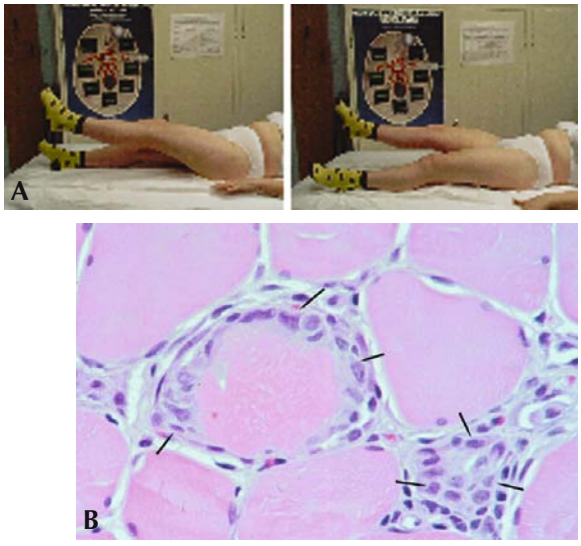

Fig. 2. Polymyositis. **A** Clinical proximal weakness on raising the leg in a patient with severe polymyositis. **B** Polymyositis showing increased infiltration of muscle fibers by macrophages and rare lymphocytes (arrows)

Distribution/anatomy

Usually affects proximal muscles with sparing of the face.

Time course

Progressive disorder with gradual onset in most cases. Occasionally acute onset is described.

Onset/age

Average age is 35 years. Can occur in children, but usually in those greater than 20 years of age.

Clinical syndrome

Polymyositis is more common in women (9:1). It usually results in a progressive, subacute weakness with muscle pain in approximately 50% of subjects. There is usually proximal weakness of limb (Fig. 2A) and neck flexor muscles, dysphagia, and occasional weakness of respiratory muscles. Cardiac involvement with EKG changes may also occur.

Pathogenesis

There is targeted, cell mediated lymphocyte toxicity against muscle fibers. An increase in CD8-T lymphocytes and macrophages is seen in affected muscle fibers. Muscle fibers may be destroyed by cytotoxic T cells possibly by produc-

tion of the pore forming protein perforin, by upregulation of Fas-induced apoptosis, or by induction of oxidative intermediates such as nitric oxide and peroxynitrites due to upregulation of nitric oxide synthase. There is also upregulation of anti-apoptotic molecules for example Bcl-2 on the surface of muscle fibers, implying that loss of muscle cells eventually occurs by necrosis and not apoptosis.

Diagnosis

Laboratory:
An elevated CK, at least 5–10 times normal, AST, and LDH may be observed. The following antibodies may be positive: Anti aminoacyl t-RNA synthetases e.g. JO1, and PM1.

Electrophysiology:
On EMG, there is increased insertional activity with short duration polyphasic motor unit action potentials. Nerve conductions studies are usually normal.

Imaging:
In early polymyositis, the muscle may be homogeneous on MRI. At sites of active inflammation there may be increased signal with gadolinium or on T2 weighted images. In chronic disease the muscle may be replaced by fat and show atrophy.

Muscle biopsy:
Evidence is found of focal areas of inflammation within perimysial connective tissue and surrounding blood vessels (Fig. 2B). There is usually scattered muscle fiber necrosis and an increase in CD8-T positive cells that traverse the basal lamina and focally compress and replace segments of muscle.

Differential diagnosis

- Dermatomyositis
- Inclusion Body Myositis
- Muscular Dystrophies
- Polymyalgia Rheumatica

Therapy

- Prednisone: 1 mg/kg P.O. per day, up to a maximum of 100 mg/day.
- Intravenous immunoglobulin (IVIG): 1 g/kg I.V. monthly.
- Azathioprine: 2–3 mg/kg P.O. per day. Especially in adults over the age of 50 and those who are severely weak.
- Mycophenylate mofetil 500–2000 mg/day P.O. in divided doses.
- In resistant individuals: cyclophosphamide or methotrexate may be required.
- General management includes dietary counseling, twice yearly eye evaluations for cataracts and glaucoma, supplemental calcitriol 0.5 mg/day, elemental calcium 1,000 mg/day, a regular graded exercise program, CK monitored at 2–4 weekly intervals coupled with strength testing and regular monitoring of serum electrolytes and glucose.
- Once the patient is stable or improved, the prednisone is tapered by approximately 10%, to an every other day dosage at 4 weekly intervals. The dose should be maintained at a steady state if the patient shows a decrease in strength or elevation of their CK level.

Prognosis

Generally good with most patients showing response to therapy.

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Dermatomyositis (DERM)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
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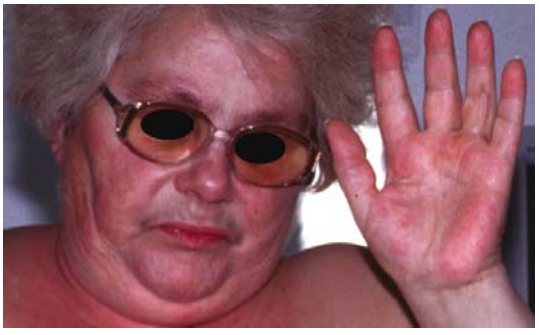

Fig. 3. Patient with dermatomyositis. There is evidence of a hyperememic rash on the upper chest, face and palm

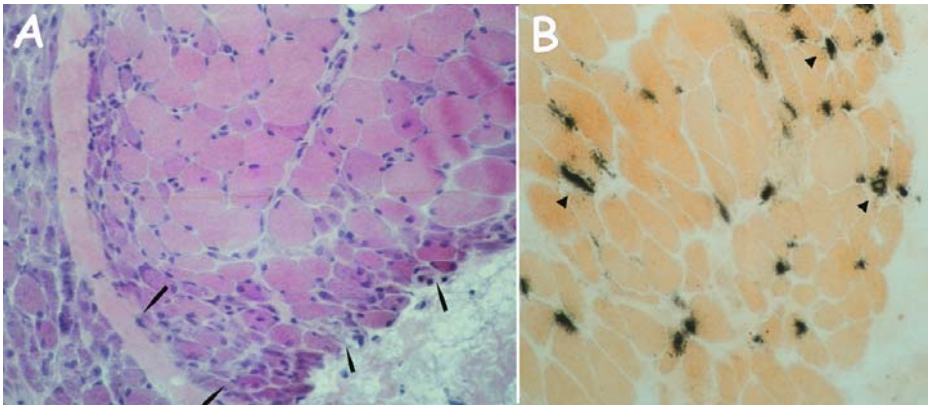

Fig. 4. Dermatomyositis. **A** Typical perifascicular regeneration (arrows). **B** Necrotic capillaries demonstrated by dark precipitates on alkaline phosphatase (arrow heads)

Distribution/anatomy

Usually affects proximal muscles and bulbar muscles.

Time course

Progressive disorder with gradual onset in most cases.

Onset/age

Any age, bimodal frequency 5–15 years and 45–65 years.

Clinical syndrome

Equally common in men and woman. Symptoms include myalgias, with subacute development of muscle weakness and dysphagia. Patients may also develop a rash (Fig. 3) with arthralgias, joint contractures and systemic symptoms related to cardiac or pulmonary involvement. DERM is associated with proximal muscle weakness, including weakness of the neck flexors, dysphagia and ventilatory failure. This is associated with erythema and telangiectasis over

the face with a violet discoloration (heliotrope) around the eyes, papular erythematous changes may be present on the knuckles called Gottron's papules, dilated capillaries at the base of the fingernails (Keinig's sign), nail fold capillary infarcts, dry and cracked skin on the palms (mechanic's hands). Necrotizing vasculitis may affect several organ systems including the retina, kidneys, gastrointestinal tract, heart and lungs.

Pathogenesis

In DERM there is myonecrosis with evidence of immunoglobulin and complement deposition in the microvasculature, suggesting a systemic immune-mediated response. There is probably an increased risk of cancer in subjects within 3 years of diagnosis of DERM. DERM following treatment with interferon α2b has also been observed.

Diagnosis

Laboratory:
Serum CK is elevated in more than 90% of patients with DERM. The following antibodies may be positive: Mi-2, MAS, sometimes Jo-1, anti t-RNA synthetase (anti-synthetase syndrome – myositis, polyarteritis, Raynauds, interstitial lung disease).

Electrophysiology:
Evidence of increased insertional activity with fibrillations and positive waves on EMG. Complex repetitive discharges may be seen with polyphasic motor units, many of which are short duration. With advanced disease the motor units may be frankly myopathic.

Imaging: May show evidence of inflammation and atrophy in chronically affected muscles.

Muscle biopsy:
Perifascicular muscle fiber atrophy (Fig. 4) is specific for DERM and occurs in 75% of patients. There may also be evidence of focal invasion of muscle fibers by inflammatory cells, although this is infrequent. There is a high proportion of CD4 positive T cells in DERM compared to PM or inclusion body myositis.

Differential diagnosis

- Polymyositis
- Inclusion body myositis
- Muscular dystrophies
- Polymyalgia rheumatica

Therapy

- Prednisone: 1 mg/kg P.O. per day, up to a maximum of 100 mg/day.
- IVIG: 1 g/kg I.V. monthly.
- Azathioprine: 2–3 mg/kg P.O. per day. Especially in adults over the age of 50 and those who are severely weak.
- Mycophenylate mofetil 500–2000 mg/day P.O. in divided doses.
- In resistant individuals: cyclophosphamide or methotrexate may be required.
- General management as for PM.

Prognosis

Generally worse than with PM.

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Callen JP (2000) Dermatomyositis. Lancet 355: 53–57
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Griggs RC, Mendell JR, Miller RG (1995) Evaluation and treatment of myopathies. FA Davis, Philadelphia, pp 154–210

Inclusion body myositis (IBM)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
-	+++	+	+/-	+++

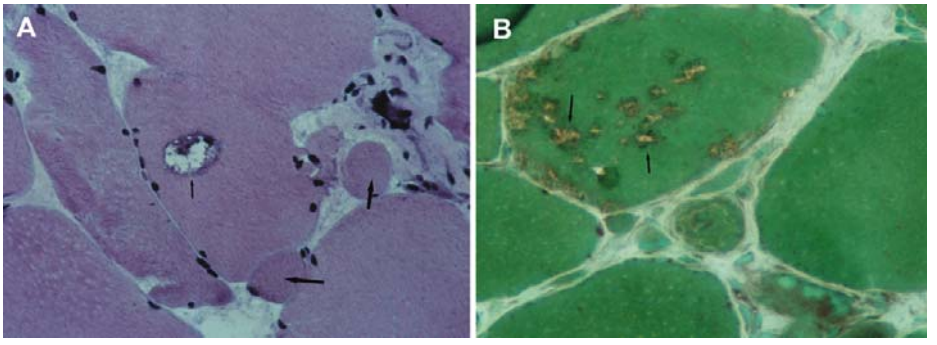

Fig. 5. Inclusion Body Myositis. **A** Hematoxilin and eosin stained tissue showing a typical rimmed vacuole in the center (small arrow) and atrophy of muscle fibers (large arrow). **B** Acid phosphatase stain showing rimmed vacuoles (arrows)

Distribution/anatomy

Affects proximal and distal muscles in upper and lower extremities, with distal muscles affected predominantly in 20% of patients. Wrist and finger flexors and quadriceps are often more severely affected. Proximal arm, hand and face muscles are spared.

Time course

The disorder is progressive over 5 to 25 years

Onset/age

More common in males over age 50 years.

Clinical syndrome

Weakness and atrophy occurs in the distribution described above. Muscle weakness is often asymmetric unlike PM and DERM. Dysphagia is seen in 30% of patients. Tendon reflexes are normal or decreased with disease progression. A mild sensory neuropathy is observed in some patients. Systemic involvement is rare.

Pathogenesis

Unknown. No association with malignancy. An association with myxovirus has not been confirmed, inflammation is present but it is unknown if it is primary or secondary. The β-amyloid protein may result in muscle fiber apoptosis, and some cases are inherited (HaD).

Diagnosis

Laboratory:
Mildly elevated CK, at least 2-5 times normal, but may be normal. The ESR is usually normal. There may also be an elevation in muscle AST and LDH up to

20 times normal. May be associated with various HLA types including DRb1*0301, DRb3*0101, DRb3*0202 and DQb1*0201. Genetic testing for inherited cases is not clinically available at this time.

Electrophysiology:
Nerve conductions studies are usually normal. EMG shows increased insertional activity. Short duration polyphasic motor unit action potentials, mixed with normal and long duration units are frequently observed. The presence of longer duration, polyphasic units may be misinterpreted as a neurogenic condition such as motor neuron disease.

Imaging:
Similar to dermatomyositis, but of limited clinical value.

Muscle biopsy:
Endomysial inflammation (mainly CD8+ T cells and some macrophages), with myopathic changes and groups of small fibers. Muscle fiber hypertrophy is more common than in polymyositis, and small groups of atrophic fibers of mixed histochemical type may be seen similar to that observed with denervation of the muscle. Frequently rimmed vacuoles are seen with granular material and filaments measuring 15 to 18 nm (Fig. 5). These may comprise several proteins including b-amyloid, desmin, and ubiquitin.

Differential diagnosis

- Polymyositis
- Dermatomyositis
- Motor Neuron Disease
- Muscular dystrophies
- Distal myopathies

Therapy

No effective therapy. A high dose of IVIG is reported to be effective in some patients.

Prognosis

Survival is usually good, although weakness is progressive and may be debilitating.

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Focal myositis

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
-	+++	+	++	+++

Fig. 6. Calf hypertrophy. This patient had a unilateral right calf hypertrophy in a case of focal myositis

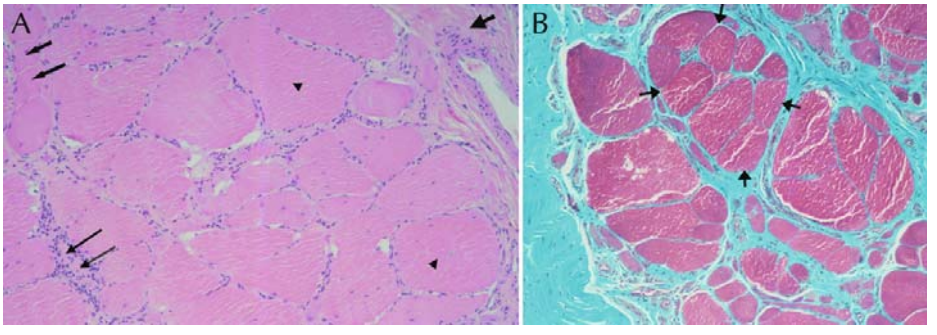

Fig. 7. Focal Myositis. **A** Atrophic fibers (arrows top left), inflammatory response (arrows bottom left), hypertrophied fiber (arrow head), increased connective tissue (top right). **B** Lobulated fibers outlined by bands of collagen (arrows)

Distribution/anatomy

May involve any muscle, although the quadriceps; gastrocnemius, and abdominal muscles are commonly affected.

Time course

May occur at any age from childhood to 70 years, mainly 30–50 years.

Onset/age

May occur at any age but is more common in subjects between 30 and 60 years of age.

Clinical syndrome

There is an equal distribution in men and women. Symptoms include a painful, focal mass (Fig. 6) with muscle cramping. Patients may have a solitary, asym-

metric muscle mass, enlarging over several months. Strength and reflexes are usually normal. Most cases spontaneously resolve, and recurrence is unusual.

Pathogenesis

Unknown. A focal inflammation develops in isolated muscles and may represent a localized cell mediated response.

Diagnosis

Laboratory:
Serum CK and ESR may be mildly elevated, but are usually normal.

Electrophysiology:
Nerve conduction studies are usually normal. EMG shows increased insertional activity only in affected muscles. Short duration polyphasic motor unit action potentials, mixed with normal and long duration units are seen in the affected muscle/s.

Imaging:
Focal enlargement and edema, especially observed on T2 weighted images and T1 with gadolinium.

Muscle biopsy:
Muscle fiber hypertrophy and fibrosis are more common than in PM and DERM. There is formation of clusters of tightly packed fibers surrounded by fibrosis (Fig. 7). Inflammation is mild, with predominant T-lymphocytes.

Differential diagnosis

- Localized nodular myositis
- Muscle sarcoma
- Sarcoid infiltration of muscle
- Soft tissue tumors

Therapy

- Analgesics and anti-inflammatory medications.
- Corticosteroids in a short course may help some patients.

Prognosis

Usually excellent and the swelling resolves spontaneously. Recurrence may occur in a minority of patients.

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Connective tissue diseases

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
–	+++	+++	+	+++

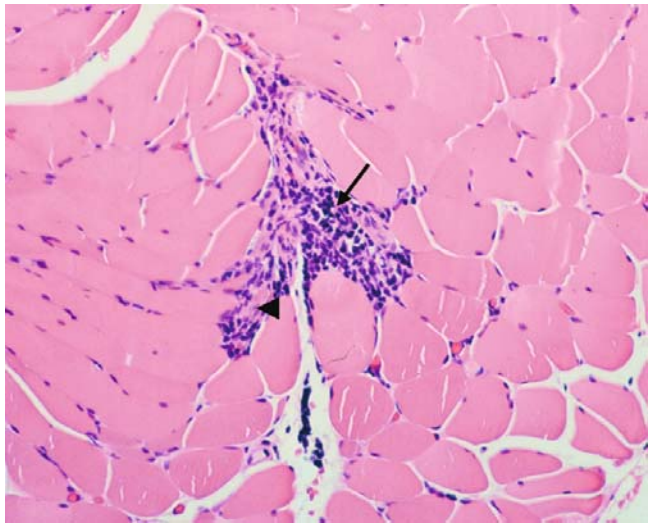

Fig. 8. Mixed connective tissue disease. A prominent inflammatory response is seen (arrow), with a degenerating fiber (arrow head)

Distribution/anatomy

Any muscle may be affected, although proximal muscles are more likely to be involved.

Time course

Variable, although involvement of muscle is unusual and tends to be seen more in chronic connective tissue disorders.

Onset/age

Can affect any age depending on the specific connective tissue disorder.

Clinical syndrome

The following types of connective tissue diseases are associated with myopathy: 1) Mixed connective-tissue disease (MCTD); 2) Progressive systemic sclerosis (PSS); 3) Systemic lupus erythematosus (SLE); 4) Rheumatoid arthritis (RA); 5) Sjögren's syndrome (SS); 6) Polyarteritis nodosa (PAN); and 7) Behçet's syndrome (BS).

- MCTD and PSS. Most patients develop a progressive weakness associated with fatigue. The weakness may be associated with an inflammatory myopathy that resembles polymyositis, or may be associated with poor nutrition and disuse atrophy.

- SLE. A true inflammatory myopathy is rare in this disorder. Other causes of weakness include a vasculitic neuropathy associated with mononeuritis multiplex or an axonal polyneuropathy. Myopathy in SLE may be related to inflammation, disuse atrophy secondary to painful arthritis, or following use of medications such as corticosteroids or chloroquin.
- RA. Causes of muscle weakness include disuse atrophy secondary to arthritis pain, inflammatory myopathy, and medications including penicillamine.
- SS. Myalgia is common in this disorder, but inflammatory myositis is rare. Weakness is often due to disuse atrophy following joint pain.
- PAN. Although muscle biopsy may show evidence of vasculitis, symptomatic myopathy as a presenting disorder is rare in PAN.
- BS. Most patients present with painful calf or thigh symptoms, rather than muscle weakness. True myositis is unusual.

Pathogenesis

The immunopathogenesis of myositis with connective tissue disease is poorly understood. The presence of anti-RNP antibodies, circulating immune complexes, and reduced complement levels all suggest activation of the humoral immune system.

Diagnosis

Laboratory:
The CK value is often very high up to 15 times normal, although CK values may only be mildly elevated in less severe cases.

Electrophysiology:
On EMG, there is evidence of an increase in insertional activity, coupled with short duration polyphasic motor unit action potentials observed in patients with connective tissue disease and inflammatory myopathy. Nerve conduction studies may also show evidence of neuropathy in many of these disorders.

Imaging:
In MRI studies, there may be evidence of increased signal on T2 weighted images, or with gadolinium, indicating areas of active inflammation and muscle necrosis. In chronic disease there may be evidence of fat infiltration and muscle atrophy.

Muscle Biopsy:
Frequently the muscle biopsy shows changes that resemble those in DERM There may be necrotic fibers invaded by inflammatory cells (Fig. 8). Atrophy of type 2 muscle fibers may be observed particularly where there is significant arthritis, joint pain and disuse atrophy of the muscle.

Differential diagnosis

- DERM
- IBM
- PM
- Causes of weakness associated with connective tissue disease e.g. polyneuropathy or mononeuritis multiplex.

Therapy

This is dependent on the specific cause of the connective tissue disease. In general immunosuppressive medication similar to that used for PM is appropri-

ate for the treatment of inflammatory myopathy associated with connective tissue disease.

Prognosis

Depends mainly on the severity of the systemic illness. With appropriate control of the disease, the myopathy may become quiescent.

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Mastaglia FL (2000) Treatment of autoimmune inflammatory myopathies. Curr Opin Neurol 3: 507–509

Infections of muscle

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
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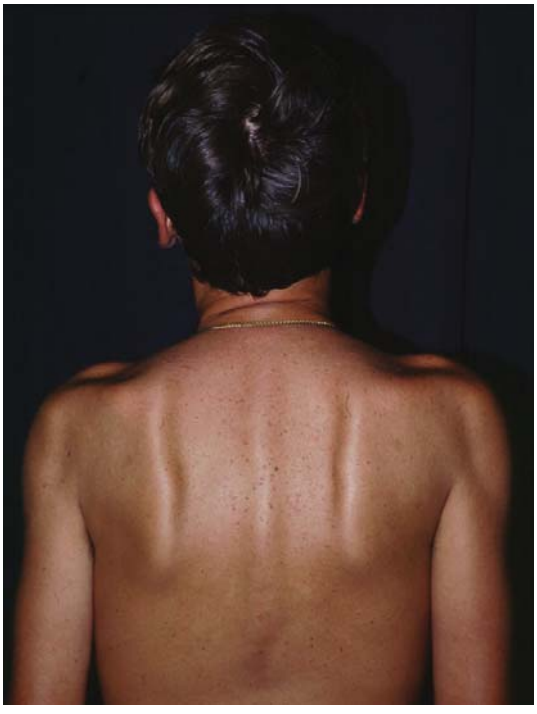

Fig. 9. HIV myopathy. Proximal arm atrophy and bilateral scapular winging in a patient with HIV myopathy

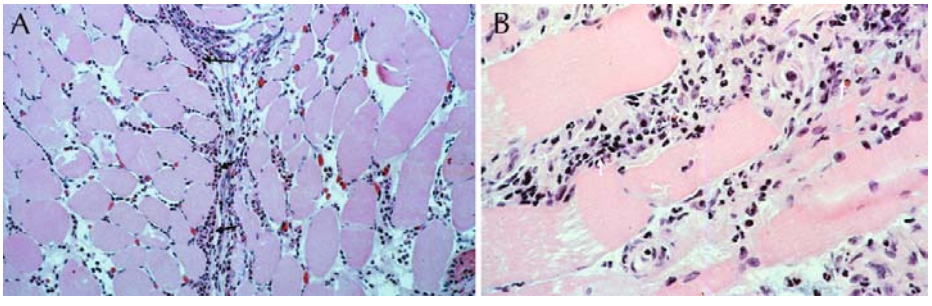

Fig. 10. Pyomyositis. **A** Marked neutrophil inflammation (arrow). The muscle fibers are textureless and have no nuclei, features consistent with rhabdomyolysis. **B** Neutrophil inflammatory response dispersed between several fibers

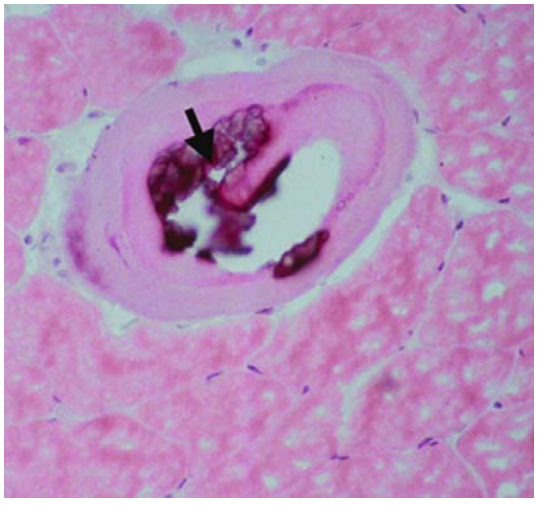

Fig. 11. Trichinella spiralis. Slide shows a calcified cyst within the muscle (arrow)

Distribution/anatomy

The distribution is variable depending on the type of infection.

Time course

Is variable depending on the type of infection.

Onset/age

Any age.

Clinical syndrome

Viral myositis

Influenza virus myositis is characterized by severe pain, tenderness and swelling which usually affects the calf muscles but may also affect thigh muscles. Myalgia is the most common symptom, and starts approximately one week after the onset of the influenza infection, and then persists for another 2–3 weeks. The disorder is usually self-limiting, however in rare cases it may be severe with myoglobinuria and a risk of renal failure. Coxsackie virus infection is characterized by a wide spread acute myositis which may be severe and may be associated with myoglobinuria. Epidemics of Coxsackie virus infection tend to occur during the summer and fall. In children aged 5–15 years there may be a self-limiting acute inflammatory myopathy. Infection is usually caused by Coxsackie virus group B. Affected patients may complain of muscle aching, often exacerbated by exercise, and weakness if it occurs may be minimal. The symptoms usually resolve within 1–2 weeks. Bornholm's disease is associated with severe pain and tenderness in the muscles of the chest, back, shoulders, or abdomen and may be associated with a more severe Coxsackie B5 infection.

The human immunodeficiency virus (HIV), and human T-cell lymphotrophic virus (HTLV) may be associated with a variety of myopathic manifestations. HIV infected patients may develop one of the following manifestations: a) An HIV associated myopathy (Fig. 9) that resembles polymyositis. b) Zidovudine myopathy, which resembles mitochondrial myopathy. c) AIDS-associated cachexia with muscle wasting. d) Opportunistic infections and tumor formation within muscle. e) A myopathy resembling nemaline myopathy. f) An HIV associated vasculitis. With HIV associated nemaline rods, the CK is often very high and

there may be evidence of muscle fiber necrosis. HIV may also be associated with a necrotizing myopathy with proximal weakness. Pyomyositis and lymphoma may also develop in the muscle, and may be associated with painful limb swelling. A variety of organisms have been associated with pyomyositis including cryptococcus, CMV, *Mycobacterium avium intracellularae* (MAI), and toxoplasma. With HIV wasting disease, which is more common in sub Saharan Africa, there is fatigue and evidence of type 2 muscle fiber atrophy.

HTLV1 may also be associated with polymyositis, as well as causing a tropical spastic paraparesis (TSP).

Pyomyositis

Pyomyositis associated with staphylococcus, streptococcal and clostridial infections are the most common forms of bacterial myositis. Pyomyositis most commonly occurs in tropical areas and may occur without any antecedent illness or other predisposing factors. It may also be associated with trauma, malnutrition, diabetes mellitus, following an acute viral infection, associated with a suppurative arthritis or osteomyelitis, or from hematogenous spread from a bacterial source within the body. Non-tropical pyomysitis may occur in elderly bed ridden patients with bed sores, intravenous drug users, burn victims, in immunosuppressed patients, e.g. AIDS or underlying cancer. In the vast majority of cases, *Staphylococcus aureus* is cultured from the abscesses, however other organisms including *Streptococcus pyogenes*, salmonella, and pneumococcus may also be isolated from the abscess. Clinically there is painful swelling of the muscle, the pyomyositis often affects the quadriceps, glutei muscles, biceps or pectoral muscles. Although the swelling may initially be hard, it rapidly becomes fluctuant as the inflammation increases and muscle necrosis occurs. Clostridial myositis is due to infection with *Clostridium welchii*, and develops after wound or muscle contamination. The clinical features of clostridial myositis include local pain, swelling, production of serosanguinous fluid, and local brownish discoloration. Patients may develop systemic signs of septicemia. Necrotizing fasciitis and myonecrosis (a flesh eating infection) is a rare but life-threatening disease, most often caused by group A β-hemolytic *Streptococcus pyogenes*. The disorder may occur postoperatively, or following minor trauma. There is destruction of skin and muscle in response to streptococcal pyrogenic exotoxin A.

Fungal myositis

Fungal myositis is uncommon in man. In immunocompromised patients, fungal myositis is becoming increasingly more common in those suffering from AIDS or with malignancies. Sporotricosis, histoplasmosis, mucormycosis, candidiasis, and cryptococcosis are all associated with myositis. In sporotricosis and histoplasmosis a single muscle or group of muscles is usually affected with formation of an abscess. Mucormycosis can spread into the orbit where it produces ophthalmoplegia, proptosis, and edema of the eyelid. In disseminated candidiasis, patients develop papular cutaneous rashes, and wide spread muscle weakness with myalgia. Toxoplasmosis may cause local inflammation within the muscle. In immunocompromised hosts it is often asymptomatic, however in other infected subjects, an acute infection may develop with lymphadenopathy which may remit spontaneously, and in some patients a polymyositis-like syndrome may develop.

Parasitic myositis

American trypanosomiasis (Chagas' disease) caused by *Trypanosoma cruzi* can cause an inflammatory myopathy coupled with evidence of a neuropathy. In

African trypanosomiasis, there is malaise and fever along with myocarditis, polymyositis and encephalopathy. Microsporidiosis is caused by the zoonotic protozoa, microsporidium, and results in polymyositis in immunocompromised patients. In addition to causing the systemic illness malaria, plasmodium falciparum can also cause acute muscle fiber necrosis. Cysticercosis results from infection by *Cysticercus cellulosae*, the larval form of the pork tapeworm *Taenia solium*. The encysted parasite may be found in skeletal and heart muscle, as well as eye and brain. The clinical features vary according to the location and number of cysts, however myalgia, fever, and vomiting may occur as part of the overall syndrome. Trichinosis is caused by the larva of *Trichinella spiralis* and may be associated with periorbital and facial edema, fever, myalgia, and proximal muscle weakness. Occasionally the disorder may mimic mild dermatomyositis. Myositis is also reported with echinococcosis, visceral larva migrans, cutaneous larva migrans, coenurasis, sparganosis and dracunculosis.

Pathogenesis

The specific mode of muscle injury depends on the particular pathogen. Several of the viral infections, including HIV may cause myositis by increasing release of cytokines and interferons. Viral infections may also cause perivascular, perimysial, or endomysial inflammation. In streptococcous pyogenes infections the pathogenic M-protein and associated proteases may prevent the normal host phagocytic response.

Diagnosis

Laboratory:
The CK value may be normal or mildly elevated.

Electrophysiology:
EMG shows evidence of focal or more diffuse muscle damage, characterized by increased insertional activity or with “myopathic” polyphasic motor unit potentials.

Imaging:
MRI studies may show evidence of a focal myositis depending on the specific pathogen.

Muscle biopsy:
The muscle biopsy changes depend on the specific pathogen. In general the features are similar to those observed in polymyositis (Fig. 10). In certain disorders such as HIV, nemaline rods may be observed. In the parasitic infections, the specific parasite may be observed, e.g. cysticercosis, trichinosis (Fig. 11), echinococcosis, and trypanosomiasis. Likewise, with the fungal infections, the specific pathogen may be identified in the muscle tissue.

Differential diagnosis

Many of the causes of infectious myositis resemble one another, and determining the specific cause may require culture of the organism, specific antibody testing and muscle biopsy with special staining. Other disorders that may resemble infectious myopathy include: 1. Polymyositis 2. Dermatomyositis 3. Mitochondrial myopathies 4. Necrotizing myopathy

Therapy

Therapy for the specific infectious myositis depends on the specific pathogen, and is beyond the scope of this book. In addition to use of specific anti-infective

drugs, patients may require surgical drainage of the abscess, or removal of the parasite. HIV polymyositis is similar to disease in non-HIV patients and may improve with corticosteroids or immunosuppressive medications. Some patients with the HIV wasting disorder, may respond to oxandrolone.

Prognosis

The prognosis depends on the specific cause of the myositis. For a non-HIV related viral syndrome, the disease is usually self-limiting and prognosis is good. Where there is HIV infection or opportunistic infection the prognosis is poor. Removal of isolated parasites coupled with anti-protozoal medications may be all that is required to treat parasitic myositis.

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Duchenne muscular dystrophy (DMD)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
+++	++	–	+	+++

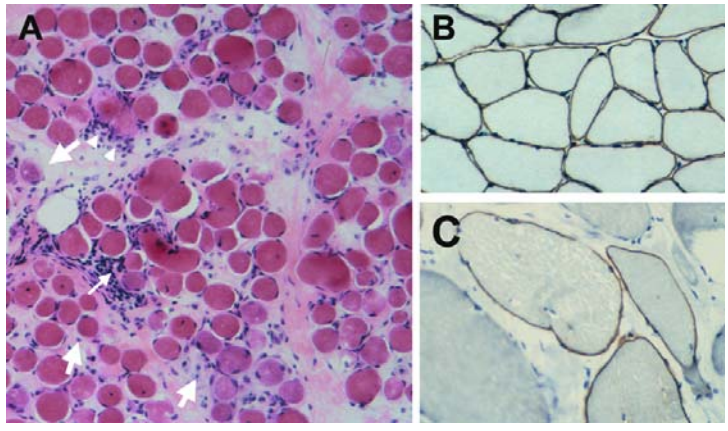

Fig. 12. Muscle biopsy DMD. **A** Hematoxylin and eosin showing an increase in endomysial connective tissue (large arrows), inflammatory infiltrates (small arrows), and degenerating fibers (arrow head). **B** Normal dystrophin staining. **C** Loss of dystrophin staining in DMD

Distribution

Proximal muscles are more affected than distal muscles. Infants may have generalized hypotonia and be described as "floppy".

Time course

Progressive disorder resulting in significant disability in most children.

Onset/age

DMD starts at age 3–5 years with symmetric proximal greater than distal weakness in the arms and legs. By 6–9 years they characteristically exhibit a positive Gower's sign, and by 10–12 years patients often fail to walk.

Clinical syndrome

DMD results in a progressive muscular weakness affecting 1:3500 male infants. They often have calf muscle hypertrophy, muscle fibrosis, contractures in the lower extremities, and scoliosis of the spine. In general the average IQ of affected children is reduced compared to the general population to approximately 85. Some patients (20%) may have more severe cognitive impairment. Other features include a retinal abnormality with night blindness, and a cardiomyopathy that develops by the mid-teens. In DMD, cardiac conduction defects, resting tachycardia, and cardiomyopathy are frequently encountered. Mitral valve prolapse and pulmonary hypertension may also be seen. Death normally occurs by the late teens to early twenties from respiratory or cardiac failure.

Pathogenesis

Most have a frameshift mutation (> 95%), although 30% may have a new mutation. The molecular abnormality is unknown. However, in DMD there is an abnormality in dystrophoglycan development at the neuromuscular junction. Dystrophoglycan may play a role in clustering of acetylcholine receptors and development of the neuromuscular junction, along with dystroglycan, α1-syntrophin, utrophin, and α-dystrobrevin.

Diagnosis

Laboratory:
Serum CK is usually very high.

Electrophysiology:
Nerve conduction studies are usually normal (except reduced CMAP in affected atrophic muscles). EMG shows increased insertional activity only in affected muscles. Short duration polyphasic motor unit action potentials, mixed with normal and long duration units are seen in the affected muscle/s.

Imaging: Focal enlargement, edema, and fatty infiltration especially observed on T2 weighted and T1 images with gadolinium. Imaging may show hyperlordosis and scoliosis.

Muscle biopsy:
Characterized by endomysial fibrosis (Fig. 12), variation in muscle fiber size, muscle fiber degeneration and regeneration, small fibers are rounded, there are hypercontracted muscle fibers, and an increase in endomysial connective tissue. Muscle dystrophin staining is absent (Fig. 12C).

Genetic testing:
Exonic or multiexonic deletions (60–65%), duplication (5–10%), or missense mutations that generate stop codons may be found. Genetic testing is helpful in most affected cases.

Differential diagnosis

- Becker's muscular dystrophy
- Congenital myopathies
- Inflammatory myopathies
- Spinal muscular atrophies (SMA).

Therapy

- Prednisone therapy may prolong the ability to walk by a few years, and reduce falling. The doses are usually 0.75 mg/kg/day as a starting dose and then changing to a weekly dose of 5 to 10 mg/kg, or Oxandrolone 0.1 mg/kg/day.
- Non-surgical treatment of contractures consists of night splints and daytime passive stretch.
- Surgical treatment of contractures consists of early contracture release, Achilles tenotomy, posterior tibial tendon transfer followed by early ambulation.
- Scoliosis – back bracing. Spinal fusion may be required where there is respiratory compromise: according to Hart and McDonald, fusion should be used before the curvature is greater than 30° and vital capacity is less than 35% of predicted.

- Patients with cardiomyopathy and pulmonary hypertension may be helped by angiotensin converting enzyme inhibitors and supplemental oxygen. Digoxin may be used in selected patients. Carriers should also be checked for cardiac defects.
- Respiratory compromise may require portable positive pressure ventilation.
- Prophylactic antibiotics should be used for dental and surgical procedures in patients with mitral valve prolapse.
- In the future, adeno-associated viruses show the greatest promise of transfer of normal DNA to affected muscles. Myoblast, DNA, and stem cell transfer are potential therapies.

Prognosis

Patients usually survive to their mid-twenties.

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Becker muscular dystrophy (BMD)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
+++	++	–	+	+++

Distribution

BMD affects proximal greater than distal muscles. Worse in the quadriceps and hamstrings.

Time course

BMD is a progressive disorder with a slower rate of progression than DMD.

Onset/age

BMD is much milder than DMD with later clinical onset. Patients may have difficulty walking by their late teens.

Clinical syndrome

BMD often causes calf pain, cramps, and myalgias. Weakness is present in approximately 20% of affected patients. Patients may have no symptoms. In general the severity and onset age correlate with muscle dystrophin levels. As with DMD, affected subjects may have calf muscle hypertrophy and contractures in the lower extremities. Patients with BMD often have a severe cardiomyopathy as part of the muscle weakness syndrome, or may have an isolated dilated cardiomyopathy. In general the average IQ of affected children is reduced compared to the general population and may be a major presenting symptom in BMD. Some patients may present with an atypical neuromuscular disorder mimicking SMA, a focal myopathy, or a limb girdle muscular dystrophy.

Pathogenesis

Most are exonic or multiexonic (70–80%), although duplications can occur in 10%, and missense mutations in < 10%. Although dystrophoglycan is reduced in BMD, the molecular abnormality is unknown although it is likely similar to DMD. In some affected subjects there is a deficiency of mitochondrial enzymes and downregulation of several mitochondrial genes.

Diagnosis

Laboratory:
Serum CK is high in 30% of subjects.

Electrophysiology:
Nerve conduction studies are usually normal. If the EMG is abnormal it shows increased insertional activity only in affected muscles. Short duration polyphasic motor unit action potentials, mixed with normal and long duration units are seen in the affected muscles.

Imaging:
Focal enlargement, edema and fatty tissue replacement is observed on T2 and T1 weighted images with gadolinium in more severely affected patients.

Muscle biopsy:
There may be variation in muscle fiber size, an increase in endomysial connective tissue, increased myopathic grouping, and evidence of degeneration and regeneration of muscle fibers. There is also evidence of reduced dystrophin staining.

Genetic testing:
Exonic or multiexonic deletions (60–65%), duplication (5–10%), or missense mutations that generate stop codons may be observed. Genetic testing is helpful in most affected cases.

Differential diagnosis

- Congenital myopathies
- SMA
- Limb girdle dystrophy
- Focal myopathies.

Therapy

- Prednisone therapy may help in more severely affected subjects.
- Treatment of contractures, cardiac, and pulmonary disease follows the outlines for DMD.
- Many subjects have mild symptoms and do not require therapy.

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Myotonic dystrophy (DM)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
+++	+++	+	–	++

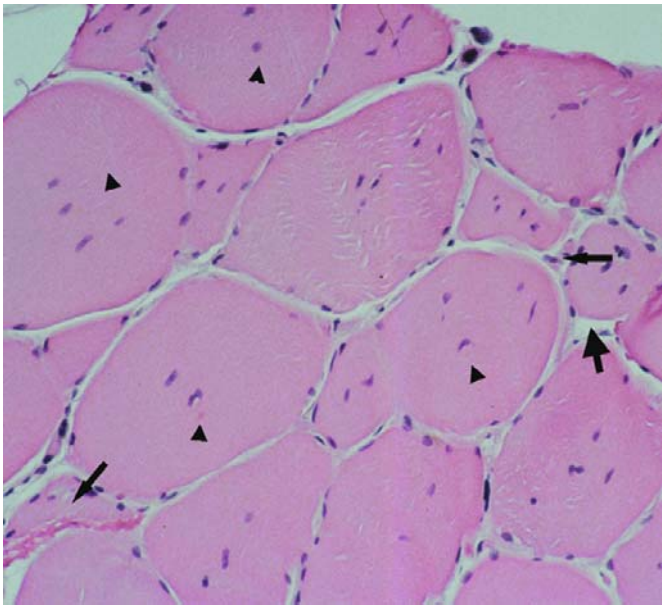

Fig. 13. Myotonic dystrophy. The muscle biopsy shows atrophied fibers (small arrows), mixed with hypertrophied fibers (arrow head), and a slight increase in endomysial connective tissue (large arrow)

Distribution/anatomy

DM affects both distal and proximal muscles, as well as many other organ systems.

Time course

Slowly progressive disorder.

Onset/age

Variable age of onset.

Clinical syndrome

DM affects approximately 1:7400 live births, although it is much rarer in sub-Saharan regions, suggesting that the mutation developed post-migration from Africa. DM1 affects many organ systems. There is considerable phenotypic variation within families. Both proximal and distal muscles are usually affected, and weakness usually follows years of myotonia. Facial muscle weakness with prominent mouth puckering, weak eye closure, and external ocular muscle weakness is common. Usually, symptomatic weakness begins in the hands and at the ankles, with hand strength and progressive foot-drop. Myotonia may be demonstrated in the thenar eminence, or tongue. Frequently affected organs

include skeletal muscle, the cardiac conduction system, brain, smooth muscle, and lens. Sinus bradycardia is common, although heart block, and cardiac arrhythmias can be present. Dilated cardiomyopathy is unusual.

Cerebral signs and symptoms may be prominent in later years. In addition to cognitive impairment, patients may have a severe personality disorder. Later in the course of the disease, hypersomnolence may become apparent. Cataracts are common in typical DM, but are less common in epidemiological studies where genetic testing is used. Another frequent problem is insulin insensitivity. Blood sugar levels are elevated and there is persistent hyperinsulinemia.

Where the expansion is small (< 100 CTG repeats), the phenotype is often very mild with cararacts as the sole manifestation, and muscle symptoms not appearing until the sixth decade.

In DM2 (proximal myotonic myopathy or PROMM) symptoms are often milder than DM1 and include proximal > distal weakness, myotonia, and white matter hyperintensity on the brain MRI.

Pathogenesis

DM1 is an autosomal dominant disease due to variable triplet repeat (CTG) mutation on chromosome 19. This region codes for myotonin protein kinase (DMPK gene). In patients with DM the mutation varies from 50 to several thousand repeats. Abnormalities in DMPK only partially explain the clinical abnormalities seen in DM. DMPK localizes to the motor endplate where it may regulate calcium homeostasis. In DMPK knockout mice there is a 40% reduction in muscle force generation. Other genes affected in DM1 are SIX5 and DMWD. Reduced levels of SIX5 are associated with cataracts in mice. The role of DMWD in DM1 is unknown. Unlike DM1, DM2 is related to an expansion of the CCTG repeat in intron 1 of the ZNF9 gene. DM shows evidence of anticipation. The repeat usually becomes larger in subsequent generations, although exceptions to this rule occur.

Diagnosis

Laboratory:
Serum CK is often normal.

Electrophysiology:
Nerve conduction studies are usually normal. If the EMG is abnormal it shows a minimal increase in insertional activity in affected muscles. There is often evidence of myotonic discharges especially in distal muscles. The myotonic discharges may be increased by cooling the muscle.

Muscle biopsy:
The muscle biopsy in both DM1 and DM2 is similar and shows type 1 fiber atrophy, central nuclei, atrophied fibers mixed with hypertrophied fibers, and a slight increase in endomysial connective tissue (Fig. 13). Ringbinden, characterized by peripheral myofilaments wrapped perpendicularly around the center of a fiber may be seen but are not pathognomonic of DM. Electron microscopy shows sarcoplasmic masses and dilation of the terminal cisternae of the sarcoplasmic reticulum.

Genetic testing:
Genetic evaluation has supplanted other tests in the diagnosis of DM. DNA testing using PCR or Southern blotting is available to measure the size of the unstable CTG repeat in blood or tissue DNA. Each test should be interpreted

with care: a small myotonic dystrophy repeat may be missed by Southern blotting techniques, while a larger repeat may be missed by PCR methods. Diagnostic (prenatal) tests include: 1) amniocentesis – this may not accurately represent CTG repeats in fetal blood 2) measuring CTG triplet repeats in mother and fetus.

Differential diagnosis

The clinical manifestions of DM are very variable, and thus the disorder may remain undiagnosed when a family history is not available. This is especially true when cardiac arrhythmia or hypomotility of the bowel is the presenting complaint and where there is no overt muscle weakness or myotonia. Other conditions to be considered are:

- Myotonia congenita
- Cold induced myotonia (paramyotonia)

Therapy

There is no specific therapy for DM. However the following are useful in management of these associated disorders:

- Monitor the EKG for cardiac disease. Gradual widening of the PR interval to greater than 0.22 msec provides a warning for impending heart block, and invasive electrophysiological testing for elective pacemaker placement should be considered.
- Hypersomnolence may occur later in life and may make employment difficult. Medication that may improve the somnolence are methylphenidate, caffeine, and imipramine.
- Cognitive impairment and personality disorders require a combined approach with medication and psychological support.
- The following medications may worsen the patient's symptoms: amitriptyline, digoxin, procainamide, propranolol, quinine, and sedatives.
- Where there are at least 300 repeats in the villous sample and 600 repeats in mother, or where there is polyhydramnnios, the pregnancy should be treated as high risk with appropriate monitoring and if necessary early induction with or without a caesarian section.

Prognosis

DM shows variable progression, even in members of the same family. Earlier onset usually implies a rapid and severe disorder. Although survival to the fifth decade is common, survival beyond 65 years is rare. Late in the course of the disease, hypersomnolence becomes more problematic. The most frequent causes of death are pneumonia and cardiac arrhythmias.

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Limb girdle muscular dystrophy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
++	++	+	–	++

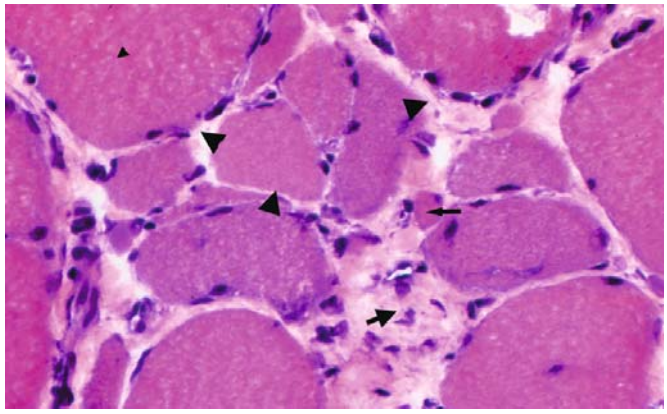

Fig. 14. Limb girdle dystrophy. There is an increase in connective tissue (large arrow), the presence of nesting muscle fibers (arrow heads), muscle atrophy (small arrow), and a hypertrophied fiber (small arrow head)

Distribution

In approximately 50% of subjects with LGMD, weakness begins in the pelvic girdle musculature (the Leyden and Möbius type), then spreads to the pectoral musculature, and in 50% (the Erb type) starts first with the pectoral girdle musculature.

Time course

Generally most causes of LGMD are slowly progressive.

Onset/age

Age of onset is variable depending on the specific cause of the LGMD. The autosomal recessive forms are more severe and start early in life, whereas the autosomal dominant forms are milder and start later. The weakness is progressive, and eventually all muscles in the body are affected.

Clinical syndrome

LGMD is a very heterogenous disorder, where the clinical presentation depends on the gene defect. It occurs approximately equally in both sexes. There is a characteristic clinical appearance: drooped shoulders, scapular winging, and "Popeye" arms (due to wasted arm muscles and spared deltoids). In the pelvic form of LGMD, sacrospinals, quadriceps, hamstrings, and hip muscles are especially involved, causing excessive lumbar lordosis and waddling gait. Facial muscles are uninvolved in LGMD until the patient is severely disabled from limb weakness. Pseudo-hypertrophy of calf muscles is unusual. Muscle tendon reflexes are preserved in the early stages, but are lost as the disease progresses. As the disease progresses, there may be respiratory failure associated with axial weakness and scoliosis.

Understanding the specific genetic mutations in this heterogeneous condition is helpful in separating out the individual pathogenetic and clinical disorders. Specific types are characterized below:

Autosomal dominant:
1A: Myotilin; 5q31
1B: Lamin A/C; 1q21
1C: Caveolin-3; 3p25
1D: 7q
Bethlem myopathy: Collagen VI

Autosomal recessive:
2A: Calpain-3; 15q15
2B: Dysferlin; 2p12
2C: gamma-sarcoglycan; 13q12
2D: alpha-sarcoglycan; 17q21
2E: beta-sarcoglycan; 4q12
2F: delta-sarcoglycan; 5q33
2G: Telethonin; 17q11–12
2H: TRIM32; 9q31–q33
2I: FKRP; 19q13.3

- Chromosome 1q21-linked LGMD (Lamin A/C deficiency): Proximal weakness with cardiac involvement.
- Chromosome 2p12 (Dysferlin) – linked LGMD: Weakness of the pelvic girdle musculature is common, and resembles chromosome 15q LGMD. In rare cases distal muscles are affected, but cardiac and respiratory muscles are spared.
- Chromosome 3p25-linked LGMD (Rippling muscle disease – caveolin-3): This autosomal dominant transmitted disorder likely results from single amino acid mutations of caveolin-3. Patient present early in childhood with a progressive aproximal muscle weakness, calf hypertrophy, cramping muscle pains, and a peculiar muscle rippling phenomenon.
- Chromosome 4q12-linked LGMD (beta-sarcoglycan): This autosomal recessive form of LGMD has been described in Amish families. The clinical features resemble those of calpain3-associated LGMD.
- Chromosome 5q31-linked LGMD (myotilin): This is an autosomal dominant form of LGMD, with age of onset ranging from 18–35 years. Characteristic clinical features include pelvic and pectoral girdle muscle involvement, weakness of neck flexor and facial muscles, dysarthria, tight heel cords, absent ankle jerks, and loss of ambulation at 40–50 years.
- Chromosome 5q33-linked LGMD (delta-Sarcoglycan): This is autosomal recessive.
- Chromosome 6q2-linked LGMD (laminin α2/merosin): This autosomal recessive disorder presents with a clinical picture ranging from a severely hypotonic infant where laminin α2 is completely absent to less severe forms of LDMD with partial deficiency. Cognition is normal, but there is evidence of severe white matter changes on the MRI. A demyelinating neuropathy may be present, but is difficult to distinguish clinically from the severe myopathy.

- Chromosome 13q12 LGMD (gamma-sarcoglycan): This autosomal recessive LGMD starts between 3–12 years and is characterized by pelvic weakness, inability to walk by 20–30 years, calf hypertrophy and cardiac involvement.
- Chromosome 15q15-linked LGMD (Calpain3): There is considerable variation in the severity of this disease initially described among Amish families and families from La Reunion. Onset is usually before age 10 years, with a wide range of time before loss of ambulation and death. Shoulder and pelvic girdle muscles are affected, facial muscles are spared, calf muscle hypertrophy is common, and the degree of clinical heterogeneity makes it difficult to distinguish from other forms of LGMD.
- Chromosome 17q11-12-linked LGMD (telethonin deficiency): This autosomal recessive LGMD starts ages 2–15 years and results in difficulty in the patient walking on their heels, proximal weakness of the arms and distal and proximal weakness of the legs. Facial and extraocular muscles are spared. There may be cardiac involvement and muscle hypertophy.
- Chromosome 17q21-linked LGMD (α-sarcoglycan, primary adhalinopathy): In this autosomal recessive form of LGMD, the dystrophin-associated glycoprotein adhalin is absent in muscle fibers. Adhalin is primarily expressed in skeletal muscle, but may also be found in heart muscle. The clinical severity of myopathy in patients with adhalin mutations varies considerably, and is most severe in patients homozygous for null mutations, who lack skeletal muscle adhalin expression. Missense mutations cause relatively milder phenotypes and variable residual adhalin expression. The clinical picture is very similar to other forms of LGMD. In addition, clinically indistinguishable secondary adhalin deficiency and LGMD may be associated with loss of γ-sarcoglycan, coding to chromosome 13q12.
- Chromosome 21q-linked LGMD (Bethlem myopathy – collagen V1 gene mutation): This autosomal dominant LGMD begins in infancy. It is associated with flexion contractures of the ankles, elbows and fingers, and affects both sexes equally. The progression is very slow, and most patients remain ambulatory until late in life.
- ITGA linked LGMD (α7 integrin deficiency): This is a severe form of LGMD with onset in infancy and associated with torticollis.

Pathogenesis

LGMD is a heterogenous disorder with a wide range of molecular defects. LGMD1A is associated with a a missense mutation of the myotilin gene on chromosome 5q. It is not clear why these patients develop LGMD, since it is difficult to demonstrate a reduction, or accumulation of myotilin. LGMD1B is due primarily to missense mutations of the gene for lamin A and C which play a critical role in the structure of the nuclear membrane and are involved in DNA replication, chromatin organization, regulation of the nuclear pore, and growth of the nucleus. LGMD1C is likely due to a dominant negative effect since transgenic mice expressing the P104L mutant caveolin protein develop LGMD whereas knockout animals do not. Caveolin-3 is part of caveolae membranes and is likely critical in controlling lipid and protein interaction in the caveolae membrane, and possible controlling T-tubule organization. Although collagen VI is ubiqitously expressed in the body, for unknown reasons only skeletal muscle and tendon are affected in patients with Bethlem myopa-

thy. LGMD2B substitutions or deletions of the dysferlin gene (DYSF) results in non-specific myopathic changes in skeletal muscle. The phenotypical variation suggests that additional factors to mutations in the DYSF gene account for the defect. LGMD2C-2F constitute the sarcoglycanopathies. Loss of sarcoglycan results in structural weakness of the muscle cytoskeleton resulting in a clinical picture similar to Becker's muscular dystrophy. The pathological mechanisms are complex but likely involve several mechanisms including impaired mitochondrial function with energy depletion, loss of calcium homeostasis, necrosis of affected fibers, and loss of fiber regeneration. LGMD2G is due to a mutation of the gene coding for telethonin found in the myofibrillar Z-discs. It likely plays a role in control of sarcomere assembly and disassembly.

Diagnosis

Laboratory:
Serum CK is usually elevated especially in the autosomal recessive forms of LGMD.

Electrophysiology:
Nerve conduction studies are usually normal. The principal findings on needle EMG are short duration, low-amplitude motor unit potentials, increased polyphasic potentials, and early recruitment. Increased insertional activity is seen in more rapidly progressive autosomal recessive LGMD. Progressive muscle fibrosis may also result in decreased insertional activity.

Muscle biopsy:
The muscle biopsy is nonspecific and depends on the particular type of LGMD. In general there are a wide range of degenerative changes include fiber splitting, ring-fibers, and lobulated fibers. Individual muscle fibers showing hyalinization, vacuolation, and necrosis. Other changes include an increase in connective tissue with nesting of muscle fibers, and muscle atrophy (Fig. 14). Regenerating fibers with prominent nucleoli and basophilic sarcoplasm are often seen. Rarely, mononuclear cellular infiltrates are seen near necrotic muscle fibers. On electron microscopy, focal myofibrillar degeneration and distortion of the Z-disks are common, but are not specific for LGMD.

Genetic testing:
This may define the specific type of LGMD, although genetic testing is problematic for several reasons. These include the heterogeneity of the disorder, many potential causes of the syndrome have not been fully elucidated, and even when the gene abnormality is known genetic testing may currently not be available.

Differential diagnosis

- FSHMD
- DM1 or DM2
- DMD or BMD
- Congenital myopathies

Therapy

No specific therapy is known for LGMD at this time. Future therapies will have to target the specific molecular defect.

- Treatment of contractures, cardiac, and pulmonary disease follows the outlines for DMD

– Genetic counseling is complex in LGMD due to the heterogeneity of the disease. It can be difficult to convince family members that the risk of having a severely affected child may be equally as high in those subjects with mild or severe disease.

Prognosis

LGMD is a progressive disorder, although the rate of progression depends on the type. Autosomal recessive LGMD usually progresses rapidly,with inability to walk in late childhood and death in early adulthood. In contrast, autosomal dominant LGMD even of childhood onset is usually only very slowly progressive. Respiratory involvement may occur later in the disease depending on the specific type of LGMD. This may result in pneumonia and early death. Myocardial changes may also occur in LGMD, depending on the type, although they are usually less severe than in the dystrophinopathies. Affected patients may develop a cardiac arrhythmia or sometimes congestive cardiac failure.

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Oculopharyngeal muscular dystrophy (OPMD)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
+++	++	+	+	+++

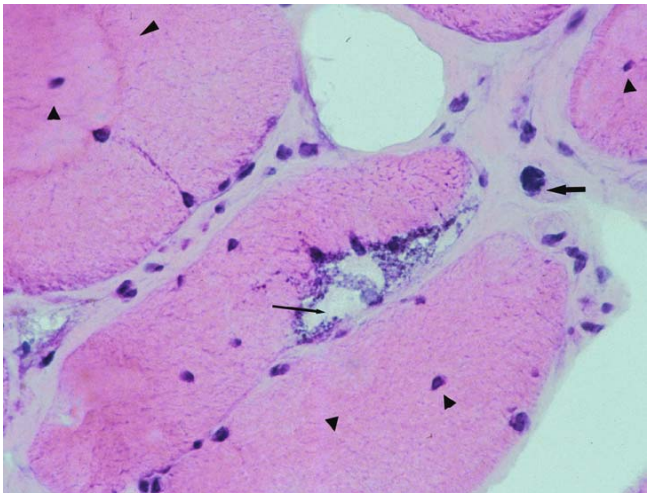

Fig. 15. OPMD with a prominent rimmed vacuole (small arrow), and a mixture of atrophied (large arrow) and hypertrophied fibers with central nuclei (arrow heads). Note prominent fiber splitting (upper left)

Distribution

In general OPMD effects the eyelids causing ptosis, the pharyngeal muscles, extraocular muscles, and to a lesser extent proximal limb muscles.

Time course

The condition is very slowly progressive in most cases.

Onset/age

OPMD most often presents in the fourth to sixth decade most frequently with ptosis.

Clinical syndrome

Autosomal dominant OPMD is more common in certain population groups: French Quebecois 1:1000, Bukhara Jews 1:600. The rarer autosomal recessive form is estimated to be much more rare. Patients hypercontract the frontalis muscle and retroflex the head so they have a characteristic looking up posture. Patients often have incomplete extraocular muscle paralysis and a superior field defect that disappears when the eyelids are elevated. Dysphagia and tongue weakness are other early symptoms and may result in repeated episodes of aspiration and may lead to aspiration pneumonia. Laryngeal weakness may result in dysphonia. Weakness in the limbs is usually mild, although it may vary, and usually affects proximal muscles with distal muscles later becoming weak in more severe cases. In rare autosomal recessive homozygotes there may be

disability due to proximal leg weakness. Mild neck weakness also occurs but seldom results in significant disability. In certain variants of the disease (Japanese variant) there may be evidence of cardiac conduction block.

Pathogenesis

The OPMD locus maps to chromosome 14q11.1. The dominant form is a genetically homogenous condition caused by short $(GCG)_{8–13}$ expansions of a $(GCG)_6$ stretch in the first exon of the PABPN1 gene. The PABPN1 is a mainly nuclear protein involved in the polyadenylation of all messenger RNAs. PABPN1 acts as a nuclear to cytosolic shuttle for the mRNA, and is released from the mRNA after translation. In its mutated form, PABPN1 is an inefficient transporter and results in cell death.

Diagnosis

Laboratory:
Serum CK is normal or mildly elevated.

Electrophysiology:
Nerve conduction studies are usually normal. The principal findings on needle EMG are short duration, low-amplitude motor unit potentials, increased polyphasic potentials, and early recruitment. Increased insertional activity may be seen. Progressive muscle fibrosis may result in decreased insertional activity.

Muscle biopsy:
In OPMD there is evidence of variation in fiber diameter, and the presence of atrophic angulated, hypertrophic, or segmented muscle fibers (Fig. 15). Rimmed cytoplasmic vacuoles and internuclear inclusions (15–18 nm in diameter) are characteristically seen. Filaments in nuclei are often tubular, and form tangles and palisades. These contain mutant PABPN1 protein, ubiquitin, proteasome components, and poly(A)-RNA. Rimmed vacuoles are seen in all biopsies, but are not numerous. These markers are more common in homozygotes. The cricopharyngeal muscle is characteristically affected.

Genetic testing:
Genetic testing for a short GCG repeat expansion in the poly (A) binding protein nuclear 1 (PABPN1) gene can be detected in both the autosomal dominant and recessive forms of OPMD.

Differential diagnosis

- Centronuclear or myotubular myopathy
- Mitochondrial myopathies
- Oculopharyngodistal myopathy – this is an autosomal dominant myopathy, more common in Japanese and French families. The onset is variable, ranging from 6–40 years. Oculopharyngeal involvement is similar to OPMD, however limb involvement starts distally in the anterior tibialis muscles and spreads proximally.
- Inclusion body myopathy with joint contractures and ophthalmoplegia.

Therapy

- Pharyngoesophageal sphincter abnormalities may benefit from cricopharyngeal myotomy.
- Lower esophageal involvement may respond to metoclopramide.
- Eyelid crutches may be used for ptosis to improve vision. Surgical correction of the ptosis is appropriate if orbicularis oculi strength is sufficient to allow closure of the eyelids after surgery.

Prognosis

Depends on the degree of pharyngeal and esophageal involvement and thus the risk of aspiration.

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Fascioscapulohumeral muscular dystrophy (FSHMD)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
+++	++	+	–	++

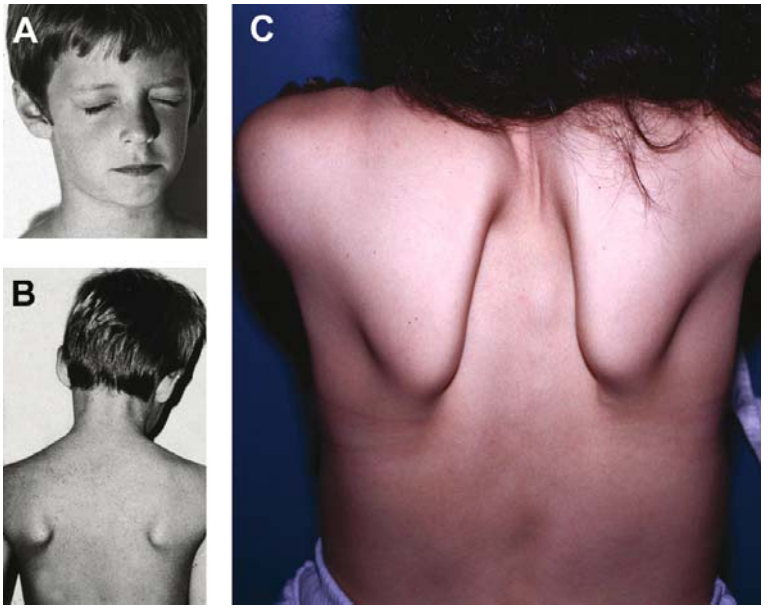

Fig. 16. Patient with FSHMD. **A** There is bilateral ptosis and facial weakness. **B** and **C** Prominent scapular winging in patients with FSH

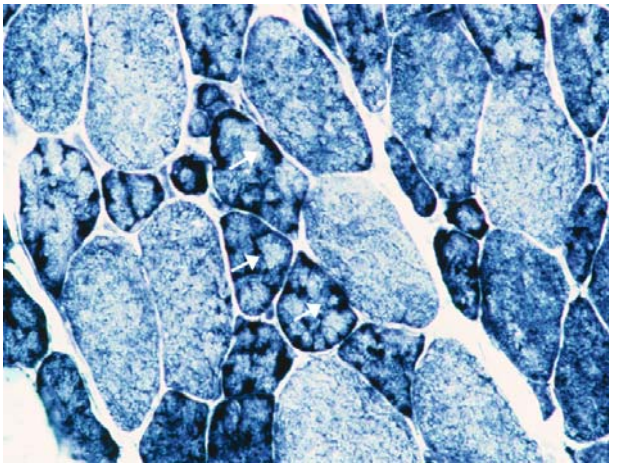

Fig. 17. FSHMD showing lobulated type 1 fibers (white arrows) that are smaller than the type 2 fibers (succinic dehydrogenase)

Distribution

FSHMD affects the face, scapula and proximal shoulder girdle and the lower extremities in a peroneal distribution.

Time course

The disorder progresses slowly and is compatible with a normal life span even in those who are symptomatic.

Onset/age

FSHMD often becomes symptomatic in late childhood or adolescence.

Clinical syndrome

In FSHMD, protruding scapulae (winging) (Fig. 16) may be noted by the parents of the child. There may be winging of the scapulae with the arms dependent, on arm abduction, or with arms straight against the wall. The pectoral muscles are often poorly developed and there is frank pectus excavatum so that the chest seems to be caved-in. Due to the scapula disorder, the arms cannot be raised to shoulder level even though strength in the supraspinati, infraspinati, or deltoids may be normal. This may result in difficulty lifting objects, however the hands maintain function for many years. In the legs there is distal muscle weakness resulting in a scapuloperoneal syndrome. Other symptoms include difficulty with whistling, closing the eyelids, and weakness of the abdominal muscles with a positive Beevor's sign. The reflexes may be either preserved or absent if muscle weakness is severe. About 10% of adults lose the ability to walk and are in wheelchairs, although in general most adult patients retain mobility. In addition to the musculature, FSHMD may be associated with hearing loss and retinopathy. Cardiomyopathy and severe limb contractures are not seen in FSHMD, and symptomatic arrhythmia is exceptional. Approximately 10–30% of all familial cases are asymptomatic.

Childhood onset FSHMD may resemble Möbius syndrome, and may be associated with severe limb weakness. Sporadic cases are more likely to have onset in childhood or infancy and have a more severe course. Hearing impairment and retinopathy are more common in childhood-onset FSHMD.

With DNA diagnosis, it is apparent that the presentation of FSHMD may be atypical with a facial-sparing scapuloperoneal myopathy, distal myopathy, asymmetric arm weakness, or limb girdle muscular dystrophy.

Pathogenesis

FSHMD is autosomal dominant. Most sporadic cases are linked to new mutations at 4q35, although 10% of families do not map to this gene, indicating locus heterogeneity. The biological basis of FSHMD is not known. Tandem repeats in telomere region 4q35 control expression of neighboring genes that may cause the biological defect in FSHMD. Candidate neighboring genes include: TUBB4q which is a probable pseudogene related to the beta-tubulin gene family; FRG-1 and FRG-2, that may be involved in RNA processing; and DUX4 that may act as a toxic gene.

Diagnosis

Laboratory:
Serum CK may be normal or mildly elevated.

Electrophysiology:
Nerve conductions studies are usually normal. In clinically affected subjects, EMG shows an increase in insertional activity in affected muscles, along with small duration, polyphasic motor unit potentials. Some motor units may appear

larger than normal, probably accounting for electrodiagnostic confusion between FSHMD and SMA in the past.

Muscle biopsy:
The muscle biopsy shows lobulated type 1 fibers (Fig. 17), with isolated angular and necrotic fibers. Moderate endomysial connective tissue proliferation may be observed. There may be variation throughout the biopsy with one area showing severe changes while another is hardly affected. Histologic abnormalities may include clusters of inflammatory cells that are seen frequently enough to be consistent with the diagnosis. Muscle biopsy is not needed if linkage to 4q35 is demonstrated. In doubtful cases, biopsy can exclude other causes of a scapuloperoneal syndrome.

Genetic testing:
In familial cases, inheritance is always autosomal dominant. Penetrance is almost complete and more than 95% are clinically symptomatic by age 20. However some cases are asymptomatic up to the eighth decade, thus a family history may be difficult to establish. There is evidence of anticipation (onset at an earlier age in successive generations) in some families; this seems dependent on a deletion rather than expansion of DNA. Recently clinical testing using pulsed field gel electrophoresis, allows us to detect deletion rearrangements associated with FSHD.

Differential diagnosis

- Spinal muscular atrophy – prior to the availability of genetic testing, some cases of FSHMD were misdiagnosed as SMA.
- Polymyositis – in FSHMD for unknown reasons, collections of inflammatory cells may be found in the muscle biopsy, although these patients do not response to steroid immunosuppression.
- Limb-girdle muscular dystrophies.
- Mitochondrial myopathy – occasionally there may be a facial, scapuloperoneal distribution in patients with mitochondrial myopathy. A muscle biopsy should be performed in at least 1 patient in any family with a facioscapulohumeral muscular dystrophy syndrome that does not link to 4q35.
- Emery-Dreifuss muscular dystrophy (emerin defect). This condition is a clinically and genetically heterogenous disorder defined by certain distinctive clinical features: cardiac arrhythmia often requiring a pacemaker, limb and spine contractures, lack of facial weakness, and X-linked or autosomal dominant inheritance. It may appear in successive generations suggesting an autosomal dominant inheritance, although none of these clinical features are seen in FSHMD.
- Dawidenkow's syndrome of scapuloperoneal neuropathy.

Therapy

Many patients require only physical and occupational therapy. Specific approaches to therapy are outlined below:

- Scapula and upper arm instability – with appropriate physical therapy, patients maintain function for many years. Where there is severe limitation of arm functions, the scapulae may be wired to the chest to give better purchase for shoulder girdle muscles.
- Foot drop – may be helped by ankle-foot orthoses.

– In a clinical trial of albuterol treatment there was an increase in muscle mass in some patients, but overall there was no significant change in strength. Individual patients may report improved function.

Prognosis

FSHMD is usually slowly progressive and survival is normal. In general, over 50% of patients continue working in occupations of their choice. Less than 20% will need a wheelchair, there are no cardiac risk factors, medical complications are few, and most women have normal pregnancies.

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Distal myopathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
+	+++	–	–	+++

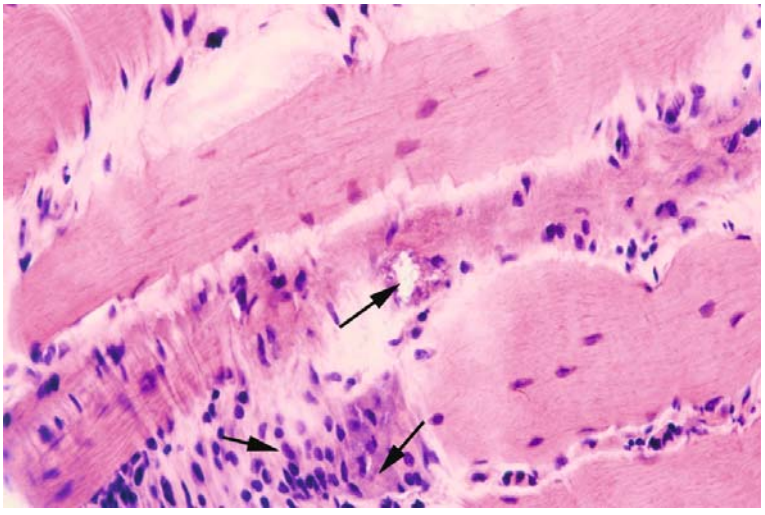

Fig. 18. Uncharacterized distal myopathy showing a rimmed vacuole (small arrow), degenerating fiber (arrow head) and minimal inflammation (large arrow)

Distribution

Characteristically affects distal leg or arm muscles.

Time course

Slowly progressive and usually limited to distal muscles.

Onset/age

May present in childhood, but typically is seen in early adulthood to middle age.

Clinical syndrome

The distal myopathies represent a genetically heterogenous group of disorders with certain shared clinical features. The classical syndromes described below may represent variants of hereditary inclusion body myopathies (HIBM). The main clinical types are:

– Welander (type 1) distal myopathy (WDM). This autosomal dominant myopathy presents most usually in middle age. In most patients the disorder starts in the arms with weakness of the hands, finger extensors, and in particular the thumb and index fingers. The long extensors of the hands and feet are the most-affected muscles. Flexor muscles may be involved at a later stage of the disease. Weakness is progressive and remains limited usually to distal muscles, with proximal muscles affected in only 15% of patients. Reflexes are usually normal, although ankle reflexes may be lost. Many patients

complain of a cold sensation in the peripheral parts of their extremities. Cold sensation may be decreased distally.
- Markesbery (type 2) distal myopathy (MDM). Like WDM, MDM is a progressive autosomal myopathy with onset usually in middle age (range 40–80 years). Tibial muscles are usually affected early, with foot drop developing only in advanced stages. MDM is usually milder than WMD, the hands are usually spared and patients remain able to walk even in late life. Many patients remain asymptomatic.
- Nonaka distal myopathy (NDM). This autosomal recessive myopathy presents in early adulthood and progresses to significant weakness of anterior tibial and then posterior compartment muscles within 10–15 years. Cardiomyopathy and conduction block may occur in some patients.
- Miyoshi distal myopathy (MIDM). This autosomal recessive myopathy begins in early adulthood with progressive weakness and atrophy of the posterior gastrocnemius muscles. Other leg and hand muscles may be affected but proximal weakness is uncommon. Reflexes and sensation are usually normal.
- Gowers-Laing distal myopathy (GLDM). This is an autosomal dominant myopathy seen in patients aged 4–25 years. Weakness begins in the neck flexors and anterior leg muscles, followed by finger extensor weakness, and ending with severe shoulder girdle weakness.
- Distal desmin body myofibrillar myopathy (DBM) are clinically similar to other distal myopathies, but cardiomyopathy and conduction defects are common.

Pathogenesis

WDN is linked to chromosome 2p13. MDM is linked to 2q31 and may affect the gene for titin, a striated muscle protein that appears to play an important role in sarcomere assembly. Other chromosome linkages include GLDM: 14q11, MIDM: 2p12, NDM: 9p12, and DBDM: 2q35. MIDM may be an allelic variant of LGMD2B, and both show an abnormality in the large and complex DYSF gene coding for the novel mammalian protein dysferlin. Dysferlin shows some sequence homology to fer-1 and therefore may play a role in muscle membrane fusion or trafficking.

Diagnosis

Laboratory:
Variable, serum CK is usually normal or mildly elevated except in MIDM where it may be > 100 times normal.

Electrophysiology:
Nerve conductions studies are usually normal except in WDM where sensory fibers may be affected. In clinically affected subjects, EMG shows an increase in insertional activity in distal muscles, along with short duration motor unit action potentials typical of myopathy. Complex repetitive discharges are common in DBM.

Imaging:
MRI studies help in diagnosis by showing the distribution of the atrophy and fatty changes in the muscle.

Muscle biopsy:
WDM shows variation in fiber size, fiber splitting, and rimmed vacuoles (Fig. 18) may be present along with filamentous inclusions (15 to 18 nm).

Characteristically there is loss of Aδ fibers on the sural nerve biopsy. In MDM, a dystrophic pattern is seen with rimmed vacuoles in 30%. Evidence of apoptosis may be observed in some muscle fibers. Rimmed vacuoles are also very frequent in NDM, but are seldom seen in MIDM. Immunostaining for desmin should be performed on muscle biopsies because DBM mimics other distal myopathies and is associated with an increased risk of cardiomyopathy.

Genetic testing:
Genetic testing is not currently clinically available for most of these disorders.

Differential diagnosis

- HMSN (Charcot-Marie Tooth disease)
- SMA
- FSHMD
- IBM
- LGMD (with distal limb involvement)
- Nemalin myopathy

Therapy

There is no medical treatment for any of the distal myopathies, although more severely affected patients may benefit from orthotics. Cardiac complications in DBM and NDM may require use of a pacemaker.

Prognosis

WDM and MBDM are slowly progressive and do not affect life expectancy. In contrast, MIDM progresses more rapidly and affected patients may be nonambulatory within 10 years from the onset of symptoms. DBM has a rapid progression and affects respiratory, bulbar, and proximal muscles. The disorder may be associated with cardiac arrythmias.

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Congenital myopathies

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
+	++	+	+	+++

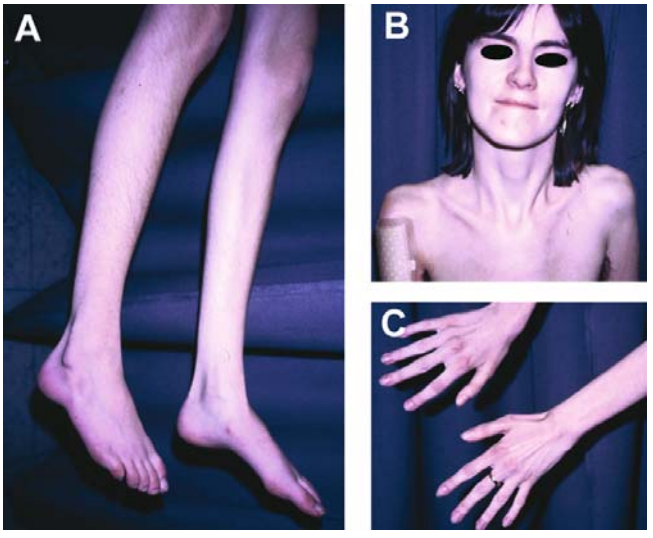

Fig. 19. Nemaline myopathy. **A** Distal leg atrophy in a patient with nemaline myopathy. **B** Atrophy of the proximal arm muscles, neck muscles, and weakness of the facial muscles. **C** Bilateral hand wasting

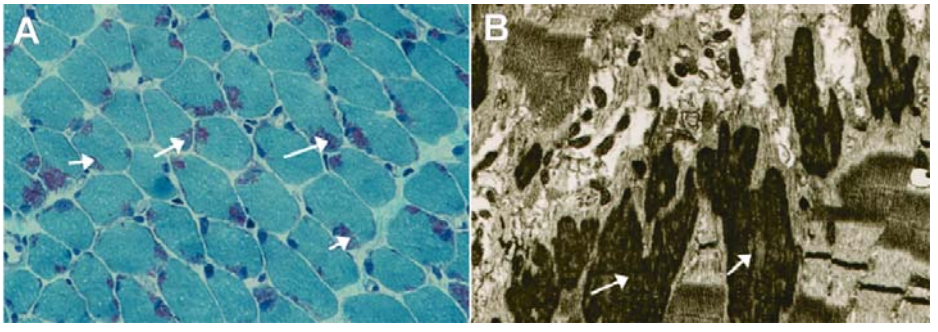

Fig. 20. Nemaline myopathy. **A** Large nemalin rod inclusions (arrows) on Trichrome stain. **B** Electron microscopy-nemalin rod inclusion (arrows)

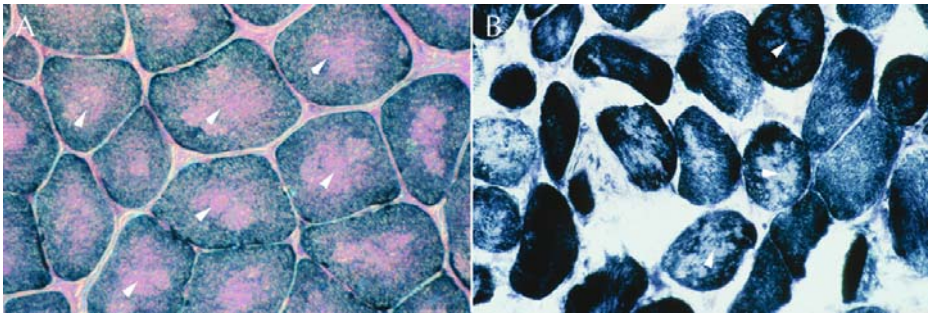

Fig. 21. Central Core Disease. **A** Central cores with trichrome and eosin staining (arrows). **B** Multicore disease – multiple cores (arrows) on NADH-trichrome stain

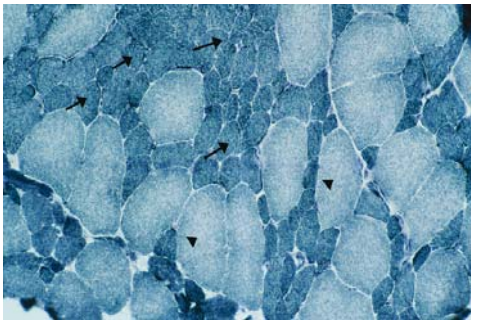

Fig. 22. Congenital fiber disproportion showing numerous smaller type 1 fibers (arrows), and normal fibers (arrow heads)

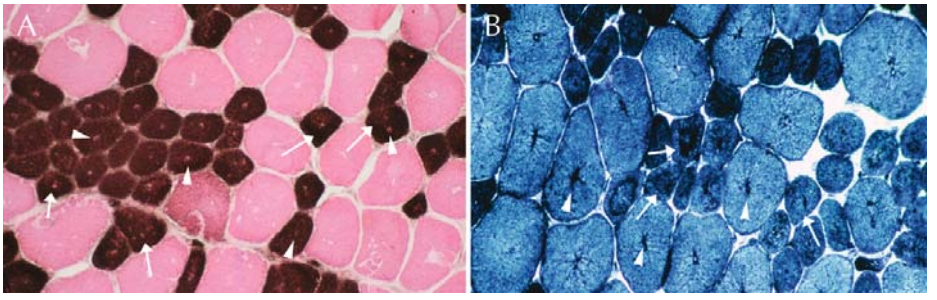

Fig. 23. Centronuclear Myopathy. **A** Adult onset subject with red stained central nuclei (arrows) seen in small type 1 fibers (arrow head). **B** NADH tetrazolium reductase showing small type 1 fibers (arrows), and central nuclei with mitochondria arranged like spokes in a wheel (arrow heads)

Distribution/anatomy

Central core disease (CCD) – generalized or limited to upper or lower limbs. In multi or minicore disease (MCD), nemalin myopathy (NM), and centronuclear myopathy (CNM) all muscle types including the face may be affected. Congenital fiber type disproportion (CFD) may affect any muscle mass, subjects often have a thin face and body. In Fingerprint body myopathy (FPM) proximal muscles are more severely affected than distal. Limb and trunk muscles may also be affected. In Bethlem myopathy (BM) proximal muscles, and extensors more than flexors are affected.

Time course

Variable. In CCD progression is slow, whereas patients with MCD may have a benign disorder with static muscle weakness or with some improvement over time. In MCD spinal rigidity becomes a significant feature restricting head mobility. In NM the progression of the disease is variable depending on the type. In CNM, the progression is more severe in the infantile form, and milder in later onset forms. Childhood and adult onset CFD develops insidiously, whereas neonatal disease progresses more rapidly. In CFD, FPM, and BM the myopathy is non-progressive and may even improve clinically as the child grows. Severely involved infants with CFD may die from respiratory failure.

Onset/age

In CCD 20% of patients present between 0 and 5 years, 30% between 6 and 20 years, 30% between 21 and 40 years, 15% over 40 years. MCD usually presents in the first year of life, however, approximately 10% of cases present in adulthood. CFD and CNM may present at any age. FPM usually begins in childhood. BM may start in childhood to the second decade.

Clinical syndrome

Consists of a variety of syndromes including 1) Central core disease 2) Multi or minicore disease 3) Nemalin myopathy (Fig. 19) 4) Centronuclear myopathy 5) Congenital fiber type disproportion 6) Fingerprint body myopathy 7) Bethlem myopathy

- CCD. Presents with slowly progressive muscle weakness. There is generalized weakness in 40% of patients, or the disease may be limited to the upper or lower limbs. Rarely the face is involved, and strength may be normal in 15% of cases. Muscle atrophy occurs in 50% and reflexes are decreased in 45% of subjects. Other associations are kyphoscoliosis or lordosis, foot deformities, congenital hip dislocations, contractures, hypertrophic cardiomyopathy, and arrythmias. There is also an association between central core disease and ryanodine receptor gene abnormalities associated with malignant hyperthermia (MH).
- MCD. The infant presents with hypotonia and delayed motor development. They may also have evidence of cleft palate, dislocated hip, or arthrogryposis. Patients may have hypotonia in infancy, although the paraspinal muscles may be rigid and the neck relatively immobile. Minimal proximal and distal weakness may be observed in several muscles. The facial muscles are not involved. The deep tendon reflexes are reduced. Despite hypotonia, patients may have a rigid spine and kyphoscoliosis that may progress in late childhood. The disease may be misdiagnosed as SMA. Approximately 20% of patients have ophthalmoplegia.
- NM. There are several types including congenital forms that vary in severity. The disorder can be characterized as follows: 1) severe congenital 2) intermediate congenital 3) typical congenital 4) juvenile 5) other. The infantile form is rapidly fatal. Infants present with severe hypotonia and facial diplegia, and may develop failure to thrive secondary to inability to suck and respiratory complications. Affected subjects are extremely hypotonic with depressed deep tendon reflexes and proximal weakness. The degree of weakness is variable. Bulbar muscles may be affected resulting in hypernasal speech. Ophthalmoplegia may occur. Patients are thin due to reduced muscle bulk and facial weakness results in loss of facial expression. Weakness of intercostal and diaphragm muscles may causes respiratory impairment. The adult form may only present with weakness in the seventh decade. The course of nemaline myopathy may be static or progressive. Most patients have progressive weakness, although occasionally weakness improves over time.
- CNM. In the infantile form, often referred to as myotubular myopathy, affected subjects may have a large head, with a narrow face, and long digits. Subjects often develop severe hypotonia, weakness of proximal and distal muscles, ophthalmoplegia and ptosis. They may also develop severe hypotonia, proximal and distal muscle weakness, respiratory insufficiency, ophthalmoplegia and ptosis. Subjects may become respirator dependent. Older patients with CNM develop weakness of proximal and distal muscles coupled with kyphoscoliosis, pes equinovarus, leg cramps, ophthalmoplegia, facial, and scapular weakness.
- CFD. There is prominant facial weakness with ptosis, variable external ophthalmoplegia, and pharyngeal muscles weakness. The tongue is thin but no fasciculations are seen. Patients are often very thin with reduced muscle mass. Tendon reflexes are often reduced. Congenital contractures, scoliosis, and foot deformities are present in a minority. Cardiomyopathy is rare in CFD.
- FPM. There is symmetric weakness of proximal greater than distal muscles, and limb and trunk. Cranial nerves are usually spared. Patients occasionally have intellectual impairment.

– BM. Congenital flexion contractures of the ankles, elbows, interphalangeal joints of the fingers are typical, although the neck and back are usually not involved. Many patients also have hypotonia and torticollis.

Pathogenesis

– CCD. There is an autosomal dominant abnormality of the ryanodine receptor localized to chromosome 19q13.1. At least 22 mutations have been described in CCD.
– MCD. Most patients have a sporadic disease. Minicores are small lesions of sarcomere disruption with Z band streaming and dissolution of myofilaments.
– NM. Five gene loci have been identified: slow alpha-tropomyosin (TPM3 on chromosome 1q) for autosomal dominant or autosomal recessive NM, nebulin (NEB on 2q) for autosomal recessive NM, alpha-actin (ACTA1 on chromosome 1q) with both recessive and dominant mutations, troponin T1 (TNNT1 on chromosome 19q) causing autosomal recessive NM, and beta tropomyosin (TPM2 on chromosome 9p) in several autosomal dominant cases.
– CFD. Most cases are sporadic, with some families having an autosomal dominant or recessive inheritance.
– CNM. The gene responsible for most cases is unknown. In some cases there appears to be an autosomal dominant inheritance, in others autosomal recessive. Some patients may have a mutation of the MYF6 gene mutation (Ala112Ser) on chromosome 12q21. The severe infantile form of CNM, X-linked myotubular myopathy, may be due to any one of over 100 mutations of the gene MTM1 on Xq28 coding for myotubularin.
– FPM. Unknown, may be sporadic or autosomal recessive.
– BM. Autosomal dominant disorder characterized by missense or splice-site mutation of one of the 3 collagen VI genes (α1, α2, α3 – COL6A1-3). COL6A1 and 2 are localized on chromosome 21q22.3 and COL6A3 on 2q37. At least 6 mutations have been described. Collagen VI is important in stabilizing the myofiber basal lamina.

Diagnosis

Laboratory:
The serum CK may be normal, but is usually high in patients with MH. The *in vitro* contracture test may be useful for MH-sensitivity: 97% to 99%, specificity: 78% to 94%. Muscle enzymes are usually normal in MCD, CNM, NM, CFD, FPM, and BM but may be mildly elevated up to 3 times normal range.

Electrophysiology:
In the congenital myopathies, nerve conduction studies are usually normal. In clinically affected subjects, EMG may be normal or there may be an increase in insertional activity in affected muscles, along with short-duration motor unit action potentials typical of myopathy.

Genetic testing:
In CCD there are a variety of mutations in the ryanodine receptor gene so genetic testing may be negative. However, in families where the gene abnormality has been identified, molecular genetic analysis can supersede all of the more traditional diagnostic methods. Similarly genetic testing may be of use in

other types of congenital myopathy, although these tests are not readily available from commercial laboratories at this time.

Muscle biopsy:

1) CCD. There is variation in muscle fiber size and presence of "cores" (Fig. 21), in muscle with reduced or absent oxidative enzyme activity. The cores run along the long axis of the muscles and sometimes the whole length of the muscle fiber. There may be an increase in the RYR 1 protein in the core.
2) MCD. Light microscopy may show normal muscle fiber architecture or slight variation in muscle fiber size. Numerous unstructured cores are observed and there is an abundance of central nuclei.
3) NM. Diagnosis depends on the finding of nemaline rods in the muscle biopsy (Fig. 20).
4) CFD. There is a predominance of small myofibers, usually type 1 (Fig. 22), with the remaining hypertrophic fibers being type 2, particularly 2b. The reverse pattern is not congenital muscle fiber-type disproportion. No necrosis is observed, however many fibers have central nuclei.
5) CNM. The muscle biopsy shows the presence of central nuclei, central pallor of the fibers on ATPase (Fig. 23). Type 1 fibers are predominant and small in many affected patients. In myotubular myopathy the central nuclei are large and resemble fetal myotubes.
6) FPM. Ovoid inclusions are seen and observed on EM to show arrays of parallel osmiophilic lamellae resembling fingerprints. Similar fingerprints are seen in DM, OPMD, CCD, and some inflammatory myopathies.
7) BM. There is fiber size variation, increased endomysial connective tissue, and rounded fibers.

Differential diagnosis

- Muscular dystrophies
- Myotonic dystrophies
- Metabolic myopathies
- SMA

Therapy

There is no specific therapy of the congenital myopathies. In CCD, anesthetics associated with MH should be avoided, while in myotubular myopathy muscle relaxants must be used with care to avoid prolonged paralysis. In NM physical therapy helps to prevent contractures. Extra-alimentary feeding may be required to prevent loss of weight. Physical therapy and chest physiotherapy and antibiotics may be required for pulmonary infections in the congenital myopathies. MCD patients with severe scoliosis require ventilatory support.

Prognosis

CCD – slow progression of weakness with a good prognosis. Virtually all affected subjects are at risk of developing malignant hyperthermia and this is increased by certain general anesthetics. Some patients may suffer from cardiac conduction defects. In CNM the prognosis is poor and leads to early death in the first 6 months. In NM, CNM, and CFD prognosis depends on the severity of the initial disorder. Myotubular myopathy is usually fatal in infancy, while BM is usually non-progressive.

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Mitochondrial myopathies

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
+	+	+	–	+++

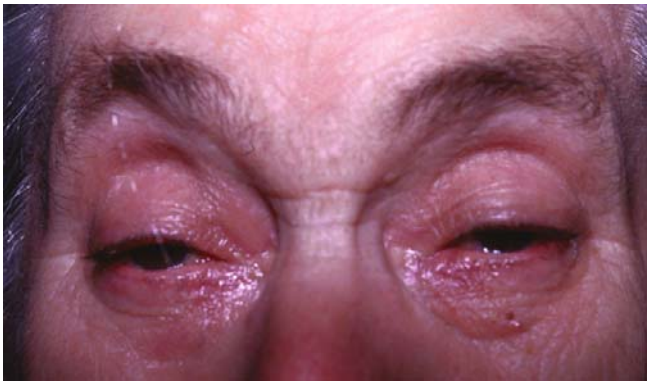

Fig. 24. Mitochondrial myopathies. Bilateral ptosis and ocular divergence due to weakness of the extraocular muscles

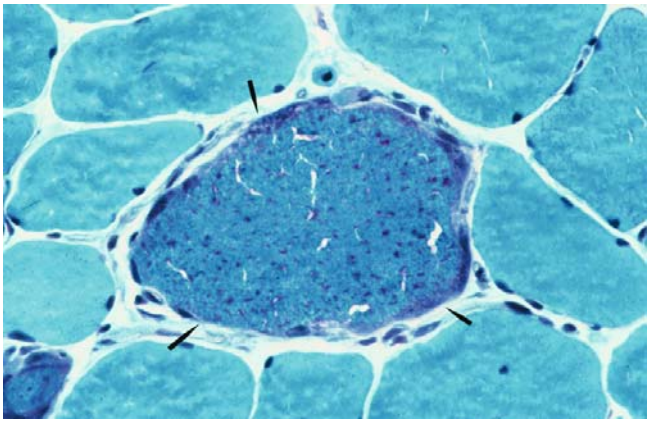

Fig. 25. Mitochondrial Myopathy. Typical ragged red fiber seen with trichrome stain (arrows)

Distribution/anatomy

Mitochondrial (Mt) myopathies may affect any muscle system in the body, although they are usually limited to skeletal muscle systems. Usually proximal muscles are affected, although extraocular, and distal muscles may also be affected.

Time course

In most cases the disorder is slowly progressive. In the adult onset forms of Mt myopathy, the disease is usually very slowly progressive and may be limited to symptoms rather than clinical weakness.

Onset/age

Can occur at any age

Clinical syndrome

Mutations in Mt DNA can be classified into three main categories: 1) large scale rearrangements in Mt-DNA, 2) point mutations in tRNAs or rRNAs, and 3) point mutations in protein coding genes. These type of defects generally take one of two forms, firstly deletions or secondly, duplications. In a duplication defect usually patients present as sporadic cases. Often symptoms are mild or absent. In contrast, deletions cause more severe symptoms. The most common and mildest variant is chronic external ophthalmoplegia syndrome (CPEO) (Fig. 24), in which clinical signs and symptoms develop during adulthood and are limited to the eyelids and eye muscles. A more severe variant is Kearns-Sayre syndrome (KSS) which is characterized by significant multisystem involvement starting usually in the second decade, and which includes cardiac conduction defects, diabetes mellitus, cerebellar ataxia, retinitis pigmentosa, increased CSF protein, and multi-focal neurodegeneration. In general Mt deletions lessen with age, and reflect the increase in the proportion of deleted Mt-DNAs developing with age.

Mutations in Mt-DNA protein coating genes

Mutations in Mt-DNA protein coating genes include: i) ATP6 mutations: NARP and Leigh syndrome. These patients have a complex phenotype that includes neuropathy, myopathy, ataxia, and retinitis pigmentosa. The age of onset is infancy through early childhood. ii) Cytochrome b mutations and Complex I mutations: subjects may have exercise intolerance, myalgia, and may or may not have myoglobinuria. iii) Complex IV (COX) subunit mutations: several different mutations have been described within this group, resulting in disorders ranging from pure myopathies to multi-system disorders.

Mutations of tRNA and rRNA

Mutations of tRNA and rRNA include: i) Mt encephalopathy, lactic acidosis and stroke-like episodes (MELAS): in this disorder there is sudden development of cerebral lesions resembling small vessel strokes, and patients may also have pre-existing migraine headaches and/or seizures. Other associated symptoms include myopathy, ataxia, cardiomyopathy, diabetes mellitus, renal tubular disorders, retinitis pigmentosa, lactic acidosis, and hyperalaninemia. The disease usually starts in the fourth or fifth decade. ii) Myoclonic epilepsy and ragged-red fibers (MERRF): symptoms start in early childhood to adulthood. Clinical findings include myoclonic and/or generalized or focal seizures, cerebellar ataxia, myopathy, corticospinal tract deficits, dementia, optic atrophy, deafness, peripheral neuropathy, cardiomyopathy, multiple symmetric lipomatosis, and renal tubular acidosis. iii) Mitochondrial myopathy and cardiomyopathy: This disorder is associated with a hypertrophic cardiomyopathy, congestive heart failure, bilateral cataracts, insulin-dependent diabetes mellitus, myopathy of very great severity, and Wolf-Parkinson-White syndrome.

Multiple Mt-DNA deletions

Multiple Mt-DNA deletions: i) this disease is characterized clinically by ophthalmoparesis and exercise intolerance with onset usually between ages 18 to 48. ii) myoneurogastrointestinal encephalopathy (MNGIE): this disorder is characterized by a progressive external ophthalmoplegia, dementia, myopathy, peripheral neuropathy, and gastrointestinal abnormalities including diarrhea, malabsorption, and weight loss with normal function of the pancreas. iii) Wolfram syndrome (DIDMOAD): this disorder is characterized by diabetes insipidus, insulin-dependent diabetes mellitus, optic neuropathy, and deafness. iv) Autosomal recessive cardiomyopathy with ophthalmoplegia (ARCO): This

disease begins in childhood and is associated with a severe clinical hypertrophic cardiomyopathy and progressive external ophthalmoplegia, and proximal muscle weakness.

Pathogenesis

In most cases of Mt cytopathy, there is a dysfunction of Mt oxidative phosphorylation. Oxidative phosphorylation is dependent on four enzyme complexes (Complexes I to IV) that comprise the electron transport chain, and are necessary for generation of ATP. Both the nuclear and Mt genomes are necessary for generation of the oxidative phosphorylation complexes. Proteins for the eighty structural subunits are encoded in the Mt-DNA, and the remainder by genomic DNA. Thus the disorders can exhibit any mode of inheritance, including maternal, autosomal dominant, recessive, or sporadic.

Diagnosis

Laboratory:
CK values may be mildly elevated, and there may be elevation in serum lactic acid levels.

Electromyography:
The nerve conduction studies are usually normal unless there is an associated neuropathy. In most cases of mitochondrial myopathy, the needle EMG is normal. In some cases there may be minimal evidence of increased spontaneous activity, coupled with small motor unit action potentials.

Muscle biopsy:
The muscle biopsy may show increased lipid accumulations, glycogen accumulations, or excessive bundles of enlarged Mt. In general most muscle fibers show evidence of typical ragged-red fibers (Fig. 25). Succinate Dehydrogenase (SDH) is the most sensitive and specific stain for Mt proliferation in muscle fibers. Trichrome stains are much less specific and sensitive for Mt proliferation than SDH. Cytochrome Oxidase (COX) stain identifies additional patients with Mt disorders. Scattered COX-fibers with ragged red fibers is consistent with a mtDNA mutation affecting Mt protein synthesis.

Genetic testing:
Genetic testing on serum, or more appropriately on muscle biopsy samples is extremely helpful in differentiating the specific Mt disorder.

Differential diagnosis

- Other metabolic myopathies
- Congenital myopathies
- Muscular dystrophies

Therapy

Currently there are no specific pharmacological treatments for respiratory chain disorders. Aerobic training improves exercise tolerance, cardiovascular function, and muscle metabolism in some patients. Strength training may help in some patients. A variety of mitochondrial enzyme supplements have been tried with variable success. These include coenzyme Q, creatine, carnitine, thiamine, nicotinamide, riboflavin, succinate, and menadione. Until the specific enzyme defects within a particular Mt myopathy are better defined, enzyme supplements will have a limited role in treatment of this disorder.

Prognosis

Depends on the specific Mt disorder. Where there is isolated myopathy, progression is usually slow and prognosis is good.

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Glycogen storage diseases

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
–	++	+	–	+++

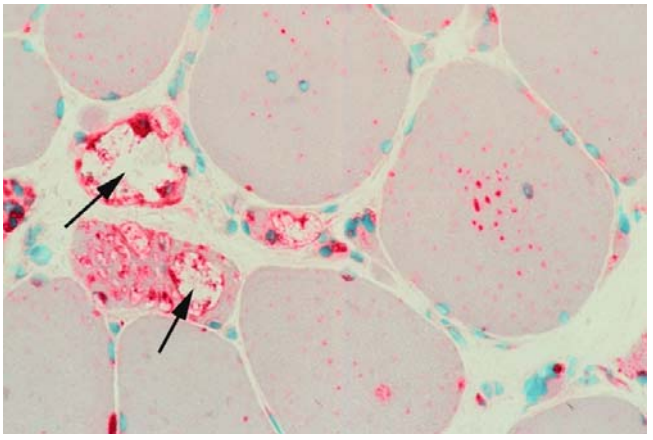

Fig. 26. Acid maltase deficiency. The muscle contains vacuoles filled with glycoprotein (arrow)

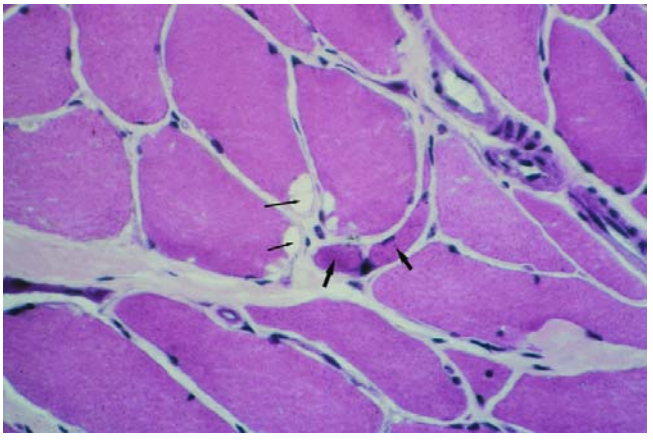

Fig. 27. McArdles disease. Subsarcolemmal vacuoles with stained glycogen (small arrows), and evidence of denervation atrophy (large arrows)

Distribution

There is either no weakness, or proximal muscles are involved.

Time course

Slowly progressive in most cases.

Onset/age

Onset depends on the specific glycogen storage disease (GSD) and can range from infantile to adult onset as outlined below

Clinical syndrome

Type I (GSD I)

Type I (GSD I – von Gierke disease) is characterized by growth retardation, hypoglycemia, hepatomegaly, kidney enlargement, hyperlipidemia, hyperuricemia, and lactic acidemia. Deficiencies in glucose-6-phosphatase (G6Pase) and glucose-6-phosphate transporter (G6PT) cause GSD Ia and GSD Ib. GSD Ib patients also suffer from chronic neutropenia and functional deficiencies of neutrophils and monocytes, resulting in recurrent bacterial infections as well as ulceration of the oral and intestinal mucosa.

Type II (GSD II)

Type II (GSD II – acid maltase deficiency) – 3 types:

- Infantile onset: cardiomegaly and heart failure, liver disease, weakness and hypotonia.
- Childhood onset: proximal symmetrical weakness with enlarged muscles due to glycogen accumulation, with respiratory failure (RF).
- Adult onset: fatigue early in the disease followed by proximal weakness, and eventually RF. RF may the presenting feature in 30% of patients. Other features include basilar cerebral aneurysms, pulmonary hypertension, sleep hypercapnia with headache on waking.

Type III (GSD III)

Type III (GSD III – debrancher deficiency) is more common in men than women (~ 3:1). GSD IIIa (85%) have liver and muscle involvement and GSD IIIb (15%) have only liver involvement. Wasting of leg and intrinsic hand muscles along with slowing of nerve conduction studies and mixed myopathic and neurogenic units may lead to a mistaken diagnosis of motor neuron disease.

- Infantile form associated with deposition in muscle and liver, with hypoglycemia, recurrent seizures, severe cardiomegaly, and hepatomegaly.
- Childhood form associated with hypoglycemia, seizures, growth retardation, weakness, liver dysfunction and hepatomegaly.
- Adult form develops in the 3rd to 6th decade and is slowly progressive. It is associated with distal leg and proximal weakness, fatigue and myalgia, exercise intolerance, respiratory failure, milder cardiomyopathy, hepatic dysfunction. Patients may develop axonal neuropathy due to glycogen storage in endoneurial cells and axons.

GSD IV

GSD IV (brancher deficiency) is associated with myopathy, cardiomyopathy, and liver disease. In addition brain and spinal cord can be affected resulting in progressive involvement of the upper and lower motor neurons, sensory loss, sphincter problems, and dementia. GSD IV can be associated with adult polyglucosan body disease and is seen especially in Ashkenazi Jews.

GSD V

GSD V (McArdle's disease) usually starts in the early teens and is more common in males. It is characterized by exercise intolerance, and severe cramping that may last several hours, myoglobinuria, proximal muscle involvement, and a "second wind" phenomenon in which the patient's symptoms may temporarily resolve. In the infantile form severe weakness and respiratory failure may be seen, and late onset GSD IV may be associated with only mild fatigue.

GSD VII

GSD VII (Tarui's disease) occurs predominantly in males of Ashkenazi Jewish or Italian ancestry. Clinical features are similar to McArdle's although the "second wind" is less common than in McArdle's. High carbohydrate meals exacerbate exercise intolerance, because the patient cannot metabolize glucose and ends up depleting free fatty acids and ketones – the "out of wind" phenomenon.

Myoglobinuria is less frequent than in McArdle's. Occasionally in children there may be a severe myopathy, respiratory failure, cardiomyopathy, arthrogryposis, seizures, and corneal opacification. GSD VII is also associated with accumulation of polyglucosan bodies over time and may result in a further deterioration in strength later in life that resembles IBM.

GSD VIII–XIII

GSD VIII–XIII are characterized by intolerance to intense exercise, cramps and/or myoglobinuria. GSD X occurs almost exclusively in blacks and heterozygotes may also have exercise intolerance.

Pathogenesis

GSD are a group of predominantly autosomal recessive disorders. GSD I is caused by deficiencies in the activity of G6Pase system consisting of two membrane proteins that work in concert to maintain glucose homeostasis, G6PT (11q23) and G6Pase (17q21). G6PT translocates glucose-6-phosphate (G6P) from cytoplasm to the lumen of the endoplasmic reticulum and G6Pase catalyzes the hydrolysis of G6P to produce glucose and phosphate. Deficiencies in G6Pase and G6PT cause GSD Ia and GSD Ib, respectively.

GSD II is an autosomal recessive disorder due to deficiency of l acid α-1,4-glucosidase coded by a gene on chromosome 17q23. GSD III results from nonsense mutations, small deletions or insertions, or splice site changes on chromosome 1p21. There is a deficiency of amylo-1,6-glucosidase (AGL) that catalyzes both a transferase and a hydrolysis reaction. In GSD V several missense, stop, start codon or frameshift mutations of 11q13 have been described. There is a deficiency of muscle phosphorylase resulting in impaired ATP generation from aerobic and anaerobic glycolysis and reduced production of pyruvate. GSD VII is due to a deficiency of 6-Phosphofructokinase (PFK – 1cen-q32). Other listed enzyme deficiencies resulting in defects of glycogen storage include: GSD XII – Aldolase A: 16q22, GSD XIII – β-Enolase: 17pter, GSD XI-Lactate dehydrogenase: 11p15, GSD IX – Phosphoglycerate Kinase: Xq13, X – Phosphoglycerate Mutase: 7p12, and GSD VIII – Phosphorylase β kinase: Xq12.

Diagnosis

Laboratory:
The serum CK is usually very high. Cardiac: in GSD II and III, EKG changes are common. The ischemic forearm test shows an insufficient rise in venous lactate, but is non-specific for the GSD, relies on patient compliance, and may have complications such as myoglobinuria. Other changes include hyperuricemia, hyperbilirubinemia, and a high potassium with exercise. GSD VII is associated with a compensated hemolytic anemia.

Electrophysiology:
Nerve conduction studies are usually normal, however in GSD III there is often evidence of an axonal neuropathy. During contractures, the muscle is electrically silent in GSD. EMG shows an increase in insertional activity in distal muscles, along with short duration motor unit action potentials typical of myopathy. Myotonic discharges may be observed, and in GSD II there may be a mixture of myotonic and complex repetitive discharges observed especially in paraspinal muscles. In GSD VII repetitive nerve stimulation at 20 Hz results in a decrement in the motor response.

Muscle biopsy:
GSD I and II are characterized by prominent PAS positive lysosomal vacuoles with enlargement of muscle fibers (Fig. 26). There is little muscle fiber degeneration. Electron microscopy shows glycogen in cytoplasm with membrane-bound, autophagic vacuoles. In GSD III, V, and VII there are subsarcolemmal and intermyofibrillar vacuoles (Fig. 27). In GSD VII, partial reductions in PFK to 20% of normal may be artifactual due to the lability of the enzyme in incorrectly handled fresh frozen muscle.

Genetic testing:
Genetic testing is not currently clinically available for most of these disorders.

Differential diagnosis

- Other glycogen storage diseases
- Other metabolic myopathies
- Mt myopathies
- Congenital myopathies

Therapy

Hypoglycemia in children needs to be treated with frequent feeding. A high protein diet may improve weakness in adult forms of GSD. In GSD VII patients should avoid high-carbohydrate meals that exacerbate the "out-of-wind" phenomenon, and a ketogenic diet may help. Other potential treatments for GSD V are pyridoxine therapy that improves symptoms in some patients and creatine monohydrate that improves anaerobic but not aerobic exercise capability. Adenoviral-mediated delivery of a myophosphorylase cDNA into myoblasts from patients with McArdle's disease restores myophosphorylase to normal levels, and may prove beneficial as a potential future treatment. Enzyme replacement therapy is also being evaluated in GSD II.

Prognosis

In GSD II (infantile form) death occurs before 1 year of age, in the childhood form before 25 years. In infantile GSD III death occurs before 4 years, childhood and adult forms survive longer. GSD V has a normal life expectancy. In other forms of GSD life expectancy may be normal unless severe myoglobinuria and muscle necrosis occurs.

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Defects of fatty acid metabolism

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
+	+	+++	–	+

Distribution

In most cases of carnitine palmitoyl transferase 2 deficiency (CPT2) there is no weakness. Proximal weakness is seen in carnitine transporter deficiency (CT – primary carnitine deficiency) and very-long chain acyl-CoA dehydrogenase deficiency (VACD).

Time course

CPT2 and MTP may have an acute onset, whereas other forms of MTP, CT and VACD produce more chronic myopathic symptoms.

Onset/age

Onset depends on the specific disease. Most cases of CPT2 start between 6–20 years, CT before 7 years of age, VACD and MTP can occur in infants or adults,

Clinical syndrome

There are several defects of fatty acid metabolism in the muscle including CPT2, CT, very-long chain acyl-CoA dehydrogenase deficiency (VACD), and Mitochondrial trifunctional protein deficiency (MTP).

CPT2

There are at least 3 different phenotypes 1. a myopathic form with juvenile-adult onset 2. an infantile form with hepatic, muscular, and cardiac involvement 3. a lethal neonatal form with developmental abnormalities. Adults patients develop pain, stiffness, and tightness of the muscles, although they do not get muscular cramps or second-wind phenomena. CPT2 is frequently associated with myoglobinuria. Symptoms develop after prolonged fasting, low-carbohydrate high-fat diets, exercise, infection, cold exposure, and general anesthesia. In most patients strength is normal. In general CPT2 deficiency is more common in males (6:1) with females having milder disease.

CT

In children CT is associated with cardiomyopathy and myopathy, and in infants with recurrent acute episodes of hypoglycemic encephalopathy with hypoketonemia.

VACD

There are 3 forms: 1) Isolated skeletal muscle involvement, rhabdomyolysis, and myoglobinuria worse than in CPT2 and triggered by fasting or exercise 2) A severe and often fatal childhood form with hypertrophic cardiomyopathy, recurrent episodes of hypoketotic hypoglycemia. 3) A milder childhood form with recurrent episodes of hypoketotic hypoglycemia.

MTP

The symptoms are variable ranging from a disorder resembling the severe infantile form of VACD to an adult form that resembles CPT2 but with a peripheral sensorimotor neuropathy showing both demyelination and axonal degeneration not described in other disorders of fatty acid metabolism. Other features are retinitis pigmentosa and hypoparathyroidism.

Pathogenesis

- CPT2: CPT2 is associated with skeletal muscle disease and the defect can be demonstrated in all tissues. The CPT2 gene is located on chromosome 1p32 and the disorder is more common in Ashkenazi Jews. There are at least 20 CPT2 gene mutations.
- CT: L-carnitine is essential for the transport of long-chain fatty acids into the Mt for β-oxidation. In primary carnitine deficiency there is increased loss of carnitine into the urine. Secondary carnitine deficiency may be due to Mt disorders, renal failure, muscular dystrophy, chronic myopathy, and liver failure. CT is usually associated with nonsense mutations of the genes encoding OCTN2, a high-affinity sodium-dependent carnitine transporter and SLC22A5, an organic cation transporter.
- VACD: VACD catalyzes most of the palmitoyl-CoA (C_{16}) dehydrogenation in skeletal muscle, liver, and heart and is the rate-limiting enzyme in long-chain fatty acid β-oxidation. VACD is coded by ACADVL on chromosome 17p13, and is associated with at least 60 mutations.
- MTP: MTP is a heterogenous disorder and includes long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency. The following genes have been associated with this disorder: HADHA and HADHB.

Diagnosis

Laboratory:
In CPT2 the CK is normal between episodes of myoglobinuria, and carnitine is usually normal. During epidoses of rhabdomyolysis, CK is high in all the disorders of free fatty acid metabolism. In CT, plasma and total carnitine levels are less than 5% of normal. Diagnosis is confirmed by carnitine uptake studies in cultured skin fibroblasts. In VACD, diagnosis is ultimately based on demonstration of reduced palmitoyl-CoA (C_{16}) dehydrogenation in skeletal muscles or cultured fibroblasts.

Electrophysiology:
Nerve conductions studies are usually normal except in MTP where axonal or demyelinating characteristics are observed. EMG is often normal or shows minimal evidence of myopathy between episodes of myoglobinuria.

Muscle biopsy:
In CPT2 the muscle biopsy is normal with the exception of a decrease in CPT activity. In CT there is increased lipid droplets in type 1 muscle fibers. In VACD the muscle biopsy may appear normal or show a diffuse increase in lipid in type 1 fibers.

Genetic testing:
Genetic testing may be helpful in some of the disorders when available.

Differential diagnosis

- Other disorders of fatty acid metabolism
- GSD II
- Other metabolic myopathies
- Mt myopathies

Therapy

In CPT2 deficiency, patients should receive a high-carbohydrate low-fat diet with frequent and regularly scheduled meals, and should avoid precipitating

factors as described above. Medium-chain triglyceride supplements and avoidance of long-chain fatty acids may be helpful, but L-carnitine has no effect because carnitine levels are normal in this disease. In CT with primary carnitine deficiency, L-carnitine supplementation (100–200 mg/kg per day) will restore plasma and liver carnitine levels. Even though muscle carnitine remains low, muscle strength and other symptoms gradually improve. In VACD patients are treated with a high-carbohydrate, low-fat diet, with or without supplementation with medium-chain triglyceride oil, riboflavin, or L-carnitine. This therapy can stop crises and improving heart and skeletal muscle function. In MTP cod liver oil that is high in docosahexanoic acid may improve the neuropathy.

Prognosis

In later onset CPT2 and treated CT prognosis is usually good. In VACD and MTP prognosis depends on the disorder type.

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Toxic myopathies

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
–	+++	+	+	+++

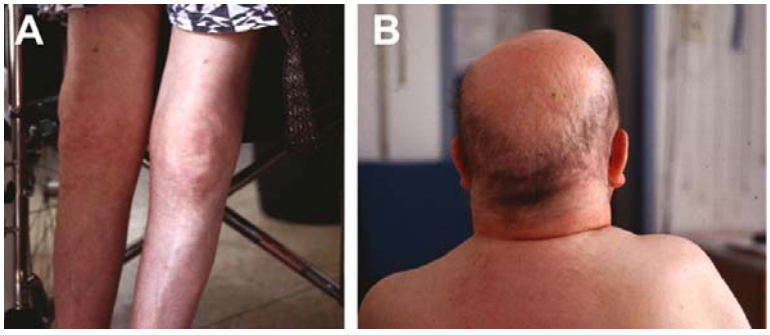

Fig. 28. Steroid-induced myopathy. **A** Proximal leg atrophy in a patient with chronic steroid use. **B** Fat redistribution around the upper torso and neck

Distribution/anatomy

Usually proximal muscles are involved, although in severe necrotizing myopathies with rhabdomyolysis, all muscles may be affected

Time course

The time course is variable, depending on the type of toxic agent

Onset/age

Can occur at any age

Clinical syndrome

There is appearance of neuromuscular symptoms after exposure to a specific medication or toxin. There may be an acute episode, with rhabdomyolysis or the disorder may develop over months. The clinical presentations include a focal myopathy, acute painful or painless weakness, chronic painful or painless weakness, myalgia alone, or CK elevation alone. In severe cases, toxic myopathy may be associated with myoglobinuria, inflammation of the muscle, muscle tenderness and myalgia. In cases of mitochondrial or vacuolar damage, the myalgia is usually painless. Steroids cause type 2 fiber atrophy that is painless (Fig. 28). Necrotic myopathies may be due to acute alcohol exposure, amiodarone, chloroquine, cocaine, emetine, clofibrate, heroin, combined neuromuscular blocking agents and steroids, perhexilline, and statins (HMG CoA reductase inhibitors). Other causes of muscle injury in necrotic myopathies include crush injuries occurring in comatose or motionless patients who are taking drugs for addiction. In cocaine-induced myopathy there may be ischemia or impaired oxidative phosphorylation. In the vacuolar myopathies there is accumulation of autophagic (lysosomal) vacuoles. This type of toxic myopathy is observed with amiodarone, chloroquine, colchicine, and vincris-

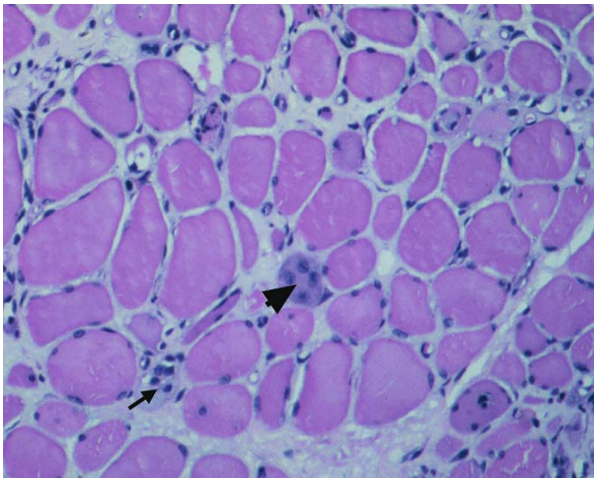

Fig. 29. Necrotizing alcoholic myopathy showing degenerating fibers (arrow), and regenerating fibers (arrow head)

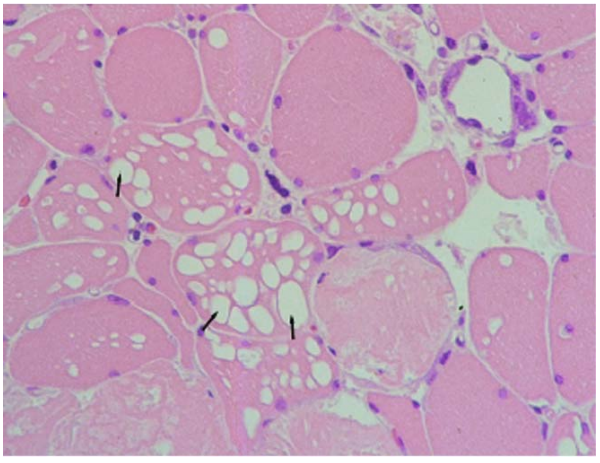

Fig. 30. Colchicine myopathy. Empty vacuoles are observed throughout the muscle, but with no inflammation

tine. The second type of vacuolar myopathy is seen with hypokalemic agents including thiazides, and amphotericin B. Mitochondrial defects are seen with anti-HIV agents that inhibit nucleoside or nucleotide reverse transcriptase and deplete mitochondrial DNA. The resulting accumulation of abnormal mitochondria results in formation of "ragged red fibers". Zidovudine (AZT) is associated with mitochondrial changes, and sometimes with inflammation. Type 2 atrophy is absorbed in steroid myopathy. Chronic alcohol use is also associated with similar changes. Another type of toxic myopathy, is the inflammatory toxic myopathy – these have similar clinical features to dermatomyositis. Typically D-penicillamine is associated with an inflammatory myopathy. A perivascular inflammation may be observed with phenytoin, procainamide, hydralazine, L-dopa, and streptokinase. Eosinophilic myositis and fasciitis associated with L-tryptophan is probably due to an allergic reaction.

Pathogenesis

A range of mechanisms lead to necrosis in toxic myopathies including damage to the muscle membrane, the presumed cause of myopathy observed with statin drugs. Other causes of muscle injury in necrotic myopathies include crush

injuries occurring in comatose or motionless patients, particularly taking drugs of addiction, and ischemia/impaired oxidative phosphorylation – as might be observed in cocaine-induced myopathy.

Diagnosis

Laboratory:
CK levels are variable ranging from normal with steroid myopathies to very high where rhabdomyolysis is observed.

Electrophysiology:
There may be increased insertional activity in inflammatory and vacuolar myopathies. EMG is usually normal in type 2 fiber atrophy. The motor units may range from small short-duration action potentials typical of myopathy, to polyphasic motor unit action potentials similar to those seen in dermatomyositis.

Muscle biopsy:
Various changes may be observed including necrosis (Fig. 29), vacuolar changes (Fig. 30), Mt defects, inflammatory changes.

Differential diagnosis

- PM
- DERM
- IBM
- Muscular dystrophies
- Mt myopathies

Therapy

There is no specific treatment for the toxic myopathies. Early recognition of a potential toxin, and removal of the toxin is essential in limiting the muscle injury.

Prognosis

This is varied depending on the degree of muscle injury. Where the toxic exposure is recognized and the toxin removed, the prognosis is usually good.

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Critical illness myopathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
–	++	+	–	+++

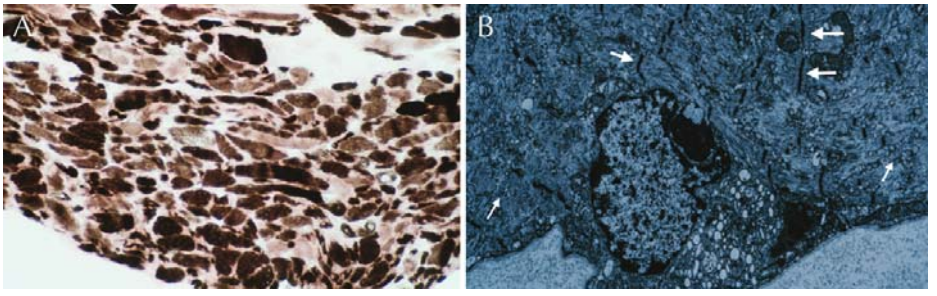

Fig. 31. Critical illness myopathy. **A** There is severe atrophy of both type 1 and 2 fibers. **B** Transmission electron microscopic image showing focal loss of myosin (small arrows), with an increase in scattered Z bands (large arrows)

Distribution/anatomy

Critical illness myopathy may affect the skeletal muscle, but is usually more severe in proximal muscles.

Time course

Time course is variable, but usually develops over days to months.

Onset/age

May develop at any age, but because of the increased risk of prolonged hospital stays or immobility the disorder is more common in older patients.

Clinical syndrome

Classic weakness of limb and sometimes respiratory muscles develops in patients following use of high dose intravenous glucocorticoids as well as neuromuscular blocking agents, aminoglycosides, or other combinations of steroids, neuromuscular blockers and antibiotics. This disorder may develop within days of treatment with high dose methylprednisone for a severe asthmatic attack, or may follow admission to the intensive care unit after surgery requiring a general anesthetic. Critical illness myopathy may also develop in some patients who have become septic or malnourished, and may not be related to use of steroids or neuromuscular blocking agents. Recovery if it occurs usually happens within days to months after removal of the offending drug.

Pathogenesis

In critical illness myopathy there is a severe acute loss of thick myofilaments from the A-band of the myofibers. The thick myofilaments in the A-band disaggregate and form a mass in the O-band. Furthermore, the disaggregated myosin monomers loose their ATPase activity and therefore are unable to generate force within the muscle, resulting in muscle weakness.

Diagnosis

Laboratory:
CK levels may be mildly elevated or normal.

Electrophysiology:
On EMG, there may be a mild increase in insertional activity, however often insertional activity is normal or minimally affected in contrast to what one observes in inflammatory myopathies. The motor unit action potentials may show evidence of polyphasic, short duration or short duration small amplitude potentials. Direct muscle stimulation may show an absent response.
NCV may show the presence of an axonal neuropathy, or focal slowing at sites of compression, if there is an associated critical illness neuropathy.

Muscle biopsy:
Muscle biopsies obtained 24 hours after the onset of symptoms often contain staining in the region of the Z-discs due to reduced A-band staining (Fig. 31). Myosin ATPase activity is markedly reduced in affected muscle fibers. There is evidence of massive loss of myofilaments in some muscle fibers.

Differential diagnosis

- Neuromuscular junction defects
- Inflammatory myopathies
- Muscular dystrophies
- Critical illness neuropathy
- Previously undiagnosed motor neuron disease

Therapy

There is no specific therapy. Any potentially causative medication should be discontinued.

Prognosis

Variable, depending on the severity of the illness. Advanced disease may take several months to recover.

References

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Myopathies associated with endocrine/metabolic disorders and carcinoma

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
–	++	+++	+	+++

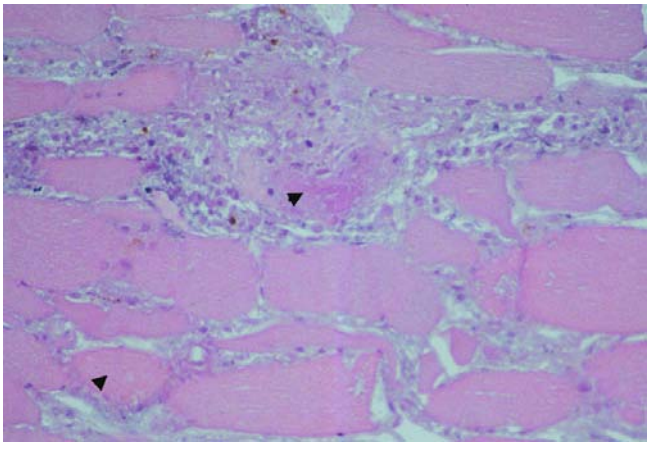

Fig. 32. Muscle from a patient with diabetes mellitus showing myolysis with degenerating fibers (arrow heads)

Distribution/anatomy

This is variable and depends on the specific systemic disorder, however proximal muscles are most usually affected.

Time course

This is variable depending on the specific cause of myopathy. Most of these myopathies progress slowly, although rapid progression of symptoms may be observed with thyrotoxicosis. If treated most endocrine related myopathies are self limiting. Myopathies related to paraneoplastic disorders are usually not treatable.

Onset/age

Any age although most are observed in adults. Paraneoplastic related myopathies are more common in older patients.

Clinical syndrome

Hypothyroidism

This disorder may be associated with a painful myopathy that can simulate polymyalgia or polymyositis. In severely hypothyroid children a syndrome characterized by weakness, slow movements, and striking muscle hypertrophy may be observed. Percussion myotonia and myoedema may be observed in patients with hypothyroidism.

Hyperthyroidism

Thyrotoxicosis is associated with muscle atrophy and weakness. It may also be associated with a progressive extraocular muscle weakness, ptosis, periodic paralysis, myasthenia gravis, spastic paraparesis and bulbar palsy. Subjects may have brisk reflexes and fasciculations similar to amyotrophic lateral sclerosis.

Hypoparathyroidism

Affected patients may have tetany, muscle spasm, and occasionally weakness.

Hyperparathyroidism

Patients may have proximal weakness, muscle atrophy, hyperreflexia, and fasciculations.

Cushing syndrome and corticosteroid atrophy

Occasionally muscle atrophy and weakness may be observed under conditions of hypercortisolemia.

Acromegaly

The muscles may appear enlarged, however this disorder is usually associated with mild proximal upper or lower extremity muscle weakness.

Diabetes

Diabetes is not associated with a generalized myopathy, however muscle necrosis or inflammation may occur in diabetic amyotrophy. In Flier's syndrome, there is muscle pain, cramps, fatigue, acanthosis nigricans and progressing enlargement of the hands and feet, and impaired glucose tolerance. Hypoglycemia may be associated with muscle atrophy as part of a motor neuron type syndrome. It does not produce primary myopathy.

Uremia and myopathy

In chronic renal failure patients may have proximal weakness and in addition myoglobinuria may occur.

Carcinomatous myopathy

This may be seen as part of an inflammatory myopathy, may also be observed in carcinoid syndrome, or may occur due to a metabolic disturbance. Direct invasion of muscle is rare although it may be observed with leukemias and lymphomas.

Pathogenesis

The pathogenesis depends on the specific muscle disorders indicated above.

Diagnosis

Laboratory:
A variety of electrolyte and endocrine changes support the diagnosis as indicated under the specific disease. The CK may be normal or significantly elevated e.g. in diabetic muscle infarction or with hypothyroidism.

Electrophysiology:
The EMG is dependent on the specific disorder, but in general there is evidence of myopathic changes in affected muscles.

Imaging:
Muscle imaging may be of value.

Muscle biopsy:
In both hypo and hyperthyroidism the muscle biopsy is often normal, although there may be evidence of mild fiber atrophy. In hyperparathyroidism and acromegaly there may be mild type 2 fiber atrophy. Evidence of inflammation and muscle infarction may be observed in affected muscle in diabetic amyotrophy. Muscle destruction following rhabdomyolysis may also be seen in this condition (Fig. 32). Inflammatory changes may be observed in carcinomatous myopathy, or as part of a paraneoplastic syndrome.

Differential diagnosis

This is wide and includes the different causes of metabolic and systemic disease associated with myopathy. In addition the inflammatory myopathies e.g. PM, DERM, and IBM may resemble these disorders. Lambert-Eaton myasthenic syndrome (LEMS) may mimic a paraneoplastic myopathy. Type 2 fiber atrophy due to any cause may mimic a metabolic myopathy.

Therapy

The therapy of the underlying systemic disease often leads to improvement of the myopathy.

Prognosis

This is dependent on the specific disorder, but if appropriate therapy is instituted the prognosis is usually good for the endocrine disorders such as hypothyroidism, hyperthyroidism, hyperparathyroidism, acromegaly, and diabetes.

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Myotonia congenita

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
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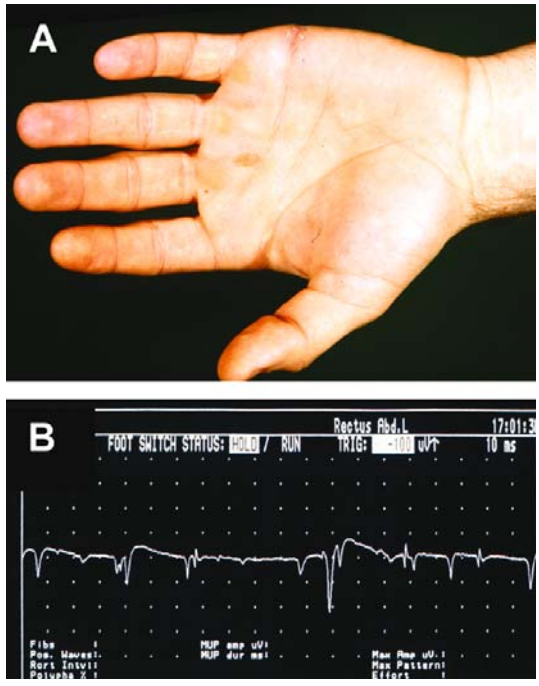

Fig. 33. Myotonia congenita. **A** Muscle myotonia in the hypothenar muscles. **B** Myotonic discharges in the EMG from affected muscle

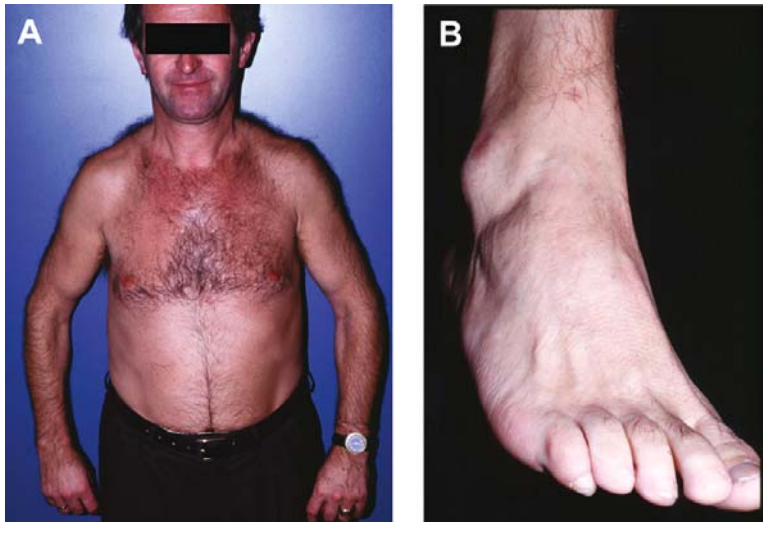

Fig. 34. Thomson's myotonia congenita. **A** Increased muscle bulk in the arms and chest in a patient with Thomson's disease. **B** Hypertrophy of the extensor digitorum brevis muscle

Distribution/anatomy

Variable, may affect both limb and facial muscles.

Time course

Progresses very slowly over a lifetime. Usually strength is spared.

Onset/age

- Myotonia congenita (Thomsen): onset in infancy.
- Myotonia congenita (Becker): onset is usually in early childhood.

Clinical syndrome

Myotonia congenita (Thomsen)

Myotonia is usually mild, approximately 50% may have percussion myotonia. The myotonia (Fig. 33) is associated with fluctuations, and may be worsened by cold, hunger, fatigue and emotional upset. Muscle hypertrophy is seen in many patients (Fig. 34), and occasionally patients may complain of myalgias. Patients may report a "warm-up" phenomenon, in which the myotonia decreases after repeated activity. Muscle strength is usually normal.

Myotonia congenita (Becker)

Patients may also have a "warm-up" phenomenon. The disease is more severe than Thomsen's, and although strength is usually normal in childhood, there is often mild distal weakness in older individuals. Strength often deteriorates after short periods of exercise. Hypertrophy may also be observed in the leg muscles, although it is less common than in Thomsen's disease.

Myotonia levior

Mild myotonia occurring late in life, with less muscle hypertrophy.

Pathogenesis

Thomsen's disease is due to a defect of the muscle chloride channel (CLCN1). Thomsen's disease is an autosomal dominant disorder, with the gene abnormality localized on chromosome 7q35. The mutation interferes with the normal tetramer formation on the chloride channel. Chloride conductance through the channel is eliminated or reduced. Normal chloride conduction is necessary to stabilize the membrane potential. Without chloride conductance there is increased cation conductance after depolarization, and spontaneous triggering of action potentials. In missense mutations of the chloride channel there is a partial defect in normal conductance of chloride. In contrast, with frame shift mutations there is complete loss of chloride conductance. In Becker's disease there is likewise a defect of the muscle chloride channel (CLCN1), with a recessive mode of inheritance linked to chromosome 7q35. A variety of genetic defects have been described including more than 20 missense mutations, and deletions. Depending on the type of mutation there may be low or reduced opening of chloride channels, or there may be chloride efflux but not influx. A final type of congenital myotonia, myotonia levior, is autosomal dominant and again is related to a mutation of the CLCN1 channel.

Diagnosis

Laboratory:
Laboratory tests are generally of limited value. CK is usually normal.

Electrophysiology:
90% of subjects with congenital myotonia will have electrophysiological evidence of myotonia (Fig. 33B). The myotonia is present even in early childhood, and is greater in distal than in proximal muscles. MUAPs are usually normal, and there is no evidence of myopathic discharges on EMG. With repetitive stimulation a decrement may be observed, especially at high stimulation

frequencies in excess of 25 Hz. Cooling does not affect the nerve response. In Becker's disease there may be a "warm-up" effect with less myotonia after maximal contraction, and unlike Thomsen's there may be occasional small, short duration MUAPs.

Genetic testing:
Testing for mutations of the CLCN1 gene may be diagnostically useful.

Muscle biopsy:
Muscle biopsy findings are variable, and are not specific for the diagnosis. Myopathic changes are more likely with Becker's, which is a more severe form of myotonia than Thomsen's disease. In more severe cases there may be increased fiber diameter variation, internalization of nuclei, and vacuolation.

Differential diagnosis

- Paramyotonia
- Hyperkalemic periodic paralysis
- Hypokalemic periodic paralysis
- Mild DM1 or DM2

Therapy

The following medications may help with symptoms, and control of myotonia: quinine (200 to 1200 mg/d), mexiletine (150 to 1000 mg/d), dilantin (300 to 400 mg/d), procainamide (125 to 1000 mg/d), tocainide, carbamazepine, acetazolamide (125 to 1000 mg/d). Procainamide is rarely used because of concerns with bone marrow suppression. Several medications should be avoided in these patients including depolarizing muscle relaxants, and β2 agonists.

Prognosis

The prognosis for Thomson's disease is good, with mild progression over many years. Patients with Becker's myotonic dystrophy may develop more significant weakness later in life.

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Paramyotonia congenita

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
++	+++	–	–	+

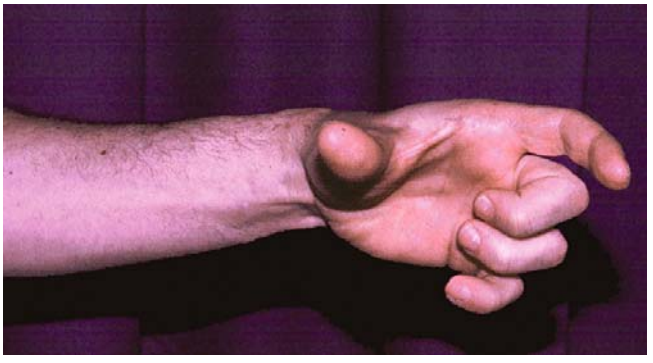

Fig. 35. Myotonia of the hand in a patient with cold induced myotonia (Von Eulenburg's disease). The patient is trying to open his hand

Distribution/anatomy

Many patients who have myotonia have only minimal or no symptoms. In more severely affected subjects myotonia may affect both proximal and distal muscles.

Time course

Many subjects are asymptomatic. In those who develop symptoms the condition either remains stable or only slowly progresses.

Onset/age

The disorder may present at any age, most commonly in late adolescence. Weakness develops in late adolescence, although myotonia may present in infancy.

Clinical syndrome

Patients may develop weakness or stiffness, which may be coupled with myotonia. Myotonia is often worse with cold and exercise and may affect the face, neck and upper extremities (Fig. 35). Episodic weakness may occur after exercise, cold exposure, or may occur spontaneously. The weakness usually lasts for a few minutes but may extend to several days. In some patients weakness may be worse after potassium load, or may be exacerbated by hyperthyroidism. Myotonia is usually paradoxical in that it worsens with exercise, in comparison to that observed in myotonia congenita.

Pathogenesis

Paramyotonia congenita is an autosomal dominant disorder associated with a gain of function mutation of the SCN4A gene on chromosome 17q23. At least eleven missense mutations have been described.

Diagnosis

Laboratory:
Laboratory studies are usually normal.

Electrophysiology:
With cooling of the muscle there is a decrease in the CMAP amplitude and with prolonged cooling it may disappear entirely. The amplitude usually recovers with warming. With cooling, the myotonia on EMG may initially worsen, but with prolonged cooling there is usually depolarization and paralysis, and the mytonia disappears.

Genetic testing:
Testing for mutations of the SCN4A gene.

Muscle biopsy:
Muscle biopsy may be unremarkable with occasional central nuclei with hypertrophic, split, rare atrophic, or regenerating fibers. In some areas there may be focal myofibril degeneration, with lipid deposits, myelin bodies, and subsarcolemmal vacuoles.

Differential diagnosis

- Myotonia congenita
- Myotonia fluctuans
- Myotonia permanens
- Acetazolamide responsive myotonia
- Hyperkalemic periodic paralysis

Therapy

Several medications may be helpful in decreasing the symptoms in paramyotonia. These include mexiletine 150–1000 mg/d, acetazolamide 125–1000 mg/d, dichlorphenamide 50–150 mg/d. Tocainide may help some patients, however there is a concern about myelosuppression.

Prognosis

Prognosis in paramyotonia congenita is usually good.

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Hyperkalemic periodic paralysis

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
+++	++	+++	–	++

Distribution/anatomy

This from of periodic paralysis usually affects proximal muscles and is symmetric. Occasionally distal muscles may be affected, or the disease may occur asymmetrically in excessively exercised muscles.

Time course

Usually progresses slowly over several decades.

Onset/age

Onset is usually in the first decade.

Clinical syndrome

Hyperkalemic periodic paralysis is characterized by flaccid, episodic weakness. The disorder frequently occurs in the early morning before eating, and may also be associated with rest after exercise. Episodes last up to 60 minutes on average, however occasionally the flaccid episodic weakness may last for hours or even days. The weakness is provoked by exercise, potassium loading, pregnancy, ingestion of glucocorticoids, stress, fasting, and ethanol use. The episodes of weakness may be relieved by carbohydrate intake or by mild exercise.

Pathogenesis

Hyperkalemic periodic paralysis is an autosomal dominant disorder of the sodium channel subunit SCN4A localized to chromosome 17q35. In hyperkalemic periodic paralysis there is a gain-of-function of the sodium channel, resulting from one or more of seven missense mutations. There is also uncontrolled repetive firing of action potentials due to a non-inactivating Na+ inward current.

Diagnosis

Laboratory:
Patients often have an elevated serum K+ greater than 4.5 mEq/l and a high urinary potassium. The serum CK is usually normal or mildly elevated.

Electrophysiology:
The CMAP amplitude increases immediately after 5 minutes of sustained exercise, and reduces by 40% or greater during rest following the exercise. In the form with myotonia, the EMG shows trains of positive sharp waves, fibrillation potentials, and myotonic discharges between attacks. The motor unit potentials are usually normal.

Muscle biopsy:
Tubular aggregates may be observed in muscle fibers, along with dilatations of the sarcoplasmic reticulum. Vacuolation may be observed, and usually vacuoles contain amorphous material surrounded by glycogen granules.

Provocative test:
An oral potassium load administered in a fasting patient in the morning after exercise may induce weakness. The study should only be done if renal and cardiac function, and the serum potassium are normal. The patient is given 0.05g/kg KCl in a sugar free liquid over 3 minutes. The patient's electrolytes, EKG and strength are monitored every 20 minutes. Weakness typically occurs in 1 to 2 hours. If the test is negative, a higher dose of KCl up to 0.15 g/kg may be required. An exercise test may also induce hyperkalemic paralysis. The subject works out for 30 minutes, increasing their pulse rate beyond 120 beats per minute. They are then rested and the serum potassium is measured. Normally potassium will rise during exercise and then fall to near pre-exercise levels. In hyperkalemic periodic paralysis there is a second hyperkalemic period with associated paralysis that occurs approximately 15 to 20 minutes after exercise.

Differential diagnosis

- Paramyotonia
- Hypokalemic periodic paralysis
- Acetazolamide responsive myotonia congenita
- Myotonia permanens
- Myotonia fluctuans
- Normokalemic periodic paralysis
- Andersen's syndrome

In Andersen's syndrome there is a potassium sensitive periodic paralysis with cardiac dysrhythmias and dysmorphic features. Acetazolamide-responsive myotonia congenita is an autosomal dominant sodium channel defect in which there is muscle hypertrophy, and "paradoxical" myotonia. The disorder is associated with muscle pain and stiffness, is aggravated by potassium, and improved by acetazolamide. It is not associated with weakness. Myotonia permanens is a sodium channel defect associated with severe continuous myotonia that may interfere with breathing. There is usually marked muscle hypertrophy in this disorder. Myotonia fluctuans is an autosomal dominant defect of the SCN4A subunit of the muscle sodium channel. In this disorder there is mild myotonia that varies in severity. Stiffness develops during rest approximately 30 minutes after exercise and may last for up to 60 minutes. Stiffness is worsened by potassium, or depolarizing agents. The stiffness may interfere with respiration if there is no weakness or cold sensitivity.

Therapy

In hyperkalemic periodic paralysis, many of the attacks are short lived and do not require treatment. During an acute attack, carbohydrate ingestion may improve the weakness. Use of acetazolamide or thiazide diuretics may help prevent further attacks. Mexiletine is of no benefit in hyperkalemic periodic paralysis.

Prognosis

This is variable, with most patients having a fairly good prognosis. One mutation (T704M) is associated with severe myopathy and permanent weakness.

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Hypokalemic periodic paralysis

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
+++	++	+++	–	++

Distribution/anatomy

Hypokalemic periodic paralysis may affect both proximal and distal muscles, although proximal muscles are often more severely affected.

Time course

The disorder gradually worsens over many years.

Onset/age

Onset usually as a teenager.

Clinical syndrome

Hypokalemic periodic paralysis is associated with acute episodes of flaccid weakness. In contrast to hyperkalemic periodic paralysis, the hypokalemic variant is associated with less frequent attacks, although the attacks are often longer and more severe than in the hyperkalemic variant. Hypokalemic periodic paralysis also is associated with a higher rate of degenerative myopathy and disabling weakness in the limbs. It is not associated with myotonia. The disorder is evoked by glucose ingestion, and improved by potassium intake.

Pathogenesis

Hypokalemic periodic paralysis is inherited as an autosomal dominant disorder. The disease may be associated with a defect in several genes. These include a loss of function mutation of the calcium channel α-1 subunit on chromosome 1q42 (CACNA1S), a loss of function mutation of the sodium channel α subunit on chromosome 17q23 (SCN4A), and a loss of function mutation of the KCNE3 gene coding for the potassium channel b subunit (MiRP2) on chromosome 11q13-14. The defects in CACNA1S, SCN4A, and KCNE3 are associated with a variety of missense mutations. The mutations of the CACNA1S gene are the most frequent.

Diagnosis

Laboratory:
Calcium levels are usually low to low normal. CK levels are usually normal, but may be increased during attacks.

Electrophysiology:
CMAP amplitudes are decreased during attacks, and increased immediately after sustained (5 min) maximal contraction between attacks. In most affected subjects, there is then a progressive reduction in the CMAP amplitude during rest 20 to 40 min after the initial increment. An infusion of glucose and insulin may provoke the symptoms, but needs to be used with EKG monitoring. During an attack there is an increase in insertional activity, and an increase in short duration, polyphasic motor unit potentials that disappear as the muscle becomes paralyzed. In most subjects the needle EMG is normal between attacks.

Genetic testing:
Testing for SCN4A, CACNA1S, l KCNE3 mutations may be useful in individual cases.

Muscle biopsy:
Clear central vacuoles are observed, along with tubular aggregates. In addition, there may be myopathic changes including variation in muscle size, split fibers, and internalized nuclei. There is vacuolar dilation of the sarcoplasmic reticulum during attacks.

Differential diagnosis

- Thyrotoxic periodic paralysis
- Hyperkalemic periodic paralysis
- Myotonia fluctuans

Therapy

Potassium supplementation of 40 to 80 mEq 2–3 times per day will often decrease the severity of the attacks. Acetazolamide sustained release tablets (500–2000 mg/d) or dichlorphenamide (50–150 mg/d) may reduce the frequency of the attacks. Use of potassium sparing diuretics (triamterene or spironolactone) in combination with acetazolamide or dichlorphenamide may also reduce the frequency of periodic paralysis.

Prognosis

With appropriate treatment the prognosis is usually good.

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Motor neuron disease

Amyotrophic lateral sclerosis

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
+	+	+	+	

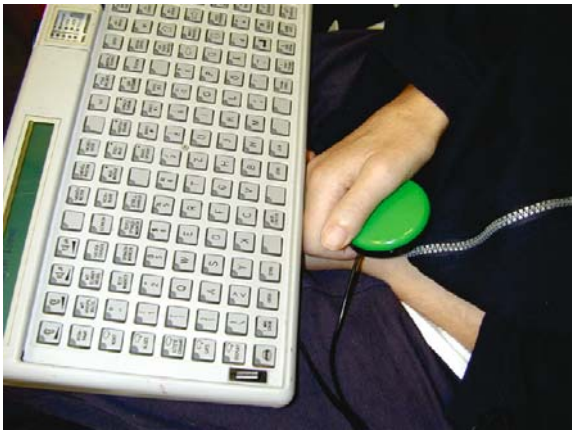

Fig. 1. ALS and communication. Progression of ALS may impose severe communicational problems. Dysarthria and inability to speak can be compensated in some patients with computer devices, such as special keyboards and a mouse

Anatomy

Amyotrophic lateral sclerosis (ALS) causes the loss of both upper and lower motor neurons. On autopsy, there is loss of the pyramidal cells of the motor cortex, with atrophy of the brainstem and spinal cord. The corticospinal tracts are degenerated and gliotic. The ventral nerve roots are atrophied, and there is microscopic evidence of muscle denervation and reinnervation.

Symptoms

ALS usually presents with painless and progressive weakness of a focal distribution that over time spreads to contiguous muscle groups. As the disease progresses, fasciculations cause muscle cramps and the patient becomes spastic. Spontaneous clonus may also occur. Weakness can lead to head drop, and contractures can lead to hand and foot deformaties.

Bulbar symptoms may be the presenting feature of ALS, but more commonly patients present with trunk and extremity weakness. Dysarthria is common and may be spastic or flaccid, or a combination of both. Dysphagia puts patients at a high risk for choking and aspiration. Spontaneous swallowing is absent, leading to drooling (sialorrhea).

Respiratory weakness is rarely the presenting feature of ALS, but becomes common with disease progression. Patients initially experience exertional dyspnea and sigh frequently when at rest. This continues on to dyspnea at rest, sleep apnea, morning headaches, and the inability to sleep supine.

Typically, mentation, extraocular movements, bowel and bladder functions, and sensation are spared in ALS. Ophthalmoplegia (ocular apraxia) has been reported. Dementia is observed in 1–2% of patients. Nearly one third of ALS patients report urgent and obstructive micturition.
Over time, muscles become atrophied and patients complain of fatigue.

Signs

As ALS affects both upper and lower motor neurons, most (80%) of patients show both upper and lower motor neuron signs. There is usually a combination of spasticity, hyperreflexia, and progressive muscle weakness and wasting.
A small percentage of patients will only show lower motor neuron signs and symptoms. On the other hand, there are rare instances where patients only have upper motor neuron disease. There is currently debate as to whether this condition, called **Primary Lateral Sclerosis** (PLS), is a separate entity. The diagnostic procedures and treatments for PLS are currently identical to those for ALS.

Pathogenesis

Most cases of ALS (at least 80%) are sporadic. A smaller number are attributable to autosomal dominant familial ALS (FALS). The cause of sporadic ALS is currently unknown, although proposed etiologies include glutamate neurotoxicity, abnormal accumulation of neurofilaments, altered neurotrophism, and toxicity from oxygen radicals or environmental sources.
The genetic cause of most FALS is unknown, but 20% of FALS cases show a mutation in the protein cytosolic copper-zinc superoxide dismutase (SOD1), found on chromosome 21q. SOD1 detoxifies superoxide anions, which can lead to cell death when they accumulate and oxidize proteins and lipids. FALS, whether caused by SOD1 mutations or not, is indistinguishable clinically from sporadic ALS; thus, there is reason to believe that oxidative damage to neurons is a common mechanism underlying all forms of ALS.

Diagnosis

The El Escorial World Federation of Neurology criteria for the diagnosis of ALS divides the body into four regions: bulbar (face, jaw, tongue, palate, larynx), cervical (neck, arm, hand, diaphragm), thoracic (back, abdomen), and lumbosacral (back, abdomen, leg, and foot). Upper and lower motor signs must be present in the bulbar region and two of the spinal regions, or in all three spinal regions. A patient with signs in two spinal regions is diagnosed with probable ALS. A diagnosis of possible ALS is given in cases where only one region is affected, or if only lower motor neuron signs are present in two regions, or if regions with lower motor neuron signs occur rostrally to regions with upper motor neuron signs.
Genetic testing can be done to determine if a case of FALS is due to an SOD1 mutation.
EMG and nerve conduction studies with repetitive stimulation are used to confirm lower motor neuron degeneration.
Imaging can be used to confirm that anatomy is normal, and exclude other pathology.
Laboratory tests used to exclude other conditions that may resemble ALS include: CBC and routine chemistries, serum VDRL, creatine kinase, thyroid studies, serum protein electrophoresis, serum immunoelectrophoresis, ANA, rheumatoid factor, and sedimentation rate.

Differential diagnosis

Neuroimaging and laboratory tests can be used to rule out the following conditions: syringomyelia, syringobulbia, paraneoplastic motor neuronopathy, polyradiculopathy with myelopathy, post-polio syndrome, multifocal motor neuropathy, motor neuron disease with paraproteinemia, hexoseaminidase-A deficiency, and heavy metal intoxication.

Therapy

Riluzole (2-amino-6-(trifluormethoxy)benzothiazole) is the only targeted treatment available. Riluzole blocks glutamate release, which may slow disease if glutamate toxicity is contributing to motor neuron loss. Riluzole is given 50 mg twice daily and may cause nausea and asthenia, but is generally tolerated well. Symptomatic treatment may be indicated for spasticity, cramps, excessive drooling, and pseudobulbar symptoms. Physical therapy, braces, and ambulatory supports are helpful. As speech becomes difficult, alternative communication devices are needed (Fig. 1). A severely dysphagic patient may choose to have a gastric feeding tube placed. Bilevel positive airway pressure ventilation is helpful for the respiratory symptoms of patients.

Prognosis

Prognosis for ALS is poor and the progression of the disease is generally relentless. The average 5-year survival is 25%. The mean duration of disease from onset of symptoms to death is 27 to 43 months, with median duration of 23–52 months.
Primary lateral sclerosis progresses much more slowly, with a mean duration of 224 months.

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Spinal muscular atrophies

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
+++	+			+

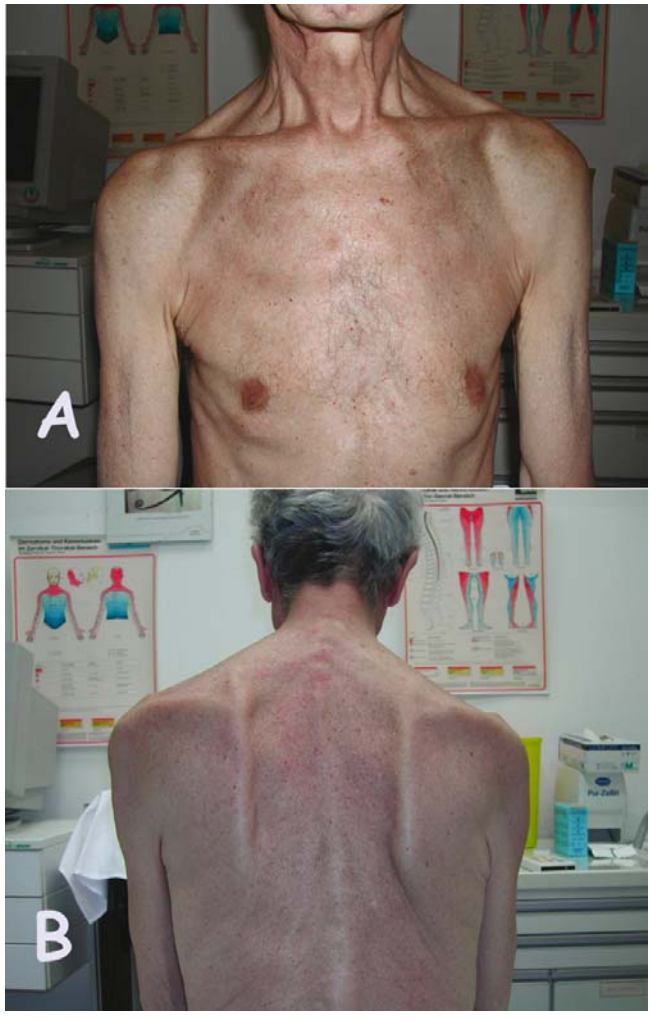

Fig. 2. SMA. Marked generalized muscle atrophy due to slowly progressive disease. Symmetric atrophy of the trapezoid muscles **A**, mild winging **B** of the medial borders of the scapula

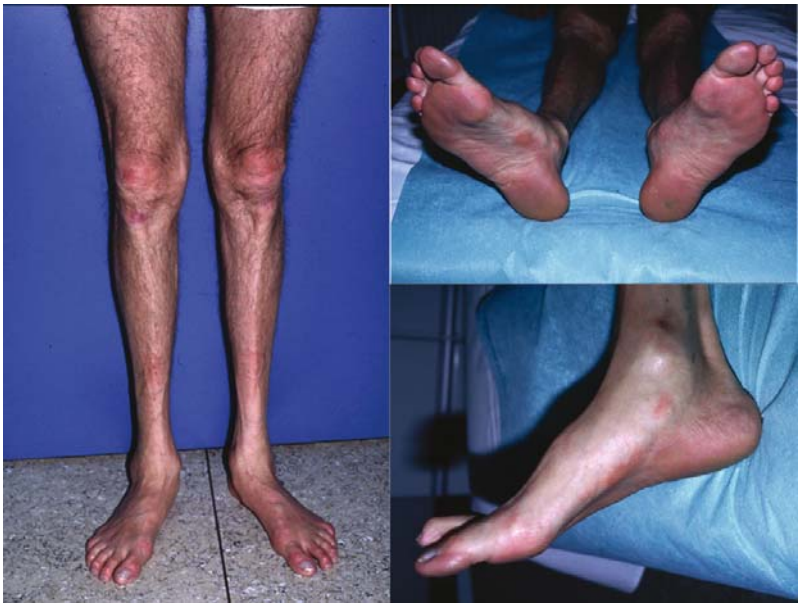

Fig. 3. Spinal atrophy. Distal atrophy of lower legs, foot deformity

Anatomy

The spinal muscular atrophies (SMAs) are hereditary motor neuron diseases that cause the loss of alpha motor neurons in the spinal cord. At autopsy, the spinal cord is atrophied, showing loss of motor neurons and gliosis. The ventral roots are also atrophied. Muscle atrophy is accompanied with signs of denervation and reinnervation.

Symptoms

The onset and severity of symptoms depends upon the type of SMA the patient has.

SMA1

SMA1 (Werdnig-Hoffmann disease) is the most severe form, with symptoms appearing in utero, or up to 3 months post-partum. Infants have severe diffuse weakness that eventually leads to fatal loss of respiration.

SMA2

SMA2 (late infantile SMA) causes weakness that appears between 18–24 months. Although less severe, these children may not be able to stand or walk, and develop scoliosis and respiratory failure.

SMA3

SMA3 (Kugelberg-Welander disease) has the mildest symptoms, and may not present until the teenage years. These patients have proximal, symmetric weakness but can still stand and walk. Deterioration of muscle function is slow and mild.

Signs

Signs of lower motor neuron loss (hypotonia, reduced or absent reflexes, fasciculations atrophy as shown in Figs. 2. and 3) are apparent, depending upon the severity of disease.

Pathogenesis

SMA is caused by mutations in one of two copies of the survival motor neuron (SMN) gene on chromosome 5q13. Loss of exons 7 and 8 in the telomeric copy of the SMN gene leads to SMA1, the most severe form of the disease. Mutations

that convert the telomeric copy of the gene to the centromeric copy cause the less severe forms, SMA2 and 3. SMA is also associated with deletions in the neuronal apoptosis inhibitor protein (NAIP) gene. These mutations occur in up to 65% of SMA patients and may modify the severity of the disease. Both genes are believed to suppress neuronal apoptosis, and thus the loss of motor neurons may be the result of misregulated apoptosis.

Diagnosis

Genetic testing in patients with appropriate signs and symptoms can reveal SMN deletions in 95% of patients. Carrier testing is available.
EMG and muscle biopsy show signs of denervation. Nerve conduction studies are normal. While these tests are often done early in the diagnosic process, they are unnecessary if a genetic diagnosis has been established.
Cerebrospinal fluid analysis and serum creatine kinase are normal.

Differential diagnosis

Infantile botulism must be ruled out in possible cases of SMA1. In botulism, impairment is detected using EMG with high frequency nerve stimulation. Stool examination for botulism can also confirm the diagnosis.
SMA2 and 3 can be distinguished from chronic inflammatory demyelinating polyneuropathy by the presence of normal nerve conduction and cerebrospinal fluid protein studies.
SMA3 may resemble hereditary motor sensory neuropathies (Charcot-Marie-Tooth disease), but again the nerve conduction studies are normal in SMA.

Therapy

There is no treatment for these diseases, although physical therapy and braces are helpful for SMA2 and 3 patients. Surgery may be indicated to correct scoliosis.

Prognosis

Half of infants with SMA1 die from respiratory failure by 7 months; 95% die by 17 months. Respiratory failure also shortens the life span of children with SMA2, although not as early as in SMA1. SMA3 patients survive to adulthood and typically maintain ambulatory function. It is not clear whether SMA3 affects lifespan.

References

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Poliomyelitis

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+	+++	+	

Anatomy

Poliomyelitis is a viral infection that causes the death of motor neurons in the spinal cord and brainstem. During the acute phase of the infection, the virus may infect the cortex, thalamus, hypothalamus, reticular formation, brainstem motor and vestibular nuclei, cerebellar nuclei, and motor neurons of the anterior and lateral horns of the spinal cord, causing an inflammatory reaction. Death of motor neurons may result, leading to muscle atrophy. The motor neurons that survive recover fully and may reinnervate denervated muscle.

Symptoms

Paralytic poliomyelitis is characterized by an initial period of muscle pain and spasms, followed by muscle weakness that peaks in severity by one week after the onset of symptoms. Patients do not experience sensory impairment, but may complain of paresthesias.

Bulbar symptoms occur in some patients and include dysphagia, dysarthria, hiccups, and respiratory weakness leading to anxiety and restlessness. In adults, bulbar disease is found in conjunction with spinal disease, but children (especially those without tonsils or adenoids) may present with a pure bulbar poliomyelitis.

Urinary retention is common during the acute phase. Patients may also complain of neck and back stiffness and pain, from meningeal inflammation.

Signs

Muscle weakness is asymmetric and typically proximal. Lumbar segments are usually more severely affected, with trunk muscles being largely spared. Tendon reflexes may be initially brisk, but become diminished or absent. Muscles progressively and permanently atrophy over a period of 2–3 months.

Loss of bulbar motor neurons occurs in some patients and can lead to paralysis of the facial muscles (unilaterally or bilaterally), pharynx, larynx, tongue, and mastication muscles.

If infection strikes the reticular formation, severe respiratory and autonomic impairment may result. Breathing and swallowing difficulties, as well as loss of vasomotor control, are serious risks for mortality and warrant intensive life support.

Pathogenesis

Acute poliomyelitis

Acute poliomyelitis is caused by infection with one of three forms of enterovirus, a single-stranded, encapsilated RNA virus in the picornavirus family. Enteroviruses spread by fecal-oral transmission. Rare cases have been attribut-

ed to live attenuated virus in the polio vaccine. The replication phase takes place 1–3 weeks post-infection in the pharynx and lower gastrointestinal tract. Secretion of the virus occurs in the saliva and feces. The severity of infection is variable, and can be classified into several categories:

Minor or abortive poliomyelitis

Most patients (95%) are asymptomatic, or exhibit pharyngitis or gastroenteritis. After this initial phase, up to 5% of infected patients may show signs of nervous system involvement.

Non-paralytic or pre-paralytic poliomyelitis

Nervous system involvement is preceded by a flu-like set of symptoms, including fever, headache, muscle aches, pharyngitis, anorexia, nausea, and vomiting. Neurological signs and symptoms include restlessness, irritability, and signs of meningitis (back/neck stiffness, Brudzinski and Kernig signs). This situation may then proceed to paralytic poliomyelitis.

Paralytic poliomyelitis

Paralytic poliomyelitis develops in only 1–2% of infected patients, anywhere from 4 days to 5 weeks following initial infection. Factors believed to predispose a patient to paralytic disease include muscle damage from recent strenuous exercise or muscle injections, increased age, tonsillectomy, weakened B-cell function, and pregnancy. Acute paralytic poliomyelitis causes fatal respi-

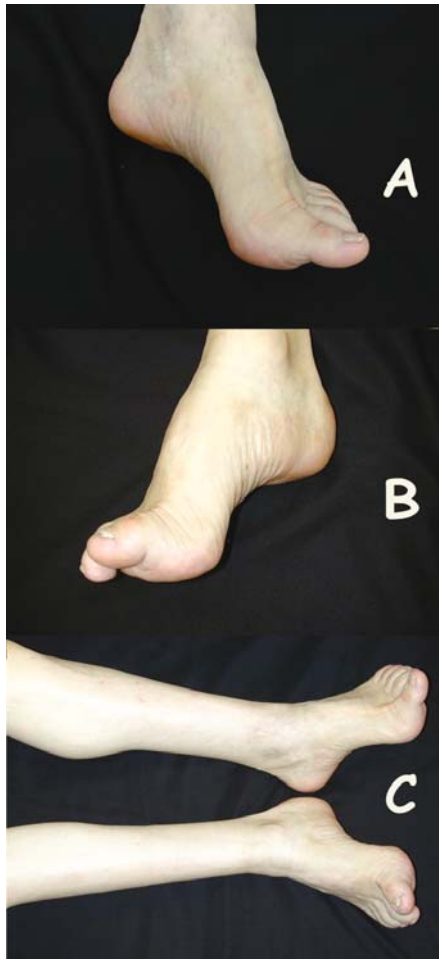

Fig. 4. Postpolio syndrome, with polio in early infancy. **A** and **B** Foot deformity reveas early onset. **C** Very often involvement of the lower limbs is asymmetric (om this case right calf is more atrophic than left)

ratory or cardiovascular problems in 5–10% of cases, or as high as 60% of cases with bulbar involvement.

Encephalitic poliomyelitis

Encephalitic poliomyelitis is extremely rare and has a high mortality associated with autonomic dysfunction. Patients present with confusion and agitation, which may progress to stupor and coma.

Post-polio syndrome

Post-polio syndrome (PPS) occurs 10 years or longer after the initial polio infection, and is characterized by slowly progressive, asymmetric increases in weakness and muscle atrophy (Fig. 4). Patients may complain of joint and muscle pain, and fatigue. PPS is not caused by the virus itself. It is believed that surviving motor neurons that have reinnervated muscle fibers become incapable of maintaining all the connections in their enlarged motor units, and begin to lose some connections. Some clinicians have suggested that excessive exercise aimed at keeping diseased muscles strong leads to this "burn-out", but studies show that the primary associative factor for PPS is the severity of disease during the acute phase of the infection. PPS may lead to weakness in muscle groups previously thought to be unaffected, but typically these muscles were originally affected and the patient developed sufficient strength and adaptation to mask the deficits until the onset of PPS.

Diagnosis

Laboratory:
Virus recovery from stool cultures during the first 2–3 weeks of disease is considered diagnostic for poliomyelitis. Virus may also be detected in throat washings, and occasionally from CSF or blood.
CBC may show increased white count.
CSF pressure may be increased. Neutrophils, and then lymphocytes, may be found in the CSF prior to neurological impairment. Slight to severe protein elevation with normal glucose may be detected.

EMG:
Early on, there is decreased recruitment and interference, with decreased motor unit action potential amplitudes. In 2–4 weeks, fibrillations will develop, with possible fasciculations. Over time, reinnervation will lead to polyphasic motor units.
Nerve conduction velocities and sensory studies are normal.

Imaging:
Inflammation of the anterior spinal cord may be detected with MRI.

Post-polio syndrome:
The diagnosis of PPS is by exclusion of other conditions and demonstration of progressive weakness over time.

Differential diagnosis

Encephalitis caused by echovirus or coxsackie virus
Meningitis
Guillain-Barre syndrome
Motor polyneuropathies
Acute transverse myelitis

Therapy

Vaccination programs have tremendously decreased the incidence of poliomyelitis in developed countries. However, rare cases are still reported in countries with good vaccine programs, frequently in isolated cultures that reject modern medical care. In countries without adequate vaccination, poliomyelitis is still common.

Once a patient has poliomyelitis, the only treatment is supportive therapy. This includes physical therapy to prevent contractures and joint ankylosis, prosthetic devices, and respiratory/swallowing therapy to minimize pulmonary complications like aspiration and atelectasis. Some clinicians recommend that patients with PPS minimize their activity, but studies suggest that exercise is beneficial for PPS, too.

Respiratory failure can be caused by central depression, weakness of the respiratory muscles, or other complications (pneumonia, edema, etc.) associated with airway obstruction. Cardiovascular collapse may also occur from infection of the brainstem. These situations require intensive care with artificial ventilation.

Prognosis

During the acute phase of polio paralysis, the mortality rate is fairly low (5–10%). Patients requiring ventilation during this period usually recover over a period of several months, during which the respiratory muscles become reinnervated and hypertrophic. Continued dependence on artificial ventilation is uncommon. In general, the prognosis for polio patients is good.

Patients that later develop PPS will experience slowly worsening weakness. This does not usually cause increased disability or mortality, although deterioration of respiratory function is a rare possibility.

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Bulbospinal muscular atrophy (Kennedy's syndrome)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
+++	+	+		+

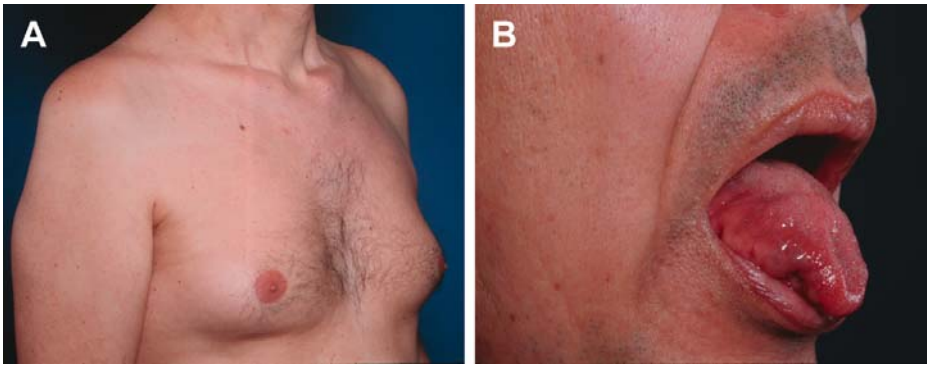

Fig. 5. Kennedy's syndrome. **A** Pt with gynecomastia. **B** Presence of tonque atrophy

Anatomy

Bulbospinal muscular atrophy (BSMA), or Kennedy's syndrome, affects the lower (alpha) motor neurons found in the brainstem cranial nerve motor nuclei and the anterior horns of the spinal cord. On autopsy, patients with BSMA show mild atrophy of the brainstem and spinal cord. Muscle atrophy is also present, with signs of denervation and reinnervation.

Symptoms

The mean onset for BSMA is 30 years (range, 15–60 years). Patients exhibit symmetrical weakness that progresses slowly over many years, and typically do not need canes or walkers until they are in their fifties or sixties. Facial, tongue, and proximal weakness are typical at presentation. Dysphagia, dysarthria, and masseter weakness are commonly observed.

Signs

As BSMA only affects lower motor neurons, there are no upper motor neuron signs. Tendon reflexes are reduced or absent. Fasciculations are common in the face (Fig. 5B). Vibratory sensation may be reduced, and patients often show a mild postural tremor. Gynecomastia occurs in 50% of patients (Fig. 5A).

Pathogenesis

BSMA is an X-linked recessive disorder, caused by a tri-nucleotide repeat expansion in the first exon of the androgen receptor gene on chromosome Xq11–12. It is unknown how disruption of the androgen receptor in this way leads to specific loss of lower motor neurons, as there are other mutations in

this gene that cause testicular feminization but have no affects on motor neurons.

Diagnosis

Genetic: Patients with appropriate signs and symptoms are diagnosed by positive genetic testing.
Laboratory: As muscles are chronically denervated, creatine kinase levels are elevated (up to 10-fold). A muscle biopsy is frequently performed and shows evidence of denervation.
EMG: Chronic denervation is also demonstrated by EMG.

Differential diagnosis

ALS: BSMA has no upper motor neuron signs, distinguishing it from ALS.

Therapy

Currently, the only treatment is supportive care when the muscle weakness becomes problematic.

Prognosis

The number of CAG repeats present in the gene directly correlates with the age of onset and severity of the disease (i.e., more repeats means an earlier onset and greater severity.)

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General disease finder

This overview will help to find neuromuscular disease patterns in the different sections

Cushing's disease: steroid myopathy Addison's disease: general muscle weakness	**Adrenal dysfunction**
Periodic paralysis Tetanic muscles	**Aldosteronism**
CN: VII Polyneuropathies: inflammatory, immune mediated, treatment related Myopathies: inflammatory, treatment related Neoplastic: Lymphoma (direct invasion) Opportunistic infections: CMV, Toxoplasmosis, Cryptococcus, HSV, Candida, Varicella, Histoplasma, TBC, Aspergillus CMV polyradiculomyelopathy Herpes zoster radiculitis Syphilitic radiculopathy Treatment related: polyneuropathy/myopathy Ddl, ddC, Foscarnet, Isoniazid Zidovudine	**AIDS**
Polyneuropathy (distal, rarely proximal, rare ulcers) Mononeuropathy-radial nerve (compression) Myopathy Acute necrotizing myopathy and myoglobinuria Chronic proximal weakness Hypokalemic paralysis Myoglobinuria Compartment syndromes (prolonged compression)	**Alcoholism**
Familial amyloid polyneuropathies Transthyretin Sensorimotor neuropathy Autonomic involvement Apolipoprotein A-1 Polyneuropathy, painful, hearing loss Gelsolin type V, VII and other CN Mild polyneuropathy *Primary amyloidosis (AL)* Deposition of immunoglobulin light chains in tissue	**Amyloid**

	Painful neuropathy Autonomic involvement Carpal tunnel syndrome Muscle amyloid Amyloidoma (trigeminal root) *Secondary or reactive amyloidosis (AA)* Chronic inflammatory diseases, rheumatoid diseases, osteomyelitis Deposition of acute phase plasma protein, serum amyloid A: polyneuropathy not significant
Anemia	Cobalamin deficiency, vitamin B12 polyneuropathy Lead poisoning polyneuropathy Thalassemia: muscle cramps, myalgia, muscle atrophy Pure red cell anemia: autoimmune disease associated with myasthenia gravis
Anesthesia	Regional: Epidural or spinal anesthesia may cause cauda equina lesions Malpositioning Upper extremity (70%): Mononeuropathies of brachial, radial, ulnar, or median nerves Lower extremity (30%): Mononeuropathies of peroneal, sciatic, or femoral nerves Cardiac bypass operations: nerve stretch, hypothermia, phrenic nerve lesions Tourniquet palsy Neuromuscular transmission disorders induced by muscle relaxants
Angiography	Peripheral: Axillary or femoral artery puncture (brachial plexus and femoral nerve) Brachial artery: median nerve Cerebral angiography: femoral nerve lesions
Anorexia nervosa	Myopathy Polyneuropahty
Asthma	Acute ICU steroid myopathy (status asthmaticus) Steroid myopathy Entrapment neuropathies and compression (ulnar, peroneal nerves) Churg Strauss syndrome
Auditory nerve	Hearing loss: Refsum's disease, Cockayne Syndrome, mitochondrial disorders, vasculitis, some types of amyloidosis and hereditary neuropathies
Bone marrow transplantation	CIDP Inflammatory myopathies MG Polyneuropathy

Carotid surgery

Facial nerve lower branch
Hypoglossal nerve
Vagal recurrent nerve

Cancer

Cranial nerves (meningeal carcinomatosis, base of the skull metastasis)

Mononeuropathies (pressure, toxic, following operations)

Radiculopathies (meningeal carcinomatosis, compression or infiltration of roots, multiple spinal metastasis), cauda equina syndrome

Polyneuropathies (treatment related and paraneoplastic, rarely infiltrative)

Myopathies: cachexia, dermatomyositis/polymyositis, necrotizing, neuromyotonia

Neuromuscular transmission: MG and thymoma, LEMS and (lung) cancer

Antineoplastic treatment associated polyneuropathy:
Cisplatinum (Carboplatin, Oxaliplatin)
Podophyllin derivatives
Procarbazine
Taxanes
Suramin
Vinca alkaloids

Radiation:

Plexopathies (brachial, lumbar, sacral)

Paraneoplastic disease
Cranial nerve: Optic nerve
Polyneuropathies (all types)
LEMS
Muscle: inflammatory and necrotizing myopathies

Circulatory disorders

Aortic disease:
- Left recurrent laryngeal nerve palsy
- Femoral nerve lesion (ruptured aneurysm, aortic surgery)
- Obturator nerve: hematoma in psoas muscle
- Radiculopathies: compression of L4,5 and S1, 2 by terminal aorta
- Ischemic monomelic: predominately sensory with causaglia like pain

Cholesterol lowering drugs:

Myopathy, cramps (Fenofibrate, benzafibrate, clofibrate, gemfibrozil, nicotinic acid lovastatin, simvastatin, pravastatin)

Embolism-compartment syndrome

Intermittent claudication

Ischemic neuropathy, angiopathic neuropathies

Muscle hemorrhage: hemophiliacs, anticoagulants: retroperitoneal, buttock, arm, calf

Neuropathy by fistula- hemodialysis

Monomelic neuropathy

Nerve compression by hematoma (femoral nerve, lumbar plexus, sciatic nerve)

	Temporary aortic occlusion (surgery)
	Venous occlusion-phlegmasia cerulea dolens
Coma	Cranial nerve lesions
	Critical illness myopathies Critical illness neuropathy
	Mononeuropathies (malpositioning)
	Steroid myopathy
	Thick filament myopathy
Complications of medical and surgical treatment	Hip and joint surgery: sciatic, femoral nerve lesions
	Hypothermia: polyneuropathy
	Injection into nerves: Mononeuropathies Nerve blockade
	Intramuscular injections
	Knee surgery: peroneal nerve, ramus infrapatellaris
	Mononeuropathies due to body position: plexus, radial, ulnar, median, peroneal, femoral nerve lesions
	Muscle: Drug induced myopathy: acute hypokalemic paralysis, necrotizing myopathy, subacute and chronic myopathies, ischemic injury during surgery
	Neuromuscular transmission: drug induced MG Neuromuscular blocking agents
	Postoperatively: GBS, postoperative apnea, malignant hyperthermia
	Radiation: Spinal cord and nerve plexus (brachial, lumbar and sacral plexus) mononeuropathies
	Spinal anesthesia: nerve roots, epidural hemorrhage, paraplegia, sensory loss, adhesive arachnoiditis
	Surgical trauma: neck surgery, mastectomy, (thoracodorsal, long thoracic, axillary nerve), median sternotomy, pelvic surgery (sciatic, obturator, femoral, ilioinguinal, iliohypogastric nerve)
	Tourniquet paralysis
Diabetes mellitus	Autonomic neuropathy Cranial mononeuropathies Mononeuropathies Muscle infarction Plexopathy Polyneuropathy; several distinct types Thoracic (truncal) radicular lesions
Immobilization	Disuse myopathy Mononeuropathies: pressure palsies

Heroin: nerve compression (coma), trauma from injection, brachial and lumbosacral plexopathies Phenylcyclidine: rhabdomyolysis Cocaine: rhabdomyolysis	**Drugs and addiction**
Hypercalcemia: muscle weakness Hypocalcemia: tetany Hypokalemic paralysis Hypokalemic myopathy Hyperkalemia: potassium retaining diuretics Hypermagnesemia muscle weakness Hypomagnesemia muscle weakness Hypernatremia: muscle weakness	**Electrolyte disorders**
Churg Strauss syndrome Eosinophilic fasciitis Eosinophilic polymyositis Eosinophilia myalgia syndromes	**Eosinophilic syndromes**
Acute abdomen: porphyria, lead poisoning-polyneuropathy Chronic diarrhea: malabsorption neuropathies, Whipple's disease, celiac disease Celiac disease: myopathy Crohn's disease: polymyositis	**Gastrointestinal disorders**
Compartment syndromes Polyneuropathy	**Ischemia/peripheral vascular occlusive**
	Hepatic disease
GBS Primary biliary cirrhosis: myopathy, neuropathy Polymyositis Polyneuropathy (hepatitis B, C) Panarteritis nodosa (hepatitis B)	**Hepatitis**
Demyelinating polyneuropathy Sensory polyneuropathy	**Biliary cirrhosis**
Hepatic myelopathy	**Acquired hepatocerebral degeneration**
Polyneuropathy	**Chronic liver disease**
Hemophilia: Nerve compression (femoral nerve, hemorrhage into iliac muscle) Ulnar nerve compression Median nerve, radial nerve, sciatic nerve, peroneal nerve Thrombocytopenia: Rarely affects peripheral nerves	**Hematologic diseases**

Complications of anticoagulation:
Brachial plexus lesions
Median nerve
Femoral nerve
Obturator nerve
Sciatic nerve

Polyneuropathy:
POEMS syndrome
Castleman's syndrome
Waldenstrom's macroglobulinemia
Lymphoma, HIV

Hyperuricemia

Median nerve mononeuropathy
Polyneuropathy
Radiculopathy

Hypnotic drugs

Polyneuropathies:
Amitryptiline
Gluthethimide
Imipramine
Li^+ carbonate
Metaqualone
Perazine
Phenelzine
Thalidomide

Immunization

Influenza, swine flu: GBS
Mumps: sensorineural deafness
Oral polio: GBS

Macrophagic microfasciitis (hepatitis A,B, tetanus)

Toxoids:
Diphtheria/tetanus: GBS
Hemophilus influenzae: GBS
Plasma derived hepatitis B: GBS

Infections

Bacterial meningitis: cranial nerve lesions

Hepatitis:
A: GBS
B: GBS, periarteritis nodosa
C: Polyneuropathy (vasculitis)

Herpes zoster:
Cranial nerves: ophthalmic, trigeminal, Ramsay Hunt syndrome
Postherpetic neuralgia

Leprosy:
Leprous neuritis

Lepromatous leprosy:
Skin, superficial nerves

Sensory loss (cool areas)
Ulnar: proximal to ulnar groove
Median: proximal to carpal tunnel
Peroneal nerve

Tuberculoid:
Mixed nerve near the tubercle
Ulnar, median, peroneal, facial nerve
Enlarged superficial cutaneous, radial nerve
Digital, sural nerves

Lyme disease:
Cranial nerves: VII (possibly bilateral)
Radiculoneuritis (Garin-Bujadoux-Bannwarth syndrome)
Polyneuropathy (unclear)
Root involvement
Truncal muscle weakness

Neurosyphilis:
Cranial nerves: pupillary abnormality
Tabes dorsalis ("Lightning pain")
Posterior nerve root, ataxia, bladder and sexual dysfunction

Tuberculosis:
Cranial nerves (meningitis): VI, III, IV
Retrobulbar with Myelitis
Tuberculous arachnoiditis: radiculomyelopathy

Tuberculomas

Typhoid fever: multifocal neuropathy

Parasitic infections:
Amebic meningoencephalitis: olfactory nerve, smell
Angiostrongyliasis: radiculomyeloneuritis
Eosinophilic meningitis: cranial neuropathies, paresthesias

Onchocerciasis: blindness

Paragonimus: optic atrophy

Poliomyelitis:
Muscle weakness
Laryngeal and pharyngeal
Facial diplegia
"Postpolio syndrome"

Trichinosis-muscle, respiration, and cardial and skeletal muscles

Viral meningitis:
Enterovirus: poliomyelitis
GBS

Mumps: deafness

Viral:
Myopathy
Herpes
Rabies

	Postviral complications: Optic neuritis: measles, rubella, mumps, varicella zoster, infectious hepatitis, mononucleosis, rabies vaccine Cranial nerves: mumps GBS: CMV, enterovirus, Epstein Barr, herpes simplex, hepatitis B, HIV, influenza A and B, measles, rabies, rubella, smallpox vaccination Deafness and vertigo: mumps, measles, varicella, influenza, HSV *Antimicrobial therapy:* Emetine induced myopathy Isoniazide neuropathy Ethambutol neuropathy Nitrofurantoin neuropathy Streptomycin-ototoxicity Sulfonamide vasculitis Metronidazole neuropathy
Inflammatory and immune diseases	Infection and immunization: brachial neuritis Cranial nerves: VI, VII, vagus Mononeuropathies: serum sickness, acute mononeuropathies: long thoracic, radial, suprascapular, musculocutaneous, femoral, sciatic, anterior interosseus nerve, intercostal, phrenic nerve Polyneuropathy: Migratory recurrent polyneuropathy GBS CIDP Postinfectious and allergic neuropathies Chronic idiopatic neuritis Collagen vascular disease Myopathies: Dermato- and polymyositis Eosinophilic fasciitis Scleroderma Lupus Multiplex neuropathy-vasculitis Periarteritis nodosa Rheumatoid arthritis Cryoglobulinemia Miscellaneous: Sarcoid Behcet's disease Lyme disease
Lipid metabolism	Alpha 1 lipoprotein deficiency: polyneuropathy A-betalipoproteinemia: polyneuropathy Hyperlipidemia: polyneuropathy
Lung disease	Lung cancer: paraneoplastic disease Sarcoid-polyneuropathy Pneumonia: phrenic neuropathy

Cranial nerves: trigeminal Mononeuropathies (median, ulnar) Polyneuropathy (sensorimotor) (see rheumatoid disease)	**Lupus, SLE**
see cancer	**Lymphoma**
Malnutrition induced myopathy Polyneuropathy Posterolateral cord degeneration Vitamin B12 deficiency	**Malnutrition**
Susceptibility in several diseases: Central core disease Duchenne's dystrophy Myotonia congenita Myotonic dystrophy	**Malignant hyperpyrexia**
Muscle weakness in: Potassium: hypokalemia, hyperkalemia Tetany, hypocalcemia Hypomagnesemia	**Mineral and electrolyte disorders**
Fabry's: corneal clouding Retinal microaneurysms: diabetes mellitus "Beaded retinal vasculature": vasculitis Myotonic dystrophy Retinitis pigmentosa: Refsum's disease, Cockayne syndrome, Bassen-Kornweig disease Sicca syndrome: Sjögren's syndrome Xerophthalmia: Sjögren's syndrome, LEMS Optic disk edema: POEMS syndrome, CIDP, GBS	**Ophthalmologic complications**
Myopathy	**Osteomalacia**
Cranial nerves: Paraneoplastic retinal degeneration "Numb chin syndrome" Polyneuropathy: Distal sensorimotor Sensory, subacute sensory neuronopathy Vasculitic neuropathy Paraproteinemic neuropathies: Monoclonal gammopathy of uncertain significance (MGUS) Anti-MAG IgM POEMS	**Paraneoplastic neuromuscular syndromes**

	Neuromuscular transmission: LEMS MG (thymoma) Neuromyotonia
	Myopathy: Dermatomyositis Necrotizing myopathy Type 2 Fiber atrophy "cachectic myopathy"
Parathyroid disease	Myopathy, bulbar and respiratory weakness Thyrotoxic periodic paralysis Polyneuropathy Ocular myopathy
Hypoparathyroid	Tetanic muscular reaction
Pituitary disease	Acromegaly: median, ulnar nerve entrapment Proximal myopathy
Porphyria	Polyneuropathy (proximal) Ascending polyradiculopathy
Pregnancy	Optic neuritis Cranial nerves: Bell's palsy Median neuropathy Lumbosacral plexus-labor Lumbosacral plexus: fetal head, forceps
	Mononeuropathies: Lateral femoral cutaneous nerve Obturator nerve Saphenous nerve Sciatic nerve Common peroneal nerve Innervation of sphincter muscle of the pelvic floor
	Myotonia and myotonic dystrophy, weakness may worsen (uterus contraction, labor) MG (relapse and remission) Arthrogryposis Polyneuropathy-malnutrition-developing countries GBS Relapse of CIDP
Psoriasis	Psoriatic myopathy
Pulmonary disease	Asthma: Churg-Strauss syndrome COPD: polyneuropathy
Renal disorders	Polyneuropathy: Distal symmetric, sensory, motor Cramps, myokymia Restless leg syndrome
	Compressive neuropathies: Ischemic myopathy related to shunt

Amyoloid deposition
Multiplex mononeuropathies

Neuromuscular junction:
Aminoglycoside toxicity

Myopathy: (type 2 fiber atrophy)
Cachexia, inanition, electrolyte disturbances, rhabdomyolysis

Rhabdomyolysis

Ethanol intoxication
Drug induced coma
General anesthesia
Heroin
Multiple organ failure
Narcotics

Secondary entrapment – compartment syndromes

Rheumatoid and connective tissue

Raynaud's syndrome

Polyneuropathy:
Systemic lupus erythematosus
Scleroderma (rare)
Eosinophilia myalgia syndrome
Mixed connective tissue disease ("Sharp syndrome")
Rheumatoid arthritis
Sjögren's syndrome with sensory ganglionopathy
Relapsing polychondritis

Trigeminal neuropathy

Muscle:
Dermatomyositis
Polymyositis
RA, scleroderma, penicillamine induced
Eosinophilic myositis/fasciitis
Eosinophilia myalgia syndrome

Bechterew: cauda equina syndrome, thoracal radiculopathies

Giant cell arteritis: cranial neuropathies, optic nerve, infarction of tongue, claudication when chewing

Polymyalgia rheumatica: muscle pain

Wegener's disesease: cranial neuropathies, neuropathy, vasculitis

Osteopetrosis: anosmia, optic nerve, atrophy, optomotor, trigeminal nerve, facial nerve, otosclerosis

Paget's disease: anosmia, optic nerve, trigeminal, deafness, caudal and cranial nerves

Therapy induced:
Gold therapy: polyneuropathy, myokymia
D penicillamine: MG, myositis
Corticosteroid: myopathy
Chloroquine: myopathy

Neurosarcoidosis

Facial nerve (bilateral)

Hypercalcemia

	Myositis: proximal muscle atrophy
	Polyneuropathy (distal sensorimotor, small fiber and autonomic) Mononeuropathy Radiculopathy GBS
Sepsis	Cachexia Critical care myopathy Critical illness neuropathy Malnutrition and avitaminosis Neuromuscular transmission disorders by: Anesthetic drugs, aminoglycosides Septic myopathy Thick filament myopathy Therapy induced: steroid myopathy
Skin changes	Angiokeratoma: Fabry's disease
	Cheilosis/glossitis: vitamin B and folate deficiency
	Dupytren's contracture: alcoholic liver disease, diabetes mellitus
	Hair loss: thallium, alopecia areata (in autoimmune disease, also in MG), hypothyroidism, thallium, Lupus
	Erythema nodosum: leprosy, sarcoidosis, inflammatory bowel disease
	Hyperpigmentation: POEMS syndrome, adrenomyeloneuropathy, adreno-leukodystrophy
	Hypopigmentation: POEMS syndrome, leprosy (patchy)
	Hypertrichosis: POEMS syndrome
	Skin rash: dermatomyositis
	Purpura: vasculitis, cryoglobulinemia, amyloidosis
	Ichthyosis: Refsum's disease
	Macroglossia: amyloidosis
	Mees' lines (nails): arsenic, thallium intoxication
	Photosensitivity: Lupus, porphyria
	Raynaud's syndrome Collagenosis, autoimmune disease
	Vitiligo: vitamin B deficiency
Starvation	Anorexia nervosa Myopathy Strachan's syndrome Wernicke's disease
Steroid medication	Chronic myopathy, type two fiber atrophy Acute myopathy in status asthmaticus Critical illness myopathy
Subarachnoid hemorrhage	Epsilon aminocaproic acid-myopathy
Thyroid disease	
	Hyperthyroidism Basedow's disease

Entrapment mononeuropathy (CTS)
Graves ophthalmopathy
Hyperthryroid periodic paralysis (Asian, Chinese)
MG and hyperthyrosis
Thyroid myopathy

Hypothyroidism
Median neuropathy
Myopathy (pseudomyotonia – Hoffman's sign)
Polyneuropathy

Toxine exposure/ working conditions

Polyneuropathies:
Acrylamide (monomer): sensory

Heavy metals:
Lead: motor neuropathy (UE > LE)
Wrist and finger extensors
Arsenic: distal axonopathy (GBS-like)
Mercury: Cranial nerves II, VIII, sensory
Thallium: Polyneuropathy, autonomic
Tin: papilledema

Organic solvents (n-hexane, methyl n-butyl ketone, carbon disulfide)

Organophosphates:
Acetylcholinesterase inhibition: fasciculations, weakness, respiration
Nicotinic effects: inhibition of neuropathy target esterase:
Distal axonopathy
(TOCP) triorthocresyl phosphate
gasoline

Trichlorethylene: cranial neuropathies

Uremia

Optic neuropathy
Mononeuropathies
Polyneuropathy
Shunt monomelic neuropathies

Visual disorders

Color vision changes: sulfonamides, streptomycin, methaqualone, barbiturates, digitalis, thiazide diuretics, antihelmintic drugs, nalidixic acid, troxidone

Optic neuropathy: chloramphenicol, isoniazid, streptomycin, ethambutol, sulfas, dapsone, chlorpropamide, chlorambucil, penicillamine, indomethacin, ibuprofen, morphine, MAO-inhibitors, barbiturates

Vitamin deficiency

Vitamin B1 (Thiamine): polyneuropathy, myopathy

Vitamin B6: isoniazid neuropathy, median neuropathy
Pyridoxine high dose: sensory neuropathy

Vitamin B12 deficiency: polyneuropathy, posterior column degeneration

Vitamin D: muscle weakness, osteomalacia

Vitamin E: myopathy, lordosis

Subject index