Eva L. Feldman
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Atlas of Neuromuscular Diseases

A Practical Guideline

Second Edition

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This book is dedicated to Professors P.K. Thomas (London, UK) and John Griffin (Baltimore, MD, USA), our mentors in neuromuscular diseases and to our families whose help and support made this book possible.

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Tools

1

Eva L. Feldman and Wolfgang Grisold

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 electromyogram (EMG) tests can be important but are less specific. Conversely, NCV and EMG are the predominant diagnostic tools for a local entrapment neuropathy like carpal tunnel syndrome. Imaging is now a standard tool in diagnosing certain nerve and muscle disorders, particularly nerve entrapments and myopathies, respectively. Some conditions will require tissue biopsy, although this is becoming increasingly less common.

The evaluation of a patient's symptoms, in particular pain, is increasingly important, as are assessments of a patient's quality of life and disability. In Europe, the International Classification of Functioning, Disability, and Health [(ICF) www.who.int] is used as a metric for a patient's overall function. In the United States, an ongoing effort is in place to assess a patient's overall functional status using a standardized National Institutes of Health Tool Box (www.ninds.nih.gov).

1.1 New Developments in Neuromuscular Disease

The first edition of this book was published in 2004. In the ensuing years, several new developments have changed our approach to patients with neuromuscular disorders. In the authors' opinion, the most important change is that the idea of "evidence-based medicine" is now widely accepted. The Cochrane Collaboration (www.cochrane.org), the European Federation of Neurological Societies (EFNS) (www.efns.org), and the American Academy of Neurology (AAN) (www.aan.com) all provide unbiased systematic reviews of treatment paradigms with evidence-based recommendations. Increasingly freely available sources such as the Directory of Open Access Journals (www.doaj.org) and PubMed Central (www.ncbi.nlm.nih.gov/pubmed) are used, which enable rapid and commonly unrestricted access to new medical information. These changes are reflected in updated content in the second edition of this atlas.

The clinical methodology of the examination of the patient with neuromuscular disease has remained unchanged and is based on a detailed case history and a systematic neuromuscular examination. The number of antibody-associated and immune-mediated neuromuscular disorders has grown modestly. In contrast, the number of newly identified neuromuscular genetic disorders has increased dramatically and continues to evolve on a monthly basis. Open access websites, including Gene Reviews (www.ncbi.nlm.nih.gov/sites/GeneTests/review) and the Neuromuscular Home Page (neuromuscular.wustl.edu), provide up-to-date genetic and clinical information for the practitioner and information on how to attain appropriate serological genetic testing.

Another major change since 2004 is the increasing use of imaging to assess the integrity of peripheral nerves and muscles. Ultrasound imaging of peripheral nerves and muscles routinely provides the initial assessment of tissue integrity and is the mainstay of neuromuscular imaging. Magnetic resonance imaging (MRI) is now also commonly used to assess the integrity of nerve roots, the brachial or lumbosacral plexus, and individual peripheral nerves. MRI imaging of muscle is increasingly employed and identifies changes in muscle integrity, including muscle tears, edema, fatty infiltration, hematomas, and tumors. MRI tractography is also currently under development for use in the peripheral nervous system.

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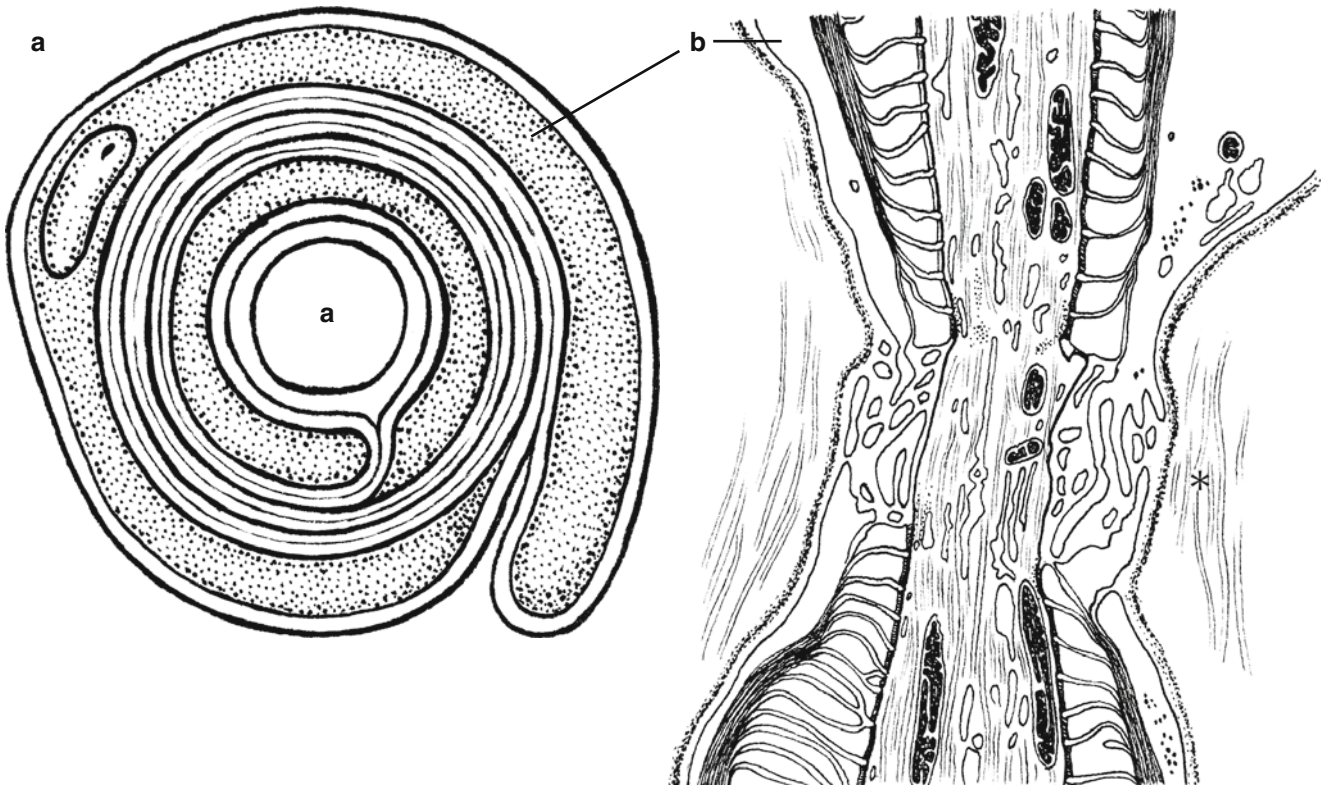
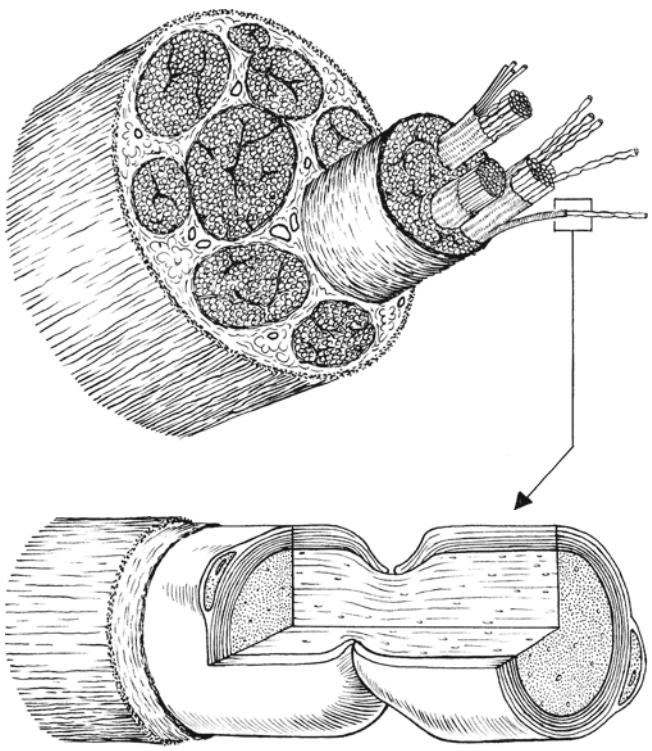


Fig. 1.1 (**a**) The axon (*a*) is surrounded by layers of Schwann cell cytoplasm and membranes. The Schwann cell cytoplasm is squeezed into the outer portion of the Schwann cell leaving the plasmalemma of the Schwann cell in close apposition. These layers of Schwann cell membrane contain specialized proteins and lipids and are known as the myelin sheath. (**b**) Peripheral axons (*a*) are surrounded by as series of Schwann cells. The space between adjacent Schwann cells is 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



1.2 The Patient with Neuromuscular Disease

The evaluation of a patient with neuromuscular disease includes a thorough clinical history, duration of the present illness, past medical history, social history, family history, and details about the patient's occupation, behaviors, and habits. The clinical history and temporal development of symptoms provide essential information to the practitioner.

Fig. 1.2 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* 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

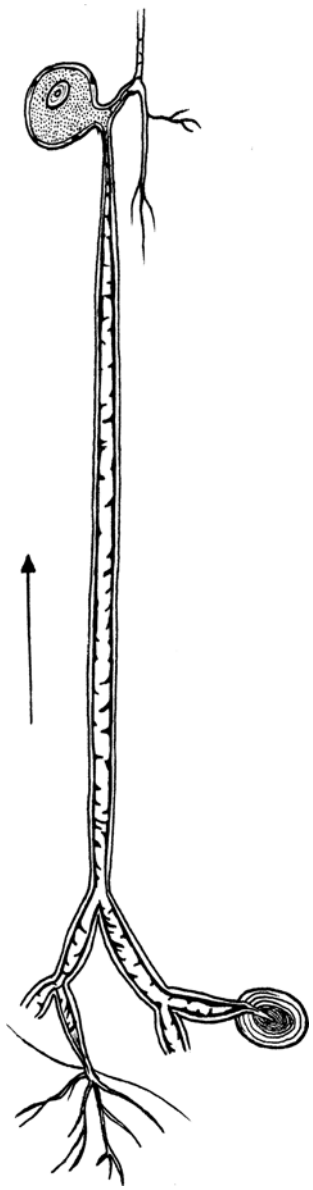


Fig. 1.3 Sensory information is relayed from the periphery toward the central nervous system through special sensory neurons. These are pseudounipolar neurons located within the dorsal root ganglia along the spinal cord. Mechanical, temperature, and noxious stimuli are transduced by special receptors in the skin into action potentials that are transmitted to the sensory neuron. The direction of the sensory system (*arrow*). This neuron then relays the impulse to the dorsal horn of the spinal cord. Motor information is relayed from the central nervous system to the muscles by the alpha motor neurons. These multipolar neurons are located within the ventral or anterior horn of the spinal cord gray matter. Impulses from the motor cortex travel down the spinal cord to the motor neurons. The motor neuron relays this impulse to the muscle inducing muscle contraction and movement

The types of symptoms (motor, sensory, autonomic, and pain) and how these symptoms are affecting the patient's activities of daily living can supply essential information required for a correct diagnosis.

The history is followed by a classical clinical neurological examination, which will assess signs of muscle weakness, reflex and sensory abnormalities, coordination, and autonomic changes, as well as give information about pain and impairment. The clinical examination is of utmost important 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) can give important clues to the precise diagnosis. 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, assessments of muscle strength [e.g., Medical Research Council (MCR) scale] and sensation (e.g., vibration threshold, Semmes-Weinstein filaments, two-point discrimination, warm-cold discrimination), patterns of atrophy, and reflex changes are useful. Digital imaging, video clips, and photographs of patients provide a precise documentation of the patient's function and are suggested when possible.

The diagnostic hypothesis is developed on the basis of history and clinical exam and can be confirmed by additional diagnostic testing. These same tests are used, in conjunction with newer quality of life scales, to monitor the impact of therapies on the disease course. Standard electrophysiological tests include nerve conduction studies (NCV), electromyography (EMG), and repetitive nerve stimulation. Complete blood counts, blood chemistries including creatine kinase, vitamin levels, serological markers of inflammation, specific antibody levels, and genetic testing are frequently required to secure a precise diagnosis. Other quantitative clinical assessments are employed when required, including autonomic function testing (Ewing test battery) and quantitative sensory testing (QST). Both neuroimaging with ultrasound and/or MRI and, if indicated nerve or muscle biopsy, are used to confirm specific diagnoses.

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

1.3 History and General Physical Examination

The detailed neurological, general medical, family, and social history, as discussed above, is essential and must be completed in a systematic manner. Upon completion, each patient should undergo a basic general physical examination. This should begin with a general inspection of the

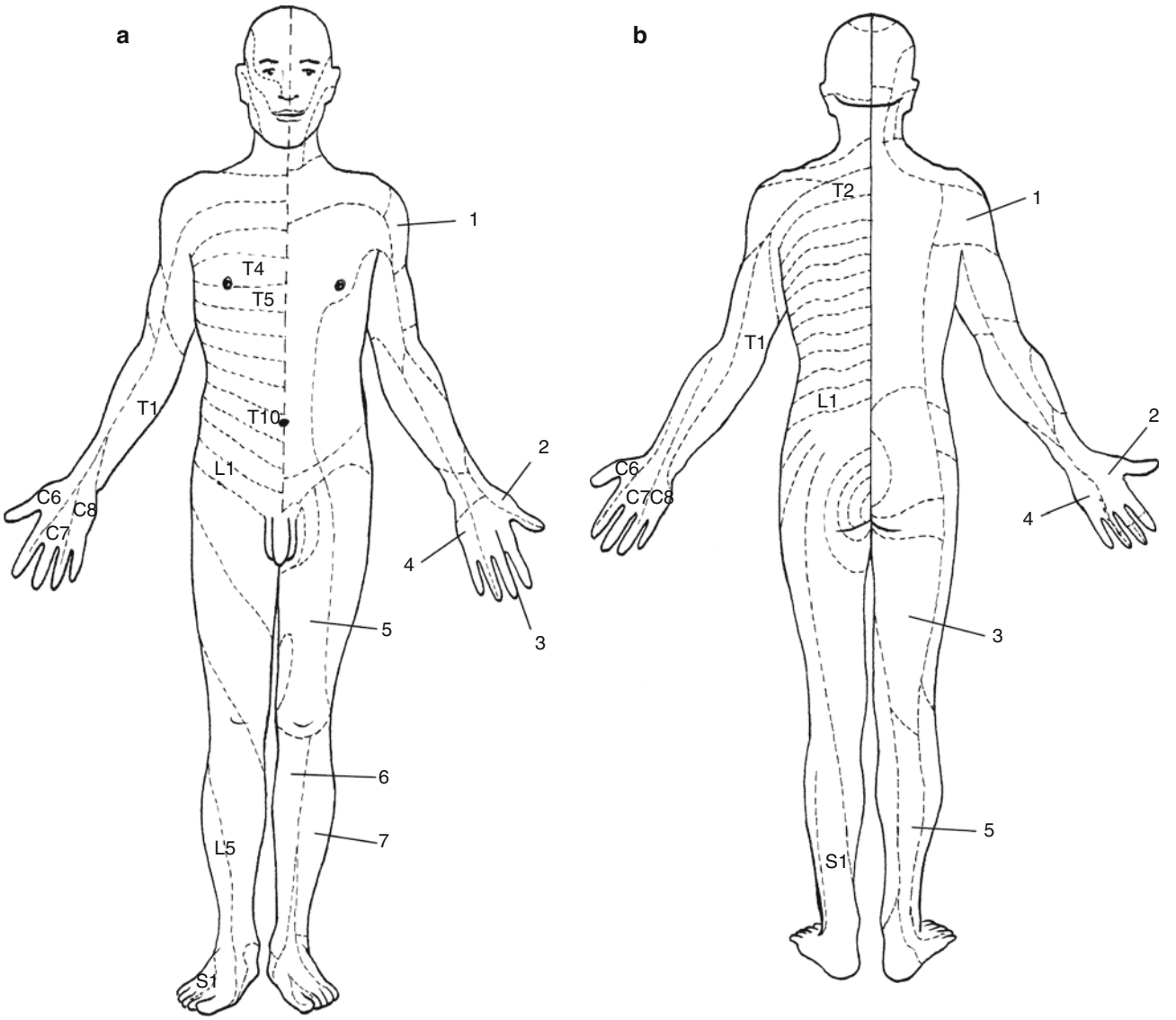


Fig. 1.4 (**a**) *1* Axillary nerve, *2* superficial radial nerve, *3* median nerve, *4* ulnar nerve, *5* femoral nerve, *6* saphenous nerve, and *7* peroneal nerve. On the right side of the body the segmental innervation is marked. (**b**) *1* Axillary nerve, *2* superficial radial nerve, *3* ulnar nerve, *4* cutaneous femoris posterior nerve, and *5* sural nerve

skin (identifying rashes, papules, birthmarks such as café au lait spots, hyperpigmentation, hypertrichosis, or other dermatological abnormalities) and the musculoskeletal system (detecting kyphosis, scoliosis, pes cavus, atrophy, hypertrophy, or any abnormal muscle movements). General inspection is followed by assessments of blood pressure and pulse and examination of cardiopulmonary function. Depending on the clinical history, a more thorough general examination may be required; for example, assessments including but not limited to the thyroid, abdomen, and lymph nodes can provide clinical information that may be required for specific neuromuscular diagnoses.

1.4 Neuromuscular Clinical Phenomenology

1.4.1 Motor Function

Motor dysfunction is one of the most prominent features of neuromuscular disease. The patient's symptoms may include weakness, fatigue, muscle cramps and pain, 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 (as in the acquired inflammatory neuropathies) or may remain discrete

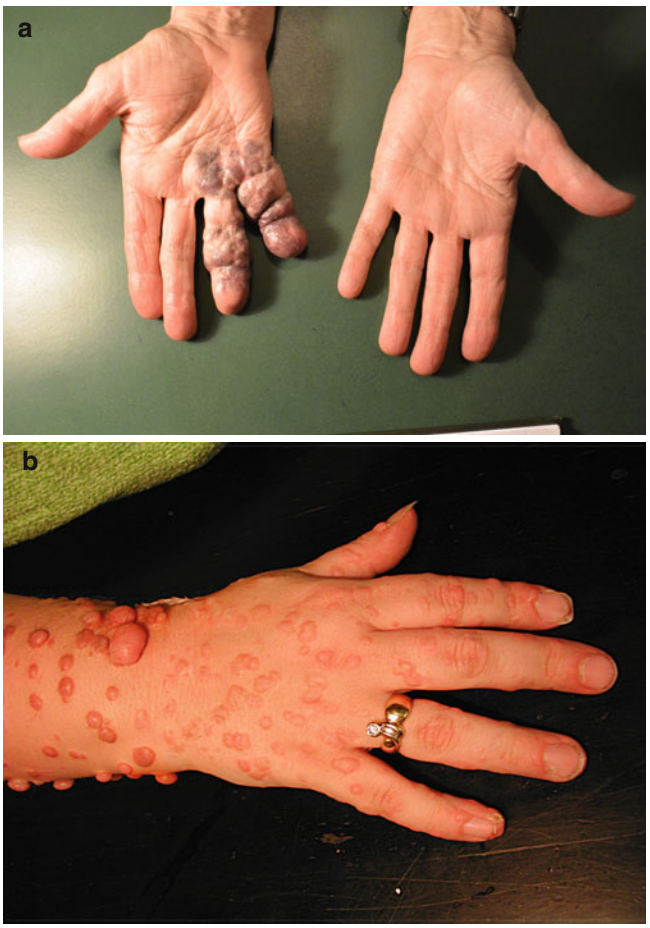


Fig. 1.5 (**a**) Hemangioma in the fourth and fifth finger and palm. (**b**) Multiple neurofibromas in NF1

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 weaknesses 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 nerves leaving the main nerve trunk. Partial lesions of proximal nerves can also result in a distinct peripheral pattern (e.g., in proximal lesions of the sciatic nerve, the peroneal nerve fibers are more vulnerable).

Muscle strength can be evaluated clinically by manual and functional testing. Typically, the British Medical Research Council (MRC) scale is used. This simple grading gives a good general impression, and most patients fall between grades 3 and 5 (3 = sufficient force to hold against gravity, 5 = maximal muscle force). A composite MRC 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 single muscles cannot be assessed individually. Handgrip strength can be measured by a dynamometer and provides a quantitative measure of muscle strength that can be followed over time.

Fatigability is present in many neuromuscular disorders. It can be objectively noted in neuromuscular transmission disorders like myasthenia gravis (e.g., ptosis time) and is also present in neuromuscular diseases like amyotrophic lateral sclerosis, muscular dystrophies, and metabolic myopathies, where it is exacerbated 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 secondary to immobilization (e.g., casting for fractures or persistent joint deformities in rheumatoid arthritis) and in wasting due to malnutrition or tumor cachexia and sarcopenia caused by cancers.

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. Finally, ruptured muscles may mimic a local hypertrophy during contraction.

1.4.2 Abnormal Muscle Movements

They can be the hallmark of a neuromuscular condition and should be observed at rest, during and after contraction, and after mechanical stimulation such as 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 diseases (amyotrophic lateral sclerosis-ALS), spinal muscular atrophy (SMA), but can also occur in polyneuropathies, and appear localized in radiculopathies. Contraction fasciculations appear during muscle contraction and are common in ALS. Ultrasound easily detects fasciculations and can be used to assess the tongue and other muscles. Fasciculations are also easily identified on EMG.
- *Myokymia* are 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 are rare and appear in neuromuscular disease with "continuous muscle

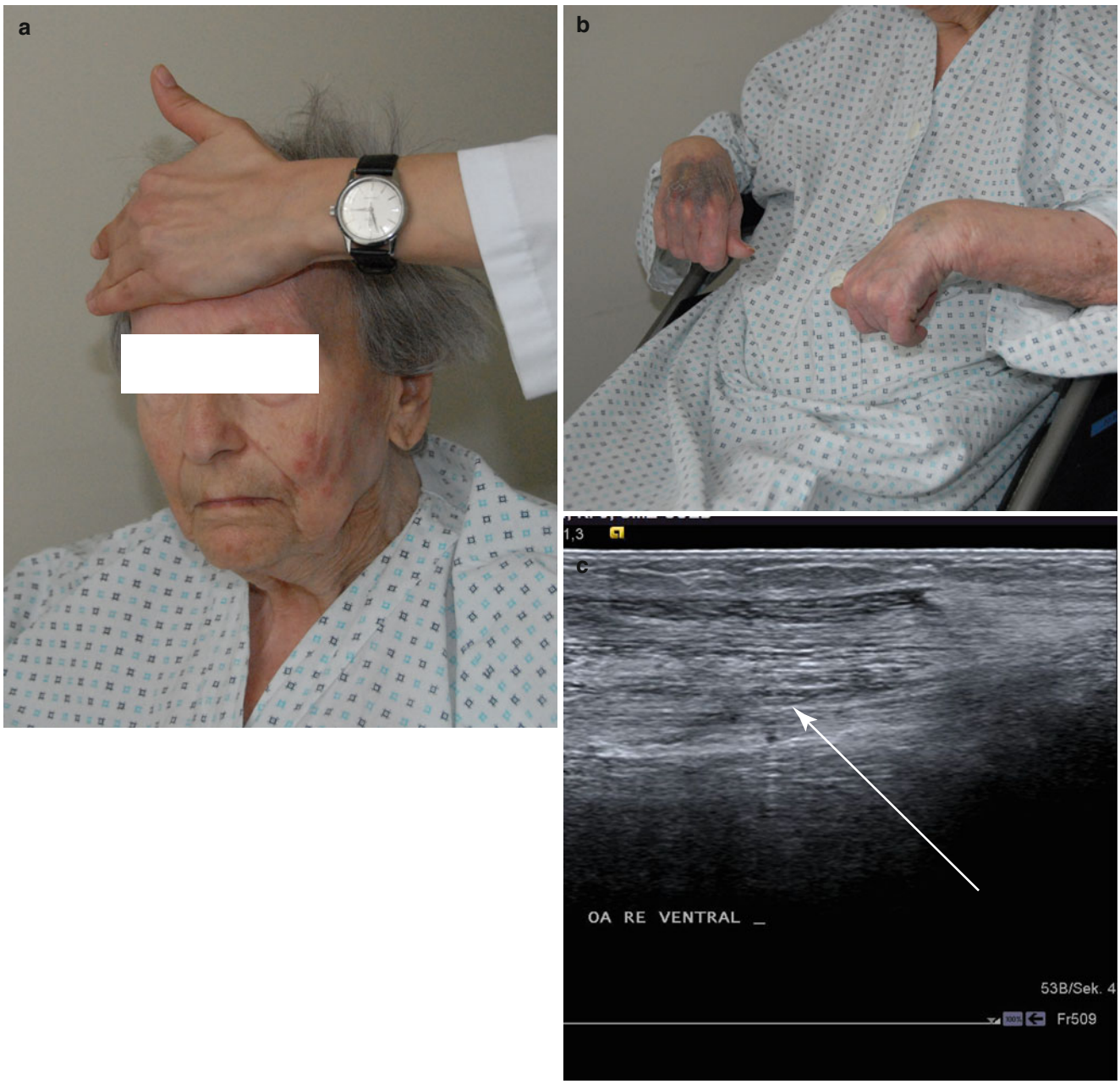


Fig. 1.6 Myopathy: clinical and ultrasound examination. (**a**) Weakness of neck flexors, (**b**) bilateral hand drop, (**c**) ultrasound of the ventral flexors show structural disarray of muscle tissue (*arrow*)

fiber activity," such as in Isaac's syndrome and in CNS disease (e.g., brainstem glioma). They may be a sequel of radiation injury to the peripheral nerves, most frequently seen in radiation plexopathies of the brachial or lumbosacral 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 and can 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 ridgelike mounding of the muscle, lasting 1–3 s. It is a rare finding and can be seen in hypothyroidism and cachexia.
- *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

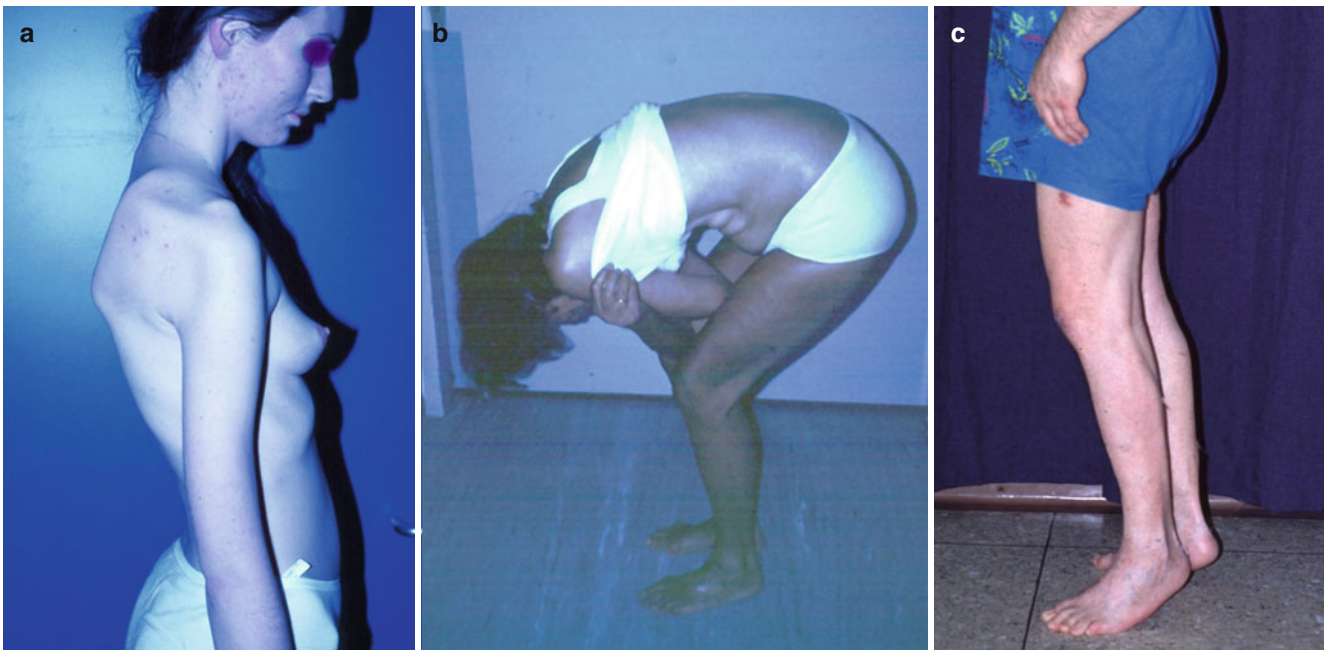


Fig. 1.7 Features of myopathy. (**a**) Hyperlordosis and scapular winging, (**b**) proximal weakness of shoulder girdle, (**c**) shortening of Achilles tendon

rippling muscle movement is associated with electrical silence in EMG.

- *Myotonia* occurs when a muscle is unable to relax after voluntary contraction and is caused by repetitive depolarization of the muscle membrane. Myotonia is well characterized by EMG. It occurs in myotonic dystrophies and congenital 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 s). 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, anterior tibialis muscle, or the tongue are examined. The relaxation is delayed, and a local dimple caused by the percussion appears, lasting about 10 s.
- *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 and neuronopathies, posterior column degeneration, and tabes dorsalis.
- *Painful legs and moving toes*: Length-dependent distal neuropathies may be associated with moving toes. This sign is maybe due to large-fiber sensory loss and has been observed in cisplatinum-induced neuropathies and other neuropathies.
- *Neuropathic tremor* resembles orthostatic tremor and has a frequency of 3–6 Hz. It occurs rarely in association with demyelinating neuropathies or hereditary 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.

1.4.3 Reflex Testing

The long reflex arc tested by the deep tendon reflex is useful for neuromuscular diagnosis. The reflex arc measures both the large fiber sensory and motor divisions of the local segment tested. Reflexes do not measure small-fiber function and are normal in isolated small-fiber neuropathies. The quality of the reflex provides information on the central nervous system input to the local segment (e.g., exaggerated, brisk, normal, or diminished). In polyneuropathies, reflex changes are symmetrical, and ankle reflexes are routinely diminished or absent, while more proximal reflex arcs remain intact until later in the disease progression. Asymmetric reflexes suggest focal pathology

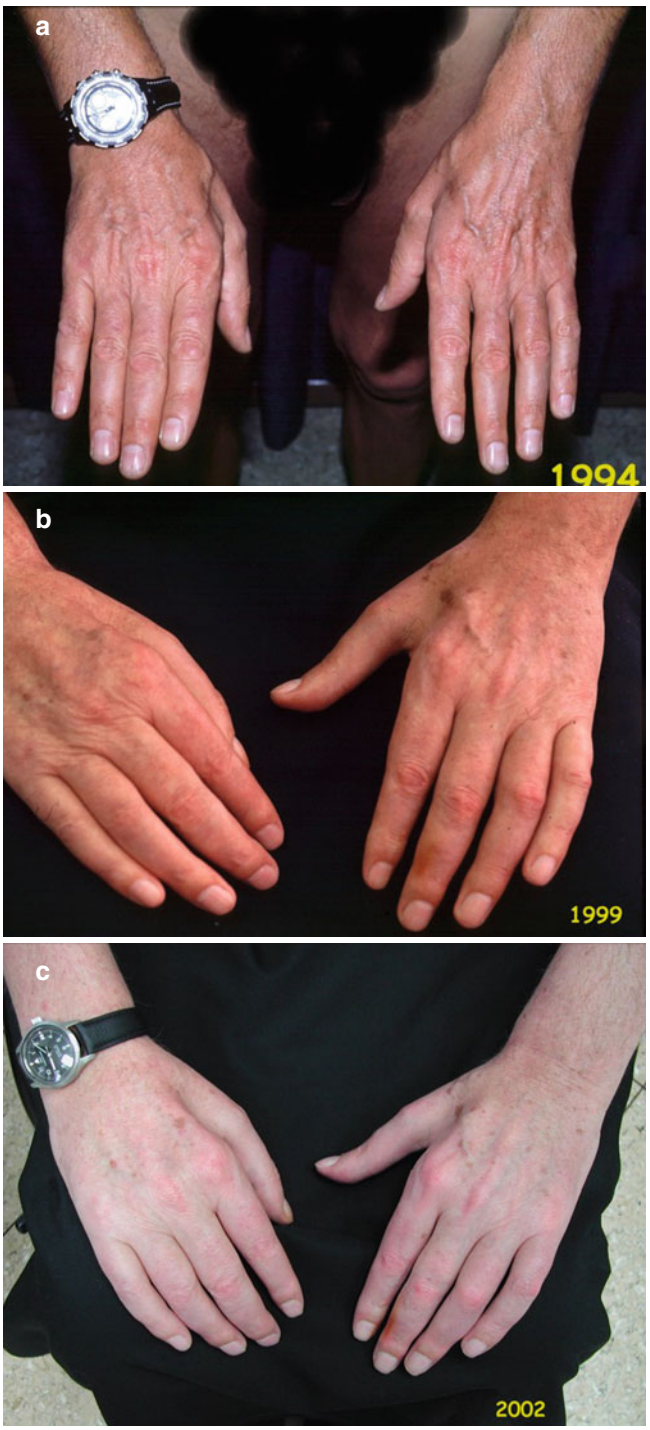


Fig. 1.8 Patient with a progressive axonal neuropathy. Follow-up over 8 years. (**a**) At the onset atrophy of the first interosseus can be noted. (**b**) 5 years later increasing atrophy. (**c**) 8 years later a severe atrophy, in particular, of the left hand of all intrinsic hand muscles developed

which can occur at the spinal cord, nerve root, or peripheral nerve level. Reflexes in myopathies are frequently diminished but preserved until late stages of the disease. 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 also be absent at rest and reappear after contraction or repeated tapping ("facilitation") as seen characteristically in the Lambert-Eaton syndrome. In summary, reflexes are useful to identify both widespread as well as local loss of nerve function and in combination with long tract signs that yield important diagnostic information.

1.4.4 Muscle Tone

Muscle tone is an important issue in motor neuron diseases, where it can be increased in ALS and decreased in SMAs. Muscle tone is assessed in parallel with reflexes.

1.4.5 Sensory Symptoms

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 paresthesias). Reports of permanent, undulating, or ictal (transient) loss of sensations should be recorded. In radiculopathies the sensory loss is rarely expressed through the whole dermatome but often confined to distal areas.

1.5 Sensory Qualities

- Negative symptoms are numbness, loss of feeling, perception, and even anesthesia.
- Positive symptoms are paresthesias, pins and needles, tingling, dysesthesias (uncomfortable feelings), or hyperpathia (painful perception of a non painful stimulus). Inadequate hyperpathia can result in allodynia. Pruritus occurs rarely.

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

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 pattern found. A patchy distribution is much rarer and can occur in the rare sensory neuritis of Wartenberg and in leprosy and sarcoid.

Transient sensory symptoms can be elicited by local pressure on a nerve, resulting in neurapraxia. In patients who have a history of repeated numbness and weakness in single nerve distribution, a hereditary neuropathy with pressure

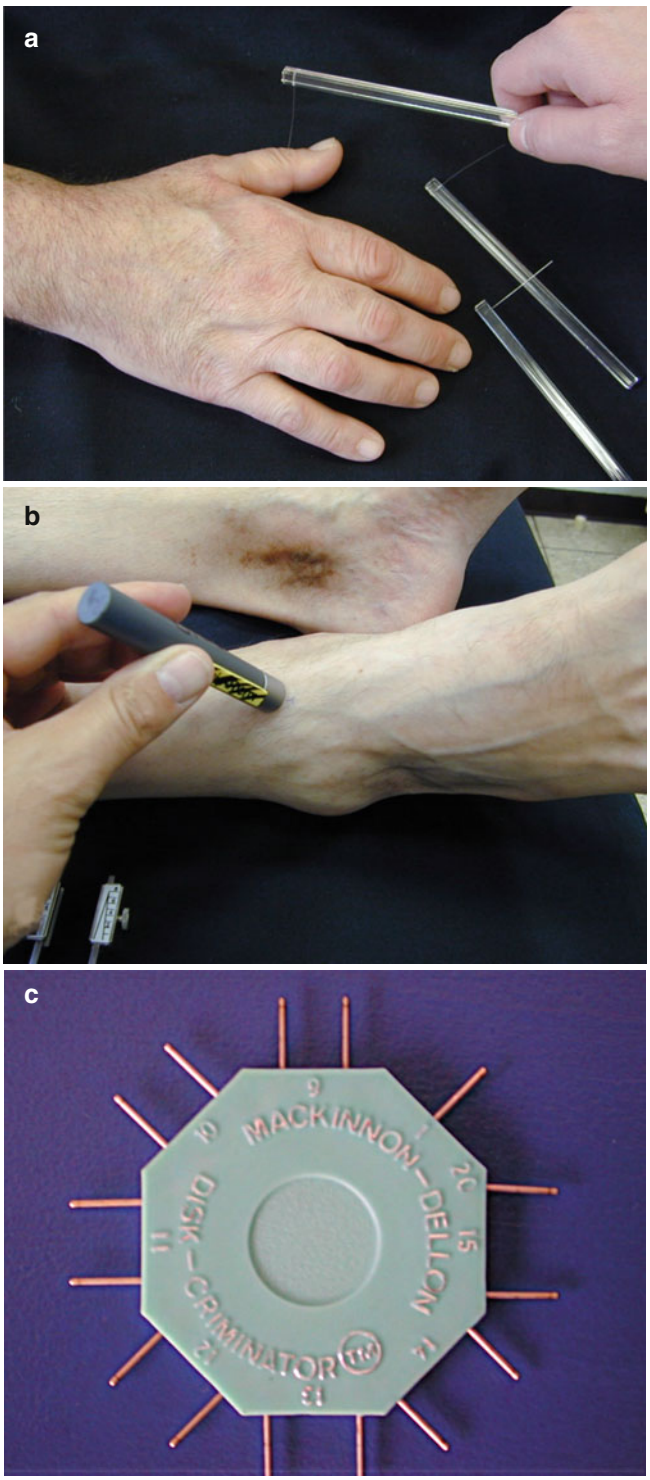


Fig. 1.9 (**a**) Weinstein filaments, (**b**) simple test for temperature discrimination, (**c**) Greulich "star" for two-point discrimination

palsy (HNPP) should be considered. Some transient sensory changes are characteristic but difficult to assess, such as perioral sensations in hypocalcemia or hyperventilation.

A characteristic sign of sensory neuropathy is the Tinel-Hoffmann 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.

Tinel has been described in carpal tunnel syndrome, cubital tunnel syndrome, radial nerve entrapment, tarsal tunnel syndrome, pronator compression, medial plantar neuropathy, superficial peroneal neuropathy, thoracic outlet syndrome, cervical radiculopathies, peripheral neuropathies, cervical plexus injuries, lateral femoral cutaneous entrapment, traumatic prepatellar neuroma, bowler's thumb, and peripheral nerve lesions.

Quantitative sensory testing includes sensory nerve conduction, testing of small fibers by cooling, and large fibers by vibration threshold and is increasingly used in neuropathies.

Distribution of Sensory Symptoms The distribution of sensory symptoms in peripheral neurology typically follows as segmental (radicular) or peripheral nerve distribution. Patchy and "atypical" sensory distributions are rare and can occur in Wartenberg's neuritis, sarcoid, and leprosy.

Small Fiber Neuropathy Small fibers can be affected predominately in some types of neuropathy, especially early in the course of the disease. In small-fiber neuropathy, clinical assessment of a patient reveals diminished pain, thermal and light touch perception, but intact vibratory and position sense. While conventional NCV studies are normal, a skin punch biopsy allows quantification of intraepidermal nerve fibers (IENF). IENF density is decreased in small-fiber neuropathies.

Raynaud's Phenomenon Occurs in connective tissue disease and has also been reported in peripheral autoimmune conditions and as a late effect in chemotherapy-induced neuropathies.

It is characterized by a discoloration of fingers and toes and is caused by an exaggerated sympathetic response causing vasoconstriction.

Other Types of Sensory/Pain Distribution In contrast to radiating pain, referred pain projects into remote cutaneous zones. These areas are sensitive to touch sometimes resulting in allodynia and hyperalgesia. A common example is an "ice cream headache" where pain from the throat and palate are referred to the sinus. Other examples include pain in the left shoulder/arm in myocardial infarction and pain in the right tip of the scapula in gallbladder pain (Kehr's sign).

1.5.1 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 and also

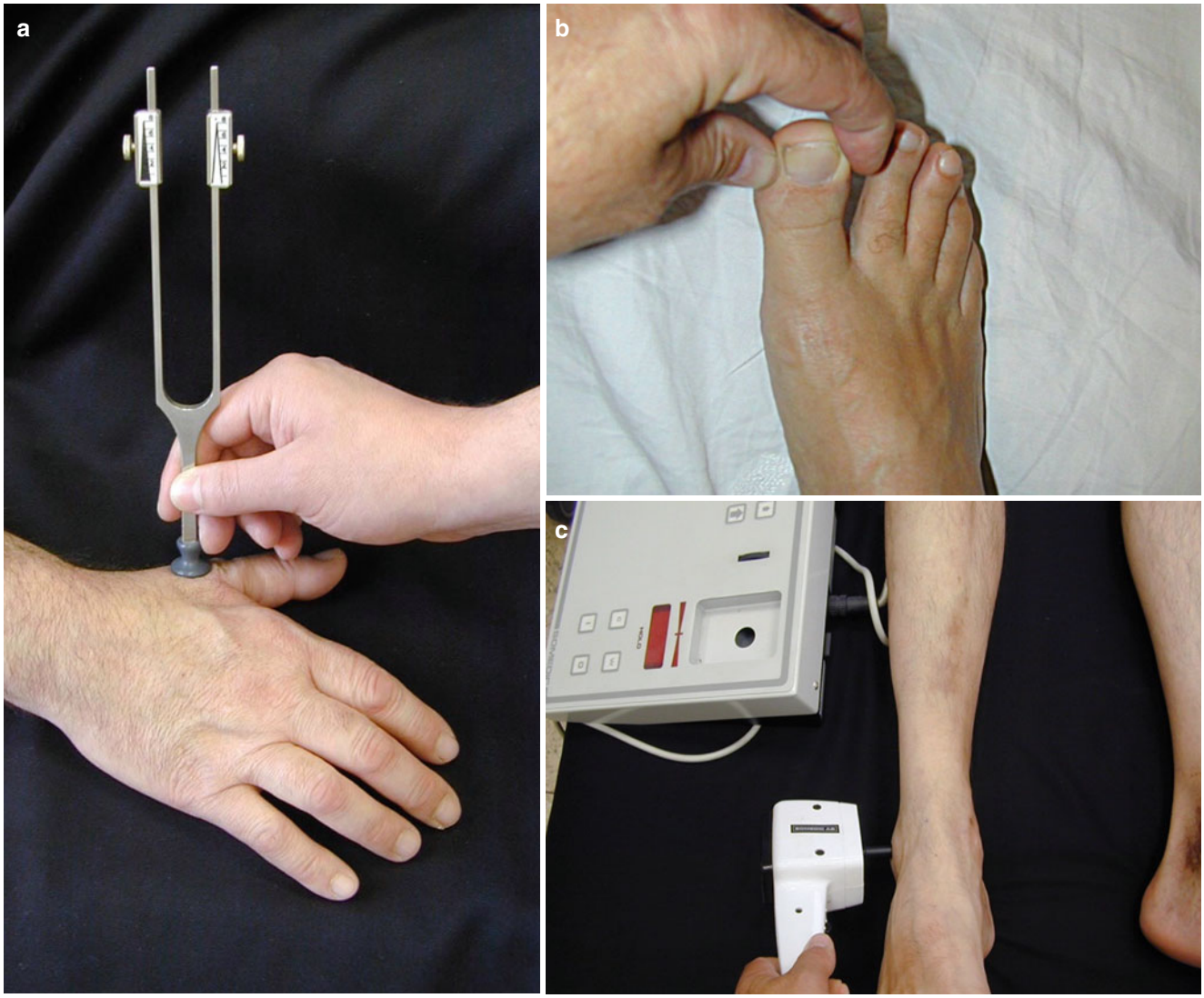


Fig. 1.10 (**a**) Vibration can be assessed with a Rydel-Seiffer tuning fork, (**b**) position sense, (**c**) vibrometer allows quantitative assessment of vibration threshold

toxic conditions (e.g., treatment with taxanes or gemcitabine). Focal muscle pain in association with exercise-induced ischemia is observed in occlusive vascular disease. Local, often severe, pain is the hallmark of compartment syndrome occurring after exercise or ischemia. Exercise-induced muscle pain in association with muscle cramps can be seen in metabolic disease.

1.5.2 Neuropathic Pain

The definition and characterization of neuropathic pain is essential for an accurate diagnosis of several neuromuscular disorders and is discussed in Chap. 4.

1.5.3 Autonomic Function

Autonomic signs and symptoms are often neglected and include loss of sweating leading to skin changes, orthostatic hypotension, tachyarrhythmias, ileus, urinary retention, impotence, incontinence, and pupillary abnormalities. In amyloidosis, autonomic neuropathy is frequently the presenting problem. In some polyneuropathies and mononeuropathies, autonomic involvement is documented revealed by skin changes at examination. The dry, anhydrotic 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 nail beds. The methods suggested for testing include RR variation testing, the

sympathetic skin response, and other components of the Ewing test battery. Autonomic function is discussed in more detail in Chap. 13.

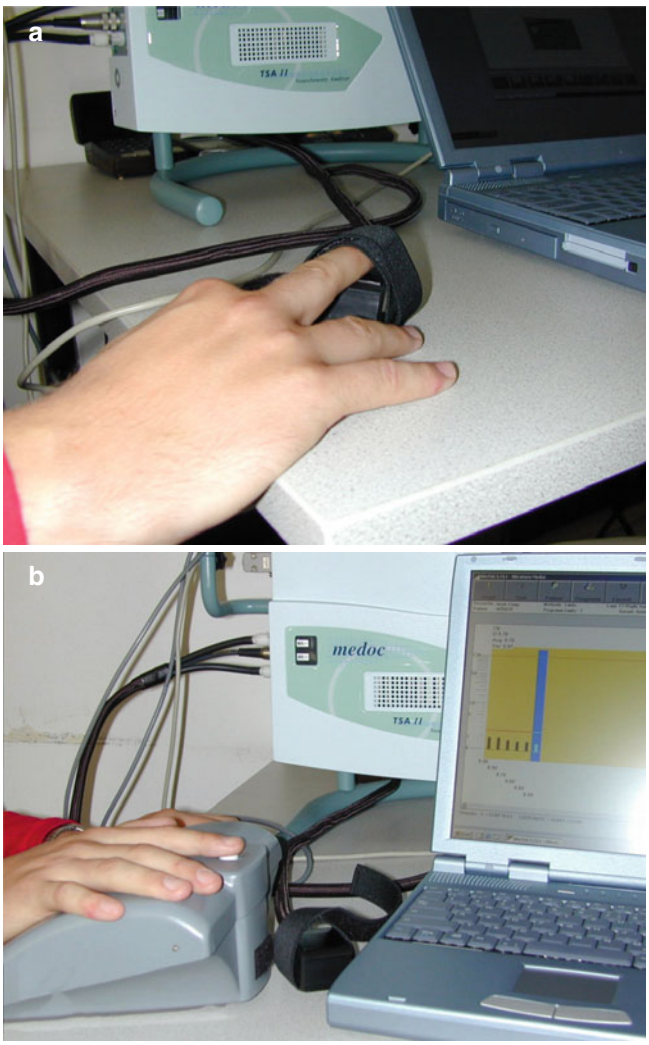


Fig. 1.11 (**a**) Small fiber, testing by thermal threshold. The finger is put on a device, which changes temperature. The patient is requested to report changes of temperature or pain. (**b**) Vibration threshold can be assessed electronically and displayed on the screen

1.5.4 Gait, Coordination

A patient's 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 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). Combinations of neuropathies and posterior column degeneration are observed in vitamin B12 deficiency. Transient gait disturbances may point to spinal claudication and also rarely to spinal arteriovenous malformations.

Deformities of the joints (Charcot joints, Charcot osteoarthropathy) can involve foot joints, the knee, and even the hip and the vertebral column. The clubfoot can be a clue to neuropathies or impaired sensory function, which can cause serious complications including spontaneous fractures, infections, osteomyelitis and necrosis, as well as neuropathic arthropathy and pain.

1.5.5 Clinical Pitfalls

There is normal variation in human anatomy that can influence aspects of both the clinical examination as well as results obtained from electrodiagnostic testing and imaging. For example, there are several anatomic variations of the peripheral nervous system including a pre- and postfixed brachial plexus and a median to ulnar anastomosis, termed a Martin Gruber anastomosis. In addition, while myotomes and dermatomes reflect radicular segmental innervation, anatomic studies show a significant degree of overlap among innervation patterns. Finally, myotome and dermatome patterns do not consider the innervation patterns of bone and joints, which can also be a source of pain and may make clinical diagnoses challenging.

Table 1.1 Sensory qualities

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	Greulich device	Large fibers

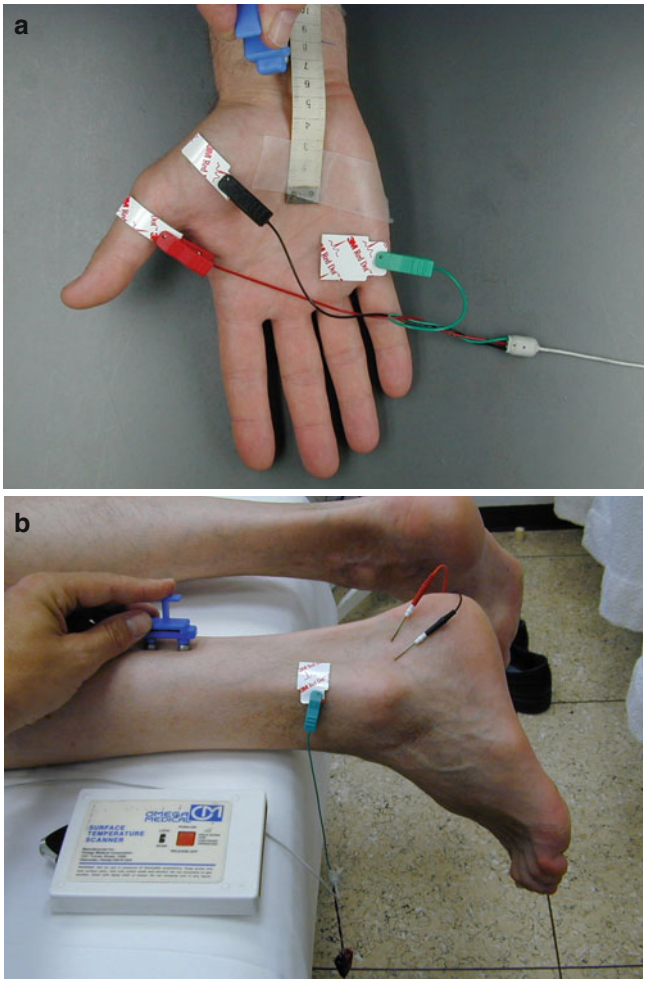


Fig. 1.12 (**a**) Motor nerve conduction (median nerve), (**b**) sensory nerve conduction, with near-nerve needle electrodes (sural nerve)

1.6 NCV/EMG/Autonomic Testing and Miscellaneous Electrophysiology

1.6.1 Motor NCV Studies

Motor nerve conduction studies 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. Both sensory and motor fibers are stimulated. The amount of time between the stimulation and muscle response (distal latency) includes the conduction time along the unmyelinated axonal endings and the neuromuscular transmission time. The difference in distal latency between two points of stimulation is used to calculate the nerve conduction velocity in m/s. The amplitude of the compound action potential 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.

NCV can be used to locate the site of entrapment in mononeuropathies. Local slowing, local impulse blockade, and decreased or absent CMAPs 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.

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 distal latencies can be assessed with certainty. Age, height, and temperature are also important factors.

Sensory NCV Studies Unlike motor conduction, where a terminal branch and synapse contribute to latency, no synapse exists between the stimulating site and recording site in a sensory nerve. Sensory nerve conduction (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 fiber populations conducting at different velocities (dispersion), which may be necessary for diagnosis in sensory neuropathies.

Sensory responses are more sensitive to temperature than motor responses in regard to conduction velocity, but not to nerve action potential amplitude. Warming of the extremity provides optimal readings; if this is not possible, correction factors exist for suboptimal recordings, but provide less useful information.

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

Late responses (F wave, M 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 an S1 radiculopathy.
- The blink reflex and the masseteric reflex are used in the evaluation of cranial nerve and brainstem function. Primary and secondary homo- 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.
- Reflex testing of deep tendon reflexes can be performed with a "trigger" hammer to elicit the reflex arc and an EMG from the respective muscle. The latencies vary between 20 and 30 ms for the polysynaptic stretch reflex, depending on the size of the person examined. In clinical practice, this technique is rarely used although it measures an extensive sensorimotor loop.
- 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 accessory, suprascapular, axillary, musculocutaneous, femoral, and sciatic nerves can be evaluated by this method.
- 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's amplitude and area are recorded and measured. Repetitive nerve stimulation allows a distinction between pre- and postsynaptic transmission disorders. MG is usually detected at 3 Hz low-frequency 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 also observed in other conditions.
- Evoked responses, in particular somatosensory-evoked responses, allow measurement of central structures like the posterior columns and provide additional insight into the peripheral-central conduction properties.
- 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 is the basic method to study skeletal muscle function. In Europe, concentric needle electrodes are mainly used, while in the United States mainly 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 and is not in routine practice.

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 belong in this category, but are usually considered spontaneous activity by the neuromuscular practitioner.
- 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. Complex repetitive discharges (CRD) stem from electrically linked muscle fibers, firing in a synchronous pattern.
- Voluntary activity
  Voluntary innervation generates motor unit action potentials (MUAP). 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 between 5 and 15 ms, has up to four phases, and has an amplitude maximum of 1–3 mV. For the assessment of MUAP potentials, duration is more constant and reliable than amplitude.
- Maximum contraction produces overlapping MUAPS, called an interference pattern in normal conditions. The spectrum of pathologic conditions 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 any 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 20–80 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 are bursts of motor unit potentials (resembling normal MUAPS) and appear 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 and 150 Hz.

1.6.2 EMG Techniques

- Quantitative EMG: Usually 20 MUAPs are analyzed for this technique. Automated or semiautomated methods are available on most 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. Quantitative EMG is the backbone of EMG studies and is performed with monopolar and concentric needle electrodes.
- Single fiber 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 the "jitter," which depends on the functional state of the 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).
- Special EMG applications:
  - Diaphragmatic EMG
  - Sphincteric EMG
  - EMG of the vocal cords (also monitoring of thyroid surgery)
  - Intraoperative techniques
  - Surface EMG
  - Polygraphy (usually surface EMG) to monitor or detect complex functions (e.g., sleep, gait, startle reactions)

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 activity. Specific (or almost specific) phenomena can appear, as well evidence of denervation, reinnervation, and acute or stable conditions. EMG is considered an electrophysiological "extension" of the neurological examination, and results should be interpreted in conjunction with the patient's clinical history, examination, and ancillary test results.

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

NCV and EMG are generally considered to be safe procedures and are in routine clinical practice. Generally the risk of a precisely placed EMG needle is low, although iatrogenic side effects have been reported for both EMG and NCV. The risk in patients with anticoagulants or on antiplatelet medication is also low, although electromyographers frequently avoid paraspinal EMG in the anticoagulated patient.

1.7 Laboratory Tests

Complete blood count and blood chemistries are routinely obtained on most patients presenting for diagnosis. Different neuromuscular disorders mandate more specialized serological testing, which is discussed in each chapter under the individual disorders. Unfortunately, there are no Class A studies available to define the spectrum of laboratory tests needed for the most common neuromuscular disorder: polyneuropathy. A fasting blood glucose, B12 level, and serum immunoelectrophoresis have the highest diagnostic yield.

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.

The CSF is often studied in polyneuropathies, particularly in acute and chronic inflammatory neuropathies. Often, inflammatory or cellular responses can be ruled out by a normal CSF white blood cell count, and elevated protein levels remain the only insignificant finding. Elevated CSF white

Table 1.2 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	GBS, CIDP	Serology
CMV-radiculitis	8/µl	Mixed cell population	Cauda equina syndrome	
Syphilis	Early: 25–2,000/µl IgG>> Late: may be normal	Lymphomonocytic cell count	Painful polyneuropathy Tabes dorsalis	Specific test
Brucellosis	15–700/µl cells	Lymphocytes, granulomatous meningitis	CN: VII, lumbar radiculopathies polyradiculopathies	
West Nile fever	Pleocytosis Protein elevation	Lymphocytic cell distribution	GBS-like polyneuropathy	
FSME ("Central European tick encephalitis")	60–2,000/µl	Lymphocytes: 20–60 % lymphocytes and 40–80 % PMN	Radiculitis, myelitis, poliomyelitis-like, CN	Antibody testing

blood cells suggest other inflammatory or infectious etiologies (Table 1.2).

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 occurring conditions, like GBS and 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 anti-myelin-associated glycoprotein (MAG) neuropathy is a typical syndrome with MAG positivity in 50–70 %. The GQ1b antibody is recorded in 95 % of patients with the rare Miller-Fisher syndrome. There are several antibodies described associated with different neuropathies. These include IgM antibodies (GalC, GalNAc-GD1a, Galop, GD1a, GD1b, GM1 ganglioside, MAG, neurofilaments, SGPG, sulfatide, and tubulin) or IgG antibodies (gangliosides as GM1, GD1b, GQ1b, GT1a, GD1a). In most cases, the role and frequency of occurrence for these antibodies is not certain. In vasculitic neuropathies, c-ANCA and p-ANCA antibodies can be found.

In paraneoplastic sensory neuropathies, the association with anti-Hu antibodies (or amphiphysin antibodies) 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 (MGUS) or point to hematologic diseases like multiple myeloma, Waldenstrom's disease, osteosclerotic myeloma, or lymphoma. Electrophoresis, immunofixation, and often bone marrow biopsies are needed, often in addition to skeletal X-ray and nerve biopsies. This is discussed in detail in Chap. 10.

1.7.1 Autoimmune Testing in Neuromuscular Transmission and Muscle Disorders

The prototypes of neuromuscular junction disorders are myasthenia gravis (MG) and the Lambert-Eaton syndrome (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 patients with typical generalized MG are seronegative for AchR antibodies; a percentage of these individuals have antimuscarinic (MUSK) antibodies, although there are patients with MG who have neither antibodies. Striational antibodies lack specificity 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, there are calcium channel autoantibodies directed against the P/Q type channels. These autoantibodies are detected in nearly 100 % of patients with LEMS. Antibodies against the N-type channel are detected in 74 % of LEMS patients. LEMS is most commonly associated with small-cell lung cancer. Serum from

patients with small-cell lung cancer is also positive for antibodies against intracellular antigens, including SOX and HU, present in 60 and 30 % of patients, respectively.

Autoantibodies to ganglionic acetylcholine receptors resulting in autonomic dysfunction have been described.

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 ryanodine receptor.

In various types of myositis, antibodies like anti-Jo 1, anti-PL 7, anti-PL 12, anti-OJ, anti-EJ, and anti-KS and several others as SRP, MI-2 are described. While some of these antibodies may help to predict disease course, prognosis, and response to therapy, the pathogenic role of these antibodies is not well understood.

1.8 Genetic Testing

Genetic testing is an important tool in the diagnosis of neuromuscular diseases, and since the first edition of this book in 2004, the field has grown tremendously. Several techniques are presently available, and with the advent of exome sequencing, it is likely that the number of identified genetic disorders will continue to increase at an even more accelerated pace.

- Cytogenetics is used to visualize large genetic anomalies like aneuploidies and some nonaneuploid or euploid cytogenetic abnormalities. Fluorescent in situ hybridization (FISH) adds an additional level of resolution and can be used to detect deletions, duplications, and rearrangements.
- DNA mutation tests are used to assess the presence of DNA deletions, duplications, or point mutations. While these changes can be assessed by a variety of methods, the most common approach is via polymerase chain reaction (PCR) of the specific gene area of interest followed by Southern blotting to visualize the distinct PCR products. In addition, assessment of restriction fragment length polymorphisms provides a method to detect point mutations.

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. Also the variability between genotype and phenotype can be considerable in several diseases. Increasingly dealing with the ethical, social, and personal issues that arise for patients and families is important, and genetic counseling and advice needs to be available to the affected neuromuscular patients.

1.9 Neuroimaging Techniques: MR and Ultrasound

MRI has become the method of choice for many conditions, although CT remains superior in the imaging of bones and calcified structures. Ultrasound is a fast and inexpensive application with the additional ability to display dynamic processes (e.g., movement of peripheral nerves and of muscles such as the diaphragm).

1.9.1 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 osseous changes.

MR spinal cord imaging is the method of choice for degenerative disk disease and is a valuable method to discriminate disk bulges and herniations. MRI is also used to identify degenerative changes of the facets and uncovertebral 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.

In addition to conventional MR studies, several techniques such as magnetization transfer and diffusion tensor imaging (DTI) are focused on imaging the course of the peripheral nerves. In addition, MR of the muscles supplied by the peripheral nerve scan can be helpful as was discussed earlier in this chapter.

1.9.2 Imaging Muscle Disease

Muscle tissue can be visualized by ultrasound, CT, and MRI.

Ultrasound is well established in pediatric neurology and is now used in adults to assess muscle integrity (muscle echo intensity, fatty degeneration, atrophy, hypertrophy) as well as functional aspects of muscle movement, such as contractions and fasciculations. Ultrasound also allows visualization of anatomical structures during interventional techniques, such as botulinum toxin injections for dystonia.

CT has been widely used for the examination of muscle disease. It allows fast images and also good resolution of deep muscle structures. In addition, spatial resolution and multiplanar reconstructions yield high-quality information on muscle integrity. Because CT subjects the patient to a high radiation dose, it is being replaced by either ultrasound or MR imaging.

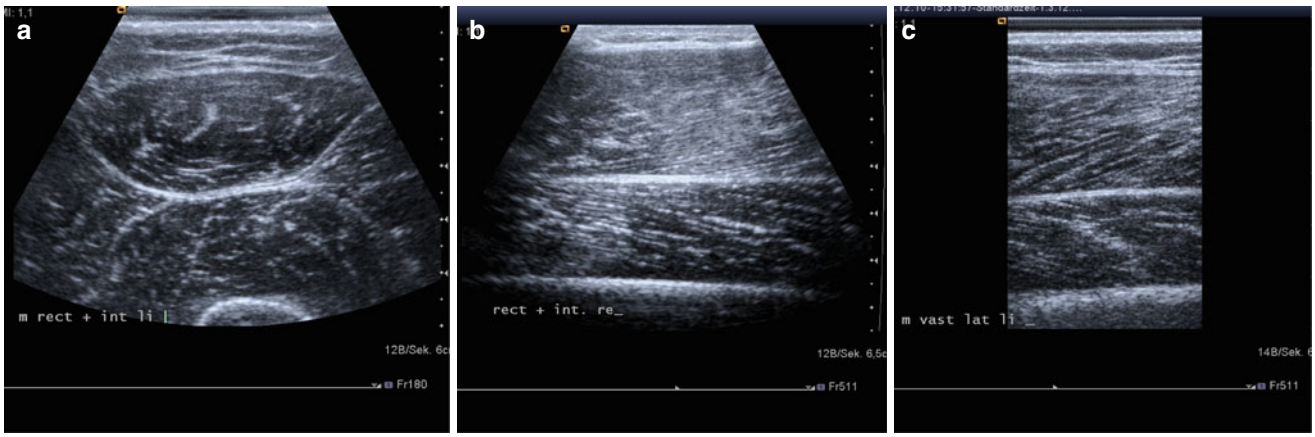


Fig. 1.13 Ultrasound images of muscle are useful for the evaluation of muscle tissue and also in intervention, such as botulinum toxin. These images show a transverse (**a**) and longitudinal (**b**) section of the rectus femoris muscle in a healthy person and a transverse section through the vastus medialis muscle (**c**)

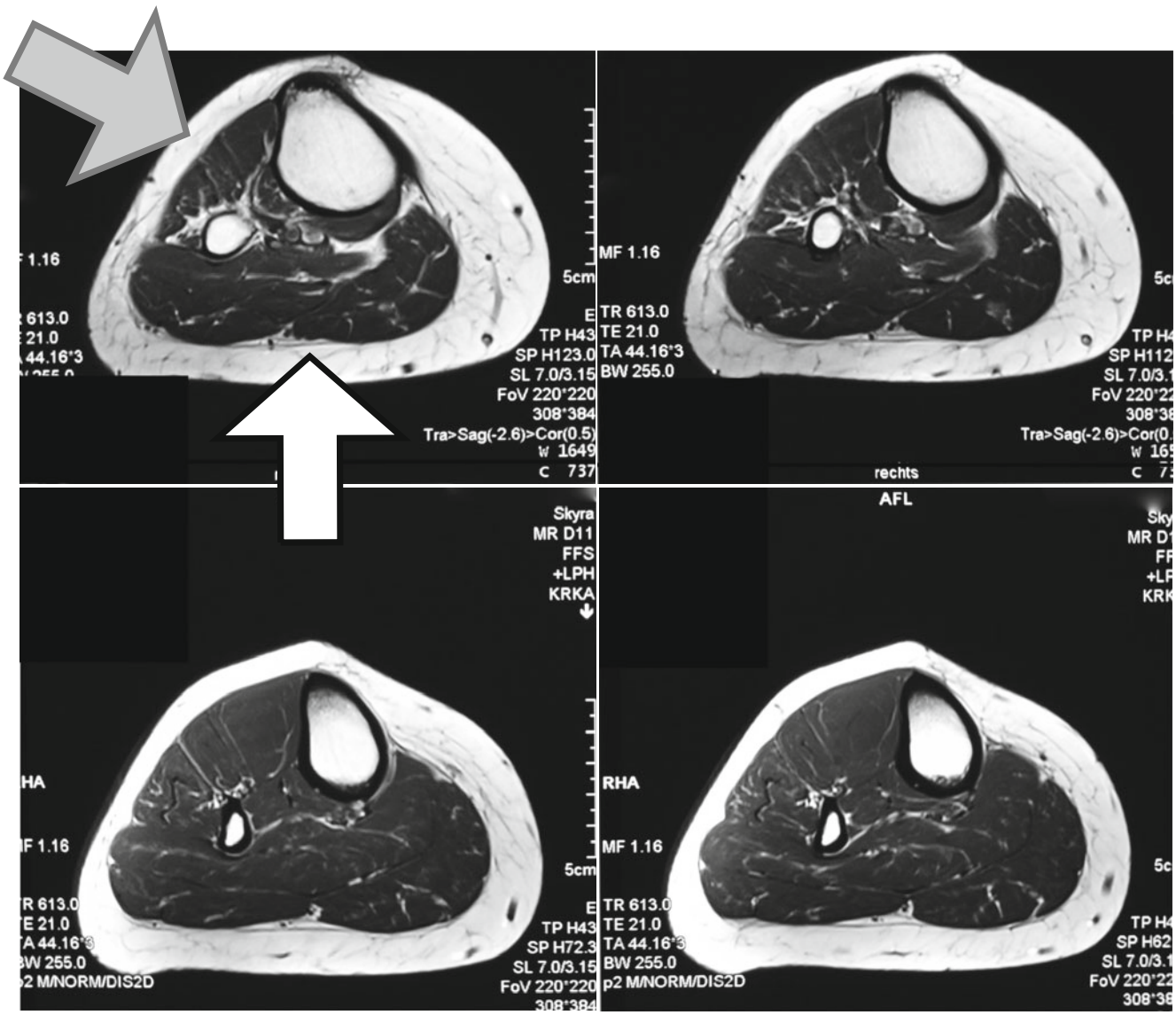


Fig. 1.14 Calf muscles. MRI of normal calf muscles: *Gray arrow* anterior compartment. *White arrow*: calf muscles

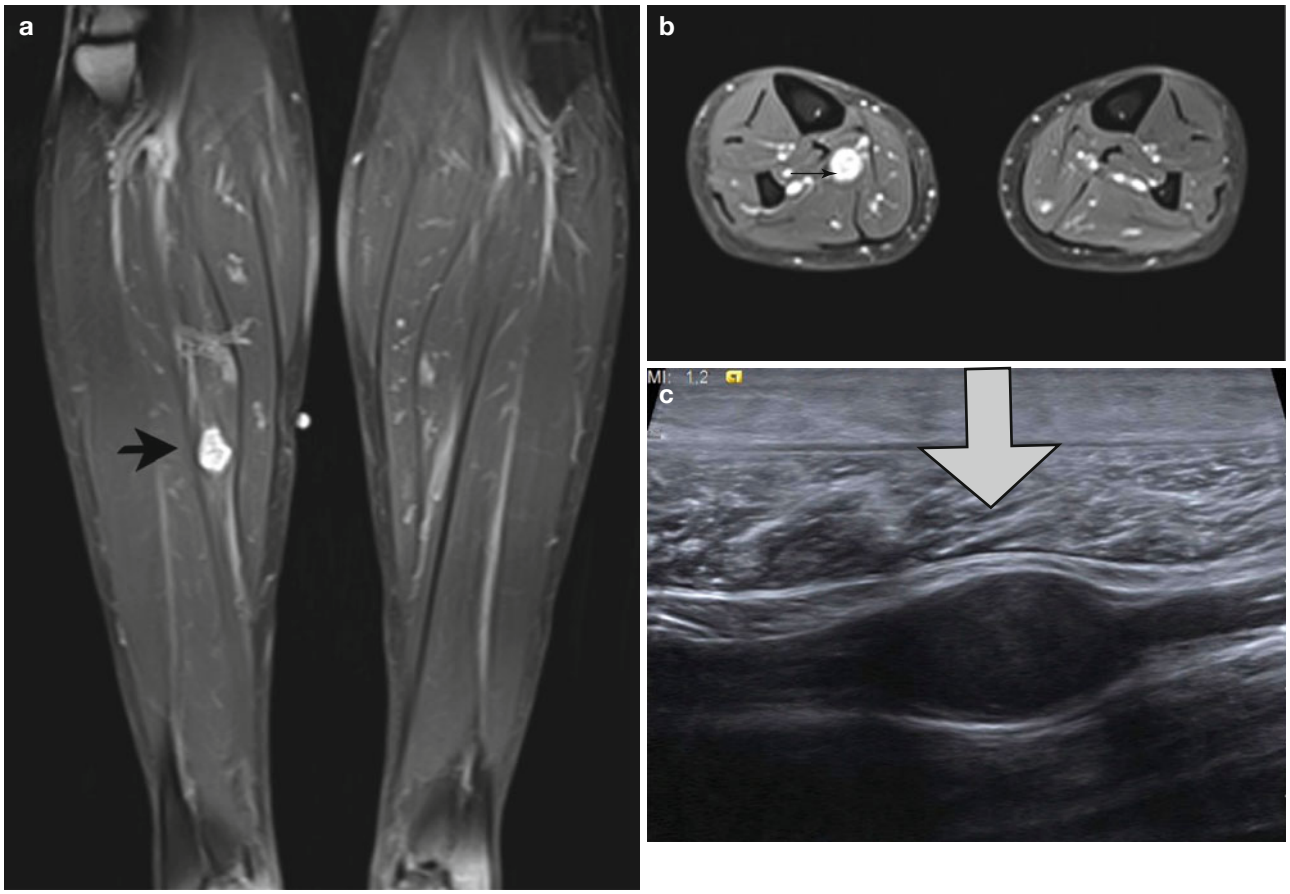


Fig. 1.15 Case: 50-year-old man complained of electric pain radiating from his lower leg into his foot. The clinical examination was normal, except for a Tinel's sign that was elicited with percussion of the lower leg. MRI (**a**, **b**) and ultrasound (**c**) showed a nerve tumor, which was identified to be a Schwannoma

MRI is increasingly used in patients with inherited, metabolic, and inflammatory muscle disorders. It allows an excellent assessment of muscle architecture using T1- and T2-weighted as well as fat suppression techniques. Whole body imaging can also evaluate all striated muscle groups. Imaging techniques and the evaluation of the distribution of pathology are often performed before biopsy. Muscle edema, which can be due to toxic, metabolic, and inflammatory changes, is easily detected by MRI.

MR spectroscopy and perfusion imaging, as well as blood flow measurements are used for specific diagnoses. Patients with muscular dystrophies, myotonic dystrophy, congenital myopathies, and also to a lesser extent muscle channelopathies and metabolic myopathies have been imaged with MR studies.

1.9.3 Imaging of Peripheral Nerves

MR neurography is becoming an important method to identify small focal lesions. Using MR to detect optic neuritis is routine in multiple sclerosis patients. Other nerves, like the inferior alveolar and mandibular nerves, can also be imaged for evidence of swelling or disruption.

The brachial plexus, which is difficult to assess by other methods, can be visualized to assess swelling and inflammation and tumors or to discriminate between radiation-induced and neoplastic neuropathy. This is also true for the lumbar and sacral plexuses, where MR imaging can resolve the nerve from the surrounding structures.

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

1.10 Tissue Diagnosis: Muscle/Nerve/Skin Biopsy

Nerve and muscle biopsy are important tools in the diagnosis of neuromuscular disease. Precise clinical, electrophysiological,

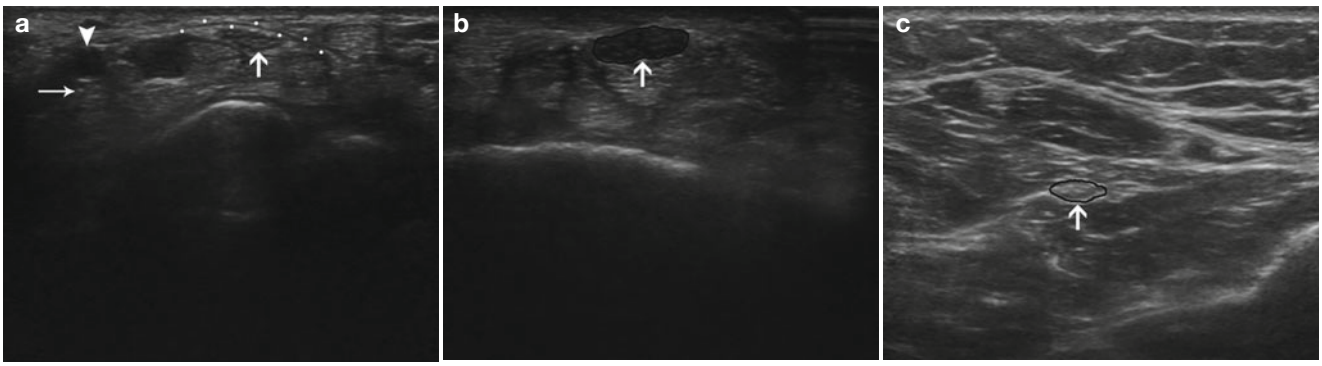


Fig. 1.16 (**a**) Median nerve (*arrow*), retinaculum flexorum (*dotted line*), ulnar nerve (*arrow head*), ulnar nerve (*thin arrow*). (**b**) Enlarged nerve proximal to the carpal tunnel in CTS (*arrow*). (**c**) Median nerve in the forearm. The diameters of the distal nerve (**b**) and the nerve at the forearm allow intraindividual comparisons. The circumference of the median nerve is marked with a circle

and laboratory diagnostics must be done and assessed before a biopsy is done. The biopsy must be taken from the correct tissue. 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, neoplastic infiltration, or florid polymyositis. The number of nerve biopsies performed on patients is decreasing due to the increased power of genetic testing as well as the sufficiency of clinical and immunological criteria for some diseases like CIDP and MMN.

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.

1.10.1 Nerve Biopsy

The sural nerve is the most frequently biopsied nerve. Some schools prefer the superficial peroneal nerve or the radial nerve, and biopsies from other nerves such as the pectoral nerves can also 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 materials may be necessary in cases of vasculitis.

The histologic examination includes hematoxylin-eosin sections, staining for myelin, and special stains depending on the clinical 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 affections such as neoplastic involvement or deposition of amyloid. Several complications have been reported although generally nerve biopsy is safe.

1.10.2 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, inclusion body myositis), structural abnormalities, and finding additional morphologic indications 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 punch biopsy allows an estimation of epidermal innervation. It is the diagnostic tool of choice in small-fiber neuropathy.

1.11 Neuromuscular Approaches to Intervention: Effects of Regional Anesthetic Procedures

Complications of local anesthetics: Local anesthesia can cause long lasting neuromuscular complications, including paresthesias, numbness, and motor dysfunction. The overall incidence of long-term nerve injury ranges between less than 0.02 and 0.4 %, depending on the definition of injury and the

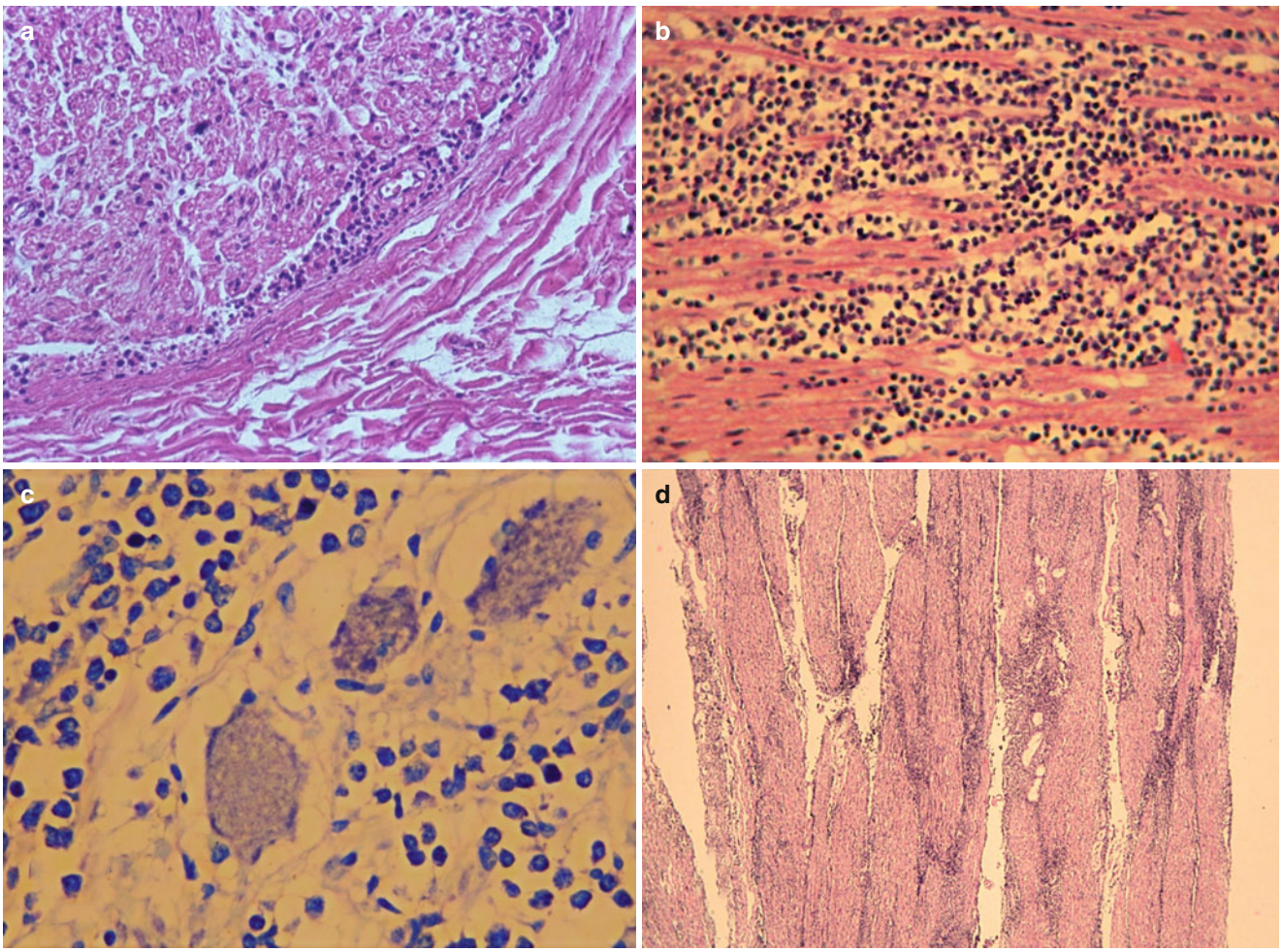


Fig. 1.17 Tissue diagnosis is often important in neoplastic nerve disease. Lymphoma: (**a**) small lymphoma infiltration in a nerve fascicle, (**b**) diffuse cranial nerve Infiltration, (**c**) dorsal root ganglion with sparse lymphocytic infiltration, (**d**) cranial nerve invasion in a more patchy fashion

length of follow-up. The mechanisms are speculative and include ischemia, inflammation, and mechanical trauma during procedures. In addition postprocedural positioning may cause peripheral nerve damage. All local anesthetics in clinical concentrations can be myotoxic causing myonecrosis; this is particularly true of bupivacaine. The differential diagnosis of postprocedural nerve or muscle damage requires clinical examination, electrophysiology, and imaging.

Quantification of function, impairment, disability, treatment outcome, and quality of life are parameters which require 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. As discussed in the beginning of this chapter, European physicians use the ICF as a metric to assess a patient's overall function while American physicians are using a standardized National Institutes of Health Tool Box (www.ninds.nih.gov) for specific neuromuscular diseases. These newer metrics employ components of older but well-standardized motor, sensory, spasticity, respiratory, and disability scales. Pain scales are now more widely used in assessing the level of a patient's discomfort and monitoring success of therapeutic interventions. A new addition to the field of neuromuscular disease is the emphasis on quality of life as both a patient-centered outcome and a measure of disease efficacy. Specific quality of life-outcome tools are now available for neuropathies, myopathies, and motor neuron diseases.

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Principles of Peripheral Nerve Surgery

2

R. Schmidhammer

2.1 Defining the Problem

The loss of afferent and efferent signal transduction following traumatic peripheral nerve injury has immediate and long-term effects on target organs (e.g., muscles and sensory receptors) as well as somatosensory and motor brain areas. The goal of surgical peripheral nerve repair is to mitigate these negative outcomes by restoring the continuity of the damaged peripheral nerve to allow axonal regeneration and reinnervation of target tissues. A complete understanding of the organizational complexity of peripheral nerve architecture reveals that a peripheral nerve is more than just a "cable" connecting central neurons to peripheral end organs. The outcome of nerve repair depends on many factors, not only at the site of injury but also in the central nervous system, which can undergo functional cortical reorganization in response to post-injury axonal outgrowth.

Peripheral nerve injuries are a major challenge for reconstructive surgeons, and several factors influence outcome, including age of the patient, severity and level of the nerve lesion, length of the nerve defect, and associated injuries. While age appears to be the primary determinant of recovery, surgical technique and the general surgical management of the injury have a definite impact on the final outcome. The introduction of microsurgical techniques using microsutures and the operating microscope has improved patient outcomes. Management also includes neurorehabilitation immediately after surgery and the management of restorative/reconstructive procedures following nerve repair.

2.2 Timing of Nerve Repair

The timing of nerve repair depends on several factors, including the type of nerve injury (open versus closed), condition of the wound (e.g., infection), general condition of the patient (polytrauma), and the extent of soft tissue and bone damage. In cases of sharp nerve transections with no or minimal crush components, a clean wound, and good blood supply with adequate soft tissue cover, primary nerve repair is the best option for neurotization of a distal nerve stump, reinnervation of the target organ, minimizing apoptosis of neurons, and functional central neuronal reorganization.

Primary nerve repair is performed within 7 days after nerve injury. If immediate repair is not possible, secondary nerve repair is indicated (after wound healing approximately more than 3 weeks after the trauma). Arguments for secondary nerve repair are reduced risk of complications (problems in vascular repair, bone, and skin have been solved), and induced fibrosis of damaged tissue may be completed 3–6 weeks after trauma. Secondary repair is also preferable in blunt nerve injuries. Lack of clinical and electrophysiological signs of regeneration 3–6 months after injury warrants surgical exploration. An overview of open and closed nerve injury management is given in Fig. 2.1a, b.

2.3 Restoration of Nerve Continuity

2.3.1 End-to-End Coaptation (Direct Nerve Repair)

Neurotization of a distal nerve stump using end-to-end coaptation of healthy conducting elements is called "direct nerve repair." Direct nerve repair is the option of choice when the nerve defect is small and nerve stumps can be approximated with minimal tension. For optimal nerve regeneration after repair, nerve stumps must be precisely and atraumatically coapted without tension and repaired with minimal number of sutures. End-to-end nerve coaptation techniques include epineurial repair (coaptation of the nerve using stitches through the epineurium), group-fascicular repair (coaptation of fascicle groups), and fascicular repair (coaptation of fascicles if fascicles do not show group formation). Epineurial repair is a commonly used technique following sharp nerve injury of proximal portion of nerves without nerve tissue loss and for partial injuries

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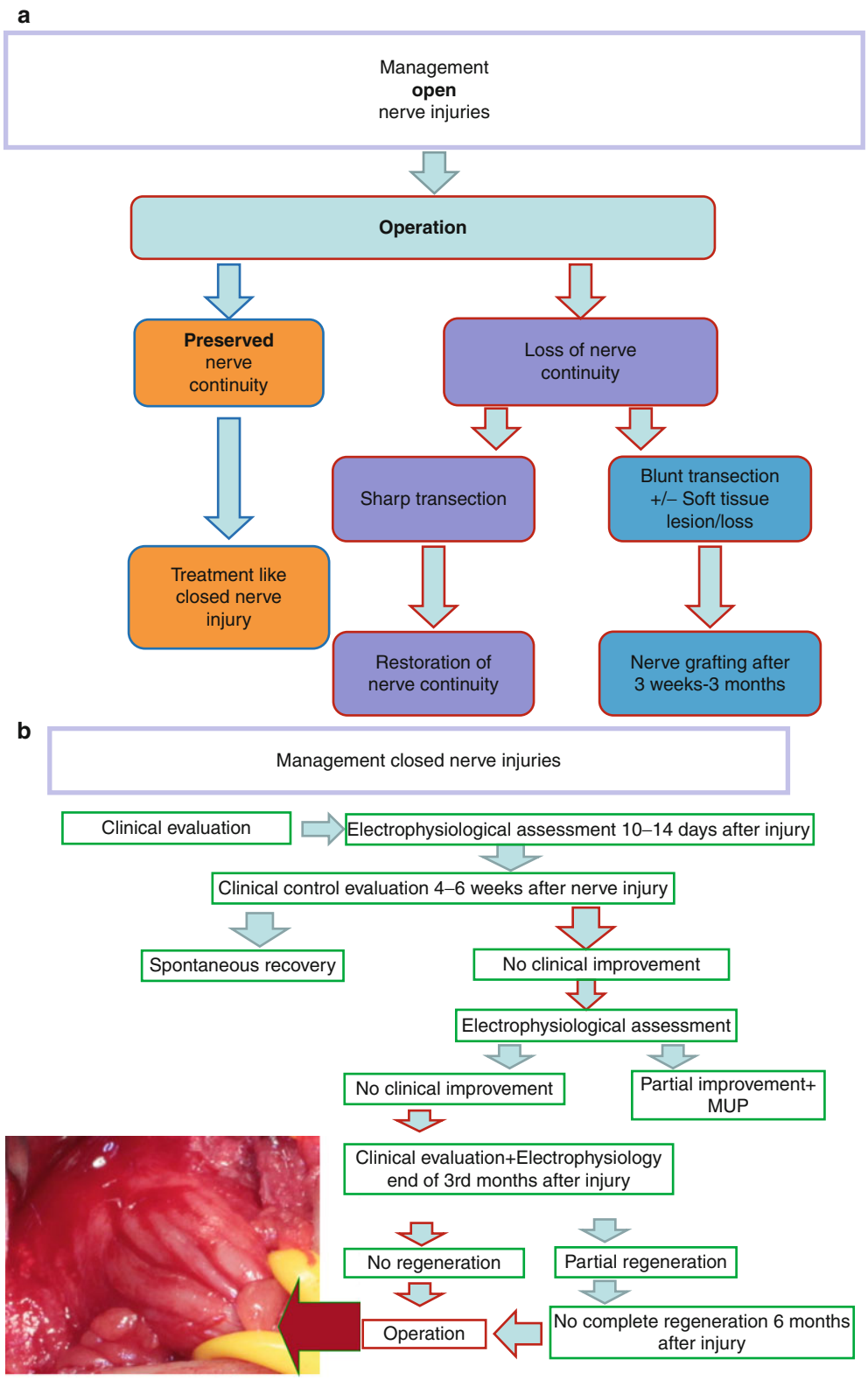

Fig. 2.1 Management of open (**a**) and closed (**b**) nerve injuries

with good fascicle alignment. The main goals of epineurial repair are to obtain continuity of the nerve stumps without tension and with proper fascicular alignment. Correct fascicle positioning can be confirmed by the continuity of the nerve's surface structures such as blood vessels (vasa nervorum) within the epineurium.

2.3.2 Nerve Grafting

When primary end-to-end coaptation cannot be performed without tension due to segmental nerve loss, restoration of nerve continuity using interfascicular nerve grafting according to Millesi (1976) is necessary. Nerve grafts produce superior results when compared with direct repairs performed under undue tension, which results in nerve ischemia. While tubulization techniques using various biological or artificial materials as scaffolding are feasible for gaps less than 3 cm, autologous or allogeneic nerve grafting is required for restoration of nerve continuity across larger gaps.

Autologous Nerve Grafts (Nerve Autografting)

The free interfascicular autologous nerve grafting technique is the gold standard for reconstruction of segmental nerve defects. The axons of the harvested fascicular graft undergo Wallerian degeneration, but the graft provides Schwann cells and mechanical guidance for the regenerating axons of the proximal stump. Autologous nerve grafts provide a permissive and stimulating scaffold for growing axons that includes Schwann cell basal laminae, neurotrophic factors, and adhesion molecules.

Clinical observations show that smaller caliber grafts result in better outcomes. Sensory cutaneous nerves are commonly used as donor nerves for autologous nerve grafting because their harvest results in acceptable morbidity, mainly sensory loss in the area supplied by the harvested sensory branch. While the lateral antebrachial cutaneous nerve, the anterior division of the medial antebrachial cutaneous nerve, the dorsal cutaneous branch of the ulnar nerve, the superficial sensory branch of the radial nerve, and saphenous nerves are commonly used donors, the sural nerve is most often used. Over 20 cm of the graft material can be obtained when the sural nerve proper is harvested alone and up to 50 cm (dependent on the lower limb length) when harvested with the medial sural cutaneous nerve. The small diameter of the sural nerve (2–4 mm) and presence of nutrient vessels within the nerve enable fast revascularization of the grafts. Donor site morbidity of harvesting the sural nerve ranges from sensory deficit, dysesthesia, or hyperesthesia around the lateral foot (reported as a main complaint in 9.1–44 % patients) to neuroma formation and unbearable pain noted in 6.1–8.1 % of cases. It is important to know that painful neuroma formation only occurs if the proximal stump of the sural nerve is left in the subcutaneous tissue of the leg after harvesting. The symptoms may be persistent but are generally well tolerated.

Nerve Allografts (Nerve Allografting)

While autologous nerve grafts remain the gold standard for reconstruction of segmental nerve loss, the limited amount of available nerve grafts, and to some extent donor site morbidity, can be significant limitations of this technique. Nerve allografts are an alternative, and extensive experimental studies on nerve allograft immunogenicity, immunosuppressive regimens, and allograft revascularization have led to the reintroduction of nerve allografting into clinical practice.

Results of a multicenter study on the use of processed nerve allografts without the need of immunosuppressive treatment show that processed nerve allografts perform well and are safe and effective in sensory, mixed, and motor nerve defects between 5 and 50 mm. The outcomes for safety and meaningful recovery observed in this study compare favorably to those reported in the literature for nerve autograft and are higher than those reported for nerve conduits.

Nerve Conduits (Conduit Repair)

Currently, tubulization using various natural and synthetic materials is effective only for small nerve defects up to few centimeters.

Biological Conduits Veins, arteries, mesothelial chambers, predegenerated or fresh skeletal muscle, and epineural sheath have been studied as biological conduits for nerve repair, with vein grafts studied most extensively. Good functional outcomes were demonstrated clinically, particularly in pure sensory digital nerve repair. A combined conduit where vein graft was filled with muscle to prevent graft collapse and facilitate axon guidance was applied in repair of 40 cases of sensory and mixed nerve defects (0.5–6 cm), with good results achieved in 85 % of patients.

Artificial Conduits Progress in tissue engineering has led to the introduction of artificial nerve conduits as a new method to restore segmental nerve defects. While many materials have been tested in animal models, only five products are currently FDA-approved for clinical use; four are resorbable (made of PGA, PLCL, and collagen I) and one non-resorbable (polyvinyl alcohol hydrogel). All of these artificial conduits are restricted for use in short nerve defects only. Despite significant progress in tissue engineering, restoration of segmental nerve defects exceeding 3 cm using tubulization materials remains challenging.

2.4 End-to-Side Coaptation

Neurotization of a distal nerve stump using an end-to-side coaptation technique (a denervated distal nerve stump coapted to the side of an innervated nerve, thus inducing collateral sprouting) is a promising procedure for repair of peripheral nerve injuries where the proximal nerve stump is not available. It is particularly useful in brachial plexus injuries and facial nerve reanimation. One of the major advantages of end-to-side repair is the recovery of function of the injured nerve without compromising the function of the donor nerve. Consistent results can be achieved if small donor nerves with a well-defined function are used; results are more unpredictable if mixed nerves are used.

2.5 Nerve Transfer

Nerve-to-nerve transfers are another alternative for restoration of function when no proximal nerve stump is available, representing one of the greatest advances in peripheral nerve surgery. However, there is a risk for donor nerve impairment.

2.6 Neurolysis

Neurolysis is a procedure that has to be performed if the gliding tissues of a peripheral nerve are severely impaired by posttraumatic adhesions or fibrosis. The paraneurium is a delicate gliding layer between the epifascicular epineurium and the tissue surrounding the nerve, providing the ability for the nerve to passively adapt to the different positions of the moveable extremity. The interfascicular epineurium allows the movement of fascicles within the nerve. Neurolysis is a stepwise microsurgical procedure with the aim of decompressing the fascicles when gliding tissues of the nerve have become impaired, leading to fibrosis and thus compression of the nerve fascicles.

Conclusions

The last decades have expanded our knowledge of peripheral nerve pathophysiology, and refined microsurgical skills are improving the outcomes of peripheral nerve repair. Primary end-to-end nerve repair is the first aim of reconstruction, if local and general conditions are amenable. Interfascicular nerve grafting is still the gold standard in the repair of peripheral nerve injuries when end-to-end coaptation is not possible without increased tension at the repair site. Nerve conduits and processed nerve allografts can reduce morbidities associated with autologous nerve graft harvesting with comparable outcomes, but only in short nerve gap repair. Nerve-to-nerve transfer is an additional surgical tool available for irreparable nerve lesions. Neurolysis is a beneficial additional procedure to assist in the decompression of fascicles and restoration of passive nerve movements. Despite the improvement in available techniques, further translational research is mandatory for the improvement of nerve regeneration, preservation of target organs, and neurorehabilitation programs.

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Principles of Nerve and Muscle Rehabilitation

3

T. Paternostro-Sluga and M. Quittan

3.1 Principles

Medical rehabilitation, in general, aims at improving function, activity, and participation of the patients rather than curing the disease. A widely accepted model of rehabilitation is provided by the International Classification of Functioning, Disability and Health (ICF) by the World Health Organization. Accordingly, the principle of rehabilitation of neuromuscular disorders is to improve function, which may be impaired due to motor, sensory, and autonomic dysfunction, pain, as well as tendon, muscle, and joint contractures. The interventions depend on the clinical picture, the course of disease, and, furthermore, the activity and participation as demanded by the patients. Therefore, rehabilitation always aims at enabling the patient to lead a self-determined and independent life as good as possible. The knowledge of underlying pathology and the course of disease are very important to design a proper rehabilitation program for the patient.

In regard to motor symptoms, muscle weakness, muscle wasting, muscle cramps, impaired coordination and proprioception, fatigue, gait disturbances, impaired upper limb function and fine motor skill, and impaired body posture may be present.

Sensory symptoms may be plus or minus symptoms, may result in severe pain syndromes, may result in severely impaired sensation, may result in trophic disturbances as the protective function of sensation is lost, and together with autonomic dysfunction may result in impaired wound healing.

Autonomic dysfunction affects all systems innervated by the autonomic system; clinical orthostatic hypotension, heart rate abnormalities, bladder and bowel disturbances, sexual dysfunction, papillary abnormalities, as well as skin changes can be seen in neuromuscular disorders.

Tendon, muscle, and joint contractures are serious problems in neuromuscular diseases, and despite regular stretching and range of motion (ROM), exercises sometimes cannot be prevented. Once the ability is lost to actively stand up, contractures of the ankle joint and shortening of the Achilles tendon develop easily. Contracture of the shoulder may be anticipated in shoulder girdle weakness.

The central representation of peripheral nerve and muscle function as central motor pattern has to be addressed in rehabilitation strategies. Neural plasticity helps to improve function even if the physiologically responsible structure of the peripheral nervous system is impaired. Neural plasticity may occur on all levels of the nervous system, the peripheral axon, the spinal cord, and the brain.

Treatment goals on the level of impairment are improving motor function, improving sensory function, decreasing pain, improving autonomic function, and activating neural plasticity. Additionally, in rehabilitation of peripheral nerve lesions, the need for surgery has to be recognized and planned in time (Table 3.1).

In regard to activity and participation, treatment goals are to improve function in all affected activities of daily living (ADL), to keep social participation and quality of life. Workplace issues are important and have to be discussed with the patient and the family/caregiver. As neuromuscular disorders often are progressive and peripheral nerve lesions often don't recover completely, adaptation of the working place or planning of changing the job/the workplace is very important.

3.2 Outcome Measurement

Outcome measurements are important to assess and follow up nerve and muscle disorders (Tables 3.2 and 3.3). For muscle strength testing, the Medical Research Council (MRC) Scale (Medical Research 1976), the modified MRC Scale (Paternostro-Sluga et al. 2008), and the Motricity Index (Demeurisse et al. 1980) are simple and useful assessment tools that can be performed clinically without the need for special technical equipment. Muscles with strength levels greater than antigravity strength can also be tested by a dynamometer. There are dynamometers for all parts of the

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Table 3.1 Symptoms and treatment goals in nerve and muscle rehabilitation

Symptoms	Treatment goals
Muscle weakness	Improving muscle strength Improving endurance Facilitating motor performance Training functional movements (gait training, upper limb function, trunk function)
Sensory symptoms	Improving sensory functions Decreasing pain Protecting the skin Improving motor functions affected by disturbed sensory input
Autonomic symptoms	Recognize and treat autonomic symptoms Improve orthostatic hypotension Improve bladder, bowel, and sexual disturbances Improve skin texture and avoid skin lesions
Pain	Decrease neuropathic pain Decrease secondary musculoskeletal pain Decrease muscle cramps
Musculoskeletal symptoms	Avoid/reduce joint contractures Avoid/reduce tendon contractures Avoid/reduce poor posture and scoliosis Decrease secondary musculoskeletal pain Recognize need of surgery in time
Fatigue	Recognize fatigue Improve strength and endurance Improve symptoms of depression Increase motivation

Table 3.2 Commonly used scales in nerve and muscle rehabilitation

Strength	MRC Scale (Medical Research 1976) Modified MRC Scale (Paternostro-Sluga et al. 2008) Motricity Index (Demeurisse et al. 1980)
Function	Rivermead Motor Assessment (Lincoln and Leadbitter 1979) Nine-Hole Peg Test (Oxford Grice et al. 2003) Functional Ambulation Category (Collen et al. 1990) Timed Get Up and Go Test (Podsiadlo and Richardson 1991) 6-Min Walk Test (Butland et al. 1982)
Quality of life	SF-36 health survey, SF-12 health survey
Pain	Visual Analog Scale Likert Scale (Plan et al. 2012)
Sensory qualities	Quantitative Sensory Testing
Treatment goal	Goal Attainment Scale (Steenbeek et al. 2011)

body (hand, finger, arms, trunk, legs), and especially for assessment and follow-up of strength, grades 4 and 5 of the MRC Scale dynamometric measurements are useful tools of quantification. For arm function assessment the Rivermead Motor Assessment (Lincoln and Leadbitter 1979) and 9-Hole Peg Test (Oxford Grice et al. 2003) are useful tools. The Functional Ambulation Category (FAC) (Collen et al. 1990), Timed Get Up and Go test (TUG) (Podsiadlo and Richardson 1991), and 6-Minute Walk Test (6MWT) (Butland et al. 1982) are tests to assess gait and mobility. Gait laboratories offer detailed analysis of gait pattern and may be used for the evaluation and follow-up examinations of gait disturbances in neuropathies and myopathies. These computerized gait analysis systems need high standard technical equipment and specialized technicians. Pain can be assessed by the Visual Analog Scale (VAS) or by categorized scales like the Likert Scale (Plan et al. 2012). For pain assessment in children, categorized scales are preferably used. Besides the clinical assessment of light touch, vibration, position sense, temperature, and two-point discrimination, sensory qualities can also be assessed instrumentally by the Quantitative Sensory Testing (QST). SF-36 health survey and SF-12 health survey are widely used assessment tools for quality of life. To assess autonomic functions, heart rate variability, blood pressure in certain provocative conditions (e.g., deep breathing), sudomotor functions, as well as urinary and sexual functions can be tested (Grisold et al. 2007).

There are many different diseases of nerve and muscle, many different clinical presentations, and different courses of disease; therefore, treatment goals depend on the individual course of disease and the individual needs of the patient. For this requirement the Goal Attainment Scale (Steenbeek et al. 2011) can be recommended.

There are several disease-specific scales that may be used, e.g., a quality-of-life questionnaire for chemotherapy-induced peripheral neuropathy (Postma et al. 2005), a fatigue severity scale for immune-mediated polyneuropathies (Merkies et al. 1999), the CMT Neuropathy Score (Maggi et al. 2011), or the Neuropathy Disability Scale (Van der Meche and Schmitz 1992).

One important aspect in using scales and scores is to improve test reliability by training the grading within the team.

3.3 Rehabilitation Treatment

3.3.1 Exercise and Medical Training

Exercise

Exercise therapy includes muscle strengthening, training of functional movements, training of coordination and proprioception, exercises to maintain the ROM of joints, as well as tendon and muscle stretching techniques. To train ambulation, water-based exercises might be very helpful. A sling table can also help to train with gravity eliminated. Exercises with electromyographic biofeedback were shown to improve

Table 3.3 Short description of disease-unspecific outcome measurements for motor function

Assessment instrument	What is assessed?	Scale
MRC Scale (Medical Research 1976)	Manual muscle strength testing of a single muscle or single movement; the movement tested has to be described	Scale 0–5 (6 grades) 0 – no movement 5 – normal strength
Modified MRC Scale (Paternostro-Sluga et al. 2008)	Like the BMRC scale, additionally including the range of motion (less than 50 %, more than 50 % of the feasible ROM) for which the strength grade can be achieved	Scale 0–5 (9 grades) 0 – no movement 5 – normal strength The additional 3 grades are 2–3, 3–4, and 4–5
Motricity Index (Demeurisse et al. 1980)	Three movements of the upper arm and three movements of the lower limb are tested and a sum score is calculated for each tested extremity	0 = no movement 100 = maximum score for one extremity = normal strength
Rivermead Motor Assessment Arm Section (Lincoln and Leadbitter 1979)	Function of the arm is assessed in lying, sitting, and standing position; simple and complex motor tasks are tested	Scale 0–15 0 = cannot even keep arm in elevation with support in lying position 15 = all tasks can be performed
Functional Ambulation Category (Collen et al. 1990)	It is assessed if the patient can walk and if he/she needs assistance by one or two persons; walking aids are not taken into account	0 = patient cannot walk 5 = patient walks independently
Timed Get Up and Go Test (Podsiadlo and Richardson 1991)	It is assessed if the patient can stand up from a chair, walk 3 m, turn around, and sit down again; the time needed for this sequence is taken	Four categories: ≤10 s: no limitations in mobility associated ADLs 10–19 s: some limitations 20–29 s: moderate to severe limitations, starting to lose independence >30 s: needs help for mobility associated ADLs
3- or 6-Minutes Walk Test (Butland et al. 1982)	The patient is asked to walk for 3 or 6 min and the distance he/she walked is assessed	Distance in meters
Nine-Hole Peg Test (Oxford Grice et al. 2003)	The patient is asked to place pegs in a holes of a wooden base with 9 holes	Time in seconds needed to place the pegs

muscle strength and activity for hand and arm function (Ince and Leon 1986). Strengthening of the trunk is essential in any type of neuromuscular disorder as a good trunk control and coordination improves gait and function of extremities and may prevent or decrease musculoskeletal pain and trunk deformities. The exercise program has to be tailored to the needs of the patient. A home exercise program has to be designed as the exercises have to be done regularly. The compliance of the patient has to be considered when designing the home exercise program; sometimes it is more efficient to offer the patient three simple exercises including stretching and ROM exercises which he/she accepts to perform than a complex training program which is not accepted by the patient. Moreover, the patient has to be controlled and motivated regularly for adherence to the program as well as for the course of disease in regard to strength, contracture, ADL activities, quality of life, mood, and social participation. It is known that adherence to home exercise programs can be increased by supervision (Novak 2011).

Strength Training

Resistance training aims at increasing or maintaining muscle mass and strength in neuromuscular diseases. Resistance training has to be adapted to the individual need of the patient and has to have supervision and monitoring. The concern of overuse weakness especially in myopathies is not supported by literature (DeLateur and Giaconi 1979; Hobermann 1959). In DMD it has been shown that the most significant gains can be achieved in patients with less disease progression and in the less severely affected muscle groups (Vignos and Watkins 1966). Therefore, resistance training has to start early in the course of disease. The same is true for slowly progressive myopathies where significant increases in strength and endurance for markedly to moderate weak muscle could be shown. Severely weak muscle (<10 % normal) did not improve. (Milner-Brown and Miller 1988) Moderate intensity exercises are safe and well tolerated by the majority of patients with at least antigravity strength (Lindeman et al. 1995; Van der Kooi et al. 2004). In CMT there is reasonable evidence that progressive resistance exercises can improve strength mainly in proximal muscles in patients with mild to moderately severe CMT (Chetlin et al. 2004). In post-polio syndrome resistance training is safe and potentially beneficial for muscle groups with at least antigravity strength (Agre et al. 1996). Also in ALS low to moderate intensity exercises may be beneficial (Bello-Haas et al. 2007).

Moderate resistance training can improve strength in neuromuscular disorders and strength gains tend to be greatest for muscles with at least antigravity strength (Doherty 2009). The training program has to be tailored to the need of the

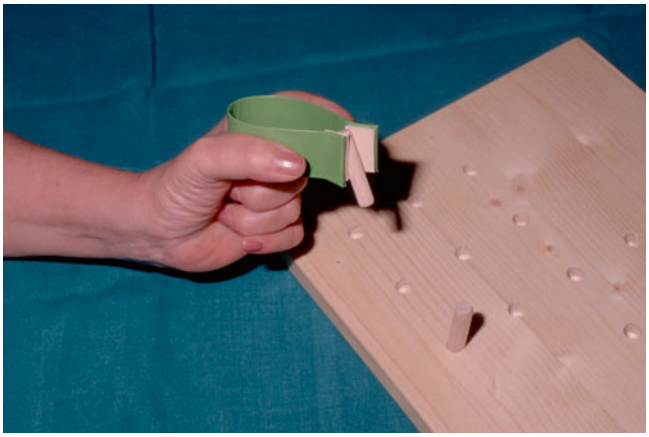

Fig. 3.1 Training of fine motor skills

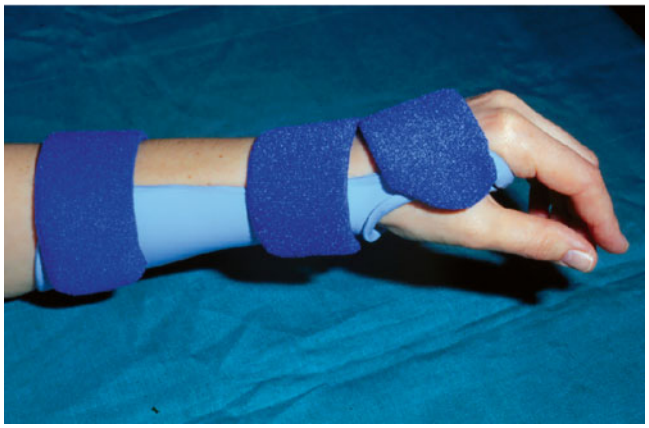

Fig. 3.2 Wrist cock-up splint

patient. In general the dosage of training has to be less intense and designed with more caution for myopathic disorders than for neuropathies.

Endurance Training

Before starting endurance training for patients with neuromuscular disorders, a cardiological testing has to be done. Studies suggest that aerobic exercise training is safe and effective for patients with moderately severe myopathies (Doherty 2009). One study included patients with facioscapulohumeral dystrophy and the other study included patients with inclusion body myositis. In regard to diabetic neuropathy, it is described that a combination of resistance and aerobic training has positive effect on blood glucose regulation, muscle strength, and perceived limitations in functioning (Otterman et al. 2011).

3.3.2 Occupational Therapy and Splints

Occupational therapy in neuromuscular disorders includes functional training, mainly aimed at improving hand and upper limb function, training of ADL activities and job activities, adaptation of working place and home environment, as well as splinting. In neuromuscular disorders hand function is frequently impaired and training of fine motor skills (Fig. 3.1) as well as sensory training helps the patient to maintain independence. In mononeuropathies, depending on the course of disease, either the recovering motor and sensory functions are trained or, in case of irreversible nerve lesion, compensatory strategies are developed. In this context, splinting may be of great importance as the splint can compensate paresis (Paternostro-Sluga et al. 2004). This is true for radial nerve palsy where a simple cock-up splint (Fig. 3.2) can stabilize the wrist and the hand can be opened by the ulnar-innervated intrinsic hand muscles (Paternostro-Sluga et al. 2003). Splinting also aims at preventing contractures by positioning splints that are primarily worn during nighttime. Splinting can protect a dysesthetic skin area of being touched, and this may be an important pain relief for the patient. Desensitization training decreases pain and sensory training increases sensory function. The principle of sensory training in the presence of a permanent nerve lesion or neuropathy is to learn a new central pattern for recognizing objects by touching them with the remaining peripheral skin receptors (Dellon et al. 1971). The training is done with different textures with and without visual control.

3.3.3 Orthoses

Orthoses are prescribed for lower limb involvement, peroneal splints for foot drop, and knee orthosis for knee extensor weakness. Whole lower limb orthoses are prescribed for myopathies like Duchenne muscular dystrophy to enable the affected child to walk for a short distance despite high-grade paresis or to stand. Nowadays there are robotics that enable patients with high-grade paresis to walk on a walking band, but mostly these robotics are designed for central nervous system disorders. Orthoses are also provided to avoid or reduce contractures, e.g., for the ankle joint, these positional splints/orthoses are predominantly worn during nighttime.

3.3.4 Neural Plasticity

Neural plasticity can be seen as continuous adaptive mechanisms of the central and peripheral nervous system (Grisold et al. 2007). In physiological conditions the nervous system adapts during all stages of life from birth to the aging process. In neuromuscular disorders neural plasticity can help to restore function. In motor impairment neural plasticity helps to regain motor function by, e.g., including agonist muscles to perform a manual task, e.g., ulnar-innervated intrinsic hand

muscle helps to open the fist in the presence of radial weakness and paresis of extrinsic radial-innervated finger extensors. A very impressive example of neural plasticity and motor relearning is the method of bionic extremity reconstruction. In this rehabilitation setting after arm amputation, the pectoral muscle is surgically denervated and reinnervated by the median and ulnar nerve and serves as amplifier for the arm prosthesis. Thinking of opening the hand activates the ulnar-innervated pectoralis muscle parts; thinking of closing the hand activates the median-innervated pectoralis muscle part. The patient learns to guide the prosthesis by thinking the movement (Aszmann et al. 2008; Kuiken et al. 2009). For sensory recovery, neural plasticity helps to relearn sensory pattern, an important principle of sensory training, which mostly is provided by the occupational therapist.

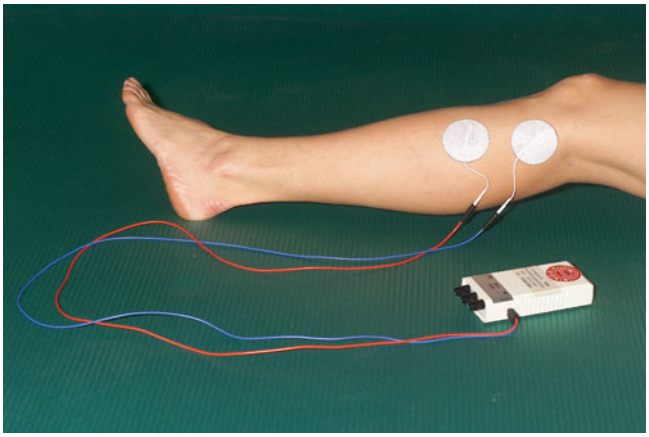

Fig. 3.3 TENS stimulation of the peroneal nerve at the fibular head

3.3.5 Surgery

Primary nerve surgery is indicated where nerve regeneration cannot proceed due to scar tissue or neuroma or neurotmesis. In these cases early surgery is recommended to increase the chance of successful regeneration and functional recovery. The time between onset of lesion and primary nerve surgery is important as the delay should not be more than maximum 1 year, preferable 1–6 months (depending on the clinical features of the lesion) as the capacity of regeneration decreases with time. If there is no evidence of spontaneous recovery, a reconstructive plan should be formulated. Muscle transfers or muscle transposition is performed to reconstruct function, e.g., musculus pronator teres transfer to reconstruct active extrinsic finger extension in high-grade radial palsy. For joint and tendon contractures that occur in neuropathies as well as myopathies, surgical release is performed. It is important to provide an effective after-surgery rehabilitation treatment (ROM exercises, gait training, strengthening, lymphatic drainage) to keep, e.g., the surgically achieved range of motion, to avoid deterioration due to inactivity after surgery, and to regain walking ability as soon as possible. Scoliosis is another important indication for surgery in neuromuscular disorders and is provided in specialized centers.

3.3.6 Physical Modalities

Electrotherapy

Electrotherapy in neuromuscular disorders has two principle treatment goals. Electrotherapy may be used as pain treatment or electrotherapy may be used to improve motor performance either to facilitate movement or to strengthen the muscle.

For pain treatment low-frequency stimulation between 2 and 100 Hz is used. TENS machines are easy to apply and well known. Self-adhesive electrodes are placed in or around the painful area. In the presence of dysesthesia or allodynia, the peripheral nerve which supplies the painful area is stimulated, e.g., for painful dysesthesia on the dorsum of the foot, the peroneal nerve may be stimulated at the fibular head (Fig. 3.3). Stimulation time should be 30 min or more, and the stimulation may be applied several times a day. Treatment can be considered effective if pain intensity is reduced at least by 30 %.

To facilitate motor performance the affected muscle groups have to be stimulated. The patient is asked to contract the muscle together with the electrically induced contraction or an EMG-triggered electrical stimulation is used. In the latter the volitional contraction of the muscles is recorded by EMG surface electrodes and triggers the electrical stimulation of the muscle. This is very useful in mild recovering paresis like in Guillain-Barre syndrome or chronic long-term paresis with at least antigravity strength (Rakos et al. 1999). In cases of high-grade paresis or no volitional activity, the patient can be asked to "think" the movement in order to keep/improve central motor representation. Stimulation times between 15 and 30 min are recommended and stimulation intensity has to elicit a clearly visible muscle contraction.

To strengthen a denervated muscle or to reduce atrophy by electrical stimulation, application time of at least 30 min and high (as high as possible) stimulation intensities are mandatory. It was shown that in completely denervated muscles in patients with complete cauda lesions of muscle fiber diameter, histologic and metabolic mechanisms could be markedly improved by long-term and high-intensity electrical stimulation (Kern et al. 2010). Denervated muscles have special electric characteristics, and impulses with long duration of 100–500 ms, preferably slowly rising, are necessary.

In myopathies electrical stimulation may be used. It has been shown for DMD children that electrical

stimulation of the quadriceps muscle with at least antigravity strength could shortly improve strength but no long-term effect.

Massage, Lymphatic Drainage

Massage techniques aim at relaxing the muscle and counteracting pain. In nerve lesions and polyneuropathies affecting the upper arms, painful hypertension of the cervical and trunk muscles occur. This type of musculoskeletal pain can be treated by massage.

In painful muscle cramps in neuropathies as well as in myopathies, especially in the legs, massage can reduce these symptoms.

Lymphatic drainage aims at reducing swelling; this is helpful in motor weakness which may be associated with limb swelling, due to reduced muscle activity and/or reduced mobility.

Thermotherapy, Ultrasound

In acute nerve lesions mild cooling of the extremity might be indicated, especially if there is a risk of developing a complex regional pain syndrome (CRPS) type II.

Heat therapy (e.g., hot packs) is indicated for secondary musculoskeletal pain, e.g., in the lumbar or cervical region, associated with neuropathies and myopathies due to weakness and poor posture. Also the knee joint or the tendons of the shoulder may develop degenerative alterations earlier due to weakness and muscular imbalance in neuropathies and myopathies, and warm therapy may relieve pain as an adjunct to exercises, medication, and infiltration according to the needs of the patient.

Ultrasound has a focal warming effect and can be used in entesopathies and focal painful muscle hypertension. Ultrasound therapy may decrease symptoms and improve nerve conduction values in mild to moderate carpal tunnel syndrome (Page et al. 2012).

3.3.7 Treatment Options for Autonomic Symptoms

Treatment depends on the specific autonomic system affected. Diarrhea and constipation can be treated by adequate diet; gastroparesis can be treated with metoclopramide. Symptoms of postural hypotension may be decreased by compression stockings and abdominal binders; patients have to take care when changing position. For impotence, a common sequel of diabetic neuropathy, urological counselling, and treatment has to be started. Neurogenic bladder patients should be encouraged to void regularly; intermittent catheterization may be necessary. Regular skin care is important to avoid skin lesions and infections (Grisold et al. 2007).

3.4 Mononeuropathies

Mononeuropathies have different etiologies. Very often they are mechanically induced, either traumatic or entrapment neuropathies. Mononeuropathies might also be induced by malignant infiltration or are primary nerve tumors, and neuritis may present as mononeuropathy.

Rehabilitation strategies depend on the affected nerve, symptoms, and prognosis and aim at improving strength and function, keeping ROM free, and controlling for pain. Workplace issues have to be addressed early.

3.4.1 Median Neuropathy

Carpal Tunnel Syndrome (CTS)

In mild CTS a night splint to keep the wrist in neutral position, ergonomic instructions, and local ultrasound therapy (Ebenbichler et al. 1998; O'Connor et al. 2003) are indicated. If symptoms increase, surgery has to be considered. A local corticosteroid injection may be indicated in mild to moderate CTS or if surgery is not indicated due to a poor general medical condition of the patient (Marshall et al. 2007).

In the presence of motor and sensory deficits, after-surgery occupational therapy may provide functional motor and sensory training to improve hand function.

Median Lesion at the Elbow or Higher

A high median nerve lesion leads to loss of grip and sensory loss and impairs hand function significantly. There is no agonist muscle group for the long flexors of the fingers and the ulnar-innervated intrinsic hand muscles only flex the MCP joints. The patient looses the ability to grasp and hold, to write with the affected hand, and many other ADLs. Moreover, severe neuropathic pain may be present. Exercise therapy wants to keep the joints ROM free, to counteract shortening of the tendons, to strengthen the trunk muscles, and to improve body posture. Occupational therapy wants to improve fine motor skills and sensation. A positional splint should be worn during the night to counteract contractures of the finger joints. TENS therapy is applied for pain treatment in addition to pain medication. If recovery is unlikely, workplace issues have to be discussed early in the course of disease. Primary nerve surgery and/or reconstructive surgery may be necessary.

3.4.2 Ulnar Neuropathy

Paresis of ulnar-innervated intrinsic hand muscles decreases fine motor skills and grip strength. Atrophy of the small hand muscles and pain in the ulnar distribution are common. Surgery for ulnar entrapment at the elbow has to be

considered early in the course of disease as spontaneous recovery is rare. Functional and sensory training helps to restore hand function; ergonomic instructions and TENS therapy for pain treatment may be helpful.

3.4.3 Femoral Neuropathy

Femoral neuropathy is associated with motor and sensory symptoms. Paresis of quadriceps muscle leads to major gait impairment. Knee orthosis may help, but it is still difficult to walk and patients may need crutches, especially in the first 3–4 weeks after onset of the lesion. Patients with femoral palsy show a hyperextended knee in the stand phase. Rehabilitation aims at strengthening the muscle, training the gate pattern, preventing falls, and creating a home exercise program. Water therapy is indicated to train walking with gravity eliminated. In the presence of neuropathic pain, TENS therapy should be applied additionally to pain medication. Electrical muscle stimulation of the quadriceps muscle should be performed; in the absence of recovery, it is advisable to finish after 3 months; in the case of ongoing recovery, it is advisable to continue until knee extension against gravity is achieved.

3.4.4 Peroneal Neuropathy

Peroneal neuropathy leads to foot drop; neuropathic pain may or may not be present. Foot drop can be compensated very well with a peroneal splint that keeps the ankle joint in neutral position. With the splint the walking pattern normalizes. Care has to be taken in regard to skin breakdown at the edges of the splint. Exercise therapy aims at facilitating motor recovery and relearning of motor pattern. Gait training and training of proprioception is important as paresis of peroneus longus and brevis muscle leads to instability of the ankle joint. Electrical muscle stimulation is applied to facilitate active dorsiflexion of the foot. In the absence of recovery, it is advisable to finish after 3 months; in the case of ongoing recovery, it is advisable to continue until foot dorsiflexion against gravity can be performed.

3.4.5 Tibial Neuropathy

In tibial neuropathy very often neuropathic pain is the prominent symptom and is affecting the patient's quality of life. Pain medication and local pain treatment with lidocaine or capsaicin patches are indicated. TENS stimulation should be applied to the tibial nerve at the ankle or knee level. Paresis of plantar flexion and hypesthesia of the foot sole interferes with walking as well as driving a car (unable to press the pedal). Exercise therapy is training plantar flexion, proprioception, and gait. In contrast to peroneal palsy, there is no splint to compensate for plantar flexion paresis.

3.4.6 Plexopathies

Rehabilitation strategies in plexus lesions depend on the affected structures. In upper brachial plexus lesion, recovery of strength, maintenance of shoulder ROM, and avoidance of cervical musculoskeletal pain are important treatment goals. In lower brachial plexus palsy, recovery of hand function, maintenance of finger and wrist ROM, and neuropathic pain control are the prominent treatment goals. In lumbar plexus palsy treatment goals are similar to femoral neuropathy, only that hip flexion is more severely affected and therefore gait is more impaired than in pure femoral neuropathy. In lumbosacral/sacral plexopathy neuropathic pain is an important treatment issue. In regard to the motor deficits, knee flexion paresis and gluteal weakness aggravate gait impairment. Water therapy for gait and strength training is strongly recommended for lower limb involvement.

3.5 Polyneuropathies

There are many different types of polyneuropathies; rehabilitation strategies depend on the affected structures, the clinical symptoms, the course of disease, and the prognosis. Treatment goals are improving strength, improving function, keeping ROM free, controlling for pain and autonomic symptoms, and supporting quality of life. Workplace issues have to be addressed early.

As an example for an acute polyneuropathy, the rehabilitation treatment for Guillain-Barre syndrome is discussed. In the acute phase parallel to the intensive care interventions, positioning of the patient to avoid contractures and musculoskeletal pain is important. Once vital parameters are stable ROM exercises to keep the joints free as well as to activate proprioceptors and produce afferent input to the brain will start. As soon as volitional activity restarts, motor performance will be trained, gradually increasing training intensity adapted to the course of recovery. Splinting of hands, fingers, and ankle is important as contractures develop quickly. Depending on the severity crutches and walking splints (peroneal splint) have to be provided; also intermittent wheelchair use may be necessary. TENS and electrical muscle stimulation may be applied if needed. EMG biofeedback training was shown to improve muscle performance of the upper extremity in Guillain-Barre syndrome (Ince and Leon 1986).

In diabetic neuropathy motor, sensory, and autonomic symptoms are present. It has been shown that strength and endurance training improves function and even improves metabolic

parameters. Patients with diabetic polyneuropathy should start early with strength and endurance training. They should be instructed to take care of their skin and feet. Shoe wear has to fit well and support the architecture of the foot and avoid pressure on the foot. Strict control of blood glucose level is crucial to counteract deterioration of polyneuropathy. Electrotherapy should be used for pain control; there are promising reports that a high-frequency stimulation can reduce pain in diabetic polyneuropathy effectively (Pieber et al. 2010).

In hereditary neuropathies progression often is slow and rehabilitation strategies have to anticipate and follow the course of disease. It is important to consider the course of disease when deciding which profession to choose. Exercises, resistance, and endurance training should be started early in the course of disease. Crutches, orthoses, splints, footwear, pain control, and surgical procedures may all be part of the rehabilitation treatment according to the needs of the patient. In regard to costs and healthcare providers, patients should be supported when applying for refunding of treatment costs.

3.6 Myopathies

In myopathies muscle weakness and fatigues are prominent symptoms. It is shown that resistance training is safe in myopathies and antigravity muscles benefit most (Doherty 2009). In regard to the musculoskeletal system, myopathies lead to joint and tendon contractures, muscle cramps, poor posture, and scoliosis. Walking is impaired and wheelchair prescription might be necessary. Splinting and orthosis aim at keeping the joints free and supporting weak muscles. Respiratory function may be impaired and a respiratory muscle training has to start early. Mechanical respiratory support may be necessary during the night and later on also during the day. Nutrition and diets are important issues as activity is highly reduced in later stages of the disease and overweight as well as malnutrition should be avoided. Rehabilitation treatment depends on the diagnosis, course of disease, prognosis, treatment goal of the patient, and his/her family/caregiver. Anticipation of symptoms, regular medical controls, sufficient rehabilitation therapy, and good healthcare management will help to achieve the individually optimal outcome for the patient.

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Chronic Pain in Neuromuscular Disease

4

Hsinlin Thomas Cheng and Anne Louise Oaklander

4.1 Introduction

Pain is a nocifensive sensation that protects animals from harm. Potentially injurious stimuli of various modalities are transduced and transmitted towards the spinal cord and brain by specific peripheral neurons (nociceptors) to generate unpleasant feelings and induce reflex and conscious responses. Peripheral pain-sensing axons, also known as "small fibers," consist of thinly myelinated (Aδ) and unmyelinated (C) fibers which, along with sympathetic axons, comprise some 80 % of peripheral axons (Fig. 4.1). Normal nociceptive pain fades quickly as an injury resolves, but in neuromuscular conditions chronic pain can reflect continual injury, such as in inflammatory myopathies. Such pain usually responds to anti-inflammatory and other first-line pain medications, not to mention disease-modifying treatments for the underlying cause. The far larger problem is pain caused by prior injury to peripheral and/or central pain neurons. Because neuropathic pain can develop or persist without associated tissue injury, diagnosis can be difficult, and treatment is different than for acute or nociceptive pain. A confounding feature of neuropathic pain is that unlike the inevitability of acute pain after injury, not all patients develop neuropathic pain even after identical injuries or illnesses (e.g., shingles). Neuropathic pain is a complex disorder with endogenous as well as exogenous causes. Pain caused by injury to the spinal cord or brain is outside the scope of this discussion, but is generally even more difficult to treat than peripheral neuropathic pain.

4.2 Clinical Approach and Treatments to Neuropathic Pain

4.2.1 Diagnosis

Pain is a subjective symptom, thus diagnosis is based on clinical judgment. Pain intensity is usually assessed using an 11-point Likert scale, and pain qualities are most often

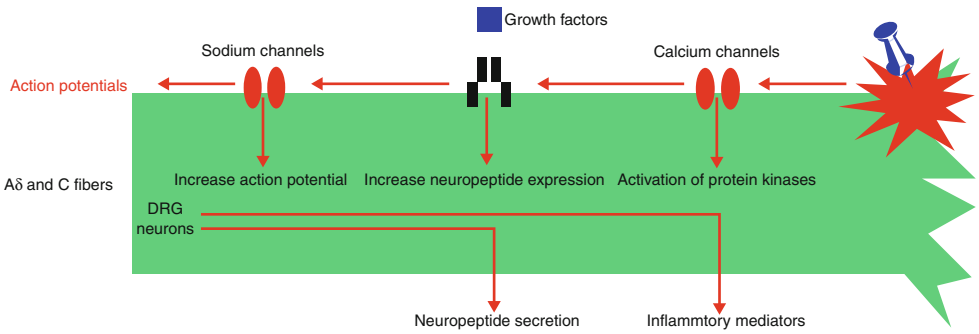

Fig. 4.1 Molecular mechanisms of neuropathic pain. After nerve injury or neuropathy, injured **Aδ** and C fibers produce increased frequencies of action potential to generate neuropathic pain. This phenomenon is mediated by several mechanisms: (1) Changes of gene expression of nociceptive sodium channels, such as Na(v) 1.3, Na(v) 1.7, Na(v) 1.6, and Na(v)1.8 to potentiate inward sodium current and facilitate retrograde action potential transmission. (2) Increased nerve growth factor (NGF) expression to enhance the expression of nociceptive peptides, including substance P (SP) and calcitonin gene-related peptides (CGRP). (3) Increased activity and opening of the **α2-δ** calcium channel, transient receptor potential (TRP) cation channel subfamily, and voltage-gated calcium channels activate downstream intracellular protein kinases to alter the gene expression for nociceptive ion channels and peptides to enhance pain perception. (4) Increased expression of algogenic inflammatory mediators including nitric oxide, histamine, prostaglandins, tumor necrosis factors, cytokines, and chemokines. These often not only potentiate inflammation but also enhance the excitability of nociceptive axons

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captured with the short-form McGill Pain Questionnaire. Several questionnaires can suggest a neuropathic profile, e.g., the Neuropathic Pain Questionnaire (NPQ) and the Neuropathic Pain Scale. Standardized examination forms include the Leeds Assessment of Neuropathic Symptoms and Sign Pain Scale (LANSS) and the Minnesota Neuropathic Symptoms Index (MNSI) (Bril et al. 2011).

Patients with neuropathic pain often have other signs and symptoms that help identify their pain as neuropathic, localize it anatomically, and suggest cause. Otherwise, unexplained chronic pain that co-localizes with weakness, hyporeflexia, or large-fiber-mediated sensory functions is most likely neuropathic. Patients with pure sensory or pure small-fiber axonopathies pose diagnostic challenges. Many will have co-localizing reduced sensation (hypalgesia) to modalities transmitted by the damaged axons. Deficits to light touch and vibration implicate large-fiber sensory axonopathy whereas pin-prick losses are most sensitive for small-fiber axonopathy. Furthermore, since small fibers have efferent vasomotor and trophic functions, for instance, antidromic release of vasoactive neuropeptides including calcitonin gene-related peptides (CGRP) and substance P (SP), co-localizing signs such as dysfunctional sweating or microvascular tone (e.g., edema, abnormal skin color, and temperature) are valuable clues.

Objective diagnostic tests can be valuable adjuncts. Conventional electrodiagnostic testing is insensitive to pure small-fiber neuropathy; electromyogram (EMG) results remain normal because small fibers do not activate muscles, and surface nerve conduction studies (NCS) are insensitive to small-fiber conduction, which is low amplitude and scattered. Microneurography may be required for electrophysiological diagnosis. For anatomical diagnosis, biopsy of a sensory nerve was once required. Now, in most cases neurodiagnostic skin biopsy (see Chap. 1) and/or autonomic function testing (see Chap. 13) are the primary diagnostic tests for small-fiber polyneuropathies.

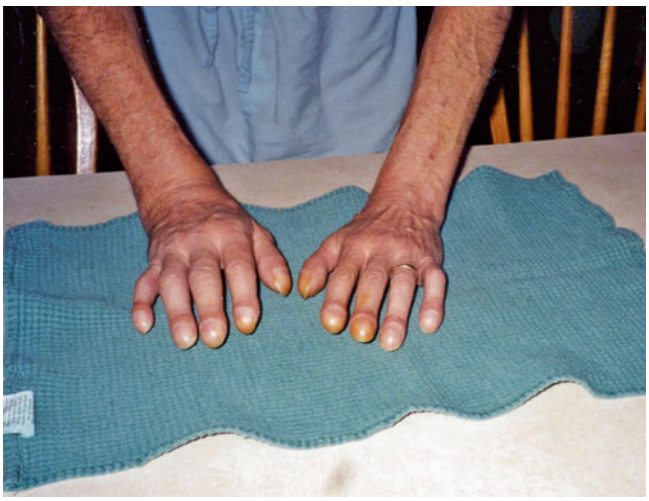

Fig. 4.2 Total body pain from sensory ganglionopathy/neuronopathy. This man with chronic total-body pain of unknown etiology was treated by pain specialists with very high doses of pain medications including opioids. These were ineffectual, and his requests for dose escalation raised concerns about feigned symptoms. Examination by a neurologist revealed nicotine-stained, clubbed fingers, suggesting paraneoplastic sensory neuronopathy/ganglionopathy associated with small-cell lung cancer. He died of cancer with unrelieved pain before immunomodulatory therapy could be initiated

4.2.2 Common Patterns of Peripheral Neuropathic Pain

- Polyneuropathies (see Chapter 9): Widespread small-fiber axonopathy caused by systemic disease is a common cause of neuropathic pain. There are metabolic, infectious, rheumatologic, toxic, paraneoplastic, autoimmune, and hereditary causes. Most painful polyneuropathies are length-dependent and begin with pain in the feet that can progress proximally in a stocking-and-glove pattern over time. Occasional patients with patchy, proximal, or total-body pain (Fig. 4.2) have widespread ganglionopathy/neuronopathy (discussed further below). Because some causes of painful polyneuropathy are curable, a diagnosis mandates additional testing for etiology. Diabetic polyneuropathy, which affects 16 % of patients with diabetes, is perhaps the best recognized, but even here 40 % of cases remain untreated (Bril et al. 2011; Callanghan and Cheng 2012).
- *Painful mononeuropathies or oligoneuropathies* affecting discrete nerves:
  - Cranial mononeuropathies: Any nerve that transmits nociceptive sensation can be the source of neuropathic pain that localizes to the region innervated by that nerve's sensory axons. In the head and neck, this includes VII and IX in addition to V (see Chapter 5 for discussion of trigeminal neuralgia). Although any type of lesion or injury can trigger neuropathic pain, the most common painful cranial neuropathies are due to vascular compression (e.g., tic douloureux, glossopharyngeal neuralgia) or zoster (e.g., herpes zoster ophthalmicus, Ramsay Hunt syndrome).
  - Peripheral mononeuropathies (see Chapter 8): These are most often caused by traumatic injury to a nerve that contains nociceptive axons. While originally associated with military trauma, medical injuries are more common now in developed countries. Less frequent causes include internal impingement, entrapment, scarring, or inflammation. Because some causes are curable or require independent treatment (e.g., leprosy, tumor, aneurysm), a diagnosis mandates additional testing for etiology. Induction or exacerbation of the

pain by percussing the involved nerve (Tinel's sign) can help with localization. Of note, pain can spread outside the dermatome of the affected nerve due to irritation of nearby neurons within nerve trunks, nerve roots or the DRG, the dorsal horn, and occasionally even the sensory homunculus.

  - Complex regional pain syndrome (CRPS): This term describes a phenotype of posttraumatic neuralgia/neuropathic pain accompanied by other manifestations of small-fiber injury including microvasculopathy (e.g., edema, skin-color changes) and changes in sweating and bone innervation. The underlying nerve injury may be evident (CRPS-II) or occult (CRPS-I), particularly when there are small or partial injuries to sensory-only nerve branches (Oaklander and Fields 2009).

- *Plexopathies:* Pain is usually regional and localized to the dermatome of the affected roots, but often in a patchy or incomplete pattern. Common causes include autoimmunity (e.g., brachial plexitis), tumor or radiation therapy, diabetes, and tissue entrapment. Typically, motor fibers are affected as well, and pain is exacerbated by movements that irritate the affected plexus. Cervical plexitis can trigger headache and neck pain. Brachial plexopathy causes pain in the shoulder or upper limb. Additional causes include Pancoast lung tumors and thoracic outlet syndrome.
- *Ganglionopathies or neuronopathies:* Insults to the cranial or spinal ganglia (dorsal root ganglia) cause pain centered on the peripheral distribution of these ganglia. Motor function is usually spared since motor axons bypass most sensory ganglia. The most common focal ganglionopathy is shingles (herpes zoster), which can be painful acutely and leaves a proportion of patients with long-lasting postherpetic neuralgia (PHN). Since the infection spreads distally via axonal transport to the skin, some patients have co-localizing motor damage (Fig. 4.3). Multiple sensory ganglia can also be affected by generalized conditions to cause widespread pain (polyneuropathy). Since sensory ganglia lack a blood-nerve barrier, they are vulnerable to autoimmune attack, such as in Sjögren's and paraneoplastic syndromes (see Fig. 4.2).
- Radiculopathy: Damage to cranial or spinal roots causes pain that often co-localizes with motor deficits in the territory of affected nerve roots. Mechanical compression or irritation at the neural foramina is the most common cause. Radiculopathy could also be caused by any space-occupying lesion, including inflammatory or neoplastic (e.g., meningioma, Schwannoma) and even Tarlov cysts.

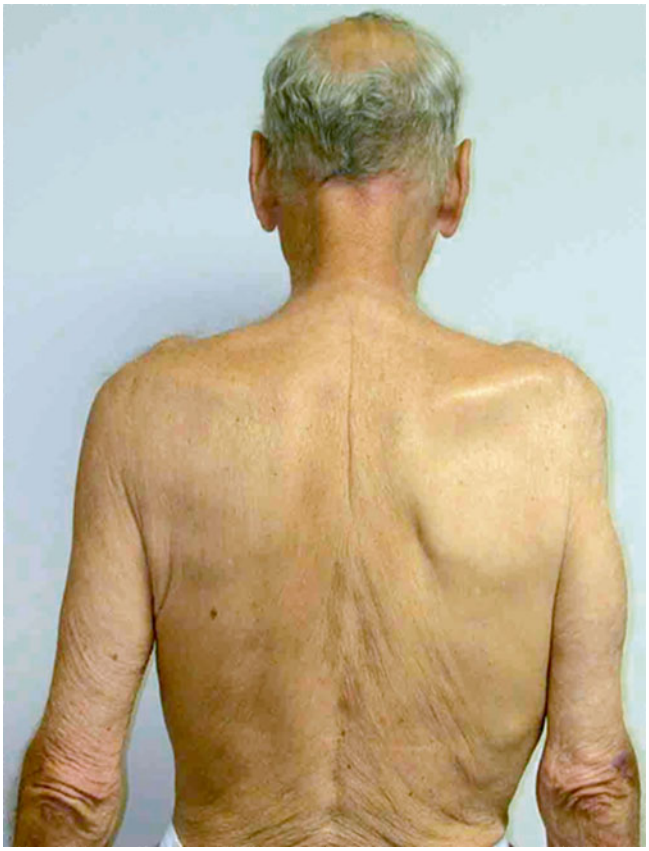

Fig. 4.3 Co-localizing neuropathic pain and motor deficits in postherpetic neuralgia. This man presented for treatment of chronic pain in his right lateral upper arm after zoster. Examination revealed weakness of right arm abduction, winging of the right scapula, atrophy of the right deltoid, supraspinatus, and infraspinatus muscles as well as punctate scars in the right C5 dermatome. Zoster infects only sensory neurons, but adjacent motor axons can sustain bystander damage. Nortriptyline and methadone were recommended for pain management

4.2.3 Pharmacological Treatments Options

A general recommendation is to begin with one of the first-line options discussed below, raising the dose until pain relief is obtained. Until pain is adequately relieved, the dose should be raised to the maximum tolerated before discontinuing that medication and trying another, preferably from a different class. If partial relief is achieved from a well-tolerated medication, the second one added should be from a different class. Too often, patients are treated with low doses of multiple medications making it difficult to assess each one's efficacy or attribute adverse effects. Medications for neuropathic pain generally have similar efficacy in various conditions, except in trigeminal neuralgia, chronic radiculopathy, and HIV neuropathy. For neuropathic pain in general, level A evidence supports tricyclic antidepressants (TCAs), pregabalin and gabapentin, tramadol and opioids (in various conditions), serotonin and norepinephrine reuptake inhibitors (SNRIs: duloxetine, venlafaxine), and topical lidocaine and capsaicin patches (in restricted conditions) (Attal et al. 2010). Which medication to try should be influenced by matching the patient and the drug profile, e.g., TCAs should be considered for patients with depression accompanying

Table 4.1 Recommended dosage and titration schedule for neuropathic pain regimens

Medication	Starting dose	Titration schedule	Common full dose
TCAs (e.g., nortriptyline, desipramine)	25 mg once daily; 10 mg in geriatric patients	Add 10–25 mg weekly	75–100 mg as single daily dose
Duloxetine	30 mg a day	Add 30 mg weekly	60 mg 1–2 times daily
Venlafaxine	37.5 mg a day	Increase to 75 mg daily after 1 week	225 mg a day
Gabapentin	300 mg; 100 mg in geriatric patients once daily	Add 100–300 mg each few days; use TID dosing	2,700–3,600 mg, dosed TID
Pregabalin	50 mg three times a day or 75 mg twice a day	Increase to 150 mg twice a day after 1 week	300 mg 1–2 times daily
Topical lidocaine	Up to 3 patches a day for 12–18 h application	Escalation not usually required	Escalation not usually required
Tramadol	50 mg tabs, can be halved for geriatric patients	Use minimum effective dose	Not to exceed eight 50 mg tablets daily, 2–3 times daily as needed
Methadone	5 mg (smallest pill); half or quarter for geriatric patients	Use minimum effective dose	Twice daily administration

their pain. Combination therapy appears useful for TCA, gabapentin, and gabapentin-opioids (Attal et al. 2010).

- Tricyclic and tetracyclic antidepressant medications (first line): TCAs with adrenergic activity are unsurpassed in efficacy for neuropathic pain. They are available in inexpensive generic formulations and have been extensively studied (Gronseth et al. 2008). Pain relief is independent of benefits for depression and sleep, although these are often added reasons to prescribe them. TCAs have multiple modes of actions, with a major one involving augmentation of descending catecholaminergic inhibition of dorsal-horn projection neurons. Side effects (e.g., dry eyes and mouth, constipation, somnolence) are common and limit use, particularly in older patients. Second generation TCAs (particularly nortriptyline and desipramine) are preferred over amitriptyline since they are equally efficacious but have fewer adverse effects. Contraindications to use include cardiac dysrhythmia or prior myocardial infarction, narrow-angle glaucoma, urethral outlet obstruction, or cognitive dysfunction. Full benefit can take 6–8 weeks to accrue.
- Serotonin-norepinephrine reuptake inhibitors: SNRIs often cost more but have fewer adverse effects than TCAs, although narrow-angle glaucoma remains a contraindication and serotonin syndrome can occur. Antidepressant effects provide added benefit.
- Anticonvulsants: Anticonvulsants that reduce neuronal firing by blocking sodium and/or calcium channels also have proven efficacy. Carbamazepine is FDA-approved for trigeminal neuralgia and oxcarbazepine is often used for this as well. Serious adverse effects include hyponatremia, hepatic injury, and rash (Gronseth et al. 2008). Gabapentin and pregabalin are widely used for neuropathic pain due to their well-documented efficacy and greater ease of use compared to TCAs and other anticonvulsants and since they have rapid onset and blood levels do not need to be monitored. Edema is a common side effect. Although they are considered a second choice (after TCAs) in healthy young patients, gabapentin and pregabalin are first-line options for the elderly and others with contraindications to use TCAs.
- Local anesthetics have powerful antinociceptive effects when administered topically as lidocaine patches, creams, or as viscous lidocaine. Their main advantage is lack of systemic absorption and hence systemic adverse effects. Their major disadvantage is limited penetration through keratinized skin, which is enhanced by occlusion.
- Opioids: These relieve pain by binding to opioid receptors in the peripheral and central nervous systems. Intermediate-term studies demonstrate significant efficacy over placebo for neuropathic pain (Eisenberg et al. 2005). Adverse events such as constipation and sedation are common but not life threatening, but long-term trials have not yet been conducted to clarify long-term efficacy, safety (including addiction risk), and effects on quality of life. Tramadol, a short-acting weak agonist with added catecholaminergic potentiation, and methadone, a long-acting agonist that also antagonizes the *N*-methyl-D-ASPARTATE glutamate receptor, are worthy of note. Both are available in generic formulations and can be divided into very small doses suitable for use in children or geriatric patients.

Various medications are worth considering as second-line options, including topical applications of capsaicin in cream or 8 % patch formulations. Capsaicin binds to TRPV1 receptors and causes nociceptive axon terminals to degenerate (Hempenstall et al. 2005). Mexiletine or continuous subcutaneous administration of lidocaine benefit selected patients (Ferrini and Paice 2004). Administering medications via injection is not generally useful for chronic neuropathic pain. Despite widespread use, the benefits of corticosteroid injection for neuropathic pain are not well documented, even for herniated intervertebral discs. Potential serious complications include injury from the needle or injectate, pressure,

and inadvertent arterial administration. Injecting local anesthetics, which have short duration of action, can be an aid to diagnostic localization of a nerve or root injury, but has no long-term therapeutic benefit. Rare patients benefit from administering medications via pump to the intrathecal space. Medications administered intrathecally include opioids, local anesthetics, baclofen, α2 agonists, and ziconotide, a voltage-gated calcium channel blocker. The chief indication is in patients with established benefit from oral therapy, but in whom systemic adverse effects limit oral use. Intrathecal delivery permits far lower doses to be used; however, implantation is costly and repeat surgeries are needed in about a quarter of patients for mechanical problems.

4.2.4 Neurosurgical Treatment Options

Prior to development of effective medications, neurosurgery was the major treatment used for neuropathic pain. Harvey Cushing, among others, established that ablation (cutting nerves leading to painful areas) is usually ineffective and in some cases triggers *anesthesia dolorosa* pain that can be intractable. Surgical decompression or removal of structural lesions that cause pain due to compression, traction, or inflammation of nerves or nerve roots is potentially curative, but requires skilled neurodiagnosis and lesion localization, particularly in cases with subtle small-fiber nerve injuries like CRPS-I.

Augmentative neurostimulation with implanted bipolar electrodes has been shown effective and used for decades. The advantage is that electrical current only affects nearby cells, unlike drugs that can spread through the body to cause adverse effects. Locations for stimulation include proximally on injured peripheral nerves, along the dorsal column of the spinal cord, on the motor cortex, or via deep-brain stimulation of the thalamus or periaqueductal gray (Nguyen et al. 2011). Since the dorsal column can be stimulated via percutaneously placed electrodes, this is most often performed, particularly to treat posttraumatic neuropathies and CRPS of the lower limbs.

The major disadvantage of neurostimulation has been the requirement for surgical implantation. However, cortical neurons can be activated externally by holding electromagnetic coils to the scalp. Repetitive transcranial magnetic stimulation (rTMS) is not considered proven for neuropathic pain, although several small trials report efficacy (Leung et al. 2009). Facial neuropathic pain may be the most responsive, partly because motor cortex devoted to the face and eye is abundant and accessible to TMS. The only major adverse effect is the small probability of provoking a single seizure. Limitations include the expensive equipment, currently mostly available in research centers, and limited insurance reimbursement.

In summary, neuropathic pain has been neglected in neuromuscular practice, with regards to diagnosis (anatomical localization of pain-producing lesions and identifying treatable causes) as well as medical and neurosurgical treatment, despite the fact that the vast majority of neuropathic pain is of peripheral origin. However, maturation of the underlying science and new objective diagnostic tests such as skin biopsy and autonomic function testing may augment interest. Social trends including the aging of the population, increased prevalence of diabetes, and need for cost containment may lead to the expectation that neuromuscular specialists diagnose and manage painful neuropathies in parallel with motor-predominant conditions.

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Cranial Nerve

5

Wolfgang Grisold

5.1 Introduction

Cranial nerves consist of 12 pairs and have several anatomical and functional peculiarities. Cranial nerves 3–12 have their nuclei within the brainstem or also in the cervical spinal cord. They can be distinguished as nuclear, parenchymatous, or having an intracranial course, a specific site of exit of the skull, or an extracranial distribution. The specificity of symptoms and signs and the combination of two or more CN lesions help to achieve a precise anatomical localization (Fig. 5.1).

This chapter helps describe the individual cranial nerves, in regard to the anatomical lesion and etiology.

Fig. 5.1 Cranial nerve anatomy. Anatomical preparation: showing the cranial nerve distribution below the base of the skull. The mandibula has been removed. In addition to imaging as CT and MR, several nerves can be demonstrated by ultrasound

5.2 Olfactory Nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	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 cribriform plate to synapse in the olfactory bulb. The olfactory bulb is located beneath the surface of the frontal lobe. Axons leave the olfactory bulb via the olfactory tract and connect to the prepyriform cortex.

Symptoms The term parosmia describes a qualitative change in smell, while the 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 and taste. Impact from a fall causes anteroposterior 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 inadvertent postsurgical damage. Other less frequent causes are listed in Table 5.1.

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Table 5.1 Etiologies of parosmia and anosmia

Vascular	Metabolic	Toxic	Infection	Inflammatory	Degenerative and aging	Genetic
ACA giant cell aneurysm	Renal insufficiency	Drugs[a]	Meningitis	Granuloma[b]	Alzheimer's disease	Congenital and hereditary
	Diabetes		Herpes	TB	CJD (new variant)	
			Influenza			
	Hypothyroidism		Diphtheria	Syphilis	Huntington's disease	
			TB	Rhinoscleroma	Korsakoff syndrome	
			Postinfections		Parkinson's disease	

[a]Drugs include allopurinol, analgesics, antibiotics (amphotericin B, ampicillin, ethambutol, lincomycin, tetracycline), antihelminthic, local anesthetics, chemotherapy (doxorubicin, methotrexate, carmustine, vincristine), colchicine, diuretics, immunosuppressants (azathioprine), muscle relaxants, opiates, and statins

[b]Wegener's granulomatous, sarcoid. Mass lesions can also produce parosmia and anosmia, including abscesses, aesthesioneuroepithelioma (blastoma), craniopharyngioma, meningiomas, mucocele, nasopharyngeal tumors, olfactory meningioma, olfactory neuroblastoma, tuberculum sellae tumors

Diagnosis is based on history, signs upon clinical testing, and in rare cases olfactory evoked potentials. If loss of taste accompanies loss of smell, electrogustometry is used. Smell charts are increasingly used, also for the assessment of neurodegenerative disorders.

Differential Diagnosis The perception of loss or altered smell may be actually due to altered taste secondary to dysfunction in 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.

5.3 Optic Nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Other clinical tests
	+	Aquaporin	+	+
	VEP	abs	MRI, ultrasound	Color vision
				ERG

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 the central vision. At the optic disc, the axons turn posteriorly through the lamina cribriformis 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.

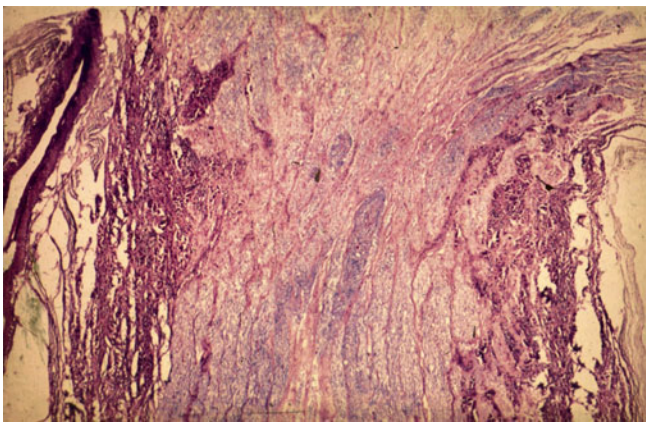

Fig. 5.2 Optic neuropathy: (photomicrograph of a histological slide). The nerve is compressed by tumor cells ("cuffed") in meningeal carcinomatosis, resulting in blindness of the patient

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

- Anterior to the chiasm (monocular field defect or blindness)
- Medial and temporal compression of the chiasm (hemianopia)
- Posterior to the chiasm

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

- *Compression:* Apoplexy of the pituitary (associated with headache), carotid aneurysm, endocrine orbitopathy.
- *Inflammatory causes of compression:* Arachnitis optochiasmatica-cisterna optochiasmatica, syphilis, tuberculosis.

- *Hereditary:* Optic atrophy 1, Leber's hereditary optic neuropathy, lysosomal disease, mitochondrial myopathy, Kearns-Sayre syndrome, storage disease (Tay-Sachs), spinocerebellar disease. Ataxias: Friedreich's ataxia; mitochondrial (NARP syndrome (neuropathy, ataxia, retinitis, pigmentosa)); 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.
- *Immune mediated:* Optic neuritis in Devic syndrome, multiple sclerosis (MS).
- *Infectious:* Meningitis, sarcoid, syphilis, tuberculosis.
- *Focal infection:* Granulomatous disease, orbital tumors, sinusitis.
- *Inflammatory:* Devic syndrome, optic neuritis due to demyelinating diseases (MS, neuromyelitis optica).
- *Metabolic:* Diabetes, thyrotoxicosis, uremia.
- *Nutritive:* Alcohol ingestion, B12 anemia, Cuban neuropathy, methylol toxicity, Strachan's syndrome.
- *Paraneoplastic:* Rarely involved in paraneoplastic dysfunction – CAR antibodies (carcinomatous retinopathy).
- *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.
- *Toxic optic neuropathy:* Alcohol, amoproxan, aniline dye, ara-C (high dose), arsenic, aspidium (antihelminthic drug), Cafergot, carbon disulfide, carbon tetrachloride, chinin, chinoline derivates, chlorambucil (edema of the retina), chloramphenicol, digitalis, disulfiram, paclitaxel/docetaxel – may cause visual sensations ("visual field flash") – ethambutol, isoniazid, lead, mercury (Hg), nitrosourea and radiation, nitrous oxide (N_2O), thallium, vincristine.
- *Vascular:* Ischemic optic neuropathy due to amyloidosis, arteritis cranialis, herpes zoster, retrobulbar optic neuropathy, systematic lupus.
- *Trauma:* "Blowout" fractures, gunshot wounds, penetrating trauma, trauma of the orbit, traumatic optic neuropathy (TON).
- *Tumors:* Metastasis, melanocytoma, meningeal carcinomatosis, nasopharyngeal tumor that can compress the nerve and chiasm, neurofibromatosis (NF 1), orbital tumors, 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 craniopharyngioma (in childhood), meningioma of the tuberculum sellae, aneurysm, tumors of the chiasm itself (spongioblastoma, meningioma, neurinoma, or retinoblastoma).

Diagnosis Diagnosis is based on X-ray, CT, or MRI imaging, visual function and color discrimination tests, ophthalmoscopic exam, visual evoked potentials, and electroretinogram. Also special ultrasound techniques allow a partial identification of the optic nerve.

Differential Diagnosis Other causes of papilledema should be considered, including increased intracranial pressure and pseudotumor cerebri.

Therapy Treatment depends upon the cause of the lesion.

Prognosis Depending on the etiology.

5.4 Oculomotor Nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Lee screen
		+	+	

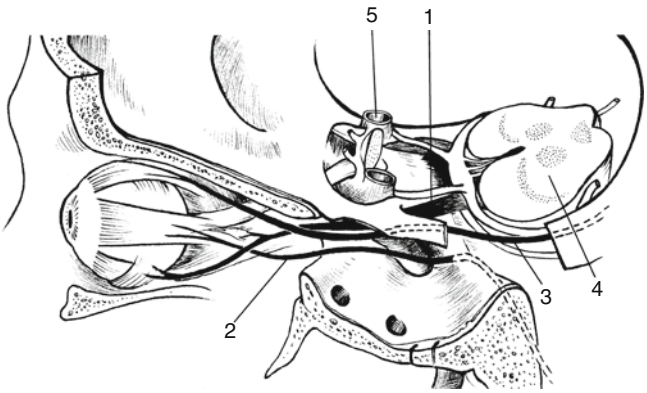

Fig. 5.3 Anatomy of oculomotor nerve: *1* Oculomotor nerve, *2* abducens nerve, *3* trochlear nerve, *4* cross section through brainstem, *5* internal carotid artery

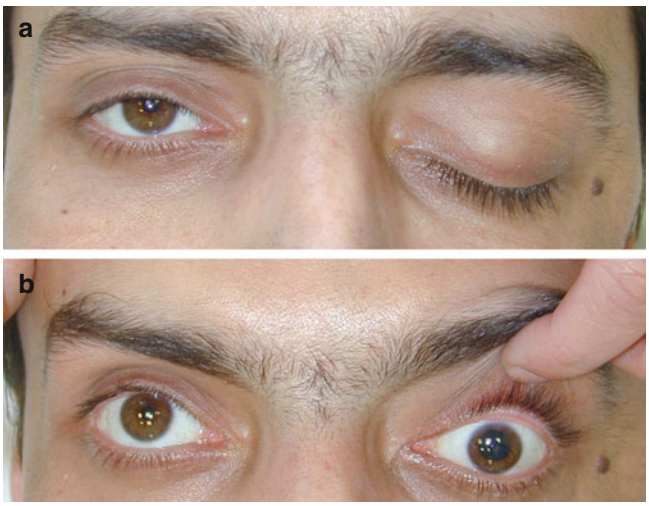

Fig. 5.4 Oculomotor nerve paresis: (**a**) complete ptosis, (**b**) Upon lifting of the lid lateral deviation of left bulbus. Mydriasis signals affection of the parasympathetic fibers for the sphincter pupillae

Table 5.2 Oculomotor nerve structures: from the nuclei to the orbit

CN III	Brain parenchyma	Intracranial and CSF	Exit of cranial vault	Extracranial lesion
III	Nuclei (see neuro-ophthalmology)	Clivus (pressure)	Fissura orbitalis superior	Orbital
	Fascicle	Cavernous sinus tumors, meningeal carcinomatosis		Orbital neuroma
	Brainstem syndromes			
		Aneurysms		
Autonomic	Edinger-Westphal nucleus	Inferior portion		Ciliary ganglion

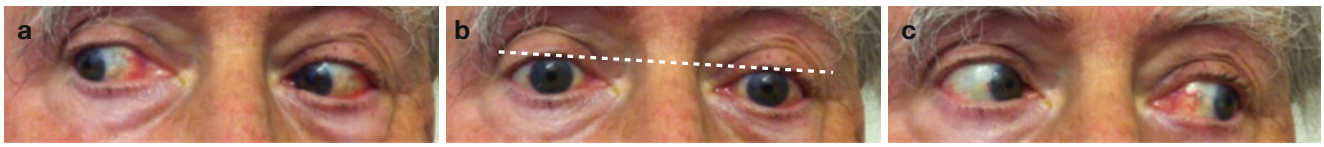

Fig. 5.5 Lymphoma of the left lacrimal gland. The patient presented with blurred vision, then diplopia. (**a**) Normal look to the left. In (**b**) the left eye is lower than the right, (**c**) also at glance to the left

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 anteriorly. 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.

Topographical Location of Lesions Brain parenchyma:

- *Nuclear lesions:* Nuclear lesions are rare and usually of vascular etiology.
- *Fascicular lesions:* Occur during the passage through the mesencephalon and 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.
- *Transtentorial herniation:* Impairment of consciousness and other signs of raised intracranial pressure.
- *Clivus and plica petroclinoidea:* In herniation or local tumors.
- *Cavernous sinus:* Associated with other CN involvement (IV, V1, VI). The pupil can be spared. "Pseudo-pupillary sparing" means that pupillary involvement by an oculomotor nerve lesion is masked by a concomitant Horner's syndrome.
- *Extracranial pathway/orbit:* Passage through the superior orbital fissure – superior division (levator and superior rectus) and 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 alleviate 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 accommodation. 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 toward 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 pupillary reaction contralaterally). Internal ophthalmoplegia involves the parasympathetic pupillary fibers exclusively. External ophthalmoplegia involves only the extraocular eye muscles while sparing the parasympathetic fibers.

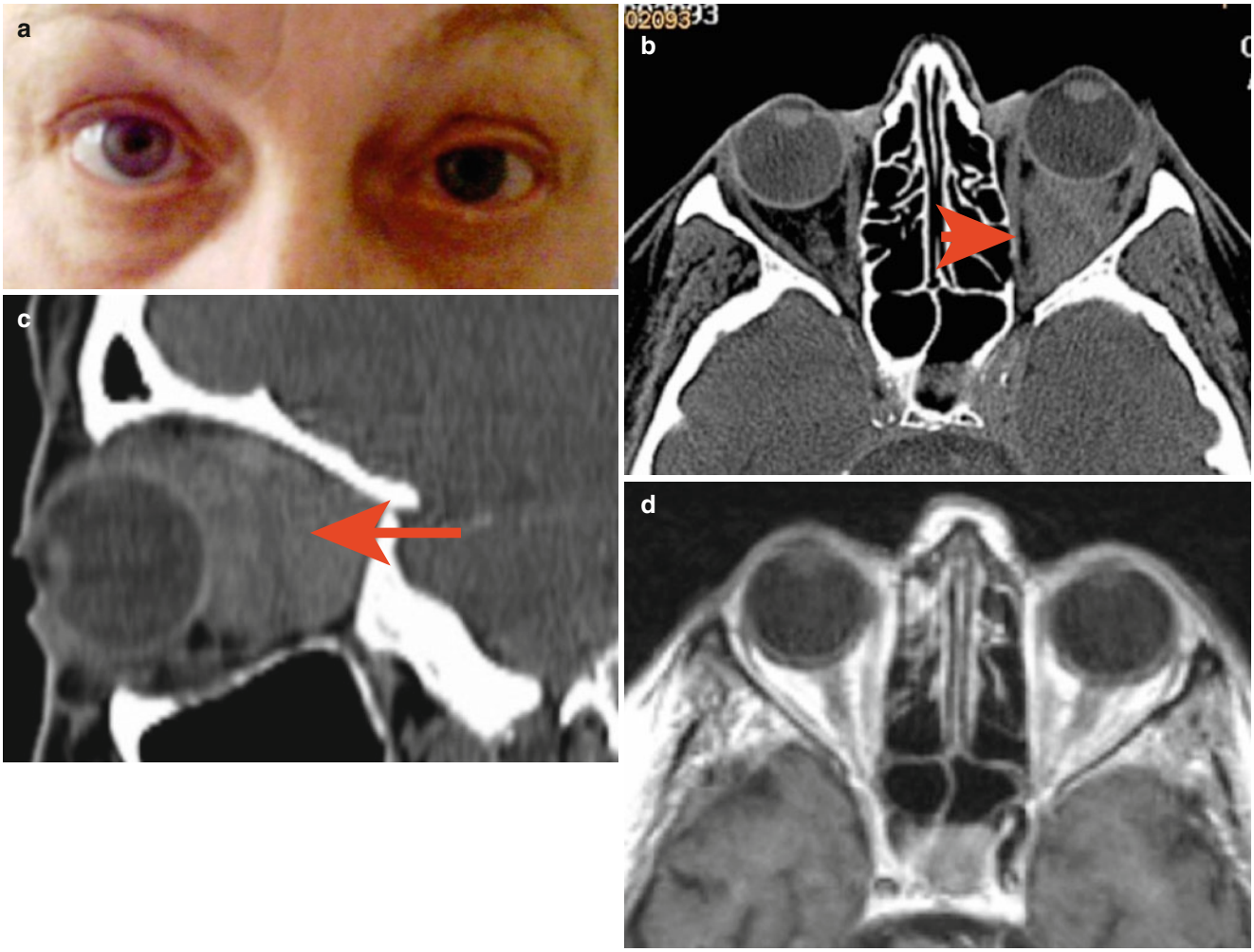

Fig. 5.6 This patient presented with orbital pain and diplopia; the left eye is hypotropic (**a**). (**b**, **c**) Mass in the orbit (*arrows*). The diagnosis of lymphoma was made at a different site (abdomen). (**d**) Regression of the lymphoma after chemotherapy

Pathogenesis Cranial nerve III is the second most frequently affected of the ocular cranial nerves. Incomplete lesions are more common. Sixty to seventy percent of lesions are isolated, the rest being associated with lesions of IV and/or VI.

- *Congenital* (nucleus usually unilateral).
- *Compressive:* Herniation of the temporal lobe, neurosurgical procedures, pathologic conditions in the cavernous sinus.
- *Idiopathic:* 20–25 % in adults, in pediatric cases up to 40 %.
- *Infections:* Botulismus, herpes zoster, mumps, syphilis, TBC, or tetanus.
- *Inflammation:* GBS (rare), meningitis – with other cranial nerve involvement.
- *Metabolic causes:* Diabetes – often painful – with sparing of the pupil. Usually self-limiting with a recovery in 4 months.
- *Toxic:* Alcohol, arsenic, carbon monoxide, and lead; carbon disulfide or dinitrophenol poisoning; or diabetes mellitus.
- *Neoplastic:* Leptomeningeal carcinomatosis, multiple myeloma, neurinoma.
- *Trauma:* Cranial trauma with or without fracture, blowout fractures, traumatic aneurysm. Differential diagnosis may be confused with impairment of orbital movements due to generalized swelling. Regeneration after trauma may be aberrant, and posttraumatic innervation may cause erroneous innervation of adjacent muscles; e.g., upper lid may

retract on attempted downward gaze (pseudo-von Graefe sign). Also, the pupil can restrict on adduction.
- *Vascular:* Aneurysm: often painful and involves the pupil. Diabetes mellitus.
- *Nuclear, fascicular:* In combination with brainstem infarcts.
- *Others:* Migraine – ophthalmoplegic migraine. Pediatric oculomotor lesions: congenital, traumatic, and inflammatory causes are most common. Isolated third nerve palsy in adults may be due to aneurysm, vascular, or undetermined causes.

Diagnosis Laboratory (exclude diabetes). Imaging, to exclude aneurysm, MR techniques (hrMRI) identifies nerve lesions.

Differential Diagnosis Botulism (involvement of pupil), brainstem disorders, CANOMAD syndrome, chronic progressive external ophthalmoplegia, congenital lesions, Miller Fisher syndrome, myasthenia gravis, and myopathy.

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.

5.5 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 level, 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 V1, CN III, and sometimes V2. It enters the superior orbital fissure and passes above the tendinous ring, crossing medially along the roof of the orbit and then diagonally across the levator palpebrae. The nerve breaks into three or more branches as it enters the superior oblique muscle.

Symptoms Patients experience vertical diplopia that increases when the gaze is directed downward 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.

Topographical Localization of Lesions Lesion sites include the midbrain, subarachnoid space, cavernous sinus, superior orbital fissure, and orbit.

Pathogenesis An 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 VI.
- *Compression:* Cavernous sinus, orbital fissure lesions, inflammatory aneurysms (posterior cerebral artery, anterior superior cerebellar artery), tentorium.
- *Infection:* Mastoiditis, meningitis.
- *Inflammatory:* Ophthalmoplegia or diplopia associated with giant cell arteritis.
- *Metabolic:* Diabetes.
- *Neoplastic:* Carcinomatous meningitis, cerebellar hemangioblastoma, ependymoma, meningioma, metastasis, neurilemmoma, pineal tumors, trochlear nerve sheath tumors.
- *Pediatric:* Congenital, traumatic, and idiopathic.
- *Trauma:* Head trauma causing compression at the tentorial edge, lumbar puncture or spinal anesthesia, subarachnoid hemorrhage, surgery. The trochlear nerve is the most commonly injured cranial nerve in head traumas.
- *Vascular:* Arteriosclerosis, diabetes (painless diplopia), hypertension.
- *Another type of involvement:* Superior oblique myokymia.

Diagnosis Diagnosis can be facilitated by the Bielschowsky test:
- Hypertropia of the affected eye.
- Diplopia is exacerbated when the affected eye is turned nasally.
- Diplopia is exacerbated by gazing downward.
- 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 of the affected eye.

Differential Diagnosis Skew deviation, a disparity in the vertical positioning of the eyes of supranuclear 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 nonselected cases.

5.6 Trigeminal Nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	(+) SEP Reflexes: masseteric, blink reflex EMG of masseteric muscle		+	

Qualities *Branchial motor:* anterior belly of digastric muscle, mastication muscle, mylohyoid muscle, tensor tympani muscle, tensor veli palatini. *General sensory:* bulb of eye, conjunctiva, face, meninges of anterior and middle cranial fossa, mucous membranes of paranasal sinus, nasal and oral cavity, tongue, teeth, part of external aspect of the tympanic membrane, scalp.

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 (Meckel's) cave in the floor of the middle cranial fossa. The three major divisions of the trigeminal nerve, V1, V2, and 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 (Figs. 5.7, 5.8, 5.9, and 5.10).

The extracranial pathway has three major divisions:

- *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
- *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. V2 is most frequently affected in trauma. Sensory loss of the cheek and lip is a common symptom. V2 can also be injured during facial surgery.
- *V3, the mandibular nerve:* The mandibular nerve's major branches are the auriculotemporal, inferior alveolar, and

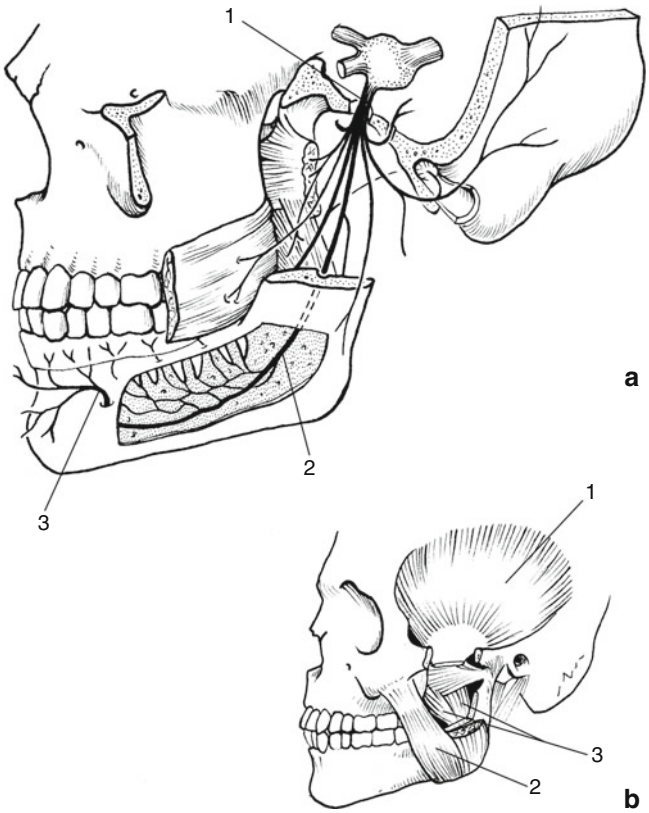

Fig. 5.7 Trigeminal nerve: Motor and sensory innervation. (**a**) *1* Mandibular nerve, *2* inferior alveolar nerve, *3* mental nerve. (**b**) *1* Temporal muscle, *2* Masseteric muscle, *3* pterygoid muscles

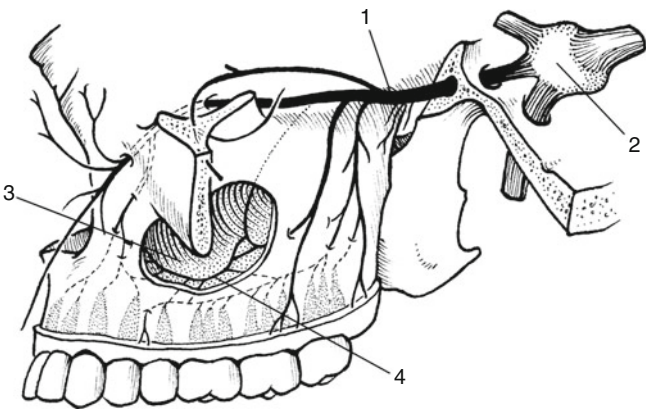

Fig. 5.8 Trigeminal nerve: sensory innervation of the maxilla. *1* Maxillary nerve, *2* trigeminal ganglion, *3* the maxilla (bone removed), *4* branch of superior alveolar nerve

lingual nerves. A separate motor division innervates the temporal and masseteric muscles and the tensor tympani, pterygoid, mylohyoid, and tensor veli palatini muscles. The mandibular nerve also has meningeal branches. Lesions of the V3 may result from dentistry, implantation, mandible resection, hematoma of the lower lip, or bites.

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

Signs 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 the trigeminal nerve distribution may be also caused by central (brainstem) lesions and follow an "onion skin" pattern. 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.

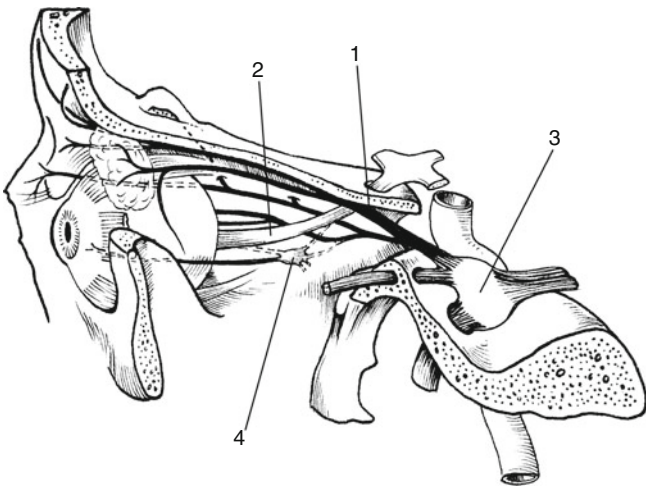

Fig. 5.9 Trigeminal nerve: sensory innervation of the eye and orbit. *1* Ophthalmic nerve, *2* optic nerve, *3* trigeminal ganglion, 4 ciliary ganglion

Pathogenesis

- *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 by some.
- *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 the 2nd or 3rd molars from the medial side, and wisdom teeth). Bronchoscopy can rarely lead to lingual nerve damage. Abscesses and osteosynthetic procedures of the mandibula can affect the lingual nerve. Clinically, patients suffer from hypesthesia and hypalgesia of the tongue, floor of the mouth, and lingual gingiva. Patients have difficulties with eating, drinking, and their sense of taste.
- *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:* Characterized by abrupt onset, usually affecting one or two branches unilaterally; numbness (may disturb motor coordination of speech);

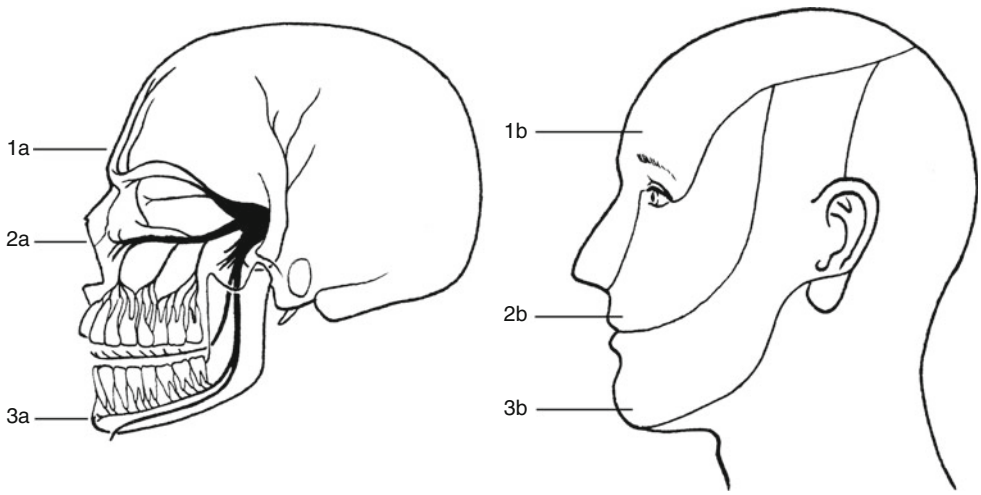

Fig. 5.10 Trigeminal nerve: 3 branches: *1a* Ophthalmic nerve, *2a* maxillary nerve, *3a* mandibular nerve, *1b–3b* sensory distribution

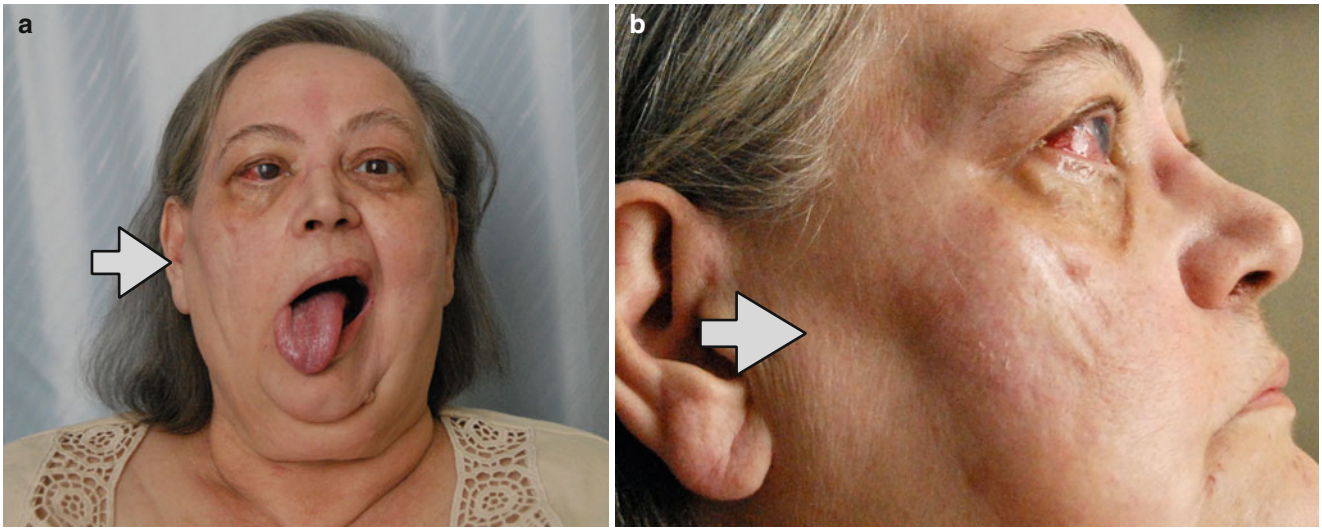

Fig. 5.11 Base of the skull metastasis with cranial nerve lesions and lesion of the trigeminal nerve: temporal and masseteric atrophy (*arrow*); in addition also VI, VII, and XII paresis occurred, due to the base of the skull metastasis

and pain. Etiologies include sensory trigeminal neuropathy, subacute sensory neuropathy, sensory trigeminal neuropathy (connective tissue disease), Sjögren syndrome, scleroderma, SLE, and progressive sclerosis. "Numb chin syndrome" or mental neuropathy has been described as an idiopathic neuropathy or resulting from mandibular metastasis.

- *Neoplastic:* "Amyloidoma" (gasserian ganglion syndrome); cholesteatoma; chordoma; leptomeningeal carcinomatosis that may compress or invade the nerve or trigeminal ganglion, either intracranially or extracranially; metastasis to the base of the skull.
- *Toxic:* Trichloroethylene (TCE).
- *Trauma:* Cranial fractures can 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.
- *Vascular:* Medullary infarction may cause trigeminal sensory deficits (e.g., "onion skin") and pain.
- *Other conditions*:
  - Association of the trigeminal nerve with polyneuropathy: Amyloidosis, diphtheria, leprosy, syphilis, thallium neuropathies, Waldenström's macroglobulinemia.
  - Cavernous sinus lesions: The ophthalmic nerve can be injured by all diseases of the cavernous sinus. Neoplastic lesions can be caused by lymphoma, metastases, myeloma, sphenoid tumors, and tumors of the nasopharynx. Typically, other cranial nerves, particularly the optomotor nerves, are also involved. The first and second divisions are also involved.
  - Gradenigo syndrome: Lesion of the apex of the pyramid (from middle ear infection) causes a combination of injury to V and VI and potentially VII.
  - Other conditions are the paratrigeminal (Raeder) syndrome, characterized by unilateral facial pain, sensory loss; Horner's syndrome; and optomotor motility disturbances.
  - An aneurysm of the internal carotid artery may also damage the cavernous sinus accompanied by concomitant headache, diplopia, and ptosis.

Trigeminal Neuralgia 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 douloureux." Trigger mechanisms can vary but often caused by specific movements such as chewing, biting, or just speaking. The neurologic examination is normal, and ancillary investigations show no specific changes. Vascular causes, like arterial loops in direct contact with the intracranial nerve roots, have been implicated as causal factors. Therapies include medication (anticonvulsants), decompression or lesion of the ganglion, vascular surgery in the posterior fossa, and rarely medullary trigeminal tractotomy (Fig. 5.13).

Symptomatic trigeminal neuralgia may be caused by a structural lesion of the trigeminal nerve or ganglion and by surgical procedures, tumors of the cerebellopontine angle, meningitis, and MS. If the ophthalmic division is involved,

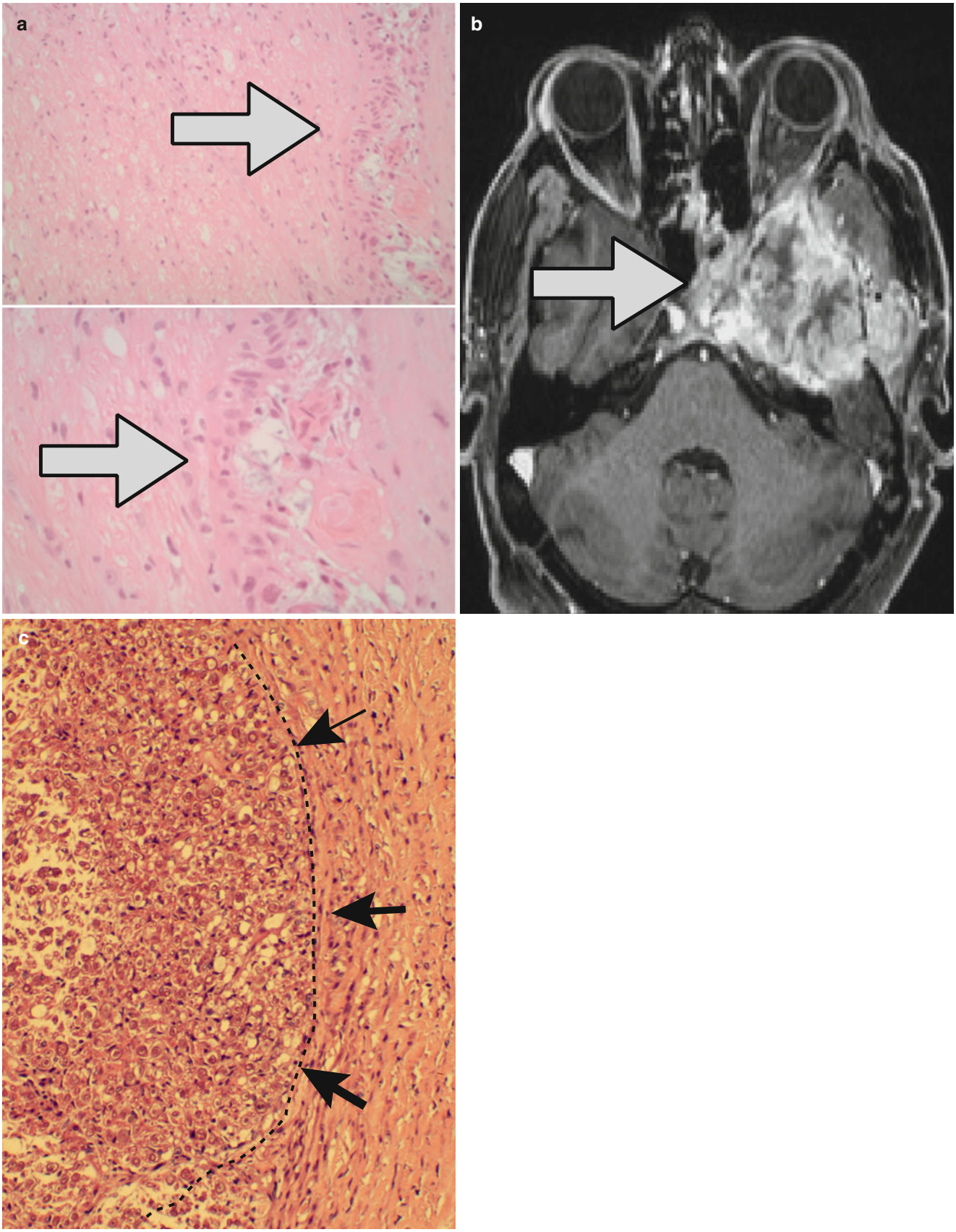

Fig. 5.12 Nerve infiltration. (**a**) Invasion of the facial nerve via the skin and retrograde spread of the tumor (*arrows*). (**b**) Malignant glioma, infiltration of the cavernous sinus. Neuropathic trigeminal pain and ophthalmoplegia due to intrasinusoidal nerve infiltration. (**c**) Nerve infiltration of a cranial nerve by a glioma in the cavernous sinus. *Dotted line:* circumference of the nerve. *Arrows:* invasion

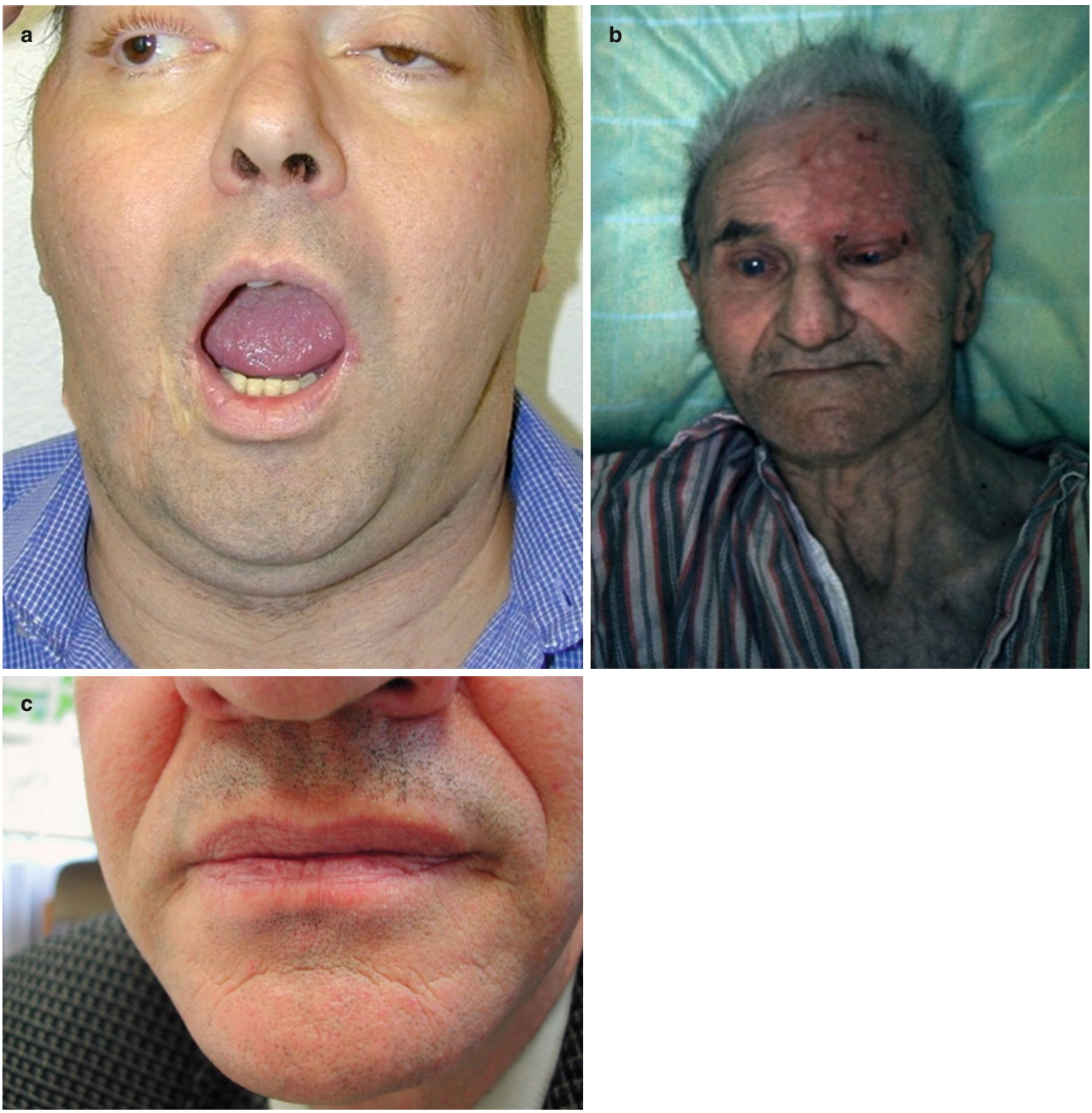

Fig. 5.13 Some features of trigeminal neuropathy. (**a**) Motor lesion of the right trigeminal nerve. The jaw deviates to the ipsilateral side upon opening the mouth. (**b**) Left ophthalmic zoster. (**c**) The patient suffers from trigeminal neuralgia. Shaving above the mouth induces attack. Note the unshaved patch that corresponds to the area, where the attack is elicited

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 boney changes and MR 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 masseteric muscles can be confirmed by EMG.

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.

5.7 Abducens Nerve

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

Quality Somatic motor, lateral rectus muscle.

Anatomy The abducens nucleus is located in the pontine tegmentum close to the midline and ventral to the IV ventricle. Axons from cranial nerve VII loop around the abducens nucleus, forming the bulge of the IV 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 anteriorly and laterally in the subarachnoid space of the posterior fossa, by 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 laterally to the carotid artery and medially to III, IV, V1, and V2. The abducens nerve enters the orbit at the medial end of the superior orbital fissure.

Fig. 5.14 Bilateral abducens nerve paresis. Inward gaze of bulbi. This patient suffered a fall from a bicycle with a subsequent head trauma

Table 5.3 Abducens nerve structures: from the nuclei to the orbit

CN VI	Brain parenchyma	Intracranial and CSF	Exit of cranial vault	Extracranial lesion
VI	Nucleus: pons, vicinity to VII fibers	Clivus pressure	Superior orbital tissue	Orbit
	Brainstem syndromes	Cavernous sinus		
		Meningeal carcinomatosis		
		Aneurysms		

Symptoms Patients report binocular horizontal diplopia that worsens when looking in the direction of the paretic lateral rectus muscle. The diplopia is also reported to be worse when looking at distant objects.

Signs An isolated paralysis of the lateral rectus muscle causes the affected eye to be adducted at rest. Abduction of

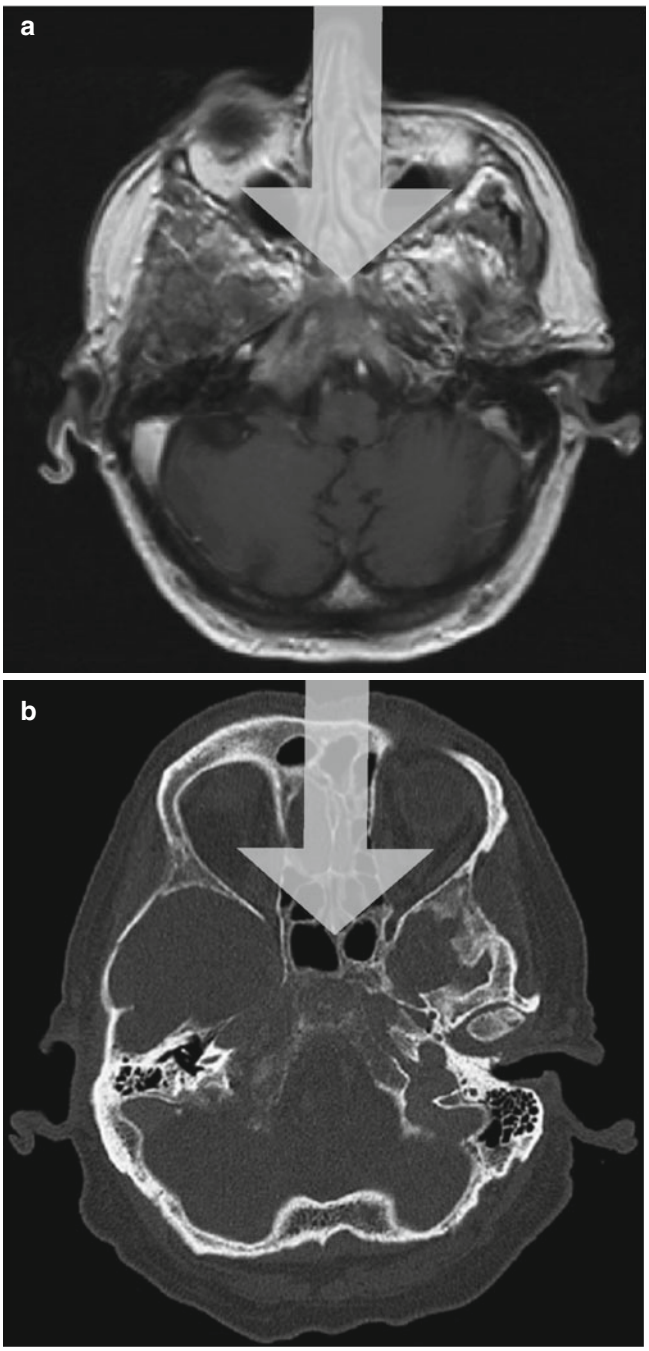

Fig. 5.15 Bilateral VIth nerve palsy caused by clivus metastasis. Bilateral VI nerve palsy in a patient with prostate carcinoma. Clinically a leptomeningeal carcinomatosis was excluded. Destruction of the sella (**a**), also visible in the image of the bone (**b**, *arrows*)

the affected eye is highly reduced or impossible, while gaze to the unaffected side is normal.

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

- *Brain:*
  - Nuclear: Fascicular lesion: demyelination, infarction, tumor, Moebius and Duane's syndrome, Wernicke's disease.
  - Intracranial course: Petrous apex: mastoid infection, raised ICP, skull fracture, trigeminal schwannoma. Subarachnoid space: basilar aneurysm, cavernous sinus, clivus tumor (chordoma, meningioma), hemorrhage, meningitis, trauma. Uncertain: microvascular infarction, migraine.
- *Causes:*
  - Compressive: Abducens palsy is a common sign of increased cranial pressure caused by hydrocephalus, pseudotumor cerebri, tumors, and lesions of the cavernous sinus (e.g., thrombosis).
  - Congenital: Duane's syndrome.
  - Infections: CMV encephalitis, cryptococcal and other meningitis, cysticercosis, HIV, Lyme disease, syphilis, tuberculosis, ventriculitis of the IV ventricle.
  - Inflammatory/immune mediated: Sarcoidosis, systemic lupus erythematosus, vasculitis.
  - Metabolic: Rarely diabetes.
  - Neoplastic: Abducens nerve tumor, cerebellopontine angle tumor, clivus tumor, leukemia, metastatic, leptomeningeal carcinomatosis.
  - Toxic: Vincristine therapy.
  - Vascular: Aneurysms of the posterior inferior cerebelli or basilar or internal carotid arteries.
  - Trauma: Fractures of the base of the skull.
  - Most frequent causes: MS, syphilis, undetermined cause, vascular disease, and diabetes.
  - Most frequent causes in pediatric cases: Neoplasm (39 %), trauma (20 %), inflammation (18 %).
  - Bilateral VI palsy: GBS, meningitis, pontine glioma, trauma, Wernicke's encephalopathy.

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

Differential Diagnosis Convergence spasm, Duane's retraction syndrome, internuclear ophthalmoplegia, myasthenia gravis, pseudo VI nerve palsy (lesion in the 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.

5.8 Facial Nerve

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

Qualities

- Branchial motor: Stapedius, stylohyoid, posterior belly of digastric, muscles of facial expression, including buccinator, platysma, and occipitalis muscles.
- Visceral motor: Lacrimal, submandibular, sublingual glands, as well as mucous membrane of the nose and hard and soft palate.
- General sensory: Skin of concha of the auricle, small area of skin behind the ear, possibly supplements the trigeminal nerve – V3 – which supplies the wall of the acoustic meatus and external tympanic membrane.
- Special sensory: Taste of anterior two thirds of the tongue and hard and soft palate.
- Major branches: Chorda tympani: taste. Large petrosal: salivation and lacrimation, motor branches, nerve to the stapedius muscle. 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 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

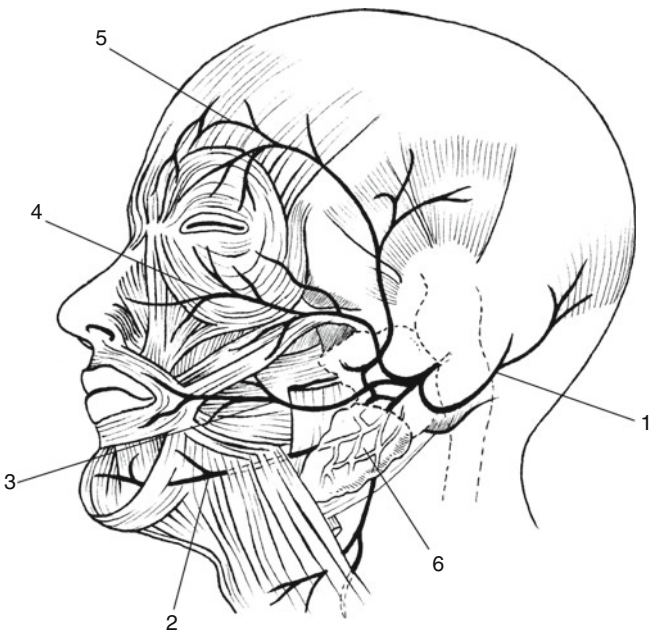

Fig. 5.16 Facial nerve: *1* Posterior auricular nerve, *2* mandibular branch, *3* buccal branch, *4* zygomatic branch, *5* temporal branch, *6* parotid gland

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.

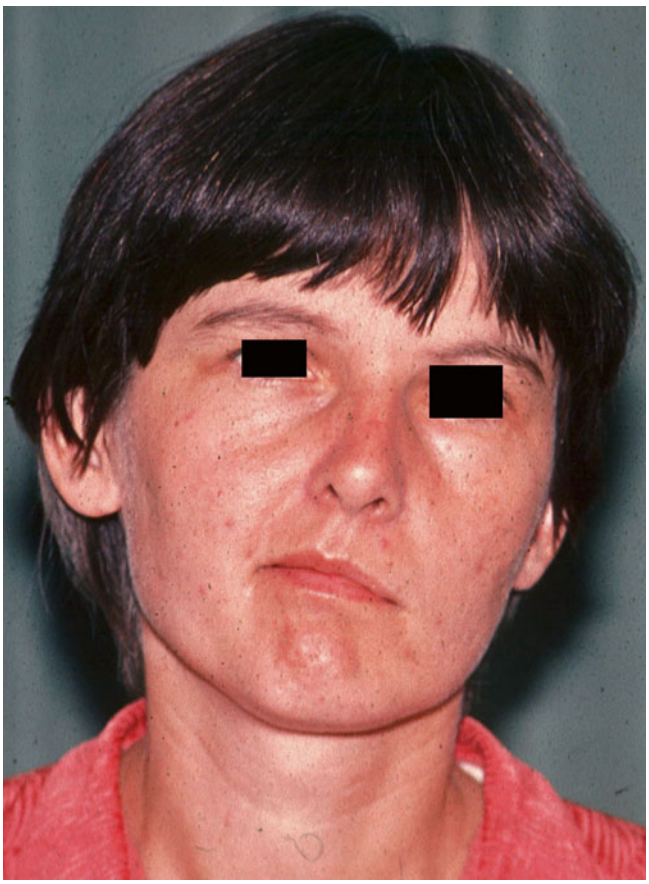

Fig. 5.17 Facial nerve palsy: this patient suffered from a right-sided Bell's palsy, which resulted into a contracture of the facial muscles. Note the deviated mouth

Topographical Lesions

- Supranuclear lesion
- Nuclear and brainstem lesions
- Cerebellopontine angle lesions
- Canalis of the facial nerve
- 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 functions 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 quadrant of the face (contralateral to the lesion). Pyramidal facial weakness: lower face paresis with voluntary motion. Emotional: face paralysis with emotion (dorsolateral pons – anterior cerebellar artery). Pontine lesion: neighboring structures: CN VI, conjugate ocular movements, hemiparesis, extrapyramidal facial: Parkinson's syndrome.
- *Peripheral lesions:* Mimic and voluntary movements of the facial muscles are impaired or absent. Drooping of the corner of the mouth, lagophthalmos. Patients are unable to whistle, frown, or show their teeth. Motor function is assessed by the symmetry and degree of various facial movements. With paralysis of the posterior belly of the digastric muscle, the jaw is deviated to the healthy side. With pterygoid paralysis, the opposite is true.

Table 5.4 Course of the facial nerve

CN	Brain parenchyma	Intracranial and CSF	Exit of cranial vault	Extracranial lesion	Multiple
VII	Central paresis: hemisphere, pons (nuclear and fascicular)	Cerebellopontine angle, meninges	Facial canal See anatomy	Parotid gland Each twig can be damaged Neoplastic retrograde infiltration	Leptomeningeal carcinomatosis, granulomatous

- *Location of peripheral lesion:*Internal auditory meatus: Geniculate ganglion – reduced salivation and lacrimation. Loss of taste on anterior 2/3 of tongue. Hyperacusis.
  - Between internal auditory meatus and stapedius nerve: Facial paralysis without impairment of lacrimation; however, loss of and salivation, taste, and hyperacusis.
  - Between stapedius nerve and chorda tympani: Facial paralysis, intact lacrimation, reduced salivation and taste. No hyperacusis.
  - Distal to the chorda tympani: Facial paralysis, no impairment of salivation, lacrimation, or hyperacusis.
  - After exit from the stylomastoid foramen: Lesions of singular branches.
  - Muscle disease: Myopathic face (facies myopathica) in several conditions.
- *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 cauda perioral muscle is seen in carotid surgery. Retrograde infiltration by skin tumors of the face can occur.

Pathogenesis *Bell's palsy:* Prevalence is 6–7/100,000 to 23/100,000 and increases with age. Paralysis progresses from 3 to 72 h. About half of the patients have pain in the mastoid or ear, and some (30 %) have excess tearing and 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 %. Symptoms may persist and contractures or synkineses may develop. Pathogenesis is not clear, but may be viral or inflammatory. Associated diseases: diabetes, hypertonia.

Therapy: Corticosteroids are effective in Bell's palsy (Salinas RA). Acyclovir, steroids, and surgery were compared: Pooled results from I and II studies showed better outcome from steroid-treated vs. non-steroid-treated patients. Steroids are probably effective, and steroids with acyclovir are possibly effective. High-quality evidence showed no significant benefit from anti-herpes simplex antivirals compared with placebo in producing complete recovery from Bell's palsy. Surgery: 104 cases were evaluated. Seventy-one showed complete recovery, 84 % with near-normal function. However a Cochrane review showed no improvement. Physical therapy was not effective in Bell's palsy. Important additional measures to consider are eye care, eyelid surgery, facial rehabilitation, and botulinus in symptomatic synkineses.

Differential diagnosis for Bell's palsy:

- Birth trauma: Cardiofacial syndrome, congenital dysfunction, hemifacial microsomia, Moebius syndrome. Prenatally: face compression against mother's sacrum, abnormal posture.
- Genetic conditions: Amyloid: gelsolin, Tangier disease.
- Granulomatous disease: Heerfordt's syndrome, sarcoid, and other granulomatous disease.
- Iatrogenic: Oxygen mask used in anesthesia (mandibular branch).
- Infection: Botulism, leprosy, Lyme disease (bilateral), otitis media, poliomyelitis, Ramsay Hunt syndrome (Fig. 5.18), syphilis, tetanus.
- Neoplastic: Acoustic neurinoma, base of the skull tumors (dermoids, large meningiomas, cholesteatoma), cerebellopontine tumors, leptomeningeal carcinomatosis, metastasis at the base of the skull.
- Trauma: Extracranial: carotid endarterectomy, gunshot, knife wound, parotid surgery. Intratemporal: motor vehicle accidents – 70–80 % from longitudinal fractures. 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. Sixty-five to eighty percent of fractures have been reported to be neither longitudinal nor transverse, but rather oblique. Severe head injury can also avulse the nerve root from the brainstem. Intracranial: surgery.
- Other conditions: Myeloma, Paget's disease, porphyria.
- Regeneration may result in involuntary movements and similar conditions: Blepharospasm, contracture (postparalytic facial dysfunction), facial myokymia, hemifacial spasm, synkinesis, tick.
- Association of CN VII palsy with neuropathies: Guillain-Barré, Lyme disease, polyradiculopathies, sarcoid.
- Periocular weakness, without extraocular movement disturbance: Congenital myopathies, FSH, muscular dystrophies (myotonic, oculopharyngeal muscle dystrophy), polymyositis.
- MND/ALS: ALS, bulbospinal muscular atrophy, motor neuron syndromes.
- Bilateral facial paralysis: AIP, leprosy, Lyme disease, Melkersson-Rosenthal syndrome, MND, Moebius syndrome, myopathies, sarcoid.

Diagnosis Aside from clinical examination, laboratory tests that may be helpful include ANA, angiotensin converting enzyme (for sarcoidosis), BSR, glucose, HIV, RA Lyme serology, microbial tests, serology, virology. CSF should be examined if an intracranial inflammatory lesion is suspected. Other tests include CT, blink reflex, EMG (facial nerve CMAP, needle EMG), magnetic stimulation, and MRI. Based on Cochrane review and conslusion of studies with steroid treatment:

Therapy Cochrane Bell and Steroids Authors' conclusions: The available evidence from randomized controlled trials shows significant benefit from treating Bell's palsy with corticosteroids.

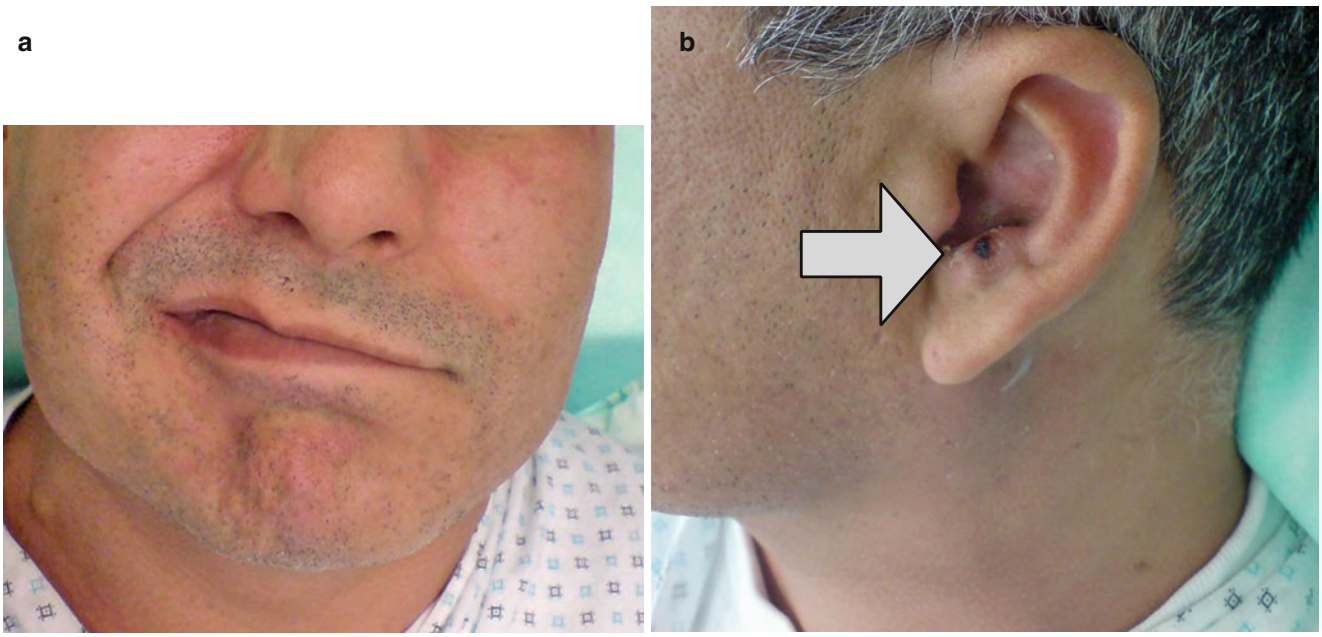

Fig. 5.18 Ramsey Hunt syndrome. This patient suffered from a left-sided peripheral facial nerve palsy (**a**). In the ear herpes sores can be seen (**b**, *arrow*)

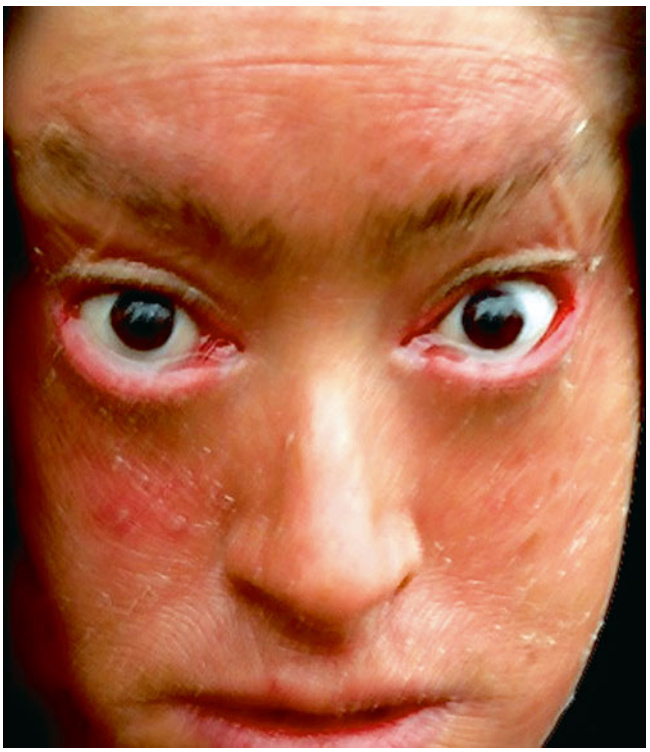

Fig. 5.19 Scleroderma mimicking bilateral "facial" paralysis. Inability to close eyes and masklike face

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 %.

The prognosis can be based on electrophysiologic tests: CMAP in comparison side-to-side – good. Blink reflex: uncertain. Needle EMG: Limited. Magnetic stimulation in side-to-side relation: good.

Qualities associated with a better prognosis for Bell's palsy include early improvement, incomplete paralysis, normal salivary flow, normal taste, slow progression, and younger age. Residual signs may occur with Bell's palsy. These include contracture (20 %), crocodile tears (6 %), facial weakness (30 %), and synkinesis (50 %).

5.9 Acoustic Nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy	Hearing tests
Familial	+ Auditory evoked potentials (AEP)		+ MR		+

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 eighth 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 brainstem, 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

- Compressive: Tumors at the cerebellopontine angle.
- Congenital: Rubeola embryopathy, thalidomide toxicity.
- Infectious: Herpes, mumps, otitis, sarcoid.
- Inflammatory/immune mediated: Cogan syndrome, paraneoplastic (anti-Hu) (very rare).
- Hereditary: Congenital hearing loss. Hereditary motor-sensory neuropathies: CMT, HMSN, and others including CMT 1A, CMT 1B, Coffin-Lowry syndrome, Connexin 31, Duane's syndrome, HMSN X (Connexin 32), neuroaxonal dystrophy (late infantile), neurofibromatosis-2, and X-linked. Dilated cardiomyopathy with sensorineural hearing loss (CMD1J; CMD1K).
- Metabolic: Diabetes, hypothyroidism.
- Neoplastic: Cholesteatoma, meningeal carcinomatosis, metastasis.
- Trauma: Temporal bone fractures.
- Toxic: Antibiotics, benzoles, carbon monoxide, cytostatic drugs, salicylate.
- 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: arteriosclerosis, conducting apparatus, degeneration of cochlea, drugs (including amyl nitrate, quinine, salicylates, streptomycin), hemifacial spasm, ischemia, labyrinthitis, otosclerosis.

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

5.10 Vestibular Nerve

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

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. Hair 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 IV 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 cerebellum and lower motor neurons of the brainstem and spinal cord (modulating muscle activation for keeping balance). In the lateral vestibular nucleus, axons project ipsilaterally and caudally into the spinal cord and vestibulospinal tract (to lower motor neurons which control 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 here between 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

- *Congenital and hereditary:* Aplasia; Arnold-Chiari; atrophy of VIII; chromosomal aberrations; Cockayne, Hallgren, and Alström syndrome; Refsum's disease; HSMN; Kearns-Sayre; OPCA; retinitis pigmentosa; sensorineural deafness; SMA; thyroid disease.
- *Cupulolithiasis* (benign paroxysmal positional nystagmus). Several subtypes have been described.
- *Immunologic disorders:* Demyelinating neuropathies, Hashimoto, leukodystrophies, MS, periarteritis nodosa, sarcoid.

- *Infection:* Labyrinthitis, specific and unspecific. Suppuration reaches inner ear by either blood or direct invasion (meningoencephalitis).
  - Bacterial: Streptococcal pneumoniae, hemophilus, Lyme disease, petrositis, syphilis.
  - Viral: AIDS may cause sensorineural hearing loss, herpes zoster oticus, Ramsey Hunt syndrome, vestibular neuronitis.
  - Mycotic: Coccidiomycosis, cryptococcosis, rickettsial infection.
- *Metabolic:* Diabetes, uremia.
- *Neoplastic:* Acoustic nerve neuroma, metastases, neurofibromatosis, schwannoma.
- *Toxic:* Alcohol, aminoglycosides, chemotherapy (cisplatin, cyclophosphamide, hydroxyurea, vinblastine), heavy metals (lead, mercury); quinine salicylate.
- *Trauma:* Blunt, penetrating, or barotrauma. Transverse fractures are often associated with additional 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 neurologic sequel to head injury, and it is a positional vertigo.
- *Vascular:* AICA aneurysm, large vascular loops, posterior communicans artery aneurysm, unruptured aneurysms, vascular lesions of the spiral ganglion, vertebrobasilar circulation (history of diabetes, hypertension).
- *Others:* Hyperviscosity syndromes (hypergammaglobulinemia, polycythemia vera, Waldenström's macroglobulinemia).

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

5.11 Glossopharyngeal Nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+ Videocinematography	

Quality Branchial motor: stylopharyngeus muscle. Visceral motor: otic ganglion, fibers to stimulate the parotid gland. Visceral sensory sensation (subconscious): 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 several parts: 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). It contains sensory fibers (posterior third of the tongue, pharynx, tonsils, middle ear, and carotid body). The parasympathetic fibers supply the parotid gland (via the ganglion oticum) and motor fibers to the stylopharyngeal muscle. There is a communicating nerve to the vagus nerve. The CN IX is involved in swallowing by innervation of the stylopharyngeal muscle, which elevates and pulls the larynx forward during the pharyngeal stage of swallowing.

Functions: It receives sensory fibers from the posterior one third of the tongue, the tonsils, the pharynx, the middle ear, and the carotid body. It supplies parasympathetic fibers to the parotid gland via the otic ganglion. It supplies motor fibers to the stylopharyngeus muscle, and it contributes to the pharyngeal plexus.

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 side of throat). Abnormal lacrimation ("crocodile tears," "Bogorad" syndrome) 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 the tongue is disturbed (taste evaluation on posterior third of the tongue). The gag reflex is reduced or absent, which may result in aspiration problems. 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) – medulla oblongata, pons, pontine tumors, Wallenberg's syndrome.
- Intracranial: Inflammatory: GBS, meningitis, "polyneuritis cranialis." Tumors: neurinoma – cerebellopontine angle, meningeal carcinomatosis, venous thrombosis.
- Exit from the cranial vault: Jugular foramen syndrome (with CN X, XI; Vernet's syndrome) caused by chordoma, fracture of base of the skull, metastasis, neurinoma.

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

Other Pathogenetic Mechanisms

- *Infectious:* Diphtheria, herpes zoster, poliomyelitis.
- *Inflammatory/immune mediated:* Cryoglobulinemia, GBS, Miller Fisher syndrome, panarteritis nodosa, sarcoid, serum sickness, SLE.
- *Metabolic:* Amyloid deposition, porphyria.
- Motor neuron disease
- Myasthenia gravis
- *Neoplastic:* Leptomeningeal carcinomatosis, leukemia, myeloma, vagal rootlet neuroma.
- *Surgery:* Tonsillectomy (rare).
- *Tardive dyskinesia:* Can involve the swallowing function.
- *Toxic:* Tetanus toxin, nitrofurantoin, salvarsan intoxication.
- *Vascular:* Brainstem lesions; see topographical lesions.
- *Trauma:* Basal fracture of the skull.
- *Association with neuropathies:* Diphtheria, GBS, paraneoplastic.

Other Syndromes

- Baroreceptor may be affected in tabes and diabetes.
- 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. The attacks are brief but can be associated with excruciating pain. Glossopharyngeal neuralgia can be associated with fainting (reflex association with vagal nerve, which can cause syncope, and bradycardia).

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

Differential Diagnosis Bulbar muscular disorder, motor neuron disorders, myasthenia gravis, pain, trigeminal neuralgia.

Therapy For neuralgia: amitriptyline, carbamazepine, gabapentin.

5.12 Vagus Nerve

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

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.

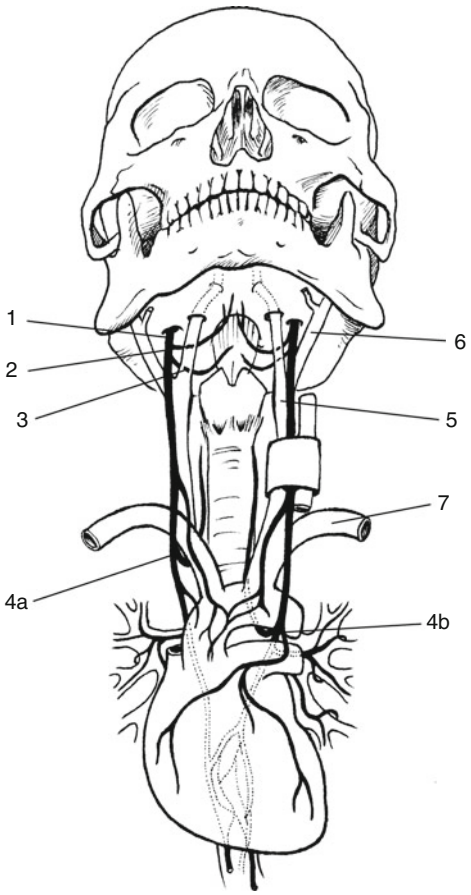

Fig. 5.20 *1* Vagus nerve, *2* pharyngeal branch, *3* internal laryngeal branch, *4a* right recurrent laryngeal nerve (across the subclavian artery), *4b* left recurrent laryngeal nerve (across the arch of the aorta), *5* internal carotid artery, *6* external carotid artery, *7* left subclavian artery

- *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 pharynx, 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). Most of the fibers are sensory and parasympathetic.

Intracranial pathway: The vagus nerve emerges from the medulla with several rootlets and exits through the jugular foramen (within the same dural sleeve as 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 the 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.

Motor divisions: The three motor divisions have a bilateral upper motor neuron innervation and consist of three branches: (1) pharyngeal branch supplying muscles of the soft palate and pharynx, (2) the superior laryngeal nerve (inferior pharyngeal constrictor and cricothyroid muscles of the pharynx), and (3) recurrent laryngeal branches innervating all other intrinsic muscles of the pharynx. The recurrent laryngeal nerve passes under the subclavian artery on the right side and the aortic arch on the left side and 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 the cardiac, pulmonary, esophageal, and gastrointestinal structures.

Symptoms Patients with vagus damage experience swallowing difficulty and hoarseness of voice.

Signs Vagus damage can cause paralysis of the palate, pharynx, and larynx according to the site of the lesion and cause hoarse voice and dysphagia. Bilateral lesions can lead to nasal voice and regurgitation through the nose. The gag reflex can be absent and the uvula deviates away from the side of the lesion as a failure of palate elevation occurs.

Pathogenesis

- *Iatrogenic:* Mediastinal tumors, mediastinoscopy, operations of the trachea and esophagus, thoracotomy, thyroid surgery (recurrent nerve).
- *Infectious:* Botulism, diphtheria, herpes, meningitis, poliomyelitis, tetanus.
- *Inflammatory/immune mediated:* Dermato- and polymyositis.
- *Neoplastic:* Jugular foramen tumor, meningeal carcinomatosis, metastasis (with CN IX involvement).
- *Metabolic:* Hyperpotassemia, hypophosphatemia.
- *Trauma:* Fractures that affect the jugular foramen (uncommon). Hyperextension neck injuries are also sometimes associated with injury to these nerves at the craniocervical junction.
- *Toxic:* Alcoholic polyneuropathy, thallium.
- *Vascular:* Medullary infarction.
- *Others:* Familial hypertrophic polyneuropathy; myopathies (Chronic progressive external ophthalmoplegia, oculopharyngeal muscle dystrophy); polyneuropathies (amyloid (some types), diphtheria, alcohol). Tardive dyskinesia can involve laryngeal muscles.
- *Special segments:*
  - *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 voice. If the superior laryngeal nerve is affected in addition and the cricothyroid is no longer functional, the vocal cords will remain in an intermediate position. This causes a breathy and weak voice and constant clearing of the throat as with a lodged foreign body or aspiration. Causes of focal damage of the recurrent laryngeal nerve include diseases of the lungs, tumors in the thoracic cavity (lung cancer), aneurysm of the aortic arch, enlarged lymph nodes, and thyroid surgery. About 25 % of cases are idiopathic.
  - *Recurrent laryngeal nerve lesions:* Hoarseness is observed in local anesthetic procedures, presumably due to excessive local anesthetic spread.
- *Other entities:*
  - Focal laryngeal dystonia, gag reflex which can be diminished in patients with schizophrenia, obesity treatment, sexual dysfunction in women after spinal cord injury, spastic dystonia, vagal nerve stimulation which has been used in the treatment of epilepsy and major depression.
  - Neuralgia of the laryngeal nerve (rare).
  - 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, motor neuron diseases, neuromuscular transmission disorders.

Therapy Treatment depends upon the etiology.

Prognosis Prognosis depends upon the etiology.

5.13 Accessory Nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

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

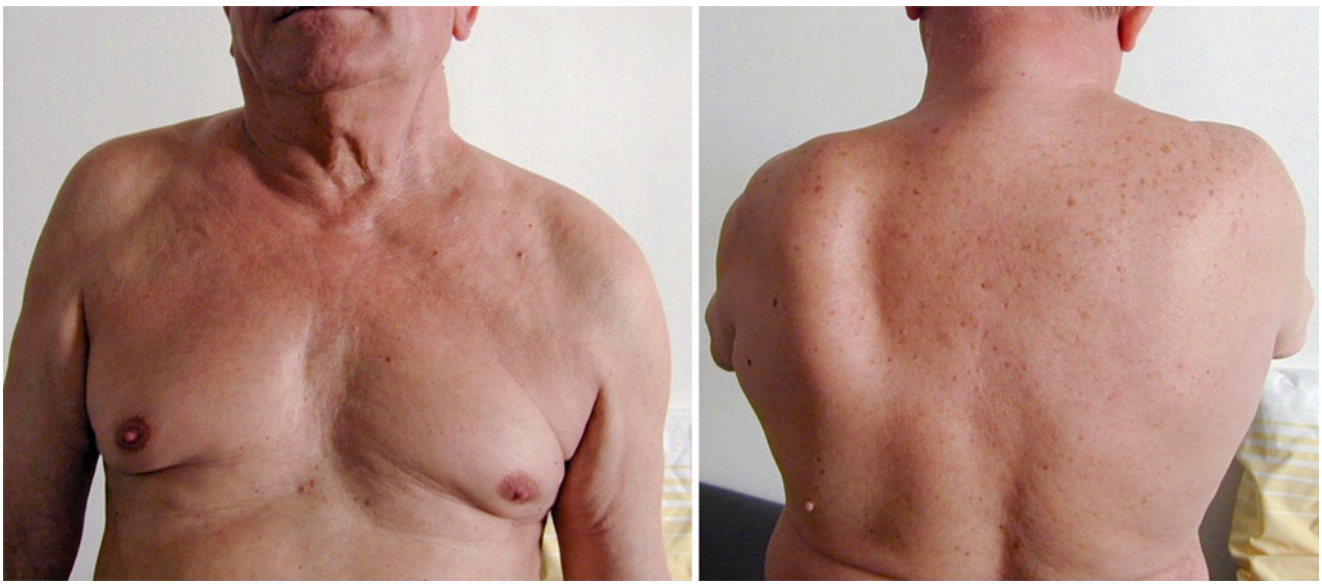

Fig. 5.21 Left accessory nerve palsy, following carotid resection: note the unilaterally missing profile of the trapezoid muscle (diagnostic clue) and the winging of the scapula with the abduction of the medial scapular border

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. Anatomically a distinction between the brainstem and spinal fibers is made, and the term of an additional "transitional nerve" has been proposed, which divides the nerve into a cranial and a spinal portion. The "transitional nerve" is involved in laryngopharyngeal innervation. 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, which has a prominent role in optomotor tracking. 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 can cause shoulder pain of variable severity, paresthesias over the shoulder and scapula, weakness of the shoulder, and shoulder drop.

Signs Lesion causes weakness of head rotation to the opposite side and trapezius weakness that results in the inability to lift the shoulder and raise the arm above horizontal. Dropping of shoulder and moderate winging of the scapula is also observed.

Pathogenesis

- *Topo*graphical lesions:
  - Intracranial part: Rare, intracranial tumors.
  - At the jugular foramen: Lesions here occur in association with the glossopharyngeal and vagus nerves – Vernet's syndrome, local tumors, schwannomas, metastasis, sarcoidosis, Siebmann syndrome, Collet-Sicard 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.
- *Other pathogenetic mechanisms:*
  - 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.
  - Neoplastic: ENT tumors, base of skull metastases (all tumors, in particular multiple myeloma, prostate, ENT). Collet-Sicard syndrome, spinal tumors, retrograde infiltration from adjacent tumors.
  - Others: Motor neuron disorders, neck surgery; spinal – tumors and syringomyelia, trauma.
  - Dystonia: A cervical lesion of the CN XI can result in cervical dystonia or torticollis (in addition to the more common cause of centrally caused dystonia).

Diagnosis

- *Sternocleidomastoid muscle:* Impaired 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.
  - 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 part.

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 exploration is warranted if no improvement occurs after closed trauma.

5.14 Hypoglossal Nerve

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

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

Anatomy *Intracranial:* The nerve originates in the hypoglossal nucleus, beneath the floor of the IVth ventricle, and extends caudally to the lower limit of the medulla. In the brainstem the fibers traverse the reticular formation and medial part of olive, then exits the medulla in the lateral sulcus. The nerve emerges in two bundles which 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 glossopharyngeal, vagus, and accessory nerves. Fibers from the first and second cervical nerve join the hypoglossal nerve close to its exit from the skull, but leave the nerve shortly after this 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

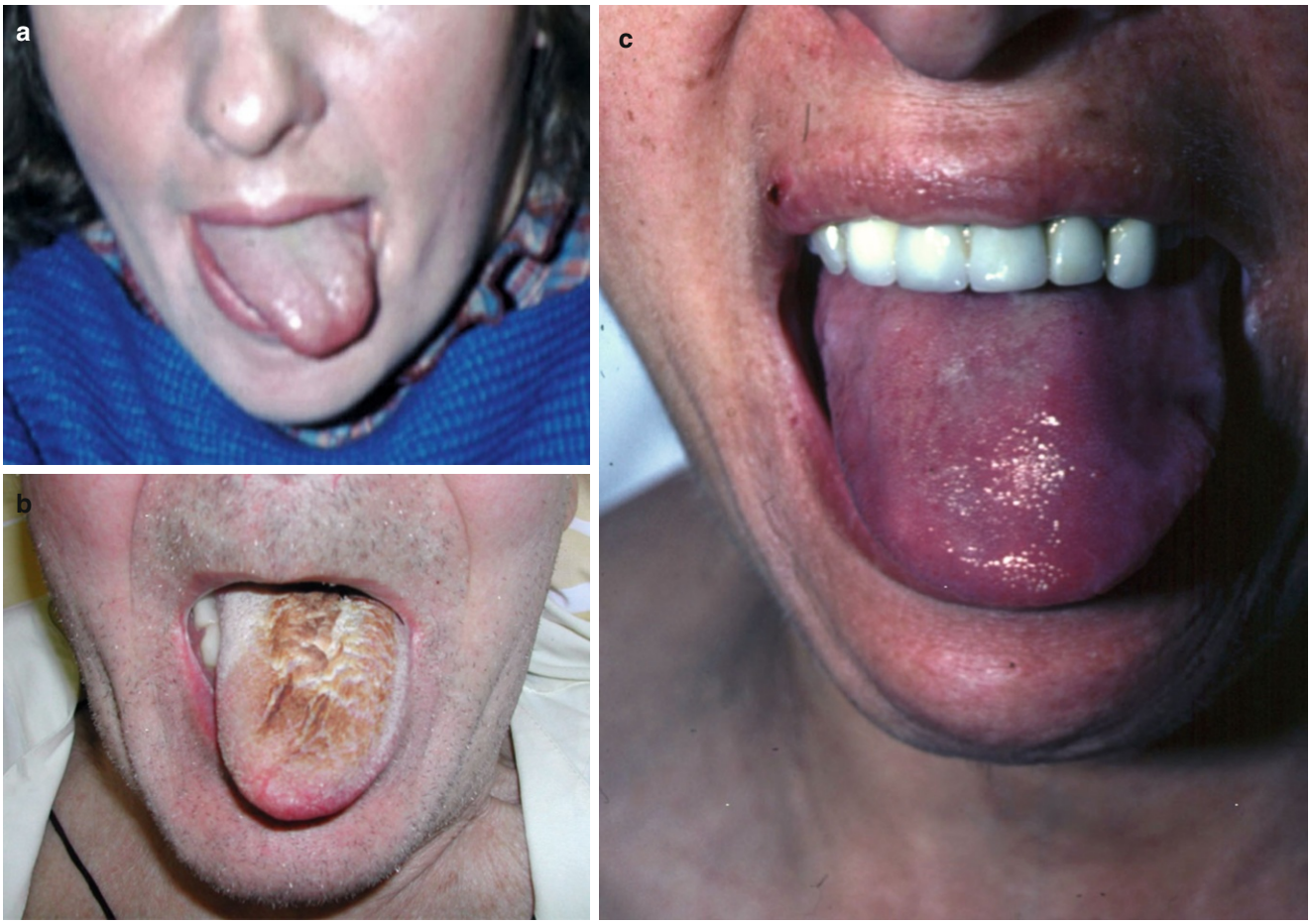

Fig. 5.22 (**a**) Left hypoglossal peripheral paresis. Note deviation of the tongue to the left. (**b**) Right-sided hypoglossal paresis, in a patient with meningeal carcinomatosis. Midline of the tongue shifted to the right. (**c**) Amyloid tongue in a patient with multiple myeloma. Patient's subjective impression was that the tongue was "too big"

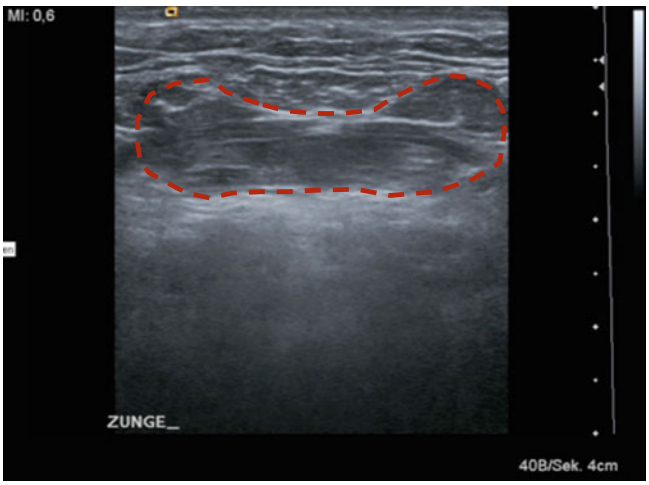

Fig. 5.23 Tongue in ultrasound. Mickey Mouse (*dotted red line*) appearance of the tongue and oral cavity in ultrasound. This technique allows a painless investigation of the tongue tissue and can detect movements as fasciculations

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 upper motor neuron lesion results in mild contralateral tongue weakness. Bilateral spasticity (e.g., ALS) in impairment of tongue movements. Unilateral peripheral lesion leads to wasting of the ipsilateral side of the tongue and excessive furring (wrinkling). Deviation occurs toward 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."

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

- *Iatrogenic:* Surgery of the oral cavity and neck, carotid endarterectomy, radiotherapy, in association with other cranial nerves, compression of the lateral part of the tongue (with lingual nerve) (laryngoscopy, etc.), following intubation, tooth extraction.
- *Idiopathic:* Isolated unexplained pathogenesis, usually reversible.
- *Infection:* Basal meningitis, infections: mononucleosis, granulomatous meningitis, postvaccination mononeuropathy, toxoplasmosis.
- *Inflammatory/immune mediated:* Rheumatoid arthritis: subluxation of odontoid process in rheumatoid arthritis, Paget's disease.
- *Neoplastic:* Schwannoma, primary nerve tumors (neurofibroma, neurinoma), metastasis to the base of the skull, meningeal carcinomatosis, clivus metastasis (can be bilateral as nerves are close to the midline), affection of hypoglossal canal by glomus jugulare tumors, meningioma, chordoma (sometimes in association with other cranial nerves). Tongue carcinoma may infiltrate the nerve and lymph nodes with Hodgkin's disease and Burkitt's lymphoma, amyloid nerve deposition in myeloma, radiation of neck tumors.
- *Trauma:* Head injury, penetrating head wound (often with other CN injuries), or dental extraction. Hyperextension of the neck. Hypoglossal tubercle or occipital condyle.
- *Vascular:* Vertebral basilar aneurysm, dissection of internal carotid artery.
- *Other causes:*
  - Malformation: Chiari malformation.
  - Bilateral CN XII lesions: Motor neuron disorders appear as bilateral hypoglossal nerve lesions. Iatrogenic: Intubation, multiple sclerosis, neoplasm – posterior tongue.

Other Syndromes

- Glossodynia: Burning pain in tongue and also oral mucosa, usually occurring in middle-aged or elderly persons.
- Burning tongue: Vitamin B12 deficiency and several internal medical diseases.

Differential Diagnosis Motor neuron disease (ALS), pseudobulbar involvement, local tumors affecting the tongue.

Therapy Treatment is based on the underlying cause.

5.15 Oral Cavity

The oral cavity is one of the most distinct entrance gates of the body. Its innervation is a combination of sensory, somatosensory, autonomic, and motor functions which is regulated both by voluntary and involuntarily controls. A brief bedside test with the patient pronouncing the consonants will help to get an impression on the function of the oral cavity regarding closure, transport of food, and initiation of swallowing.

- "**B**" entrance to the oral cavity: mouth and lips
- "**T**" the oral cavity:
  - Within: tongue, gums, mucous membranes, glands
  - Sensory motor innervation and feedback: chewing
- "**G**" posterior part: gag and swallowing

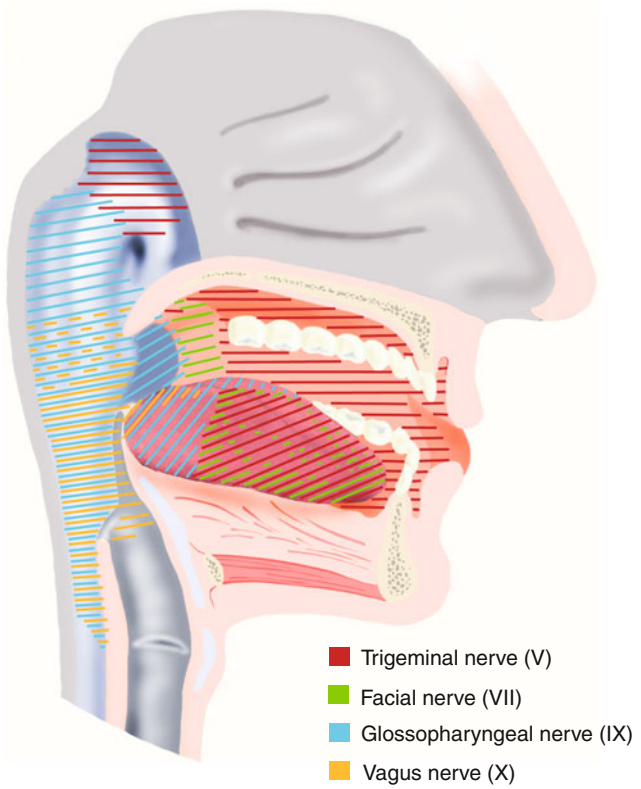

Fig. 5.24 Oral cavity. The image illustrates the innervation of the oral cavity and tongue. The taste perception of the anterior two thirds of the tongue is transmitted by the facial nerve, the posterior third by the glossopharyngeal nerve. The sensory innervation by the trigeminal nerve V3 overlapping in the buccal area with V2. The buccinator muscle, which innervates the cheeks, is innervated by the facial nerve

5.15.1 Ventral Part and Closure

The muscles of the entrance of the oral cavity are innervated by the facial nerve, and the sensory innervation comes from the trigeminal nerve. The lips are innervated in particular by the orbicularis oris muscle; the sensory innervation comes from the mental and infraorbital nerve. The closure of the oral cavity is a step in feeding; the precise lip movement and closure is as important in drinking as the movement of the lips in speaking, which is another important aspect. Both motor dysfunction (facial nerve) and sensory dysfunction (mental nerve) are reducing the ability of lip function. The causes can be central, peripheral, and within the muscle.

5.15.2 Middle Part, Oral Cavity and Tongue

The vestibule is the slit-like space between the mouth and the cheeks, lips, teeth, and gingivae. The boundaries of the oral cavity are the cheeks and lips, the hard palate, and posteriorly the oropharynx. The cheeks' sensory innervation comes from the mental and maxillary nerves; the muscle is predominantly the buccinator muscle. Both the tongue and the cheeks act as a functional unit during sucking, blowing, and chewing and act as an oral sphincter. The tongue fills the oral cavity. It consists of a root, body, and tip and is divided into an oral and a pharyngeal part. Its functions are mastication, taste (lingual papillae and taste buds), deglutition (swallowing), articulation (speech), and cleansing of the oral cavity. Squeezing food into the pharynx when swallowing and forming words during speech are its main functions. The muscle is innervated by the hypoglossal nerve, with the exception of the palatoglossus muscle, which is supplied by the pharyngeal branch of the vagus nerve. It has several intrinsic muscles. The tongue is also linked with extrinsic muscles as the genioglossus, hypoglossus, styloglossus, and palatoglossus. The sensory innervation is generated by the lingual nerve (anterior 2/3) and the glossopharyngeal nerve (posterior 1/3) and the special sensory innervation by the chorda tympani (anterior 2/3) and the glossopharyngeal nerve (posterior 1/3). The dome of the oral cavity is composed of the maxillary hard palate (2/3) and the soft palate, which is the posterior curtain-like part, composed of a fibromuscular fold, which separates the naso- and oropharynx. Posteriorly and inferiorly it extends to a curved free margin from which hangs the uvula. The muscles of the soft palate are the levator veli palatini (CN X), tensor veli palatini (medial pterygoid nerve – a branch of the mandibular nerve), palatoglossus (CN X, XI), palatopharyngeus (CN X, XI), and uvula muscle (CN X). The sensory innervation of the hard palate are branches from the ganglion pterygopalatinum. The greater palatine nerve supplies the gingivae, whereas the lesser palatine nerve, the soft palate. The anterior part of the hard palate is innervated by the nasopalatine nerve. The posterior part of the oral cavity prepares for swallowing and the gag reflex. The glossopharyngeal and vagal nerve innervate this part of the oral cavity. The function is the food passage propelling the food bolus through the pharynx, and the airway protection during food passage.

5.15.3 Posterior Part, Gag and Swallowing

Pharyngeal stage: The food is propelled by the tongue to the oropharynx. In the pharyngeal stage the two issues are (1) the passage of the food bolus through the pharynx and (2) the airway protection. The soft palate elevates and closes the nasopharynx. The base of the tongue pushes the bolus against the pharyngeal walls. The pharyngeal wall muscles contract sequentially to press the bolus downward. Several airway protection mechanisms are involved in the closure of the vocal cords; the contraction of the suprahyoid muscles and the thyrohyoid muscles pull the larynx and hyoid bone upward. The epiglottis tilts backward to seal the laryngeal vestibule. Opening of the upper esophageal sphincter (UES) (pharyngeal

Table 5.5 Cranial nerves and painful conditions

CN	Base of the skull	Cavernous sinus	Neuralgic pain	Others
II				Temporal arteritis, headache
III, IV, VI	Metastases, meningeal carcinomatosis	+	Tolosa-Hunt syndrome	Aneurysms, diabetes, giant cell arteritis, metastasis, leukemia, lymphoma, infection Orbital disease: pseudotumor, sinusitis Others: ophthalmoplegic migraine
V	Ganglion gasseri syndrome, meningeal carcinomatosis, base of the skull tumors	V1 < V2	Neuropathic pain in nerve distribution Trigeminal neuralgia	Masticatory claudication Retrograde nerve infiltration, Tolosa-Hunt syndrome
VII				Ramsey Hunt syndrome Retrograde nerve infiltration
IX	+		+ Rare "glossopharyngeal neuralgia"	
X			+ Glossopharyngeal and vagal neuralgia	
XI				Lesions in the neck region, "shoulder arm" syndrome
XII	+			Pain, anastomosis with cervical plexus (ansa cervicalis)
Multiple CN	Orbital, middle fossa, jugular foramen, occipital condyle syndrome (XII)	Parasellar		Calvarial metastasis
Cervical plexus			+	

constrictor muscles, cricopharyngeus muscle, and the most proximal part of the esophagus) is essential for the bolus entry into the esophagus. The UES is closed at rest by tonic muscle contraction. Preceding the opening of the UES, the cricopharyngeus muscle relaxes; the suprahyoid and thyrohyoid muscles contract by the force of the descending bolus. Neurologic involvement in the oral cavity manifests as burning of the tongue. Buccal alterations in DM, taste misperceptions in chemotherapy, and several pathologic conditions caused by individual lesions of the structures are involved (see above).

5.16 Cranial Nerves and Painful Conditions: A Checklist

See Table 5.5.

Other Conditions Associated with Painful Cranial Nerve Lesions

- *Neoplastic:* Chondroma, chordoma, craniopharyngioma, epidermoid tumors, giant cell tumor, meningeal carcinomatosis, meningioma. Metastases: lymphoma, multiple myeloma, nasopharyngeal, neurofibroma, squamous cell carcinoma.
- *Vascular causes:* Carotid artery aneurysm, carotid cavernous fistula, intracerebral venous occlusion, PCA, thrombosis.
- *Infections:* Fungal: mucocele, mucormycosis, periostitis, sinusitis.
- *Viral:* Herpes zoster.
- *Bacterial:* Mycobacterial, spirochetal.
- *Others:* Eosinophilic granuloma, sarcoid, Wegener's granulomatosis.

5.17 Cranial Nerve Examination in Coma

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+ Blink reflex Brainstem evoked potentials Motor evoked potentials Somatosensory evoked potentials	+ Electrolyte Endocrine Toxicity	++ Structural changes, edema	

CN examination in coma	
Pupil	Metabolic and toxic causes often spare the light reflex. Nonreacting "pinpoint pupils" point to either structural damage (pontine) or opiate intoxication. Midbrain lesions can produce large, fixed unresponsive pupils. Lids must be passively held open: anisocoria, consensual light reaction. Early manifestation of herniation syndrome – decline of pupillary reaction, usually on the side of the mass, followed by an ipsilateral mydriatic pupil. DD: miotic eye drops, organophosphates

Perception within the visual field	Can be tested by examining if the patient "blinks to threat"
Oculovestibular reflexes are dependent on the functions of 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 maneuver, caloric testing. Doll's head reflex. Deviation of eyes to one side. Eye movements in resting position: conjugate, dysconjugate, roving, bobbing, inverse ocular bobbing (dipping), nystagmus retractorius, convergence nystagmus. Lesions of the MLF with internuclear ophthalmoplegia
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 not particularly a sign of structural lesion but of metabolic or toxic influence
Pain	Pain can be elicited in the trigeminal nerve distribution. The "ciliospinal" reflex evokes a dilatation of the pupil by noxious cutaneous stimulation. Pain in the limbs and body may induce mimic changes and ipsilateral dilatation of the pupil
Trismus	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

5.18 Pupil

Genetic testing	NCV/EMG	Laboratory	Imaging	Pharmacologic
		+	+	testing

- *Innervation:* 2 antagonistic muscles: circular muscle of iris (cervical sympathetic) and pupillary sphincter (CN III).
- *Paralysis of sphincter pupillae:* Lesion 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: antidepressants, atropine, eserine, homatropine, pilocarpine, psychotropics. Cocaine causes dilatation by stimulating sympathetic nerve endings.
- *Pupillary size and equality:* Anisocoria.
- *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: CN paralysis appears first, then dilated fixed pupils (not always present).
- *Reflex iridoplegia:* Argyll Robertson pupil (syphilis).
- *Optic nerve lesions:* Swinging flashlight test.
- *Adie tonic pupils*
- *Unilateral dilatation:* Raised ICP.

Pharmacological Testing Cocaine, apraclonidine, hydroxyamphetamine, and pilocarpine are used in testing various dysfunctions of the pupil.

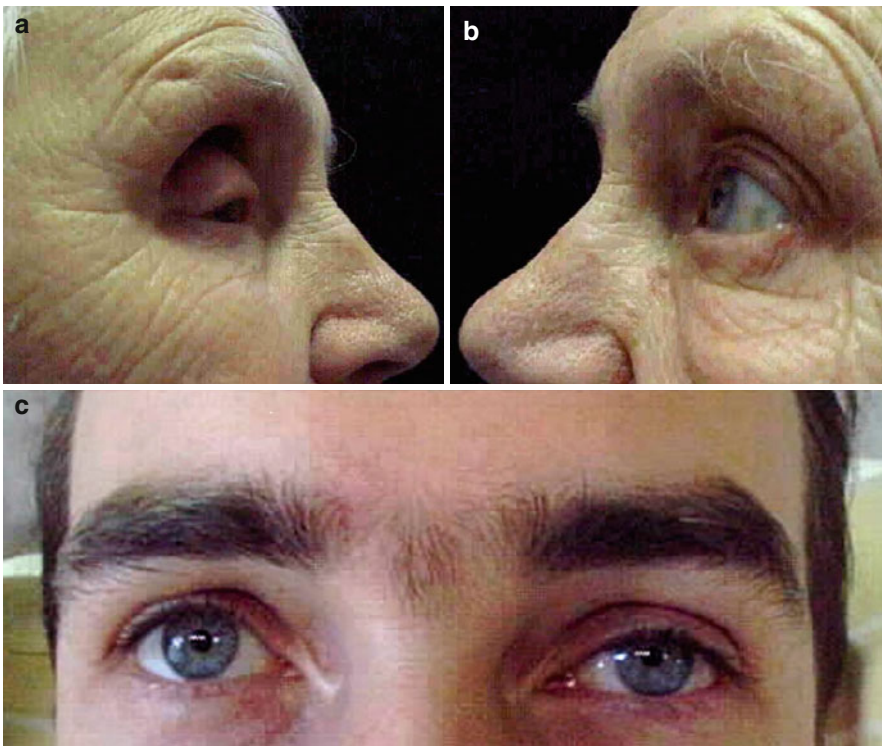

Fig. 5.25 Horner's syndrome. (**a**) Horner's syndrome of 10 y (years) duration, characterized by mild ptosis and enophthalmos, compared to normal side (**b**). (**c**) Horner's syndrome with mild ptosis and miosis

5.19 Multiple and Combined Oculomotor Nerve Palsies

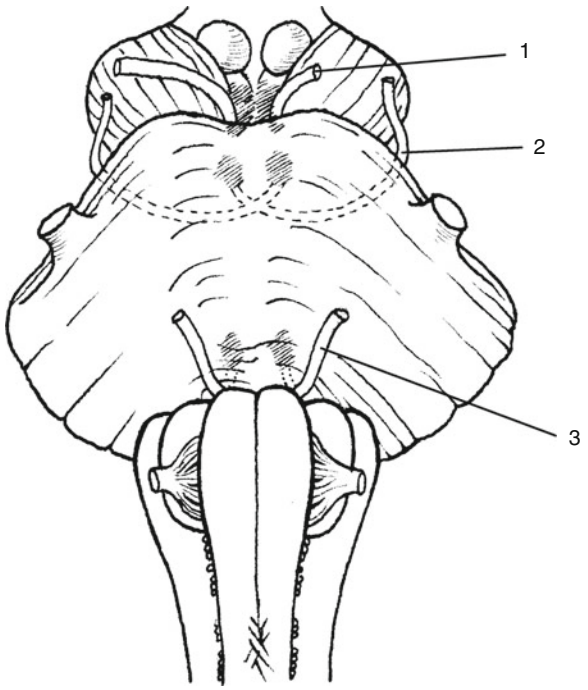

Fig. 5.26 *1* Oculomotor nerve, *2* trochlear nerve, *3* abducens nerve

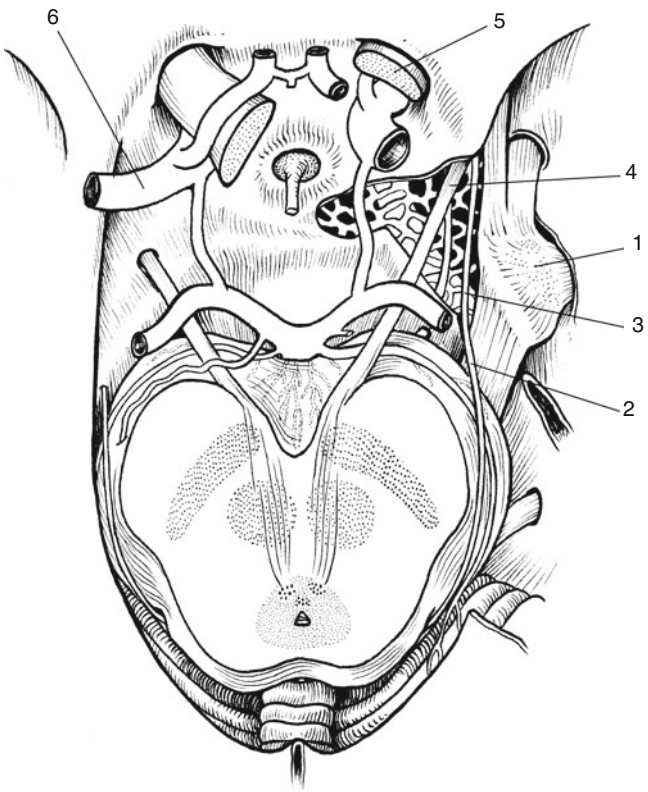

Fig. 5.27 *1* Trigeminal ganglion, *2* trochlear nerve, *3* abducens nerve, *4* oculomotor nerve, *5* optic nerve, 6 internal carotid artery

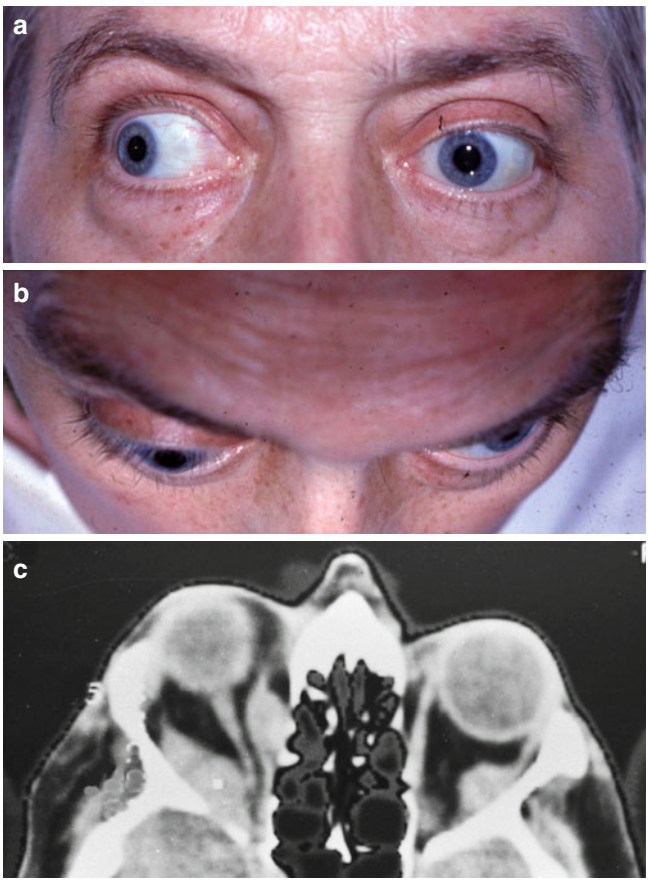

Fig. 5.28 Orbital metastasis. (**a**) Atypical optomotor function; (**b**) exophthalmos, best seen from above; (**c**) CT scan of orbital metastases

Table 5.6 Site of multiple cranial nerve lesions

CN III, IV, VI		
Site of lesion	Cause	Associated findings
Brainstem	Infarction Encephalitis Leigh syndrome Mental changes Paraneoplastic brainstem Tumor (e.g., glioma) Wernicke's disease	Brainstem signs
Subarachnoid space	Aneurysm Clivus tumor Cerebellopontine tumors LC Meningitis Trauma	Often multiple cranial nerves involved
Base of the skull	Base of the skull syndromes (Greenberg) Retrograde nerve infiltration from outside of the cranial vault, e.g., neck, sinus Infections: TBC meningitis, granulomatous diseases	

(continued)

Table 5.6 (continued)

CN III, IV, VI		
Site of lesion	Cause	Associated findings
Cavernous sinus	Aneurysm	Often V1, V2 involved
	Carotico-cavernous fistula	Orbital swelling
	Fistula	
	Herpes zoster	
	Infection	
	Mucormycosis	
	Mucocele	
	Nasopharyngeal carcinoma	
	Pituitary apoplexy	
	Tolosa-Hunt syndrome	
	Tumor: meningioma	
Fissura orbitalis superior (apex of the orbit)	Tumors, metastasis	
Orbital	Orbital cellulitis	Proptosis (particularly in advanced age)
	Orbital dysthyroid eye disease	
	Pain and vision loss: consider anterior optic pathways	
	Pseudotumor	
	Trauma	
	Tumor	
Uncertain	Cranial arteritis	Pain, polymyalgia
	Miller Fisher syndrome	Ataxia
	Oculomotor nerve palsies	Vincristine
	Toxic	
Differential diagnosis: orbital muscle disease including dysthyroid disease, MG, botulism, rare ocular myopathies		

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Radiculopathies

6

Wolfgang Grisold and Eva L. Feldman

6.1 Cervical Radicular Symptoms

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

6.1.1 Anatomy

With exception of the upper two vertebrae, the cervical vertebrae articulate with each other by an intervertebral disc, plus a pair of smaller joints between articular facets and pedicles. The intervertebral foramina are formed by the pedicles (above and below), anterior to the intervertebral discs and joints of Luschka and posterior to the facets and facet joints. The vertebral arteries course through the foramina of the transverse processes (except in the case of C7). 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. The 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 and C6; the C8 root exits between C7 and T1). The C2–4 roots merge close to the spinal column to form the cervical plexus.

6.1.2 Symptoms

The patient with a ruptured cervical disc complains of neck, shoulder, and arm pain, with or without distal radiating paresthesias. Neck "stiffness" is also a frequent symptom. 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 (paresthesias, dysesthesias, or numbness) may

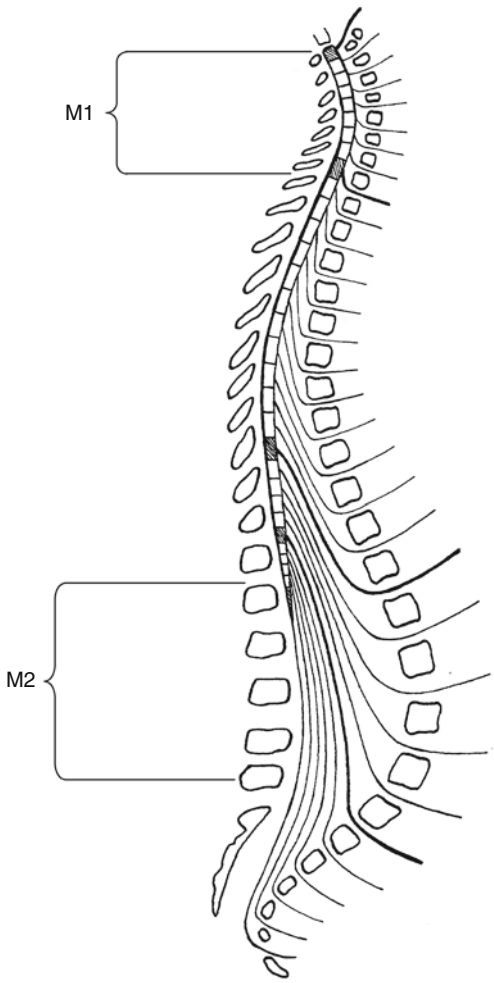

Fig. 6.1 Cartoon of the vertebral column: M1 and M2 represent the mobile parts

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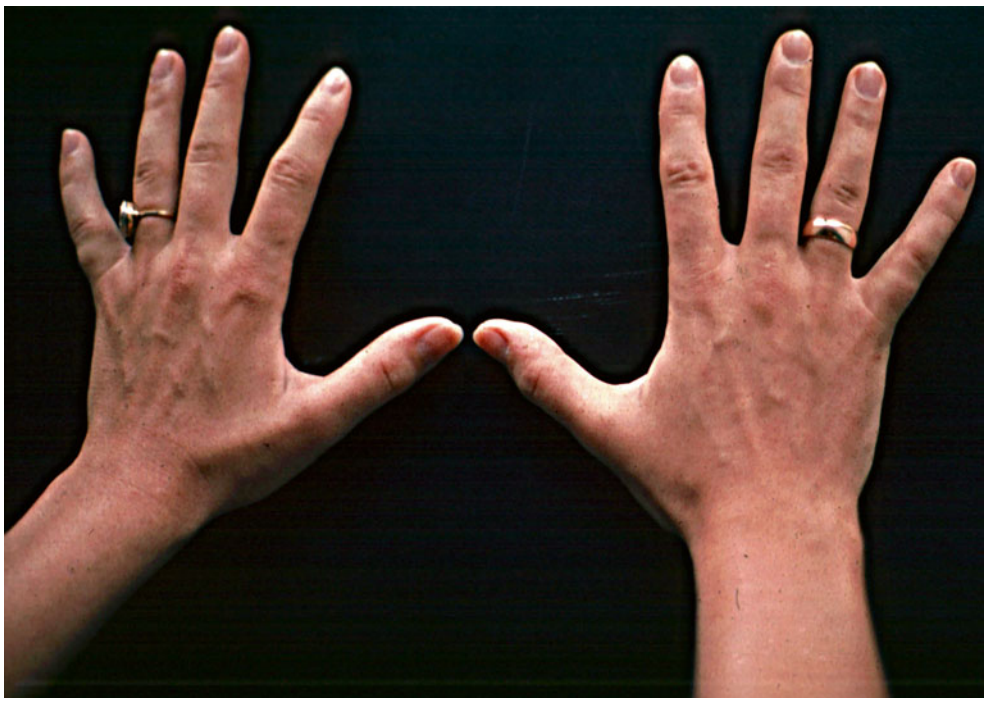

Fig. 6.2 C8 radiculopathy: this patient has atrophies of the small hand muscles due to a C8 radiculopathy, caused by leukemic infiltration

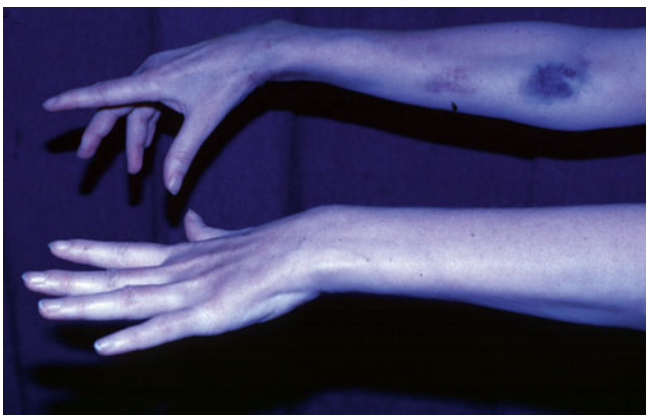

Fig. 6.3 Meningeal carcinomatosis in a patient with breast cancer with neoplastic deposits in nerve roots C6 and C7. Extensor deficits of fingers 3, 4, and 5 mimic partial radial nerve paralysis

occur in the nerve root distribution. Pain in the thumb and index finger is associated with C6, index and middle finger with C7, and ring and little finger with C8. Pain may increase with neck movement. Valsalva, sneezing, and coughing also enhance pain. C8 or T1 lesions are not common. C8 radiculopathies can be secondary to a C7 root compression in the setting of a "prefixed" brachial plexus, upper cervical cord compression with vascular compromise of the distal cervical spinal cord, intramedullary cervical cord lesions, or neoplastic involvement of the lower trunk of the brachial plexus (Pancoast tumors).

Table 6.1 Cervical radiculopathy symptoms

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: 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/or brachioradial 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		6 or 7
Sensory loss middle finger	C7	
Sensory loss small finger	C8	

Pain Quality Lancinating, shooting, or radiating into the extremity, within a narrow spatial range (2 in.). Dull aching pain is constantly felt in surrounding structures. Involved nerve roots result in weakness in a myotomal distribution.

6.1.3 Signs

Weakness and later atrophy in a myotomal distribution with corresponding diminished or absent tendon reflexes (caveat: pain may obscure the clinical examination). Reproduction of the patient's pain on cervical extension and ipsilateral rotation of the head (Spurling's maneuver) is pathognomonic for cervical root irritation and analogous to sciatica produced by straight leg raising. Neck movement may also produce paresthesia or radiating pain. Dermatomal sensory changes may occur. Percussion or pressure on the spinous process of the affected vertebral body may induce segmental, shocklike 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 weight of the arm.

Multiple Cervical Radiculopathies 13–20 % are multiple. Bilateral incidence is less likely. Multiple and bilateral lesions are atypical for simple compressive lesions, and other etiologies should be considered.

Polyradicular Lesions Extradural lesions: ankylosing spondylitis, cervical spinal stenosis, degenerative spine disease, herniated disc, osteomyelitis, Paget's disease, vertebral column metastasis, lymphoma.

Intradural-Extraaxial Arachnoiditis, leptomeningeal carcinomatosis, neurolemmoma, sarcoidosis, trauma.

Intraaxial-Medullary Encephalomyeloradiculomyelitis (e.g., post rabies 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.

6.1.4 Pathogenesis

Compressive Disc herniation: cervical disc protrusion is rarer than lumbar disc protrusion; C5/6 and C6/7 are predominately 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 the onset of pain and sensory and motor symptoms in a radicular distribution. Rarely, medial large discs can produce myelopathy – with tetraparesis, spasticity, and bladder and bowel dysfunction. In young patients, cervical radiculopathy is most commonly secondary to trauma and sports injuries. In older patients, chronic spondylotic changes often prevail, which are worsened by acute disc protrusion often causing myelopathy. Symptoms include severe pain and stiffness. Pain and sensory symptoms occur in a myotomal radicular distribution. A subacute onset is more common with chronic spondylotic changes.

Immune Mediated Ankylosing spondylitis: usually no radiculopathy but myelopathy, atlantoaxial joint involvement in rheumatoid disease, cervical intervertebral disc often affected by rheumatoid arthritis (RA) with facet instability, and encroachment of nerve root foramina and the spinal canal.

Infectious Herpes zoster occurs less frequently than in the thoracic region. Pain and vesicles occur with C2 involvement. Sensory fibers are predominately affected, rarely also motor fibers (anterior horn cells). C3–5 herpes may cause diaphragmatic paralysis. The usual pattern is a local pain syndrome, followed by the rash; motor symptoms are rare.

Inflammatory Radiculomyelitis of various etiologies, spondylodiscitis.

Neoplastic Most common tumors affecting the cervical vertebral column are breast, prostate, and lung cancer. Cervical vertebrae are less involved compared with thoracic or lumbar vertebrae. Metastases result in local pain or a radicular syndrome. Additionally, the spinal cord may be compressed, either by local extension of tumor or through nerve root foramina paraspinal metastases. Spinal cord compression and instability are the most severe complications.

Nerve Root and Spinal Nerve Tumors Schwannomas, or neurofibromas, in combination with NF1.

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.

Vascular Acute and subacute cervical radiculopathy with cervical spinal stenosis.

Cervical Spondylosis Bony changes may produce narrowing of the spinal canal and intervertebral foramina. 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 the elderly. Symptoms resemble acute herniation but are less intense. C6/7 roots are predominately affected. Head movement enhances pain. Pathologically: posterior osteophytes, as well as bone spurs projecting from vertebral bodies into the spinal canal. Additionally, the ligamentum flavum is thick and inelastic; with extension the neck buckles inward to compress the spinal cord.

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 and is the result of chronic spondylotic changes. Clinically variable combinations of radicular symptoms and myelopathy (pyramidal signs – spasticity) are observed. Although there is less pain

Table 6.2 EMG: 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 ulnaris 80 %	Flexor indicis proprius 90 %	First dorsal interosseous 80 %
Brachioradialis 80 %	Pronator teres 75 %	Anconeus 75 %	Abductor digiti quinti 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 %

and radicular symptoms, marked atrophy of hand muscles and weakness, usually in C6/7 segments, is seen. Bilateral radicular symptoms are common. Atrophy of intrinsic hand muscles and clumsiness of fingers (e.g., difficulty buttoning) are common. Long tract signs may result in spasticity and dysesthetic symptoms in the 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, with pyramidal signs ("mid-cervical reflex pattern"). MRI: intramedullary signal changes, as a sign of myelopathy. Bony changes can be seen on CT scan.

6.1.5 Diagnosis

Neuroimaging CT, MRI. CSF analysis in inflammatory disease or infection. 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 radiculopathy and focal nerve entrapments (e.g., carpal tunnel syndrome), 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.

6.1.6 Differential Diagnosis

Acute Cervical Radiculopathies Neuralgic amyotrophy, acute traumatic brachial plexopathy (with or without avulsions). Chronic cervical radiculopathies: ALS, multifocal motor neuropathy, mononeuropathies (e.g., pure motor "ulnar"). 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 a frozen shoulder. Other conditions producing pain in the neck: myocardial infarction, shoulder disease, bursitis, and arthritis (see "around the shoulder").

Other Considerations Mononeuropathies; MS (radiculopathies due to spinal cord involvement); osteomyelitis; discitis; Pancoast tumor; "pseudoradicular" symptoms; referred pain, cardiac ischemia; syrinx; thalamic lesions; "TOS."

6.1.7 Treatment

Conservative A herniated disc often diminishes in size via 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 a widely used traction is unclear. Neck manipulation and chiropractic maneuvers are not recommended.

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.

Complications Operative risks of root or cord injury, hoarseness from recurrent laryngeal nerve injury, esophageal perforation, vertebral artery injury, or bone 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 reversed lordosis, or "swan neck deformity." This approach may result in chronic pain with or without myelopathy.

6.1.8 Prognosis

Variable, depending on the cause.

6.2 Thoracic Radicular Nerves

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

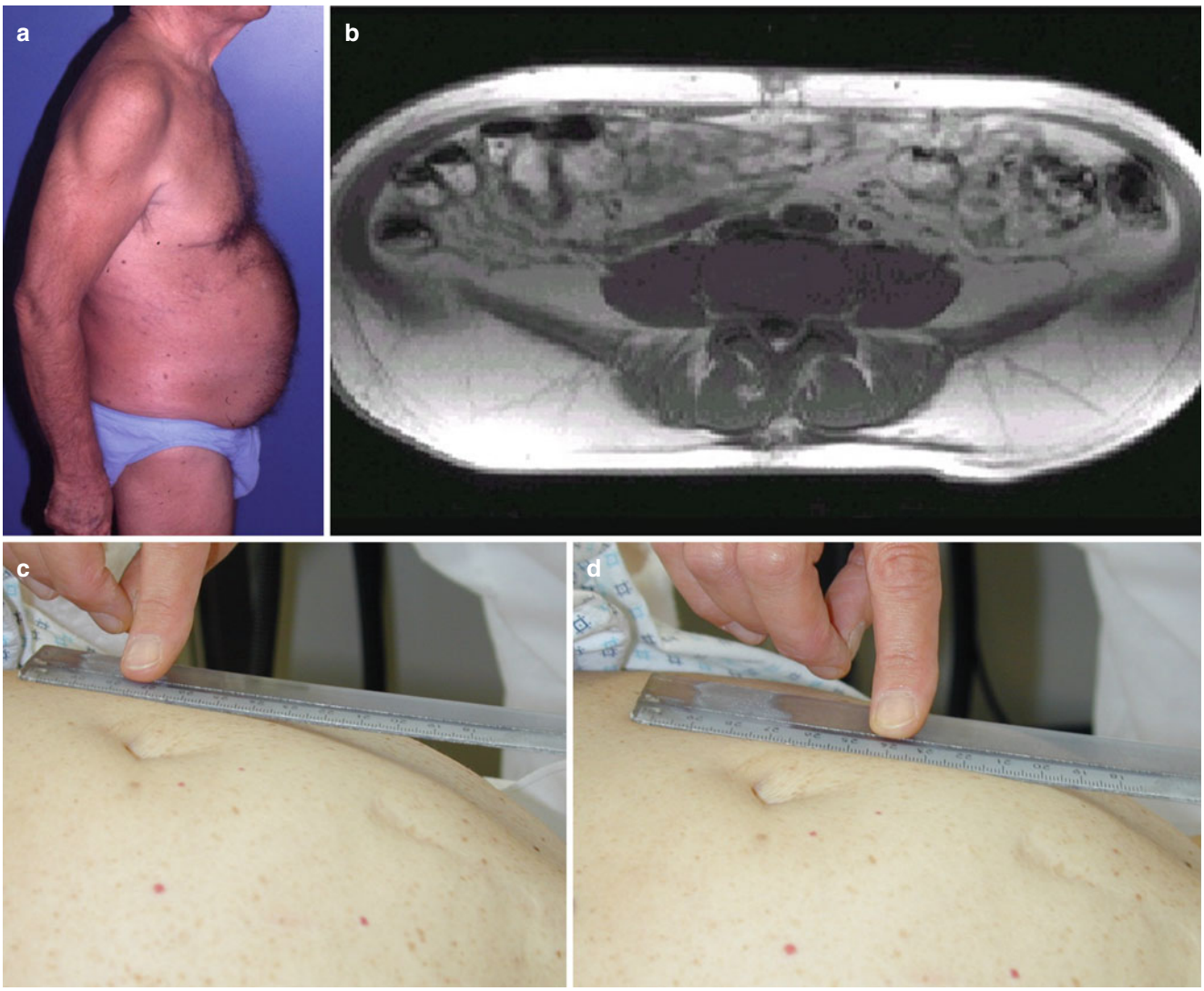

Fig. 6.4 Abdominal muscle weakness: (**a**) demonstrates effect of abdominal muscle weakness in a patient with CSF definite borreliosis. His first symptom was a feeling of distension of his abdomen. The MRT scan (**b**) demonstrates the highly atrophic ventral abdominal muscles. (**c**, **d**) The characteristic Beevor's sign in another patient with abdominal wall involvement of borreliosis

6.2.1 Anatomy

There are 12 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 and 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. T2–6 are intercostal nerves that pass around the chest wall in the intercostal spaces. Halfway 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 floor of the axilla and then crosses to the upper arm and runs together with the posterior and medial nerves of the arm (branches of the radial nerve and medial cord). The second and third intercostobrachial nerves arise from the lateral cutaneous branches of the third and fourth intercostal nerves. T7–11 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 innervating the rectus abdominis muscle. The eleventh and twelfth thoracic nerves are below the 12th rib, 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.

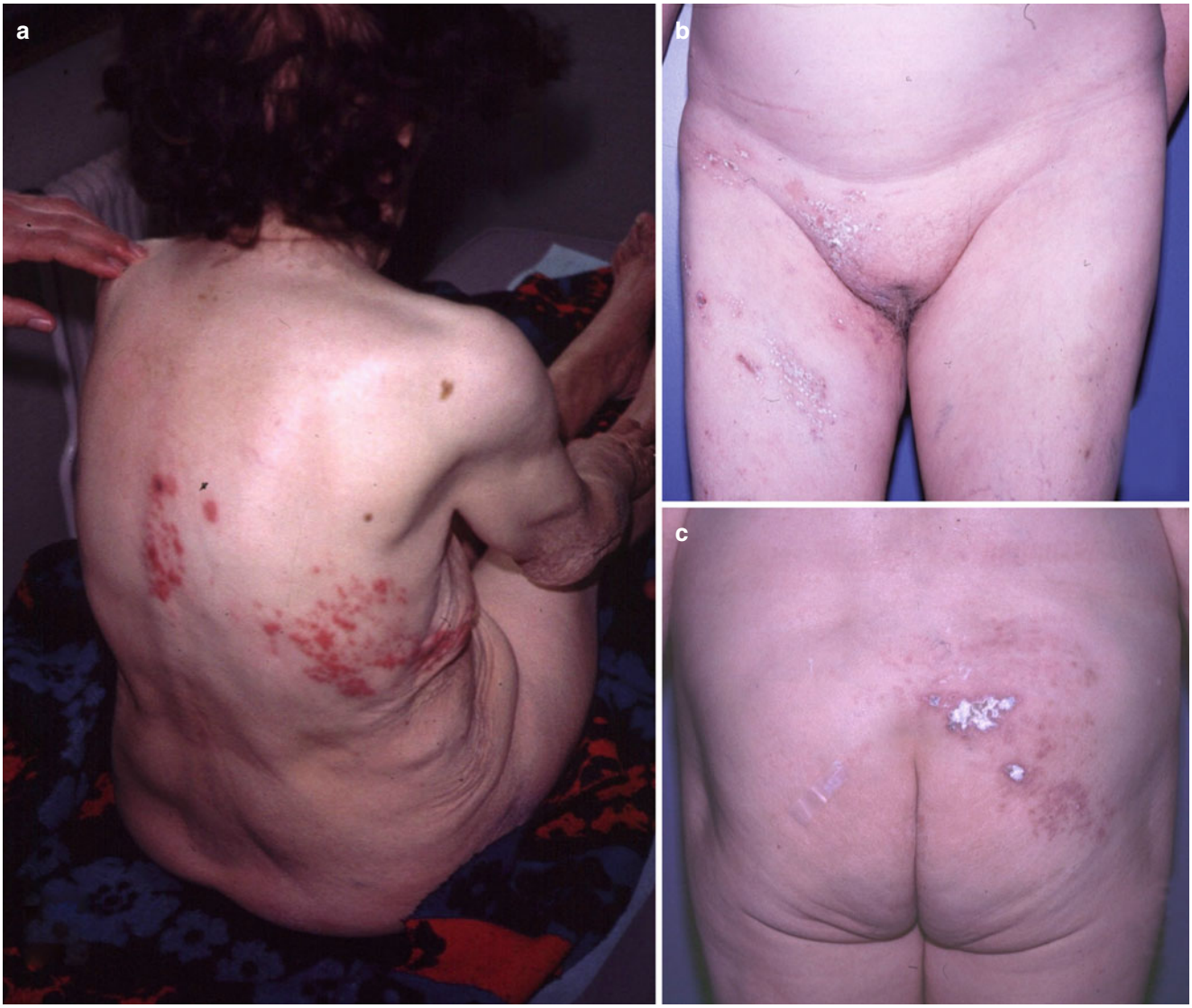

Fig. 6.5 Herpes zoster. (**a**) Classical herpes with paraspinal-thoracic vesicular lesions and radicular distribution (T8). (**b**) Herpes zoster in L1 distribution. (**c**) Sacral herpes zoster

Medial Cutaneous Nerve Entrapment The medial cutaneous nerves can be compressed at the site when they pierce the rectus abdominis muscle. Pain in the anterior abdominal wall is the clinical symptom. EMG of the rectus abdominal muscle can show denervation.

Notalgia Paresthetica Involvement of the dorsal spinal rami. Symptoms are pain, paresthesias, and "itching" sensations.

6.2.2 Symptoms

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

6.2.3 Signs

Muscle weakness is difficult to demonstrate in the intercostal spaces, but bulging of abdominal muscles can be seen or palpated. Skin lesions may be residual symptoms from herpes zoster.

6.2.4 Pathogenesis

Diabetic Truncal Neuropathy Thoracic spinal nerves: pain and paresthesias. Often "bandlike" hypersensitivity or allodynia. Motor involvement can involve the abdominal muscles. Coughing usually helps to identify the muscle weakness.

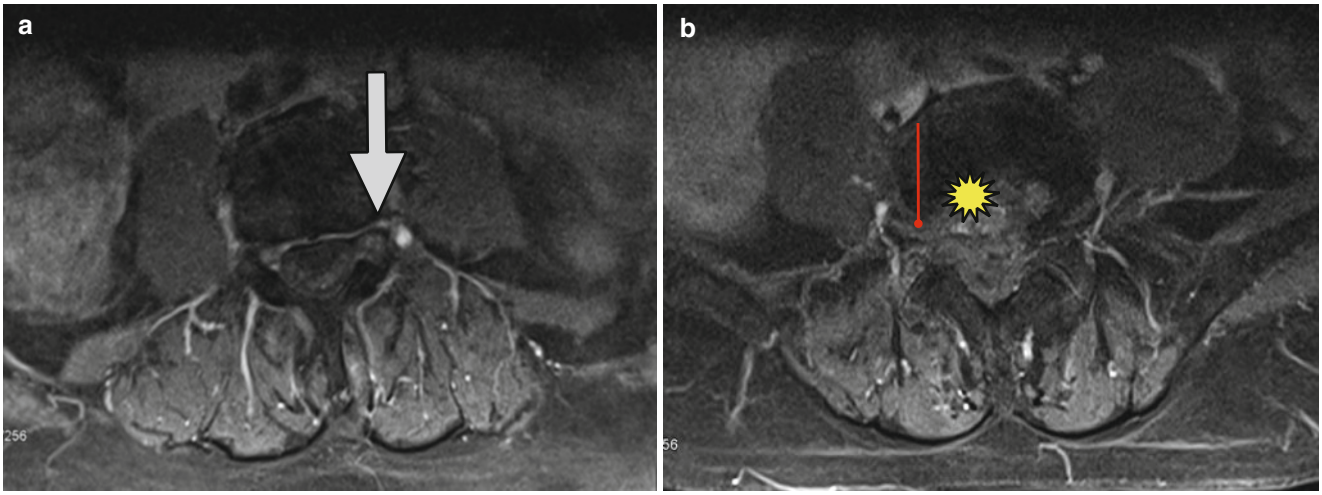

Fig. 6.6 Nerve root infiltration by cancer metastasis. (**a**) *Arrow* shows thickened nerve root. (**b**) Destruction of vertebral body (*asterisk*) and infiltration of contralateral nerve root (*red arrow*)

Disc protrusion: uncommon, 0.22–5.3 % of disc protrusions. The majority occurs in the lower third of the thoracic vertebral spine. Surgical intervention may be necessary for symptomatic spinal cord compression.

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. Polyradiculopathy is possible with HIV and acquired immunodeficiency syndrome (CMV polyradiculopathy). Lyme radiculopathy may affect thoracic roots and cause weakness of abdominal muscles.

Intercostal Neuralgia and Notalgia Paresthetica T5 paresthesias may mimic 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 the second to sixth thoracic rami. Rectus abdominis syndrome: sharp pain in the anterior wall.

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. Best technique: MRI. Leptomeningeal carcinomatosis: thoracic roots can be affected. Thoracic spondylosis: rare. Surgical intervention if myelopathy occurs.

Trauma Traumatic disc may cause cord compression. Herniation of intervertebral disc is uncommon and often caused by trauma; more frequent sites are T8–12. In T11/T12, pain, numbness, or allodynia occur with abdominal wall bulging.

6.2.5 Diagnosis

Laboratory: diabetes, paraproteinemia, herpes, Lyme. *Imaging*: plain X-ray, CT, MRI, CSF. EMG is difficult to assess in truncal muscles; paravertebral muscles can be affected in notalgia paresthetica and the rectus abdominis muscle in medial cutaneous nerve entrapment.

6.2.6 Differential Diagnosis

Borreliosis/Lyme, multiplex neuropathy, MS (root lesions), referred pain, syringomyelia, herpes zoster.

Postoperative Thoracic Pain This can be caused by several conditions: drainage in the intercostal space, injection or lesion of intercostal nerves, postmastectomy pain (spectrum from tingling to causalgia), postmastectomy phantom pain, rib retraction.

6.2.7 Therapy

Depending on the cause: surgical, conservative.

6.2.8 Prognosis

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

6.3 Lumbar and Sacral Radiculopathy

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

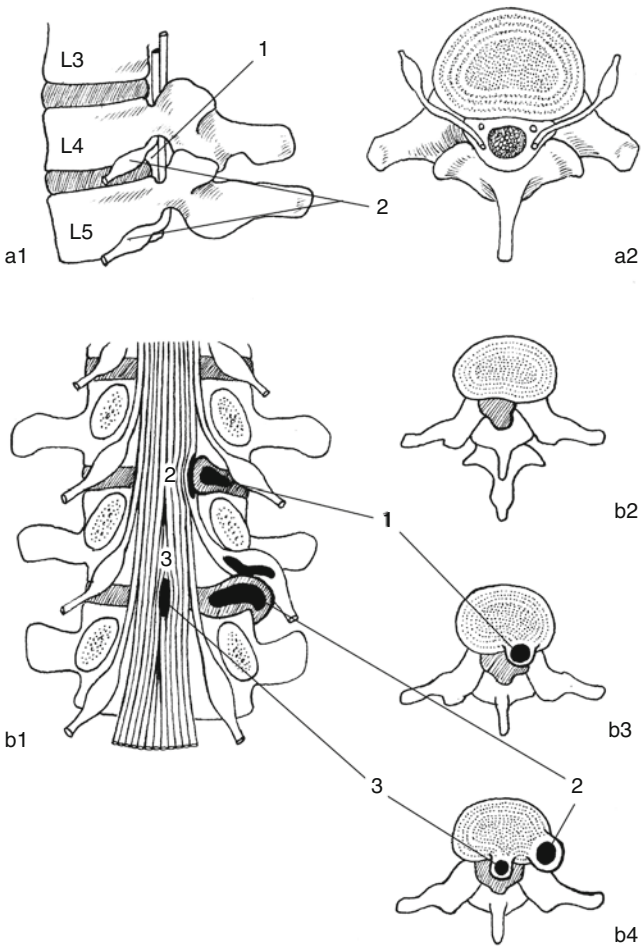

Fig. 6.7 Lumbar anatomy. (**a1**) *1* Intervertebral foramen, *2* dorsal root ganglion, (**a2**) section at L4 level, (**b1**) *1* mediolateral disc prolapse, *2* lateral prolapse, *3* median prolapse, (**b2**, **b3**) mediolateral prolapse, (**b4**) *2* lateral prolapse, *3* median prolapse

6.3.1 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 the L1 vertebrae. 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. 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 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 fibers are distributed in abdominal and pelvic structures. Patients with the most common radiculopathies (L5/S1) do not have signs of sympathetic dysfunction. The course of the nerve roots has peculiarities 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 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. Lateral disc protrusions compress the root which passes through the foramen at the same level. Also sequestrated tissue from a disc protrusion may protrude and float between segments. 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. Spondylolisthesis indicates a ventral slipping of one vertebral body, over the one below (e.g., L5 over S1). The movement of the facets narrows the foramen, and in addition the transverse process or ala of the sacrum may also compress the spinal nerve.

6.3.2 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 par-/dysesthesias occur when walking or standing. In these patients, symptoms decrease by bending forward or sitting. Differential diagnosis: in vascular claudication, it is necessary to sit down for relief. Vascular claudication is characterized by intensely cramping calves when the patient stoops or stands. Walking uphill increases symptoms of vascular claudication, but relieves neurogenic conditions. Bicycle rides are bad for vascular conditions and improve neurogenic symptoms.

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

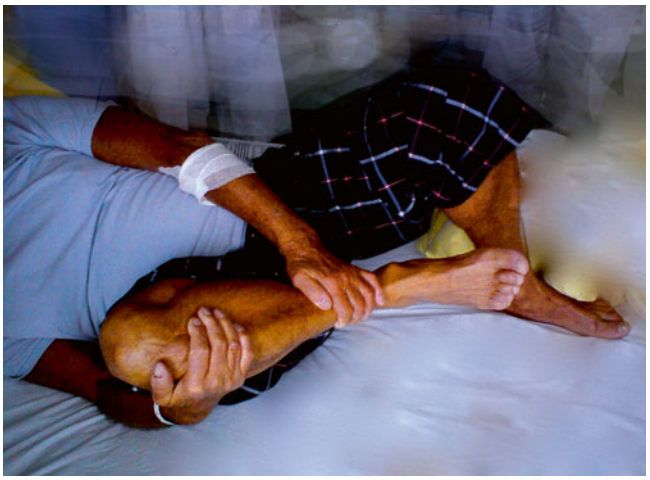

Fig. 6.8 Clinical image: acute L3 pain. In acute L3 symptoms, flexion of the hip relieves the pain. This patient took this position, which brought him some relief

Sensory Paresthesias are more suggestive for radicular (neuronal) disorders. They may be separate from pain, or pain may have a paresthetic component. Mostly, only the distal part of the dermatome is affected. Examples for "signature areas" are the dorsum of the foot and big toe, L5, and lateral aspect of the foot and little toe, S1.

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

6.3.3 Signs

Straight leg raising tests (transmitted between 30° and 70°): crossed straight leg raising test is suggestive for extensive lesions. Reverse straight leg raising test or femoral stretch test is suggested for 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).

In radiculopathies only the most distal area of the sensory segment can be affected ("signature" area). It is important to keep in mind that two or more roots can be affected in lumbar disc protrusions, due to the anatomic situation of nerve roots (see above).

6.3.4 Pathogenesis

Most Frequent Lesion Disc herniation, acute disc herniation, subacute disc herniation, bony root entrapment (in particular in older patients, where degenerative changes and disc herniation are often combined).

Table 6.3 Myotomal distribution

L1	No motor or reflex changes
L2	Weakness of psoas muscle
L3	Weakness of psoas and quadriceps muscle, knee jerk depressed
L4	Weakness of quadriceps, tibialis anterior, and posterior muscles; knee jerk depressed
L5	Weakness in tibialis anterior muscle, toe extensors, peroneal and gluteal muscles; ankle jerk is depressed
S1	Weakness of gastrocnemius muscles, toe flexors, peroneal and gluteal muscles; ankle jerk is depressed
S2	Weakness in gastrocnemius muscle, toe flexors; ankle jerk is depressed
S3	No muscle weakness, no reflex changes; bulbocavernosus and anal wink are abnormal

Table 6.4 Radicular sensory findings

L1	Sensory symptoms in upper groin and trochanter
L2	Sensory symptoms in anterior ventral thigh
L3	Sensory symptoms in anterior thigh and medial knee region and anterior (saphenous nerve distribution) medial lower leg (over the shin)
L4	Sensory symptoms over medial lower leg and ankle
L5	Sensory symptoms over anterolateral lower leg and dorsum of foot
S1	Sole and lateral border of foot, ankle
S2	Posterior leg sensory loss or paresthesia
S3	Upper medial thigh, medial buttock (without muscle weakness or reflex changes)

Congenital Tethered cord, congenital spinal stenosis.

Infectious Epidural abscess, herpes with rare motor involvement, HIV (CMV) polyradiculopathy, Lyme disease, spinal arachnoiditis, spondylodiscitis, TBC, Elsberg syndrome, and tabetic affection of small lumbar spine joints (disputed).

Inflammatory Immune Mediated Bechterew ankylosing spondylitis, sarcoidosis.

Neoplastic Chondroma, leptomeningeal carcinomatosis, ligamentum flavum cysts, metastases, neurofibroma, schwannoma.

Trauma Fractures of sacrum, spinal trauma, vertebral fractures.

Vascular Epidural hematoma due to anticoagulation therapy, AV malformation, spinal claudication.

Other Causes 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

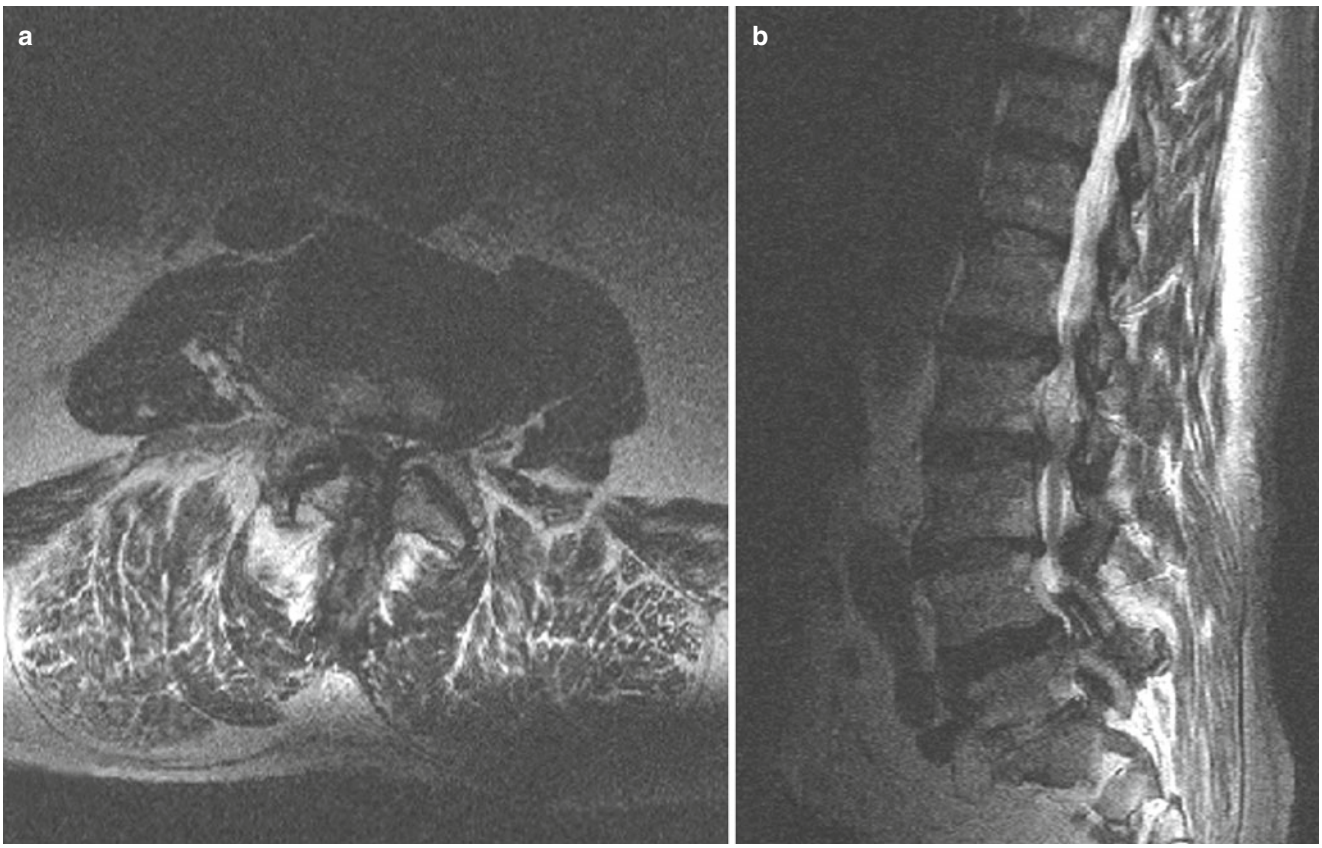

Fig. 6.9 MRI showing lumbar vertebral stenosis: note the disappearance of the spinal fluid in T2-weighted images (**a**). Lateral view shows multiple sites with narrowing of the spinal canal (**b**)

characterized by pseudoclaudication and intermittent claudication. Symptoms: pain and paresthesia when walking and standing but improves when resting and bending forward. Some patients also have weakness during the height of symptoms. Signs are often normal, or symptoms 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. Contrary to walking and standing, bicycling is usually possible. Anatomically, a narrowing of the spinal canal due to abnormal structure, narrowing of the foramina, and degenerative changes of spondylosis can be found.

Lumbosacral Spondylosis Degenerative changes of the lumbar spine involve the facet joints, intervertebral discs. Hypertrophy of the joints associated with osteophytes occurs in association with degenerative disc flattening. The lateral recess and nerve root foramen are increasingly narrowed. Bony root entrapment is more frequently found in elderly patients, they often have a long duration of back pain. Clinical examination suggests several roots to be involved.

"Pseudoradicular" The term "pseudoradicular" is often applied in the German-speaking neurologic nomenclature. It expresses that the symptoms of the patients resemble an "incomplete" radicular distribution. However, definite radicular symptoms (as 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 heterogenous and ranges from degenerative vertebral column disease to osseous disease and pathologic conditions involving the hip.

Far Lateral Disc Protrusion (with MR diagnostics 10 %, previously diagnosed in 2 %) They 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 treat this condition 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 felt worse. Complete laminectomies may result in instability. Multiple lesions are treated with multilevel lumbar laminectomies. Single

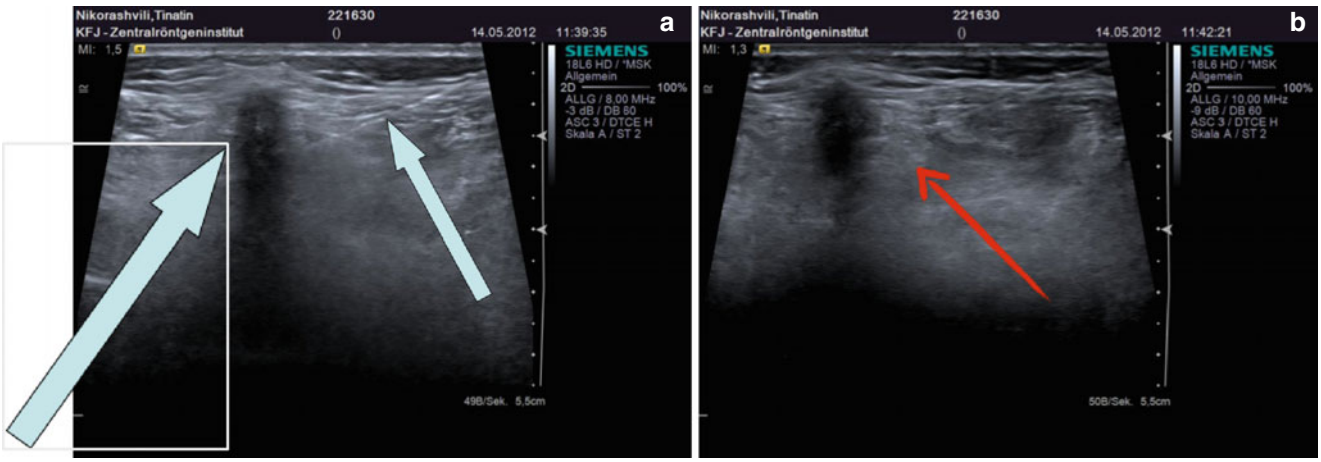

Fig. 6.10 Ultrasound-guided interventions: Blood patch and ultrasound. A patient developed a CSF fistula after repeated lumbar puncture for the prophylactic treatment of lymphoma. An initial "blind" blood patch was not effective. Under US guidance a successful blood patch was performed. (**a**) US image of the lumbar spine, the *large arrow* points to the processus spinosus for orientation. The *small arrow* points to the needle. (**b**) The *red arrow* points to the local blood patch

level disease is most common in L4/5 and surgery is successful in up to 80 %. Reoperations 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: sometimes bed rest, diminished activities, and NSRA 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.

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

6.3.5 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. Seven 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 laminectomy and older patients. Diabetics may have fibrillations in EMG. Two practical points have to be considered: the relaxation of patients with low back pain for paravertebral EMG may be difficult, and the paravertertebral 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 nerve (L5), sural nerve (S1), saphenous nerve (L4), and lateral cutaneous nerve of the thigh (L2/3) can be used.

6.3.6 Differential Diagnosis

Diabetic proximal amyotrophy ("Bruns-Garland" syndrome) (L3 in particular). Borreliosis, sacral herpes zoster, multiradicular lesions, facet arthropathy, leptomeningeal carcinomatosis, lumbar and sacral plexopathies, nerve sheath tumors. Rheumatoid conditions: as hip and sacroiliac disease, myofascial pain syndrome, spondylosis, spondylolisthesis, tabetic joint changes, tethered cord syndrome (rare in adults).

6.3.7 Therapy

Acute disc herniation surgery Urgent indication: acute cauda equina syndrome, marked focal muscle weakness (not urgent), recurrent and intolerable pain (questionable). Surgery speeds up recovery; however, long-term observations show similar results.

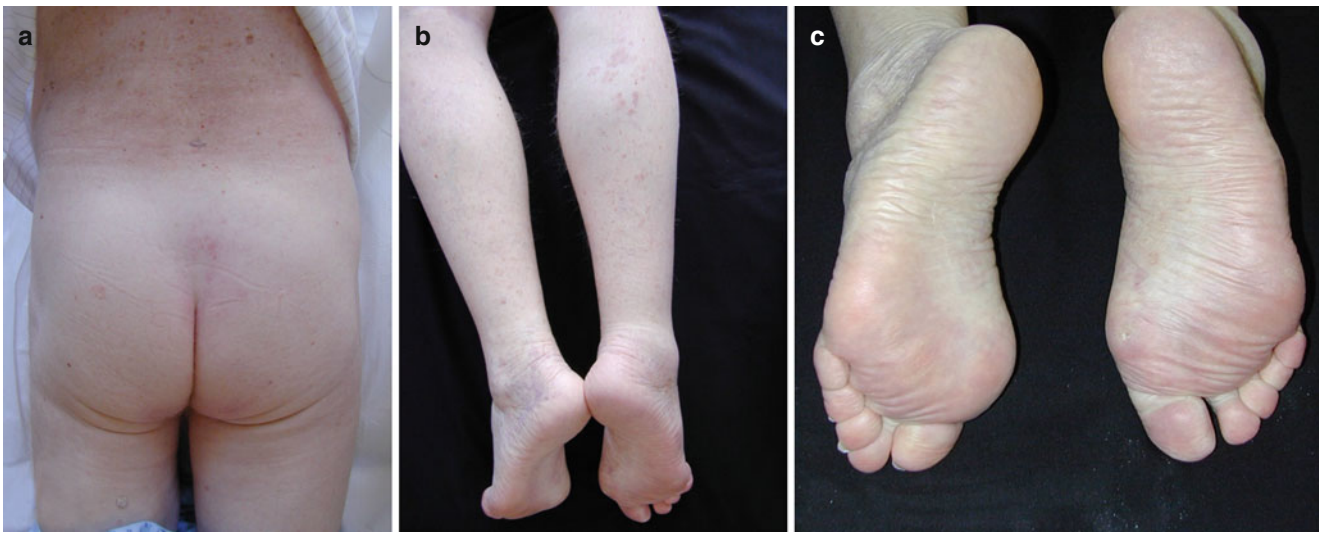

Fig. 6.11 Motor involvement following sacral herpes S1 on the right side. The vesicles can no longer be seen. (**a**) Right-sided gluteal weakness with loss of muscle definition on the right compared to the intact left side. (**b**) Discrete dry skin changes over the right half. (**c**) Wrinkling of the skin over the plantar right foot compared to left side (atrophy of the small foot muscles)

Conservative Treatment Bed rest, which was previously recommended, has no proven efficacy. Analgesics: NSAIDs, muscle relaxants, dexamethasone, and intramuscular steroids are not effective but widely used. Exercise for the back and trunk muscles is often helpful. Medications: nonsteroidal 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: biofeedback, corsets, TENS, acupuncture, and trigger point injection have little evidence. About 80 % recover without surgery.

Surgical Techniques Conventional laminectomy, microdiscectomy, percutaneous discectomy, arthroscopic disc excision, 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, and loss of sphincter control. Relative surgical indications: uncontrollable pain – functionally limiting symptoms and pain after an appropriate trial of conservative therapy (6 weeks?).

6.3.8 Prognosis

Bed rest and analgesics: resolution in 32 %, although bed rest and analgesics are disputed. *Prolonged physiotherapy:* resolution in half of the patients. Incapacitating pain or profound neurologic deficit warrants surgical intervention in up to 24 %. In an overview and analysis of lumbar disc protrusions treated conservatively and surgically within a 10 year period, remaining sensory and motor deficits were evenly distributed. Better results of surgery are seen from surgical treatment after 1 year. The only significant changes were noted in those with persistent symptoms treated with surgery during 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.

Table 6.5 Prognostic factors

Favorable	Poor
Age < 40	Age > 40
Associated with nonindustrial accident	Industrial accident
No prior surgery	Worker compensation litigation
Self-employed	
No premorbid medical conditions	Multiple other medical problems
Differential diagnosis: cauda equina tumors, malignant disease, spinal arachnitis, complications of spinal anesthesia, tethered cord, spinal AV, viral cauda equine, local infections	

6.4 Cauda Equina

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		++	

6.4.1 Anatomy

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

The lumbar nerve roots run obliquely downward 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.

6.4.2 Symptoms

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

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

6.4.3 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.

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 Similar signs as acute injury. Muscle wasting in chronic conditions may resemble chronic polyneuropathy. Chronic central disc lesion may mimic tumors of the conus medullaris and is associated with perineal pain, paresthesias, and urinary dysfunction.

6.4.4 Pathogenesis

Genetic Tethered cord (TCS).

Inflammatory/Immune Bechterew disease.

Infectious AIDS: CMV infections, herpes simplex infection. Others: cryptococcal, syphilis, tuberculosis.

Neoplastic Ependymoma, neurofibroma. Rare: dermoid, hemangioblastoma, lipoma, meningioma, paragangliomas, schwannoma.

Malignant Disease Leptomeningeal carcinomatosis, lymphoma, metastases, multiple myeloma, myeloid sarcoma (chloroma), bone tumors, astrocytoma drop metastases.

Toxic Anesthesia (spinal and epidural anesthesia), contrast media, cytotoxic drugs (e.g., intrathecal MTX), radiation: TRI (transient radicular irradiation), early radiation effect, spinal arachnoiditis.

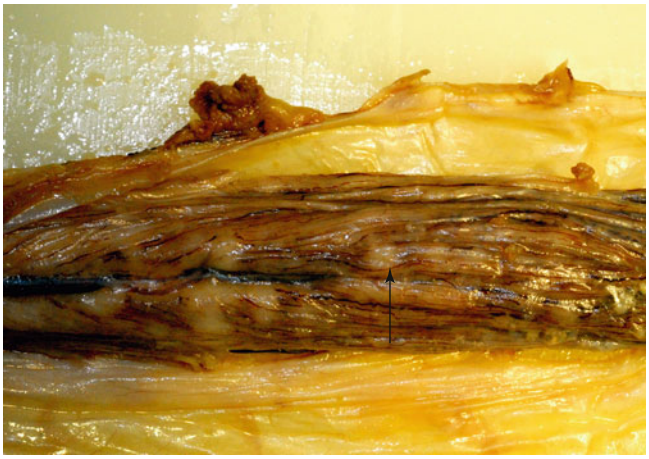

Fig. 6.12 Meningeal carcinomatosis: lumpy metastasis (*arrow*) affecting the cauda equina. The patient presented with painful neuropathy like onset; also sphincter function was impaired

Vascular AV fistulas (spinal/dural) may mimic spinal stenosis, cauda equina claudication, spinal subarachnoid hemorrhage.

Trauma Fractures of the sacrum, spinal surgery, vertebral injury.

6.4.5 Diagnosis

Imaging of bony structures and MRI. CSF in inflammatory and neoplastic conditions. Electrophysiology:

- EMG of S–S3 muscles
- Sensory conductions
- Reflex techniques (F waves, H reflex)
- Sphincter EMG including bulbocavernosus reflex
- Magnetic stimulation

6.4.6 Differential Diagnosis

Spinal cord (epiconus – medullary lesions), rapidly ascending polyneuropathy, sensorimotor neuropathies with autonomic involvement.

6.4.7 Therapy

This depends on the cause.

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Plexopathies

7

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7.1 Cervical Plexus and Cervical Spinal Nerves

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

7.1.1 Anatomy

The ventral rami of the upper cervical nerves (C1–4) form the cervical plexus. The plexus lies close to the upper four vertebrae. It descends in a loop-like structure. The skin behind the ear is innervated by the greater auricular nerve, and the occipital scalp by the lesser occipital nerve and the anterior chest down to the nipple. The dorsal rami of C1–4 innervate the paraspinal muscles and the skin at the back of neck. Horner's syndrome is often associated with a superior cervical ganglion lesion.

Cutaneous Nerves Greater auricular, greater occipital, lesser occipital, transverse cutaneous nerve of the neck, supraclavicular, and transversus colli.

Muscle Branches Diaphragm Levator scapulae: Mm. intertransversarii cervicis (C2–7), m. rectus capitis anterior (C1–3), m. rectus capitis lateralis (C1), m. rectus capitis longus (C1–3), m. longus colli (C2–6), innervation of trapezoid muscle jointly with the accessory nerve. Major motor nerve: phrenic nerve. Fibers from C2 to 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).

7.1.2 Clinical Picture

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). High cervical radiculopathies: less common, affected by facet joints. C3/4 foramen most often is involved. C2/3: site for herpes zoster, with postherpetic neuralgia possible. C2 dorsal ramus spinal nerve (or greater occipital nerve): irritation is better labeled "occipital neuropathy." In tumors: often Horner's syndrome is associated.

7.1.3 Symptoms

Pain is a prominent symptom.

Occipital Neuralgia/Neuropathy Accidents, whiplash, fracture dislocation, subluxation in rheumatoid arthritis, doubtful: spondylitic changes, neurofibroma at C2 level.

Neck-Tongue Syndrome Damage to the C2 ventral ramus causes occipital numbness and paresthesias of the tongue when turning the head (Lance). Presumably there are connections between the trigeminal and hypoglossal nerves.

Cervicogenic Headache (Controversial) Although often cited, the evidence for this condition is unconvincing. However, in oncologic conditions such as lung tumors, projections to the face and scalp occur.

Nervus Auricularis Magnus (Greater) Traverses the sternocleidomastoid and the angle of the jaw. Injury causes transient numbness and unpleasant paresthesias in and around the ear. Injury can occur during face-lift surgery, carotid endarterectomy, and parotid gland surgery (injury to the terminal branches).

Lesser Occipital Nerve Damage in the posterior triangle of the neck (e.g., lymph node biopsy). Causes numbness behind the ear.

7.1.4 Pathogenesis

Tumors Ear nose and throat (ENT), lymphoma, lung, and breast.

E.L. Feldman et al., *Atlas of Neuromuscular Diseases*,
DOI 10.1007/978-3-7091-1605-0_7, © Springer-Verlag Wien 2014

Iatrogenic Operations, ENT procedures, and lymph node biopsy.

Trauma Traction injuries.

7.1.5 Diagnosis

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

7.1.6 Differential Diagnosis

Cervical radiculopathies.

7.1.7 Therapy

Pain management, anti-inflammatory drugs, and physical therapy.

7.2 Brachial Plexus

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
(+)	+		+ MR, US	(+)

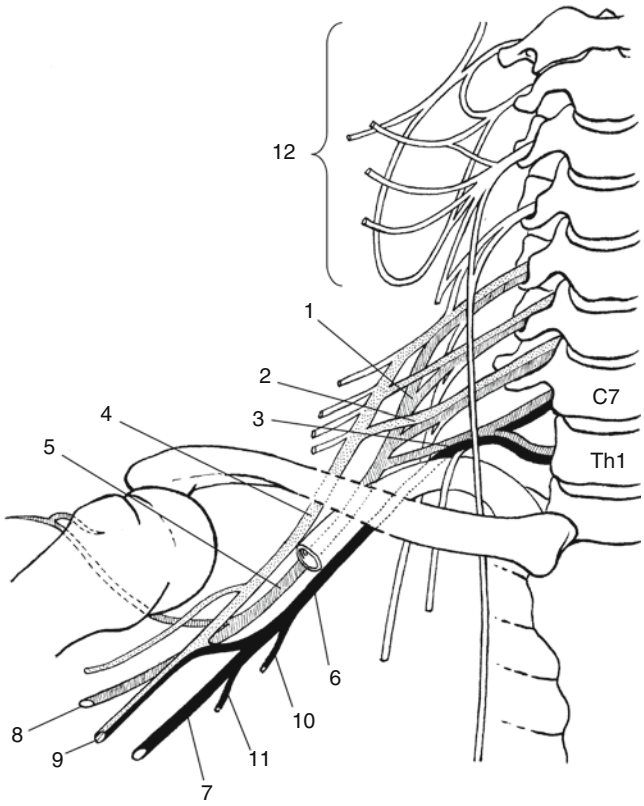

Fig. 7.1 Anatomy of the brachial plexus. *1* Upper trunk, *2* middle trunk, *3* lower trunk, *4* lateral cord, *5* posterior cord, *6* medial cord, *7* ulnar nerve, *8* radial nerve, *9* median nerve, *10* medial brachial cutaneous nerve, *11* medial antebrachial cutaneous nerve, *12* cervical plexus

7.2.1 Anatomy

The trunks of the brachial plexus are formed by the union of the ventral rami of spinal nerves C5–8. The three trunks bifurcate into anterior and posterior divisions. The ventral rami fuse to form the upper trunk, those from C8 and T1 form 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 (Fig. 7.1).

The Three Major Nerves of the Brachial Plexus

- The radial nerve is a continuation of the posterior cord and receives contributions from C5 to C8 fibers.
- The ulnar nerve fibers originate from C8 and T1 via the lower trunk and the medial cord.
- The median nerve has two components: the lateral part, which is mainly sensory, is derived from C5/6 (via the upper trunk and medial 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 nerve 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 muscle), and brachial and antebrachii nerves.

Composition of Cords

- Lateral cord: lateral pectoral nerve (upper pectoral), musculocutaneous (elbow flexors), median nerve (C5/6).
- Posterior cord: thoracodorsal nerve (latissimus dorsi), axillary (deltoid), radial nerve.
- Medial cord: medial pectoral (lower part), medial cutaneous and antebrachial 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 muscle, and the first rib. The plexus emerges from behind the lower part of the sternocleidomastoid muscles. The plexus passes under the clavicle and under the tendon of the pectoral muscle to reach the axilla.
- T1: 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:
  - Clavicle
  - First rib, infraclavicular part

- Interscalene triangle
- Supraclavicular part

7.2.2 Lesions of the Brachial Plexus (Fig. 7.2)

Supraclavicular Preganglionic and postganglionic. Upper plexus: incomplete traction, obstetric palsy, brachial plexus neuropathy. Lower plexus: metastatic tumors (e.g., Pancoast tumors), poststernotomy, thoracic outlet (TOS), surgery for TOS.
Infraclavicular Lesion of cords or branches: radiation, gunshot, humeral fracture, humeral dislocation, orthopedic conditions, axillary angiography, axillary (anesthetic) plexus block, neurovascular trauma, and aneurysm.

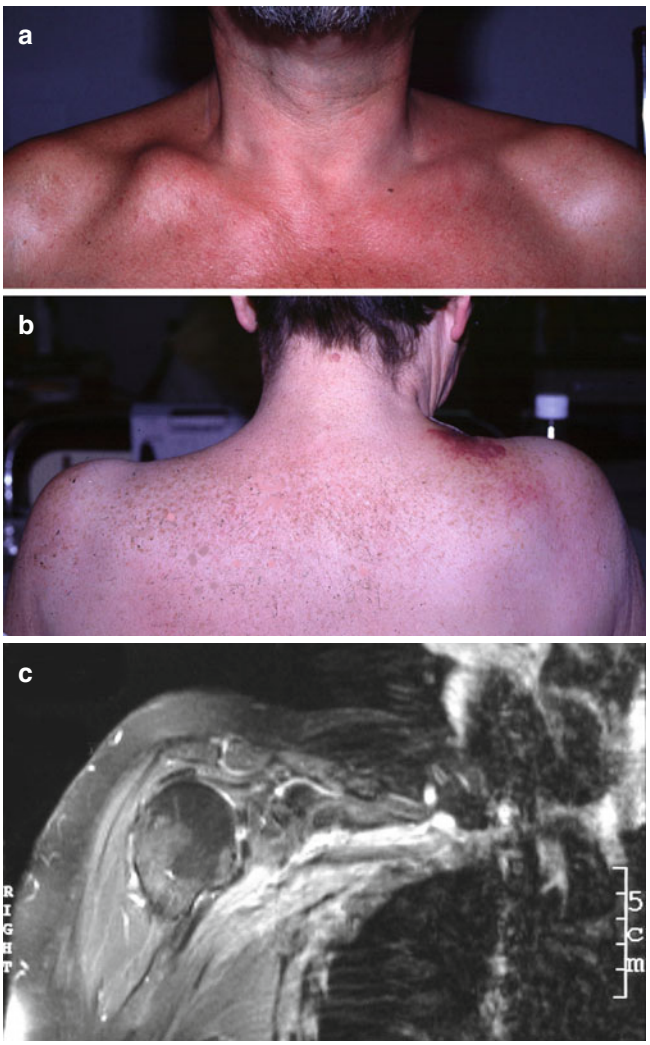

Fig. 7.2 Various types of mechanical pressure exerted on the brachial plexus. (**a**) Clavicular fracture with pseudoarthrotic joint. In some positions, electric sensations were elicited due to pressure on the brachial plexus. (**b**) A patient with arm pain and brachial plexus lesion. Note the mass over her right shoulder. The biopsy showed lymphoma. (**c**) MR scan of a brachial plexus of a 70-year-old woman, who was treated for breast carcinoma 10 years ago. Infiltration and tumor mass in the lower brachial plexus

Panplexopathy Trauma, severe traction (with or without root avulsion), postanesthetic paralysis, late metastatic disease, late radiation-induced plexopathy.

Other Classifications Upper and lower brachial plexus lesions, isolated C7 paralysis, fascicular lesions (medial, lateral, dorsal).

7.2.3 Symptoms

The symptoms depend on the site and type of lesion.

7.2.4 Signs

Trunk Lesions
- Upper trunk (C5/6): supra- and infraspinatus, biceps, pronator teres, flexor carpi radialis, brachioradialis, upper part of pectoral muscle, and deltoid.
- Middle trunk (C6/7): weakness of triceps and extensors of hand and fingers, flexor of thumb, and pectoral muscle. Teres major, latissimus dorsi, sensory: C6/7.
- Lower trunk: lower half of pectoral muscle, pronator teres, flexor carpi radialis, ulnar-innervated muscles, flexor dig superficialis, flexor pollicis longus, flexor digitorum profundus (dig 1–2), and median-innervated intrinsic hand muscles. Often associated with Horner's syndrome.

Cord Lesions
- Lateral cord: weakness of elbow flexion, forearm pronation (biceps, pronator teres, flexor carpi radialis). Sensory loss in the anterolateral forearm. Absent or diminished bicep reflex.
- Medial cord: weakness of finger flexion, extension, and abduction and of ulnar wrist flexion (all ulnar-innervated muscles, flexor digitorum superficialis, flexor pollicis longus, flexor digitorum profundus (dig 2,3), median-innervated hand muscles). 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 (latissimus dorsi, teres major, deltoid, all radial-innervated muscles). The sensory loss varies over the deltoid to the base of the thumb.

Complete Brachial Plexus Lesion Weakness of proximal and distal muscles, including levator scapulae and serratus anterior (Fig. 7.3). Sensory: complete loss in affected areas, often associated with pain.

Root Avulsion
- Clinically: usually high-velocity trauma. Functional loss may affect entire limb. Sweating intact, with severe burning, paralysis of serratus anterior, rhomboid, and spinati muscles. Associated with Horner's syndrome (if

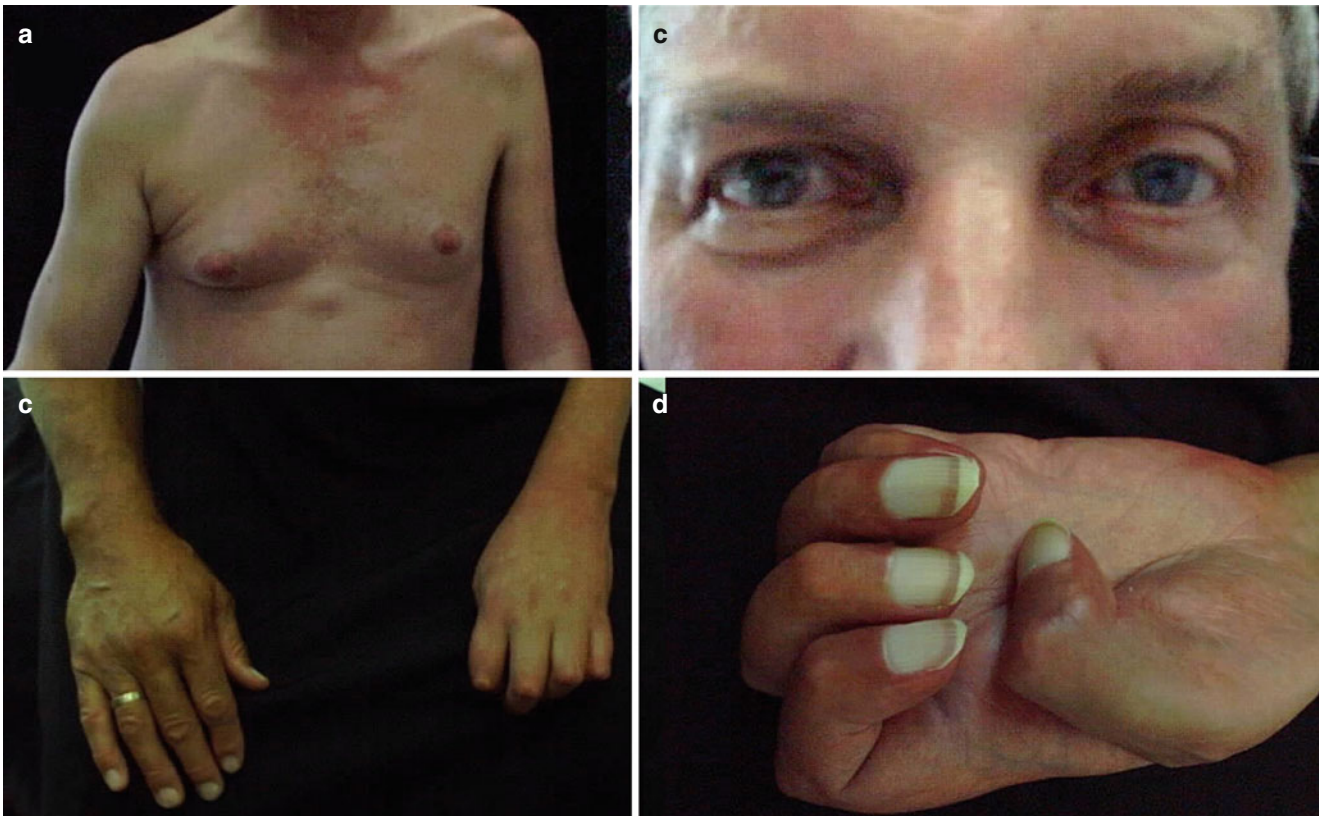

Fig. 7.3 Features of a long-standing complete brachial plexus lesion. (**a**) Atrophy of the left shoulder and deltoid. (**b**) The left hand is atrophic and less voluminous than the right hand. (**c**) Left-sided Horner's syndrome. (**d**) Trophic changes of the left hand, glossy skin and nail, and nail bed changes

appropriate root is damaged). Tinel sign can be elicited in the supraclavicular region. The neurological examination may show signs of an associated myelopathy. Radiographs may show fracture of transverse process, elevated hemidiaphragm.

- CT: spinal cord displacement, altered root sleeves, and enhancement with contrast media.
- MR: in traumatic meningoceles, root sleeves are not filled; also pseudomeningocele with spinal cord compression can occur.
- Electrophysiology: NCV: motors are unobtainable. Despite clinical sensory loss, sensory NCVs are obtainable due to sparing of the DRGs. F waves are absent.
- EMG: in addition to distal denervation also are fibrillation potentials in cervical and high thoracic paraspinal muscles.

7.2.5 Pathogenesis

Congenital 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 with flail arm and Horner's syndrome. Birth injuries are tractional lesions and may affect upper portion (Erb's type) or lower portion (Klumpke's type). However, brachial plexus lesions have also been observed after uncomplicated delivery or by Cesarean section. The diaphragm can be involved in 5 % of cases, and bilateral lesions occur in 10–20 %. Risks: high birth weight, prolonged labor, shoulder dystocia, and 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.

Genetic Conditions Ehlers-Danlos syndrome, HNA (acute attacks, pain), and HNPP (recurrent).

Neuropathy with Liability to Pressure Palsies (**HNPP**) Chromosome 17p11.2-p12; dominant, SEPT9. 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, and puerperium. Clinically: multifocal weakness: 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

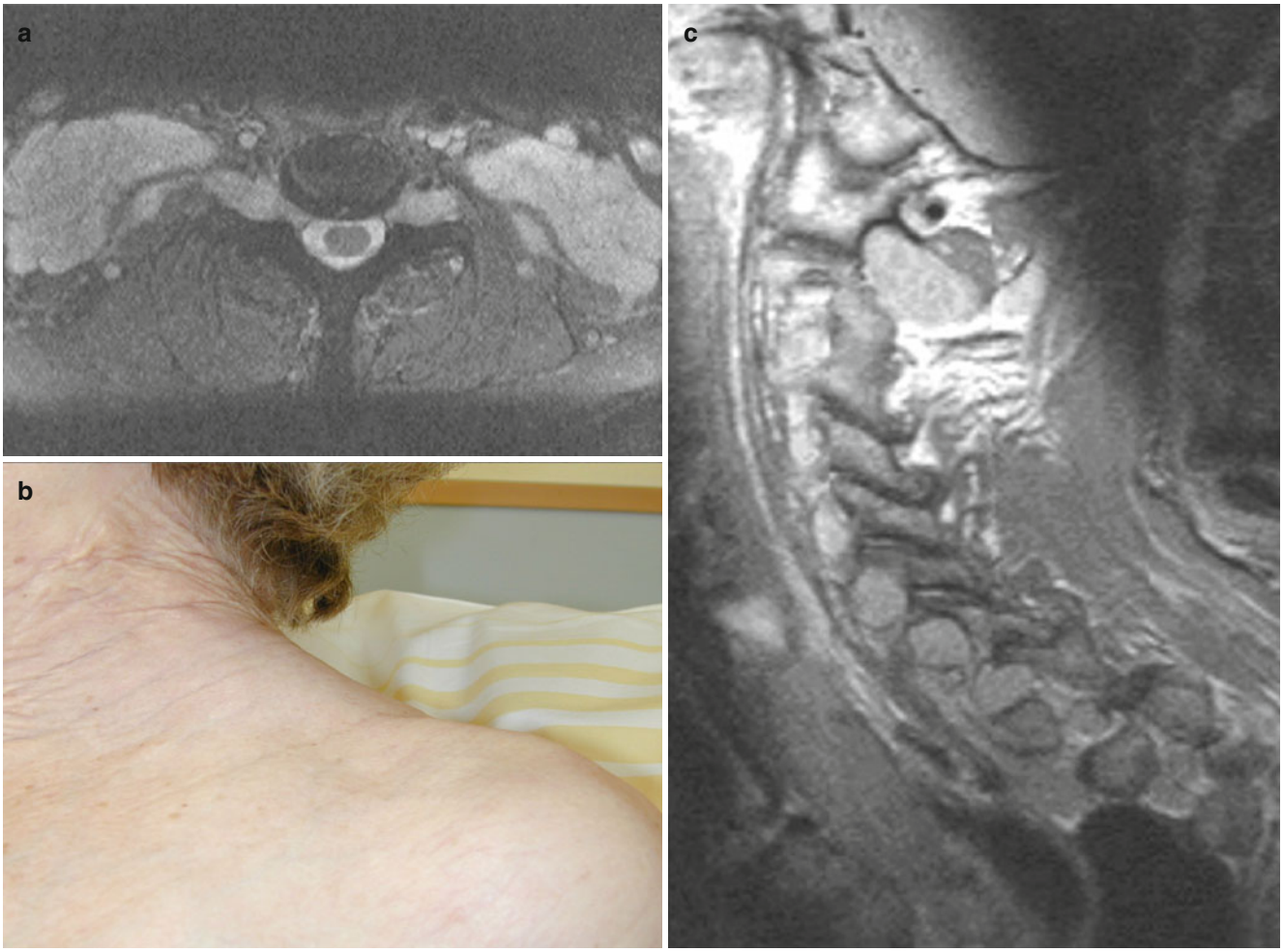

Fig. 7.4 Neurofibromatosis and the brachial plexus. (**a**) MRI of the nerve roots and brachial plexus. Note tumorous enlargement of nerve roots and (**c**) brachial plexus. (**b**) Note the palpable supraclavicular mass

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, and short stature. Prognosis: complete recovery common after each attack.

Chronic Neuralgic Amyotrophy (**HNA2**) (**Autosomal Dominant**) 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.

Chronic Neuralgic Amyotrophy (**HNA3**) (**Autosomal Dominant**: **Not Linked to 17q25**) Painful lesions of uni- or bilateral brachial plexus; phrenic nerve can be involved.

Iatrogenic

- Radiotherapy: the distinction between neoplastic involvement and radiation-induced plexopathy has not been always clear on clinical grounds (Table 7.1). The clinical distinction is usually the absence of pain and the distribution, which is more related to the upper brachial plexus (Fig. 7.5). Availability of MRI studies makes the distinction easier than before. In addition 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.

Table 7.1 Brachial plexopathy: metastasis versus radiation

Metastatic	Postradiation
Onset: pain in shoulder and hand (C8/T1)	Onset: paresthesias, median-innervated hand Slowly progressive, with or without pain
Palpable mass supraclavicularly	Infraclavicular lesion
Less than 3 months after RT	Duration: 2–4 years Onset: 4–41 years
Lower supraclavicular lesion	RT: 44–50 Gy
Metastases elsewhere	
Horner's syndrome	
"Pancoast" symptomatology	
Imaging: mass	

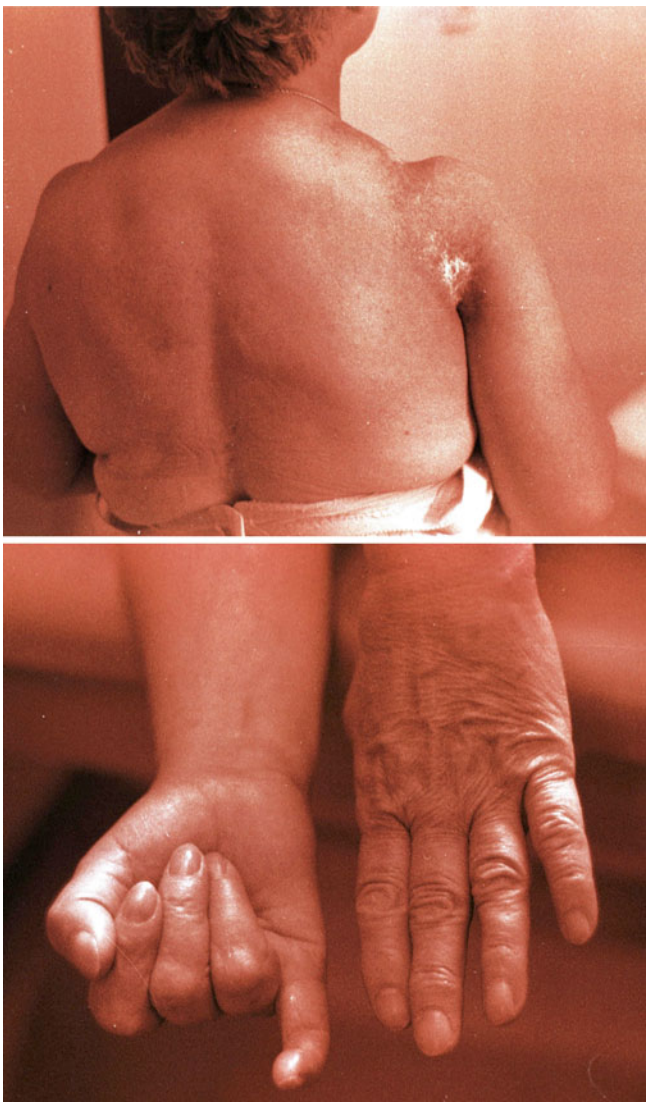

Fig. 7.5 Radiation injury of the brachial plexus: the upper picture shows the damaged skin after radiation therapy. The right hand is atrophic and has trophic skin changes. The finger movements were spontaneous due to continuous muscle fiber activity after radiation of the brachial plexus

- Electrodiagnosis: denervation, small sensory NCVs, CB across clavicle (difficult methodologically), and myokymia in EMG.
- Treatment: anticoagulation is disputed; pain therapy.
- In oncologic recurrence: surgery, chemotherapy, re-irradiation.
- 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), arthroscopy, and displacement of instrumentation (screws). Crutch use, shoulder joint replacement, shoulder arthroscopy, radical mastectomy, upper dorsal sympathectomy, humeral neck fractures. Surgery for nonspecific ("disputed") TOS (see Sect. 7.3).
- 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, and punctures of the axillary and subclavian artery and jugular vein.
- Medial brachial fascial compartment syndrome: the medial brachial fascial compartment extends from the clavicle to the elbow. Puncture of the axillary or brachial artery can produce a hematoma causing a compartment syndrome and compression of one or more of the terminal nerves (median and ulnar nerves most frequently affected).
- Postoperative brachial plexus lesion: these are usually associated with pain (and anterior interosseus neuropathies following shoulder surgery).

Infectious Botulinum toxin, CMV, EBV, herpes zoster, HIV, Lyme disease, parvovirus, and yersiniosis.

Inflammatory-Immune-Mediated Immunotherapy: interferons, IL-2 therapy, immunization and serum sickness, and vaccinations.

Neuralgic Amyotrophy (**Parsonage-Turner Syndrome**, **Acute Brachial Neuritis**) Clinically: sudden onset and pain located in the shoulder and persists 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, and 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: axonal loss in affected muscles. Abnormal lateral antebrachial cutaneous nerve in 50 % of cases. Other nerves are often unremarkable. Other nerves that may be affected include the phrenic, spinal accessory, and laryngeal. Prognosis: improvement begins after 1 or more months. Ninety percent recovery is achieved in 2–4 years. General treatment: pain control and physiotherapy. Childhood variant: onset at 3 years, after respiratory infection, with full recovery. DD: hereditary neuralgic amyotrophy, 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: intact distal NCVs. Motor NCV with supraclavicular stimulation is difficult. Sensory NCVs are not impaired. MR may show diffuse swelling of the plexus.

Mechanical Rucksack paralysis: caused by carrying of backpacks in recreational and military setting. Clinically: lesion of the upper and middle trunks, occasionally individual nerves. Pain is uncommon, and paresthesias 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.

Metabolic Coma from different etiologies—usually caused by position. The association with diabetes is uncertain.

Neoplastic Involvement of the Brachial Plexus Neoplastic: lymphoma (Fig. 7.6), metastatic breast cancer, lymph node metastasis (Fig. 7.7), Pancoast tumor (usually lung cancer,

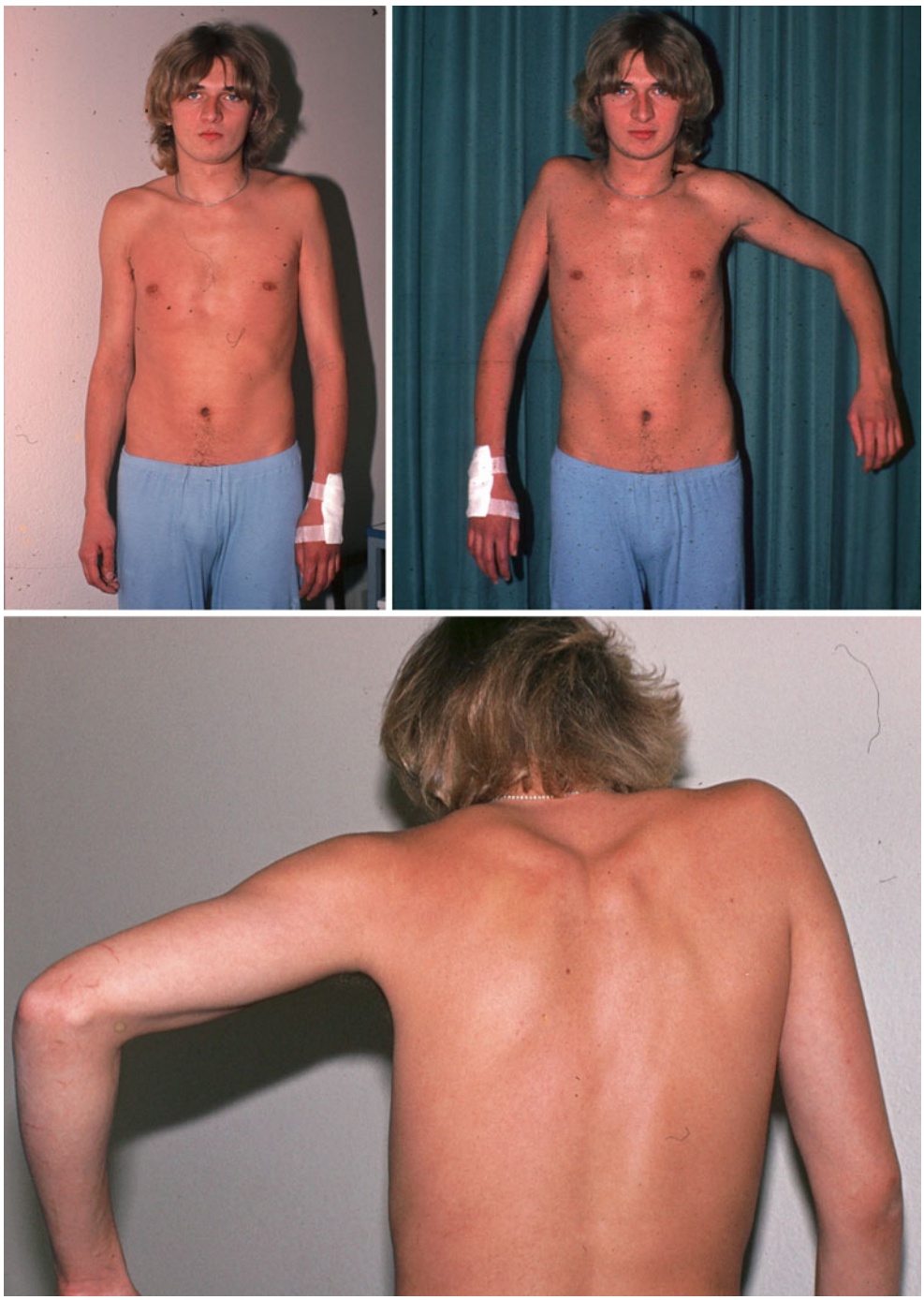

Fig. 7.6 Traumatic lesion of the left brachial plexus. Note the deltoid muscle and muscles fixing the scapula are intact. Atrophy of the lower arm and hand muscles. Note the inward rotation of the left hand while standing

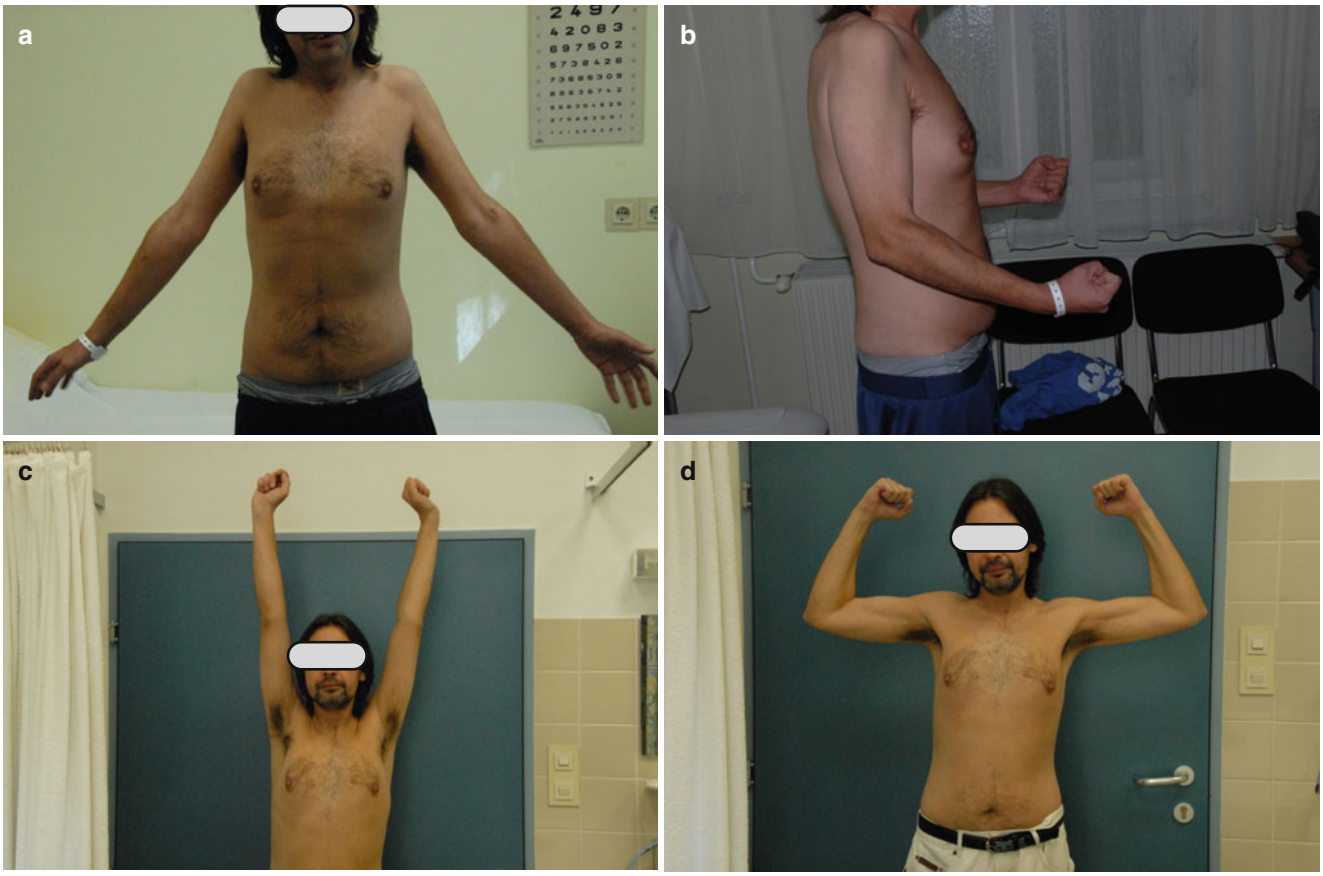

Fig. 7.7 Lyme disease. This patient presented with a shoulder girdle weakness with a duration of several weeks. There was specific symmetric pain; the CSF was pleocytotic with a mixed cellular pattern. Serology for borreliosis was positive. (**a**, **b**) Weakness of deltoids and biceps brachii; (**c**, **d**) the same patient after successful antibiotic treatment of borreliosis

Fig. 7.8), and primary brachial plexus tumors (e.g., schwannomas). Neoplastic plexus metastases have predominant involvement of C8/T1 roots or of the lower trunk. They are caused by either compression/invasion of lung tumors or lymph node metastasis. Usually neoplastic lesions are painful; often the intercostobrachial nerve is the first symptom, causing pain and numbness in the axilla. Pain is often located at the shoulder, further expanding into the medial aspects of the arm and forearm. Differential diagnoses are mononeuropathies and C8/T1 disc disease, which is uncommon. Sensory symptoms involve the 4th and 5th fingers; sensory symptoms of the medial arm often are only discovered by examination. Some patients have diffuse metastatic plexopathy or epidural tumor repetition 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. Axillary node resection sometimes causes lesions of the intercostobrachial nerve (see there). Pancoast tumor: radiation brachial plexopathy (Fig. 7.9) 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. Several atypical presentations with shoulder and elbow pain have been described.

Primary Tumors of the Brachial Plexus Rare: neurofibromas (Fig. 7.10) associated with NF-1 or intraneural perineuroma (localized hypertrophic neuropathy). DD: metastatic/RT, hemangiopericytoma, neural sheath tumors, neurofibromas about 30 % NF 1, and dumbbell tumors. Neuroneuronal: lipoma, ganglioneuroma, myeloblastoma, lymphangioma, dermoids, malignant neurogenic sarcomas and fibrosarcoma, schwannoma, and lymphoma.

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, Fig. 7.11). A frequent cause of brachial plexus lesions is 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 affected, but the plexus lesion can also be confined to the upper plexus

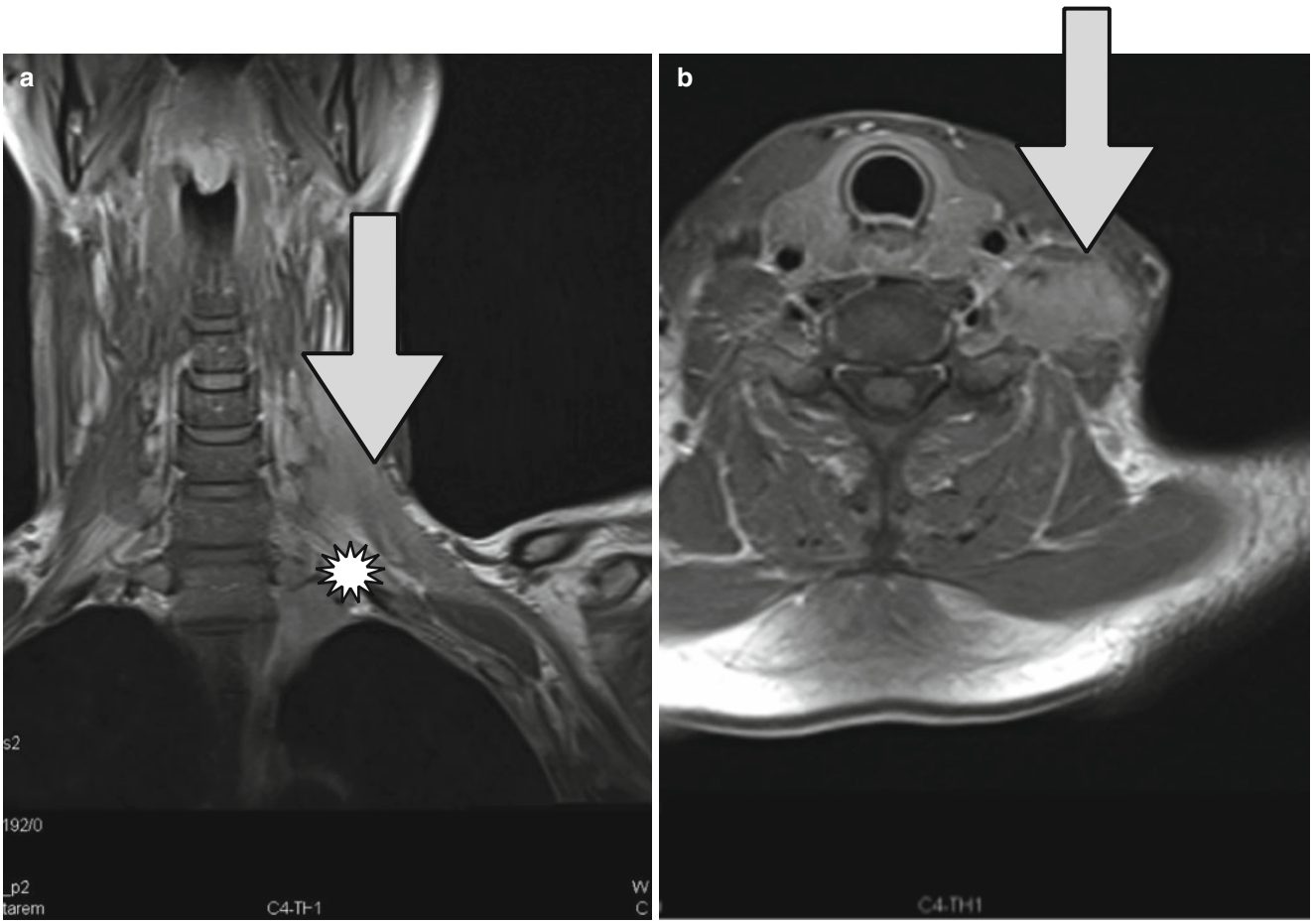

Fig. 7.8 Lymphoma. Infiltration of the brachial plexus from a lymphoma (*arrow*). Contrary to lung tumors, in this case, the upper plexus (*) is infiltrated

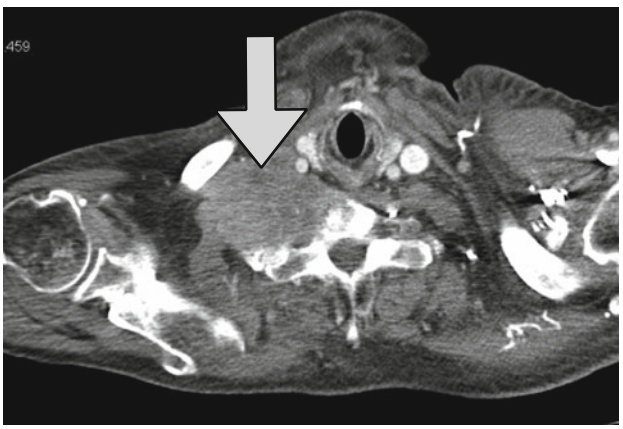

Fig. 7.9 Brachial plexus infiltration. The tumor (*arrow*) shows the tumor, which invades the vertebral column and the brachial plexus

or the whole plexus. In high-energy (traction or stretch) injuries, brachial plexus injuries and root avulsion often occur in parallel. Open plexus lesions are caused by penetration from gunshot, knife, or glass wounds. Gunshot wounds: location: infraclavicular more frequent than supraclavicular. Recovery: variable. Shoulder injuries: fractures of the proximal humerus, clavicle, and shoulder dislocation can cause injuries to the brachial plexus. The most frequent shoulder dislocation is the anterior type, which most frequently damages the axillary nerve, but also combinations with other nerves (e.g., suprascapular and musculocutaneous) occur. Clavicle fractures can damage the nerve by hematoma, bone fragments, or generation of a subclavian pseudoaneurysm. Pain is a frequently associated feature of brachial plexus trauma and is worse with root avulsion, where it may be the source of constant pain. Phrenic nerve conduction studies should be performed if a root lesion of C5 is suspected. Aberrant regeneration can occur in any traumatic plexus injury, leading to innervation of other muscle groups either with or without motor function in deltoid, biceps, and other shoulder muscles.

Toxic Alcohol, heroin: persistent proximal weakness, pain resolution over months.

Vascular Hematoma, transcutaneous transaxillary angiograms, puncture of axillary artery, and aneurysm.

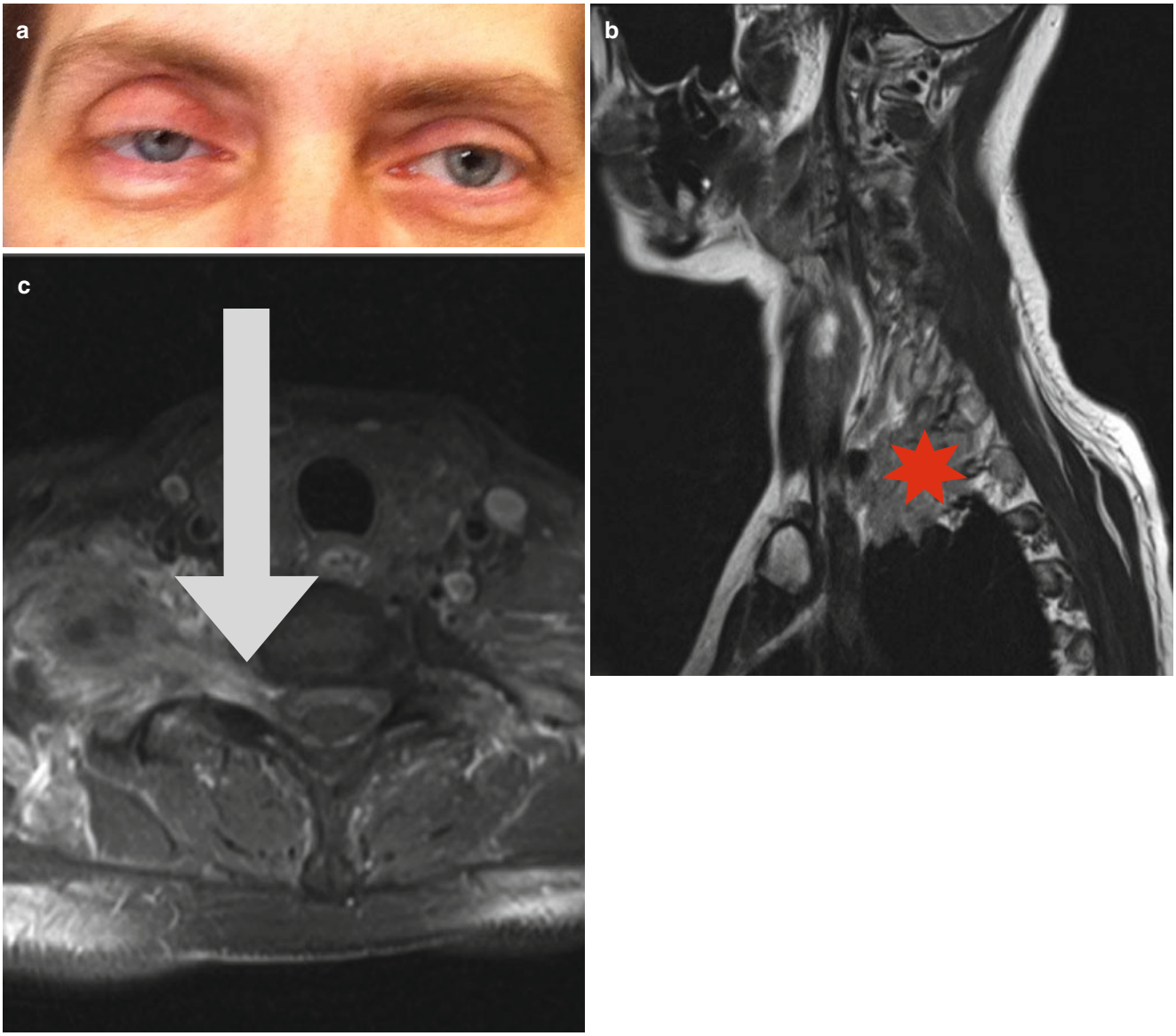

Fig. 7.10 Pancoast tumor. Some characteristics of Pancoast tumors. (**a**) Horner's syndrome, (**b**) apical lung tumor (*asterisk*), (**c**) nerve root infiltration by tumor seen in MRI (*arrow*)

Pseudoaneurysms: may result from trauma or injuries and slow low onset and development.

Others "Burner" syndrome: sudden forceful depression of the shoulder, occurs in the US football. Transient sudden dysesthesias occurs in the whole limb but may remain longer in upper trunk distribution.

7.2.6 Diagnosis of Brachial Plexus Lesions

- Upon palpation: mass
- Laboratory: genetic analysis
- Imaging: plain bone X-ray, CT, MRI, adjacent structures: lung, ribs
- US: of brachial plexus
- Electrophysiology (Table 7.2): NCV, EMG, more difficult to establish conduction block over the brachial plexus
- Sympathetic function: sweat tests (Horner in lower plexus)

7.2.7 Differential Diagnosis

Brachialgia, cervical radiculopathies, cervical radiculopathies with root avulsion, effort thrombosis, myopathies, and proximal mononeuropathies: axillary, suprascapular, long thoracic, and musculocutaneous. Shoulder injury: fracture

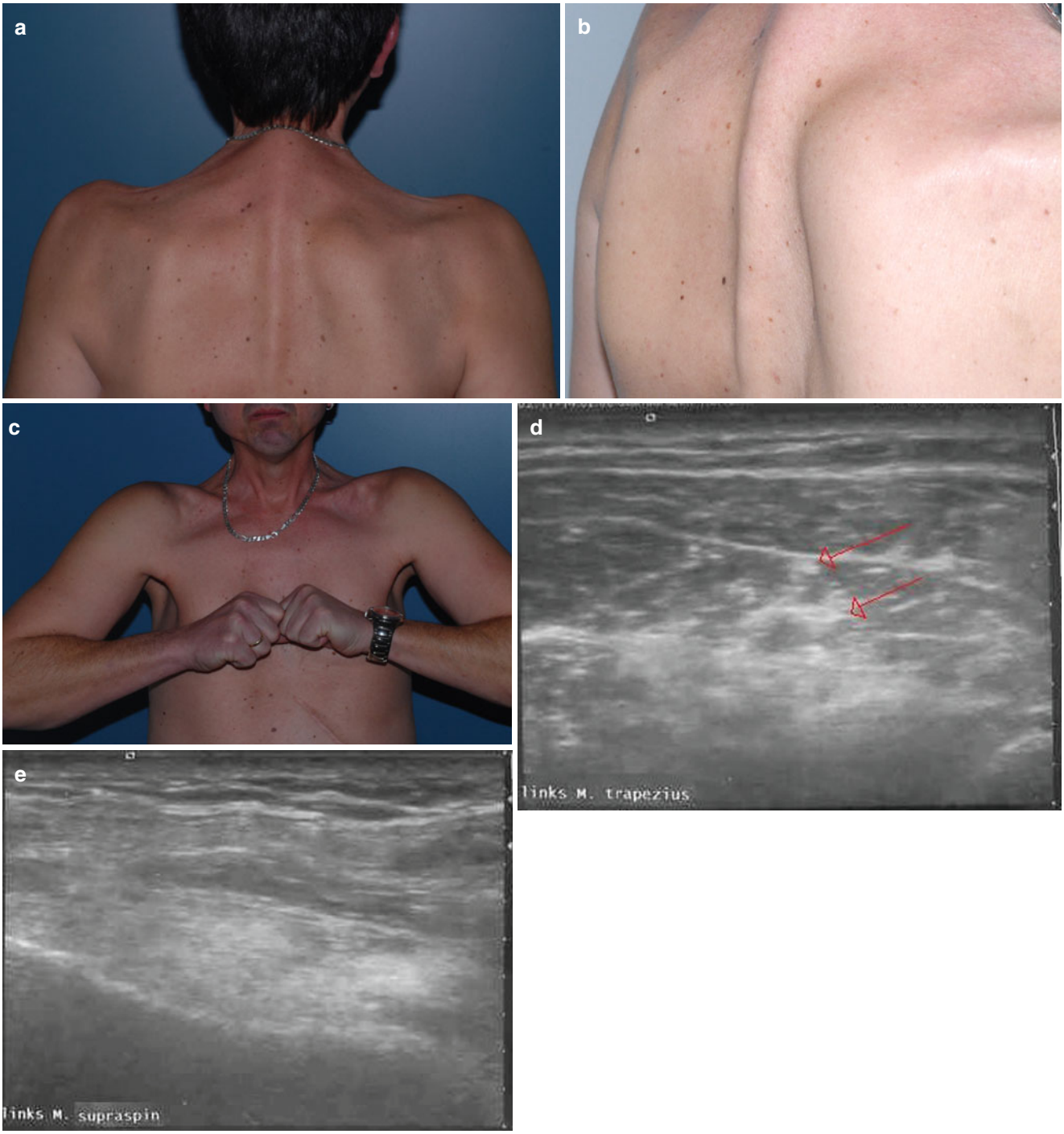

Fig. 7.11 Radiation fibrosis following radiation therapy. The patient presented with weakness and atrophies in his shoulder girdle. There is a marked atrophy of the trapezoid muscles and scapular muscle (**a**–**c**). The ultrasound shows fibrosis of the muscles (**d**, **e**); the *arrows* mark fibrotic septa

and dislocation (axillary, suprascapular nerve), rotator cuff injury (see suprascapular nerve). Shoulder joint contractures, fractures of the clavicle, and subclavian pseudoaneurysm. Orthopedic and rheumatologic conditions: "frozen shoulder," Hirayama disease.

7.2.8 Therapy

Due to the variety of brachial plexus lesions, no one therapy can be prescribed. Conservative therapy is aimed at pain management and inclusion of physiotherapy to avoid con-

Table 7.2 Brachial plexus structures and electrophysiology

Structure	EMG	Motor NCV	Sensory NCV
Upper trunk (superior trunk, C5/6)	Muscle of the C5 and C6 dermatome—not involved: rhomboids and serratus anterior	Motor latency to deltoid and biceps brachii	N. cutaneus antebrachii lateralis, median nerve (thumb), and superficial radial nerve
Middle trunk (medial trunk, C 7)	All C7 muscles, except serratus anterior	Motor latency to abductor pollicis brevis	
Lower trunk (inferior trunk, C8/T1)	Muscles of the C8/T1 myotoma	Median, ulnar nerve	Ulnar nerve
			N. cutaneus antebrachii medialis
Lateral fascicle	C5, C6, and C7 muscles innervated by musculocutaneous and median nerve	Motor latency to biceps brachii	N. cutaneus antebrachii lat, dig 1 and 2 median nerve
Medial fascicle	Muscle of the median and ulnar nerve. Radial-innervated M. ext. poll. brevis and M. ext. indicis spared	NCV from median and ulnar nerve	Sensory from ulnar nerve. N. cutaneus antebrachii medialis

tractures and ankylosis. If no improvement can be expected, muscle transfer to facilitate function can be considered. Treatment of traumatic brachial plexus lesions is often a matter of controversy. Generally speaking, a period of 4 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 reach distal muscles (see principles of nerve surgery). New developments show that avulsed roots can be reimplanted. Plastic and reconstructive surgery, orthopedic therapies, and also neuroprosthetic methods can be applied.

7.2.9 Prognosis

The prognosis is highly dependent on the cause. In traumatic plexus injury, Seddon's 5-grade classification is applied.

7.3 Thoracic Outlet Syndromes

Several entities have been described:
- True neurogenic TOS
- Arterial TOS
- Venous TOS
- Nonspecific (disputed) neurological TOS
- Combinations

7.3.1 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. Rarely is it bilateral.

Causes
- Elongated transverse process (C7)
- Rudimentary cervical rib
- A sharp fibrous band that extends from this "rib" to reach the upper surface of the first thoracic rib
- Compression by the anterior scalene muscle
- Musculotendinous abnormalities

Differential Diagnosis
Median and ulnar neuropathies: thenar wasting may be confused with CTS, lower trunk or medial cord lesions, C8 and T1 radiculopathies, and syringomyelia.

Investigations
Adson's (ipsilateral head rotation) or Allen's maneuver (contralateral head rotation), plain radiograph, CT, and MRI do not detect fibrous bands but are good to exclude other causes. Electrophysiology: to exclude CTS and ulnar nerve lesion. Characteristic: low or absent sensory NCV of ulnar and medial cutaneous antebrachial nerve. EMG abnormalities of muscles innervated by the lower trunk. Paravertebral muscles are normal. Despite symptomatic TOS, electrodiagnostic tests are often normal.

Treatment
- Conservative treatment: posture correction; stretching may relieve problems.
- Orthosis to elevate shoulder.
- Surgery: resection of the first rib.
- Botulinum toxin (Botox) injections into the scalene muscles (disputed).

7.3.2 Arterial TOS

Due to cervical rib and vascular involvement (subclavian artery compression with poststenotic compression or

subclavian artery aneurysm). Clinically, it can present with weakness and pain: resulting in unilateral hand and finger ischemia and pain.

Minor vascular involvement results in reduced arterial pulse during hyperabduction of the arm.

Occurs in young athletes and swimmers, from throwing, occlusion, stenosis, aneurysm, or pseudoaneurysm. The humeral head may compress the axillary artery. It occurs with or without cervical rib. Abnormal arteriography or venography. Electrodiagnostic tests are normal.

7.3.3 Venous TOS

This is rare and can be caused by a spontaneous thrombosis of the axillary or subclavian vein. The thrombosis occurs after effort, followed by swelling of the extremity, including cyanosis and pain. Therapy employs thrombolytic treatments followed by anticoagulation.

7.3.4 Disputed Neurogenic TOS

No rib changes. Symptoms, but no objective changes of TOS.

Symptoms are variable: pain and paresthesia in the lower trunk distribution, supraclavicular tenderness. Stable and nonprogressive. Treatment: albeit disputed, potentially the removal of the anterior scalene muscle.

7.3.5 Others

Traumatic TOS: traumatic TOS is usually unilateral and reflects supraclavicular traction injury. The medial cord is most susceptible to trauma.

7.4 Lumbosacral Plexus

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

7.4.1 Anatomy

Three nerve plexuses are commonly termed the "lumbosacral" plexus: lumbar, sacral, and coccygeal plexuses (Fig. 7.12).

Lumbar Plexus (Fig. 7.13) Formed by the ventral rami of the first to fourth lumbar spinal nerves (Fig. 7.14). Rami pass downward and laterally from the vertebral column within the psoas muscle and form the dorsal and ventral branches. The subcostal nerve frequently communicates with T12. The L2–4 ventral rami of the lumbar bifurcate into an anterior and posterior primary division. The anterior division supplies muscular branches to the psoas major and quadratus lumborum muscles. Both primary divisions then enter the lumbar plexus and give rise to peripheral nerves. The cranial portion gives rise to the iliohypogastric and ilioinguinal nerves. The caudal branch

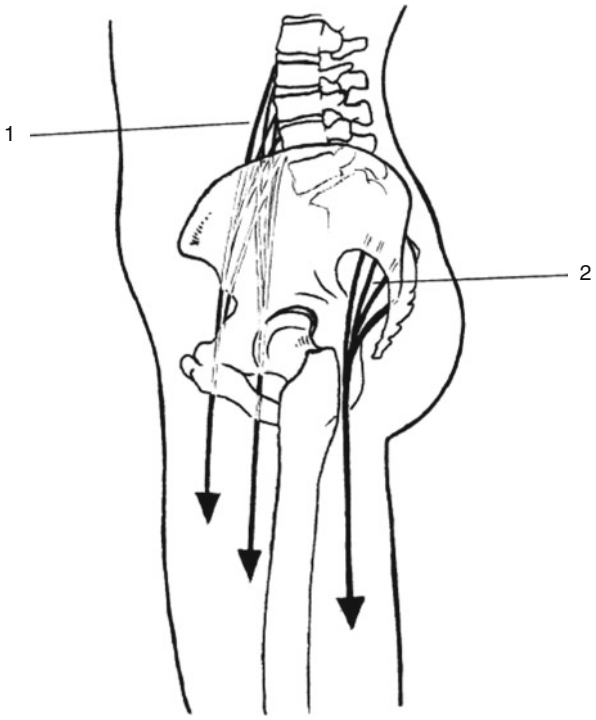

Fig. 7.12 Topical relations of lumbar and sacral plexus

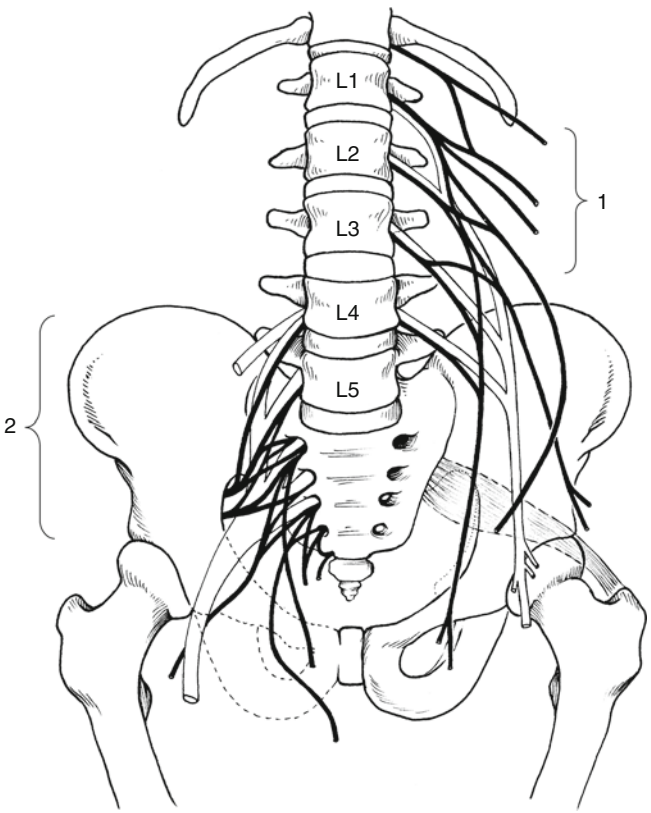

Fig. 7.13 *1* Lumbar plexus, *2* sacral plexus

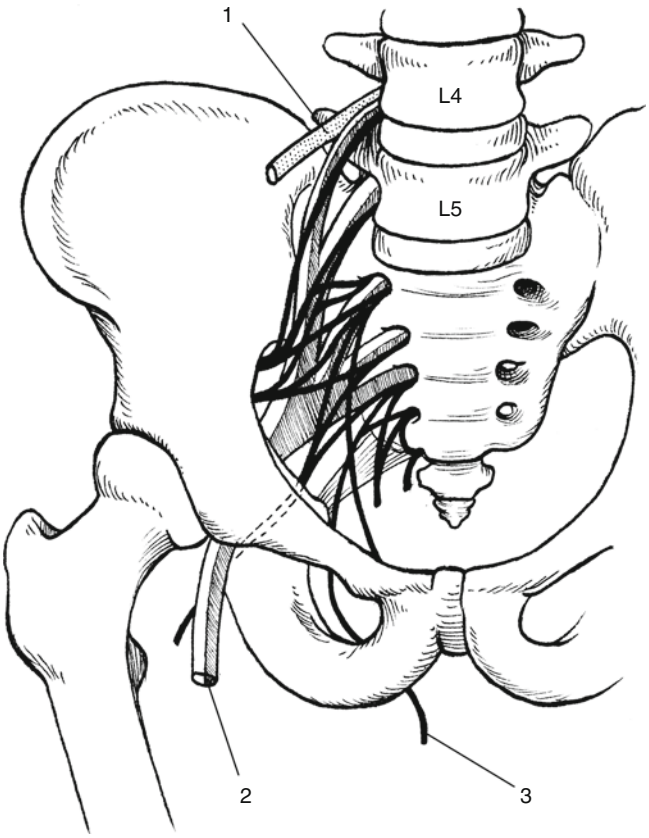

Fig. 7.14 *1* Branch to lumbar plexus, *2* greater sciatic nerve, *3* pudendal nerve

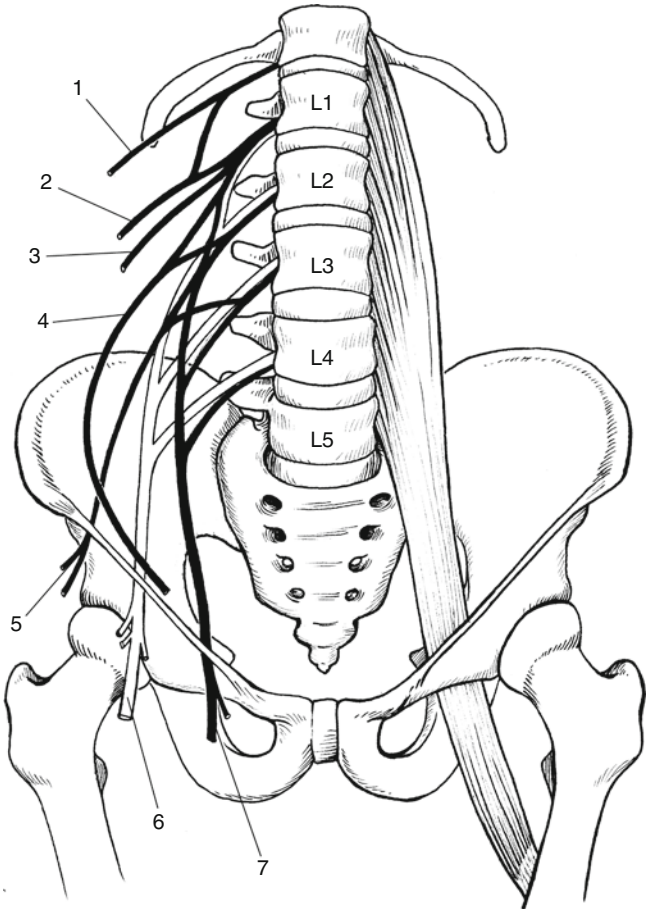

Fig. 7.15 *1* Subcostal nerve, *2* iliohypogastric nerve, *3* ilioinguinal nerve, *4* genitofemoral nerve, *5* lateral cutaneous femoris nerve, *6* femoral nerve, *7* obturator nerve

of L1 forms with the anterior division of L2, the genitofemoral nerve. The obturator nerve arises from the ventral branches of L2–4 and emerges from medial border of the psoas, within the pelvis (Fig. 7.15). The dorsal branches of L2–4 rami constitute the femoral nerve, which emerges from the lateral border of the psoas muscle. The femoral nerve passes through iliacus compartment and courses distally through the inguinal ligament. The lateral femoral cutaneous nerve arises from the posterior divisions of the L2 and L3 roots. 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 the sacroiliac joint.

Sacral Plexus The sacral plexus (see Fig. 7.13) is formed by the union of the lumbosacral trunk and the ventral rami of S1–4. The plexus lies on the posterior and posterolateral walls of the pelvis, with its components converging toward the greater sciatic foramen and continuing as the sciatic nerve. Sacral ventral rami divide into ventral and dorsal branches: the dorsal branches of the lumbosacral trunk (L4, 5) and the dorsal branches of the S1 and S2 spinal nerves join to give rise to a lateral trunk. The lateral trunk forms the peroneal nerve. 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 muscles of the pelvis and hip (piriformis muscle, internal obturator, quadratus femoris muscle). Autonomic fibers are found within lumbar and sacral nerves. The area of the sacral plexus and the proximal sciatic nerve is surgically termed "no-man's land," as the approach to this region which is created by the bony and soft tissue confines of the peritoneal cavity, retroperitoneum, pelvis, and gluteal region is difficult. The sacral plexus has direct branches to the piriformis muscle, internal obturator, quadratus femoris, sciatic nerve, pudendal nerve, and coccygeus plexus.

Pudendal and Coccygeal Plexus The pudendal plexus receives fibers from S1 to S4. The motor fibers innervate the muscles of the pelvic floor including the external urethral and anal sphincter. The sensory branches stem from the inferior rectal and perineal nerves. The coccygeal plexus is formed fibers from S1 and Co1. It forms the anococcygeal nerve.

7.4.2 Symptoms

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

Sacral Plexus Sensation is disturbed, and pain radiates in the gluteal region and in the external genitalia. All lower limb muscles display weakness, except those innervated by the femoral and obturator nerves. Motor function: in some pelvic muscles, gluteus muscles, tensor fasciae latae, hamstrings, and all muscles of the leg and foot, weakness can be caused by sacral plexopathies.

7.4.3 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 focused in L5–S1 resulting in weakness of the sciatic nerve-innervated muscles. Proximal muscles that exhibit weakness include the gluteus maximus muscle, but the gluteus medius muscle is usually spared. Sensory symptoms can also involve proximal areas, such as the distributions for the pudendal nerve and the posterior cutaneous nerve of the thigh. Sphincter involvement can occur.

7.4.4 Pathogenesis

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

Episodic Weakness of Lumbosacral Plexus: DD: cauda equina, peripheral occlusive, and ischemic plexopathy (rare).

Genetic Neuralgic amyotrophy, HNPP.

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.

Infectious Iliopsoas abscess: abscess, Lyme disease, immunizations, EBV, HIV, CMV. A bilateral lumbar and sacral plexopathy can occur in HIV. Inflammatory-immune mediated: injury caused by immune vasculopathy is characterized by older age at onset, asymmetric proximal weakness, and variable sensory loss. The course is progressive over weeks and months, sometimes associated with diabetes. Laboratory investigations show elevated sedimentation rate. Nerve biopsy demonstrates inflammatory cells around small epineural blood vessels. Treatment with corticosteroids induces recovery. The term nondiabetic lumbosacral radiculoplexopathy has similar features as the diabetic type. A similar condition can be induced by vaccination and resembles serum sickness. Hypersensitivity in drug addicts using IV heroin can cause limb dysfunction, bladder dysfunction, and rhabdomyolysis.

Metabolic Diabetic amyotrophy: this entity has received several names, one of them diabetic femoral neuropathy, although usually not only the femoral nerve is affected. Diabetic amyotrophy is usually a unilateral (but rarely bilateral) proximal plexopathy affecting the hip flexors, femoral nerve, and some adjacent structures. Vasculopathies, metabolic causes, or vasculitic changes have been described. The characteristic features are as follows: 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 CSF pleocytosis may occur. An important clinical feature is severe weight loss before the neurological disease. Pain is the dominant symptom, radiating into the hip or anterior thigh, and weakness and atrophy occurred. Hip flexors, gluteal muscles, and quadriceps show weakness, and adductors can be involved, demonstrating clearly that this is not an isolated femoral neuropathy. The PSR disappears, and quadriceps atrophy occurs. After stabilization, slow recovery can be expected. Biopsies from the sural and superficial peroneal nerves display vasculitic changes. Therapy is confined to adequate pain control, as no effective treatment is available.

Neoplastic

- Cancer associated: lumbar plexus: malignant psoas syndrome (see below). In addition, treatment-related coagulopathies can cause psoas hematoma. Sacral plexus: malignancies are colorectal, breast, cervical carcinomas, sarcomas, and lymphomas. Characterized by insidious pelvic or lumbosacral pain, radiating into the leg; paresthesia; and variable involvement of bladder and bowl function. Gait abnormalities and lower limb edema may occur. Most commonly they are the result of direct tumor extension: pelvic, abdominal, and retroperitoneal tumors. Metastases are rare. Rarely lymphoma and neurolymphomatosis occur.
- Others: tumors: plexiform neurofibromas (NF), malignant nerve sheath tumors.

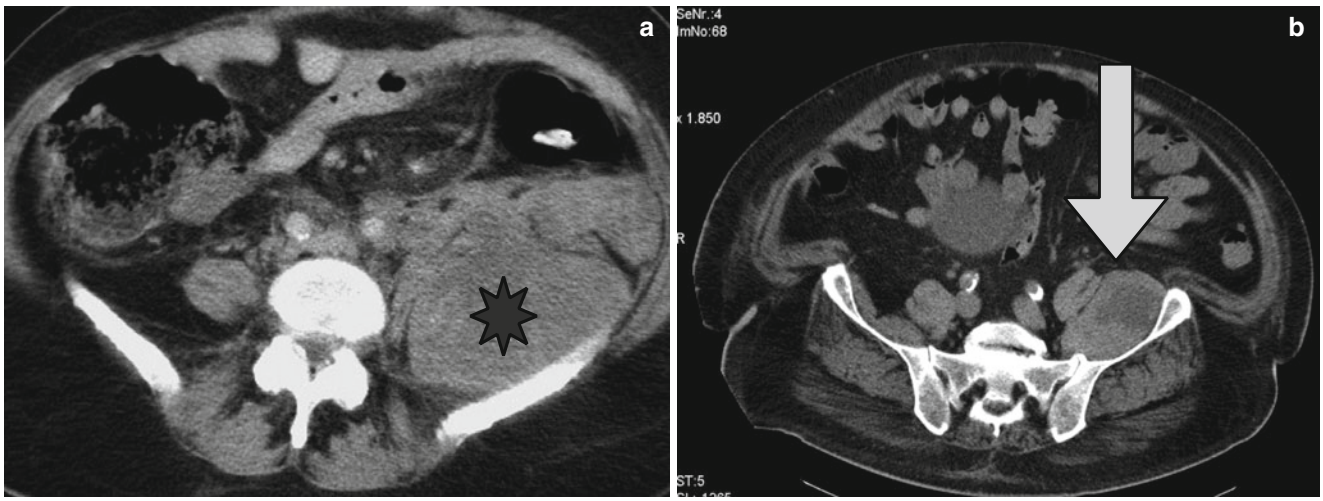

Fig. 7.16 (**a**) A large tumor invading the psoas muscle (psoas syndrome) (*). (**b**) The iliac syndrome (*arrow*) has a similar symptoms, however the knee jerk is preserved, as clinical sign

Specific Syndromes Observed in Cancer Patients Malignant psoas syndrome (lumbar plexus) Fig. 7.16a: para-aortic lymph nodes, with infiltration of the psoas muscle, can be caused by bladder, prostate, and cervical tumors. Causes anterior thigh pain. Hip held flexed to relieve pain. Warm and dry foot syndrome (sacral plexus): injury to postganglionic axons, often by cervical or uterus cancer, and associated with lower limb pain. Examination: "warm and dry foot." Bilateral caudal sacral symptoms can occur if the most caudal fibers are affected, as both sacral plexuses are near the midline. Neurolymphomatosis is a rare involvement of peripheral nerves by lymphoma.

Pregnancy Maternal lumbosacral plexopathy (maternal paralysis): the fetal head pushing against the pelvic rim can compress the lumbosacral trunk, superior gluteal, and obturator nerves. This can occur intrapartum but also in the third trimester. Symptoms: buttock pain, L5 distribution, and foot drop. Sensory loss at the lateral leg and dorsum of the foot. Motor symptoms: foot drop.

Other causes: protracted labor, cephalopelvic disproportion, and midpelvic forceps delivery. Also the femoral and obturator nerve can be compromised.

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

Radiation Plexus Lesion Lumbar plexus: is rarely affected. Sacral plexus: after a latency of months to years, weakness and atrophies occur. Usually a high radiation dose of > 55 Gy has been applied. Pain is usually not a feature. In EMG, myokymia is observed. MRI could demonstrate fibrosis. Bilateral RT of para-aortic and ipsilateral lymph nodes (e.g., testicular cancer) can cause sensory and also motor symptoms in the legs.

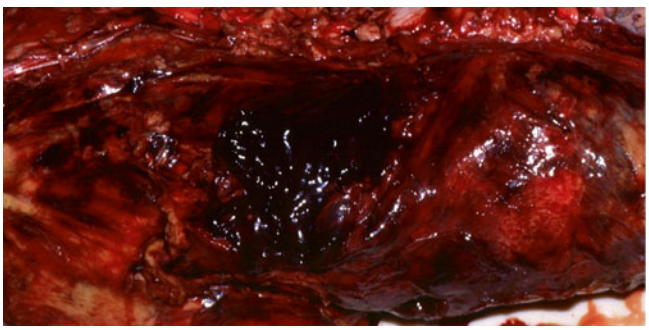

Fig. 7.17 Psoas hematoma: autopsy site shows large hematoma in the psoas muscle, in a patient with anticoagulant therapy

Differential diagnosis: neoplastic versus radiation damage of the lumbosacral plexus: neoplastic: pain, unilateral weakness, short latency, reflexes unilaterally, mass on imaging, palpable mass, leg edema, and hydronephrosis. Radiation therapy characteristics: indolent leg weakness, bilateral weakness, long latency (usually delayed for months or years), bilaterally absent, normal study, or fibrosis, myokymia in EMG, paraspinal fibrillations, and RT more than 55 Gy.

Vascular Ischemic plexopathy: hemorrhage (thrombopenia, anticoagulation therapy) can cause hematoma in the psoas muscle and induces weakness in the obturator and femoral nerve territories. The femoral nerve can also be directly compressed. Knee jerk is lost. Also iliac hematoma can cause weakness due to hemorrhage into the iliac muscle (iliac muscle syndrome). Usually in this condition, the knee jerk is preserved (Figs. 7.16b, 7.17, and 7.18).

Retroperitoneal Hematoma Can be due to anticoagulation therapy and ruptured aortic aneurysm or occur spontaneously. It can also occur in trauma in association with vertebral

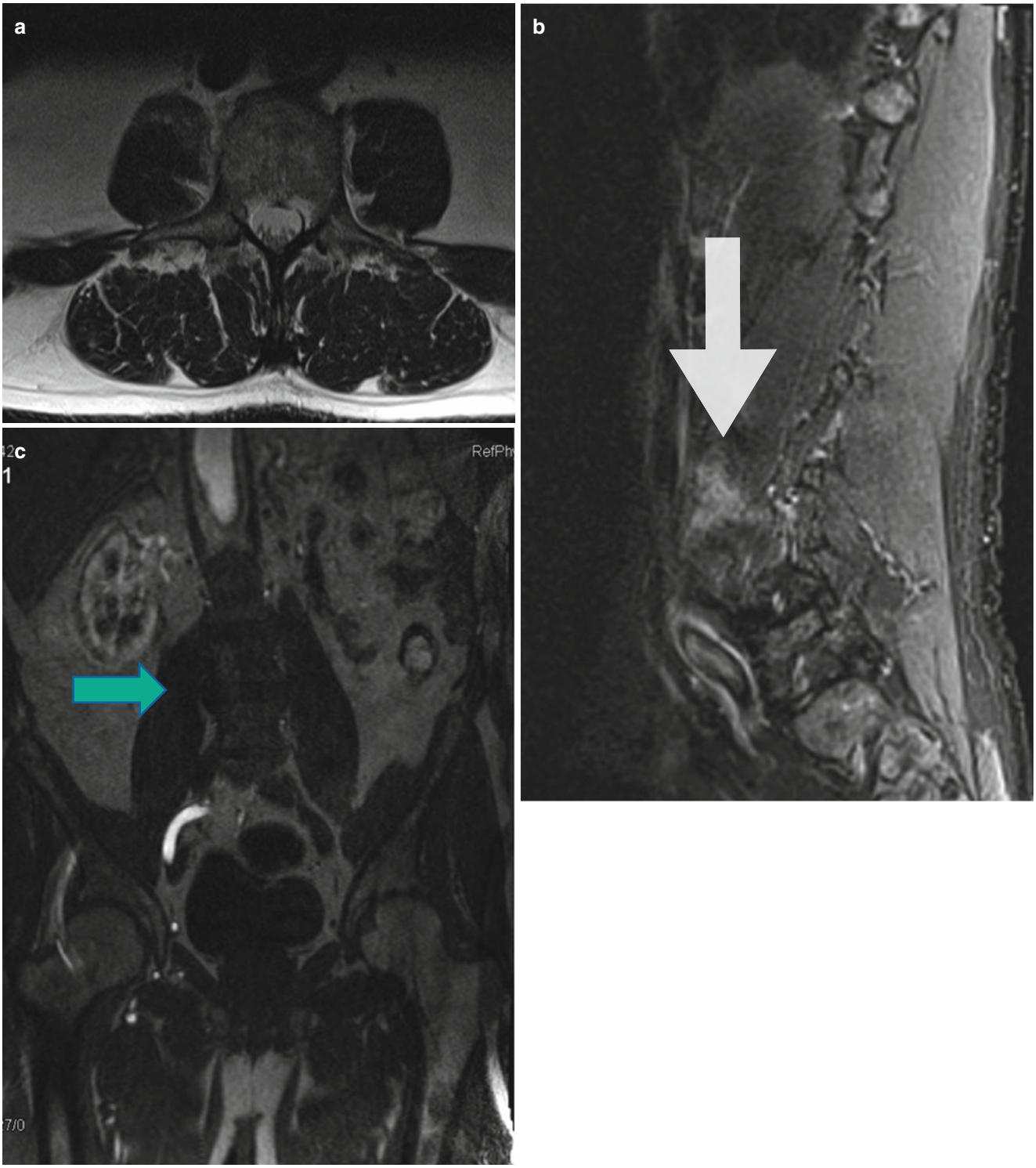

Fig. 7.18 Lumbar artery occlusion: Painful ischemic lesion of lumbar plexus due to lumbar artery occlusion. A 69 year old male with acute onset of burning pain and paresthesia of the right femoral and saphenal nerve 3 days before admission. The patient did not suffer from diabetes mellitus but had a longstanding medical history of peripheral arterial occlusive disease. Neurological examination revealed a severe weakness of the right hip flexors, a mild paresis of the right knee extensors and adductors. The right knee jerk was absent. He had severe pain with no sensory deficit on the thigh, hypesthesia below the knee, and hyperesthesia in the saphenal nerve distribution. Imaging showed a normal lumbar spine. (**a**) The proximal part of the psoas muscle was edematous (*arrow*) suggesting an ischemic lesion of the muscle (**b**). The MR angiography revealed an occluded right third lumbar artery (*green arrow*) (**c**)

column fractures, hemorrhages from iliac crest, and bone marrow biopsy or harvest. Arterial injections in the buttock can cause ischemic sciatic nerve and plexus lesions. The onset varies from minutes to hours. Ipsilateral pelvic muscles or blood vessels can be involved. Intra-arterial injection of cis-platinum or fluorouracil into internal iliac artery can cause plexopathy.

Aortic Aneurysms Can cause compression injury but also vascular cord lesions. Also common and internal iliac artery aneurysms can cause a unilateral compression. Aortic thrombotic occlusion: can cause lumbosacral plexopathy. Rarely, episodic ischemic lumbosacral plexopathy (claudication) 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. Causes include bilateral stenoses of the iliac arteries or distal abdominal aorta and 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, and this is termed iliac muscle syndrome (Fig. 7.18). These hemorrhages may cause lumbar plexopathy. Trauma: uncommon. Exceptionally violent trauma, road accidents, falls, rarely gunshots. Lesions of the sacral plexus are often associated with different types of bony fractures of the pelvic ring or acetabulum or rupture of the sacroiliac joint. 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. Severe lesions, including root avulsions, can occur in severe pelvic fractures ("open-book fracture"). Gunshot: greater chance of involving the upper plexus. Other causes: toxic in heroin abuse, endometriosis, and amyloidosis.

7.4.5 Diagnosis

- Laboratory: to exclude diabetes.
- Imaging: plain film radiography, CT, and MR. Plain film radiography and CT for surrounding structures (e.g., sacral destruction). CT or MR angiography for suspected vascular lesions. Ultrasound. CSF: when cauda equina lesion or inflammatory lesion is suspected.
- Electrophysiology: motor and sensory studies: NCV, late response, needle EMG, evoked potentials (SEP, MEP). Sensory NCVs are important in distinguishing plexopathy from radiculopathy. As the DRGs are often (but not always) located outside of the neuroforamen, this distinction is not absolute. Paraspinal muscle involvement should be excluded in plexopathies.

Lumbar Plexus

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

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 V pedis: S1, 2

7.4.6 Differential Diagnosis

Polyradicular lumbosacral involvement (Lyme disease, neoplastic involvement), inflammatory asymmetric conditions, and mononeuropathy multiplex.

7.4.7 Therapy

Depending on the cause.

7.4.8 Prognosis

Depending on the cause, variable.

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Mononeuropathies

8

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and Wolfgang N. Löscher

8.1 Introduction

Mononeuropathies are an essential part of clinical neurology. Their clinical diagnosis depends on knowledge of anatomy, presentation of clinical syndromes and their numerous other 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 a differential diagnosis is proposed. Therapeutic aspects and the prognosis, if available, 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 subsection.

8.2 Mononeuropathies: Upper Extremities

8.2.1 Axillary Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+	+		+

Anatomy

Fibers originate from the 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 muscle 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. The superior lateral cutaneous nerve of the arm (or superior lateral brachial cutaneous nerve) is the continuation of the posterior cord of the axillary nerve, after it pierces the deep fascia (Fig. 8.1).

Symptoms

Weakness in elevation of upper arm.

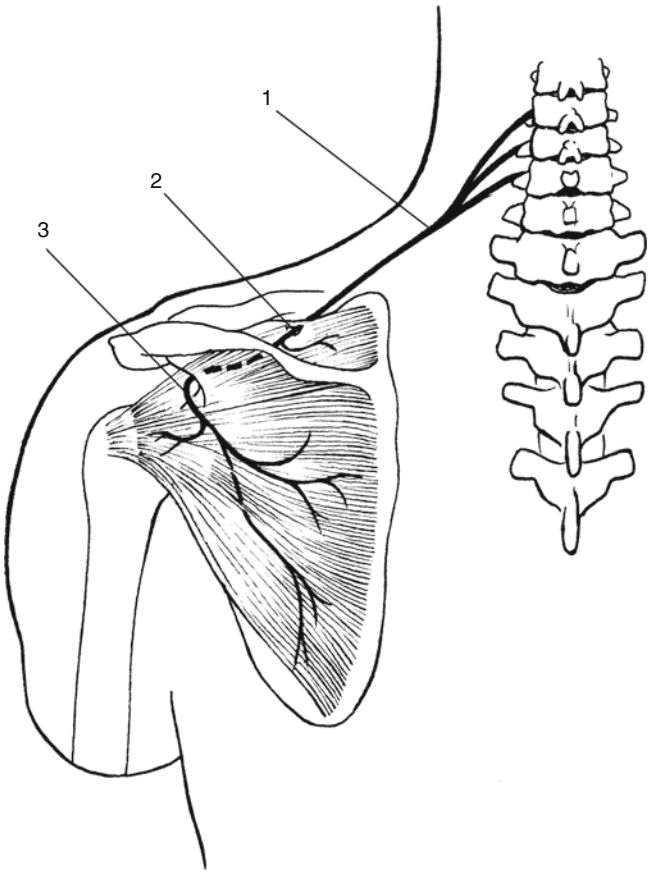


Fig. 8.1 *1* Axillary nerve. *2* Deltoid muscle. *3* Teres minor muscle

E.L. Feldman et al., *Atlas of Neuromuscular Diseases*,
DOI 10.1007/978-3-7091-1605-0_8, © Springer-Verlag Wien 2014

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). Compensatory abduction in axillary nerve palsy has been attributed to the action of the supraspinatus, biceps, coracobrachialis, and pectoralis major. During abduction in internal rotation, compensatory abduction is impaired, clearly indicating deltoid muscle dysfunction. Shoulder abduction is the most clinically relevant deficit as the other muscles are well compensated. Sensory: deficits are variable and may be absent, involving the lateral shoulder and upper arm. The superior lateral cutaneous nerve of the arm or superior lateral brachial cutaneous nerve is the continuation of the posterior cord of the axillary nerve, after it pierces the deep fascia.

Causes

Acute Trauma Anterior dislocation of the humeral head, fractures of the proximal humerus or scapula. Risk factors are the time between dislocation and reduction, presence of hematoma, and age. Birth trauma.

Blunt Trauma Heavy objects striking shoulder, contact sports, falls on shoulder.

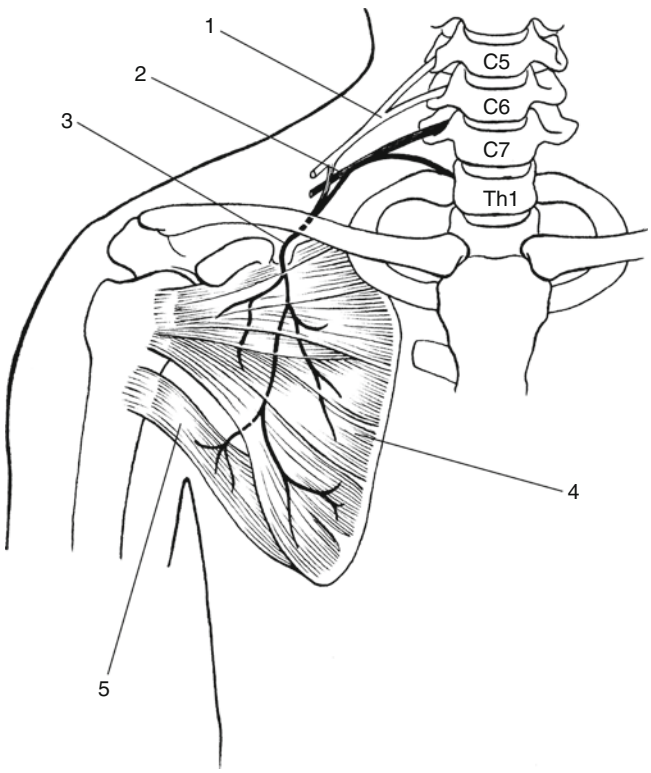


Fig. 8.2 Quadrilateral space. *1* Teres minor. *2* Teres major. *3* Medial and lateral-caput longum of triceps muscle. *4* Neck of humerus. *5* Circumflexor humeri posterior artery

Burner Syndrome Anterior nerve lesion associated with other nerve structures due to blows to upper shoulder.

Infections Measles.

Malpositioning Anesthesia, sleep.

Neuralgic Amyotrophy Usually associated with other nerves, particularly with the suprascapular nerve; rarely isolated.

Open Injury Arthroscopy, gunshot wounds, intramuscular injection.

Quadrilateral Space Syndrome Neurovascular compression syndrome, with pain, paresthesias (non-anatomic distribution throughout the limb), shoulder tenderness.

Stroke Associated with shoulder subluxation.

Surgical Interventions Humeral nailing.

Tumors Benign nerve sheath tumors, osteochondroma.

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.

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 show posterior humeral artery occlusion with shoulder abduction and external rotation.

Axillary Arteriogram, **Duplex Scan** Pseudoaneurysm.

Differential Diagnosis

Brachial plexus posterior cord lesion, radicular C5 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. *Operative*: Trauma: severe axonotmesis, neurotmesis. Extrinsic space-occupying lesions.

Prognosis

Good.

8.2.2 Musculocutaneous Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+	+		

Anatomy

Fibers stem from C5-C7 and travel via the lateral cord in the brachial plexus. The nerve innervates the coracobrachialis, biceps and brachialis muscles (Fig. 8.3). The sensory branch is the lateral antebrachial cutaneous nerve which innervates the radial aspect of the forearm: see antebrachial nerves.

Symptoms

Wasting of biceps muscle, difficulty flexing and supinating the elbow (rotating inward), reduced sensation along radial border of forearm. After lesion of the cutaneous nerve, paresthesia/causalgia (chronic compression or after venipuncture) is common. Local forearm pain can be caused by 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. Absence of biceps tendon reflex.

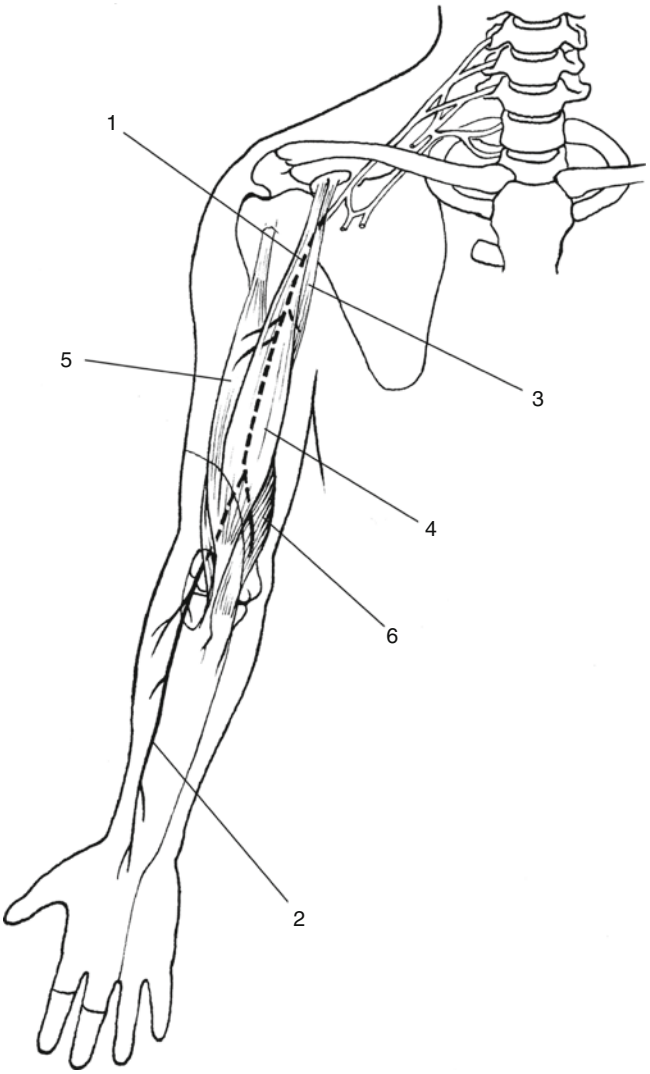


Fig. 8.3 *1* Musculocutaneus nerve. *2* Cutaneus antebrachii lateralis nerve. *3* Coracobrachialis muscle. *4* Short head of biceps muscle. *5* Long head of biceps muscle. *6* Brachialis muscle

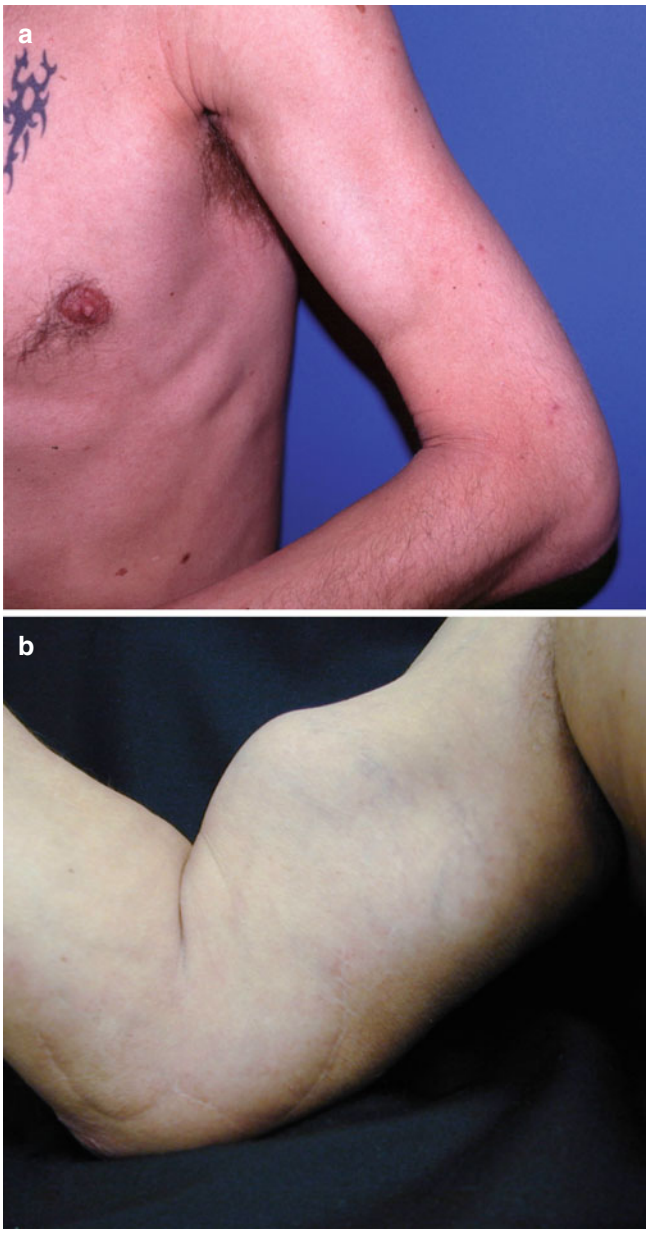


Fig. 8.4 (**a**) Atrophy of the biceps brachii in a patient with neuralgic shoulder amyotrophy. Note the absent relief of the muscle. (**b**) Biceps tendon rupture. Typical clinical manifestation with flexion of the elbow

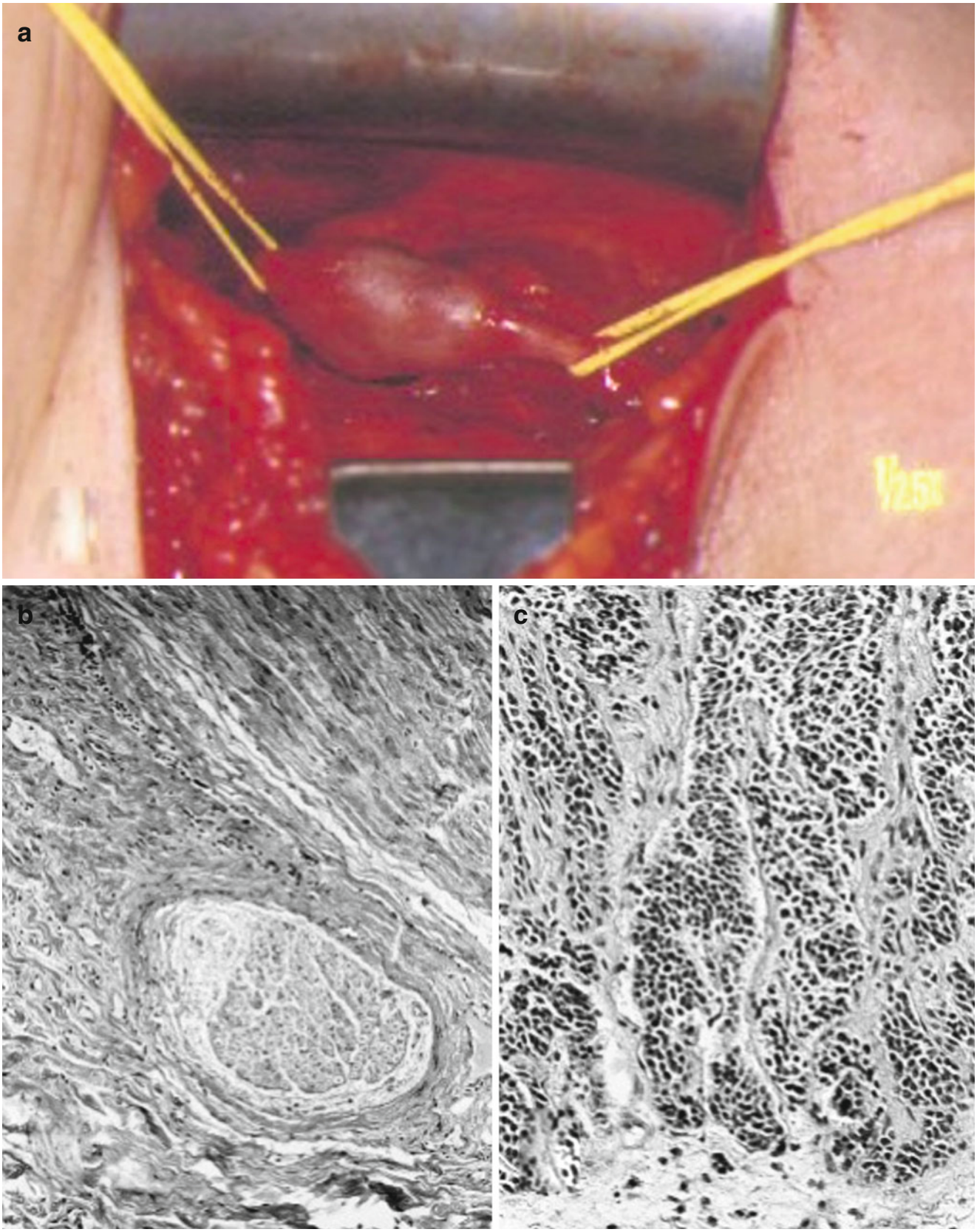


Fig. 8.5 Nerve metastasis of a carcinoid tumor in the musculocutaneous nerve. (**a**) Intraoperative site. (**b**) The nerve fascicles are closely connected to the tumor tissue. (**c**) Tumor strands within the nerve

Causes

Abnormal strenuous exercise (carpet carrier, weightlifter).

Entrapment Strap of a bag carried across the antecubital fossa, or entrapment while passing through coracobrachial muscle.

Iatrogenic Malpositioning during anesthesia, venipuncture (lateral antebrachial cutaneous nerve), tight bandages. Neuralgic amyotrophy (isolated and in combination).

Trauma Anterior dislocation of shoulder (frequently associated with axillary nerve), humerus fractures and dislocations, traumatic arm extension, missile injuries. Surgical interventions in the axilla: direct trauma; most common, especially proximal humerus fracture.

Tumors Proximal humeral osteochondroma, nerve tumors, false aneurysm, rarely nerve metastasis (Fig. 8.5).

Shoulder Dislocation, **Rotator Cuff Tear** Less common than axillary and suprascapular damage. During anesthesia. Rapid extension of forearm, strenuous exercise, lesion between Erb's point and axilla, entrapment: passing through coracobrachialis.

Nerve Grafting C5 fibers into the musculocutaneous nerve in brachial plexus lesions.

Diagnosis

NCV: CMAP and SNAP (compared to unaffected side), EMG, imaging of nerve. In cases of trauma and dislocation, the MR distribution of affected muscles is helpful.

Differential Diagnosis

C-6 radiculopathy, ruptured biceps tendon.

Therapy

For isolated complete trauma: consider surgery; otherwise, conservative.

Weakness or loss of biceps function is a concern in brachial plexus injury and causes severe functional deficits.

Prognosis

Usually good.

8.2.3 Nerves Around the Elbow

- Nerves passing the elbow
- Muscle
- Sensory and joint innervation
- Tennis elbow

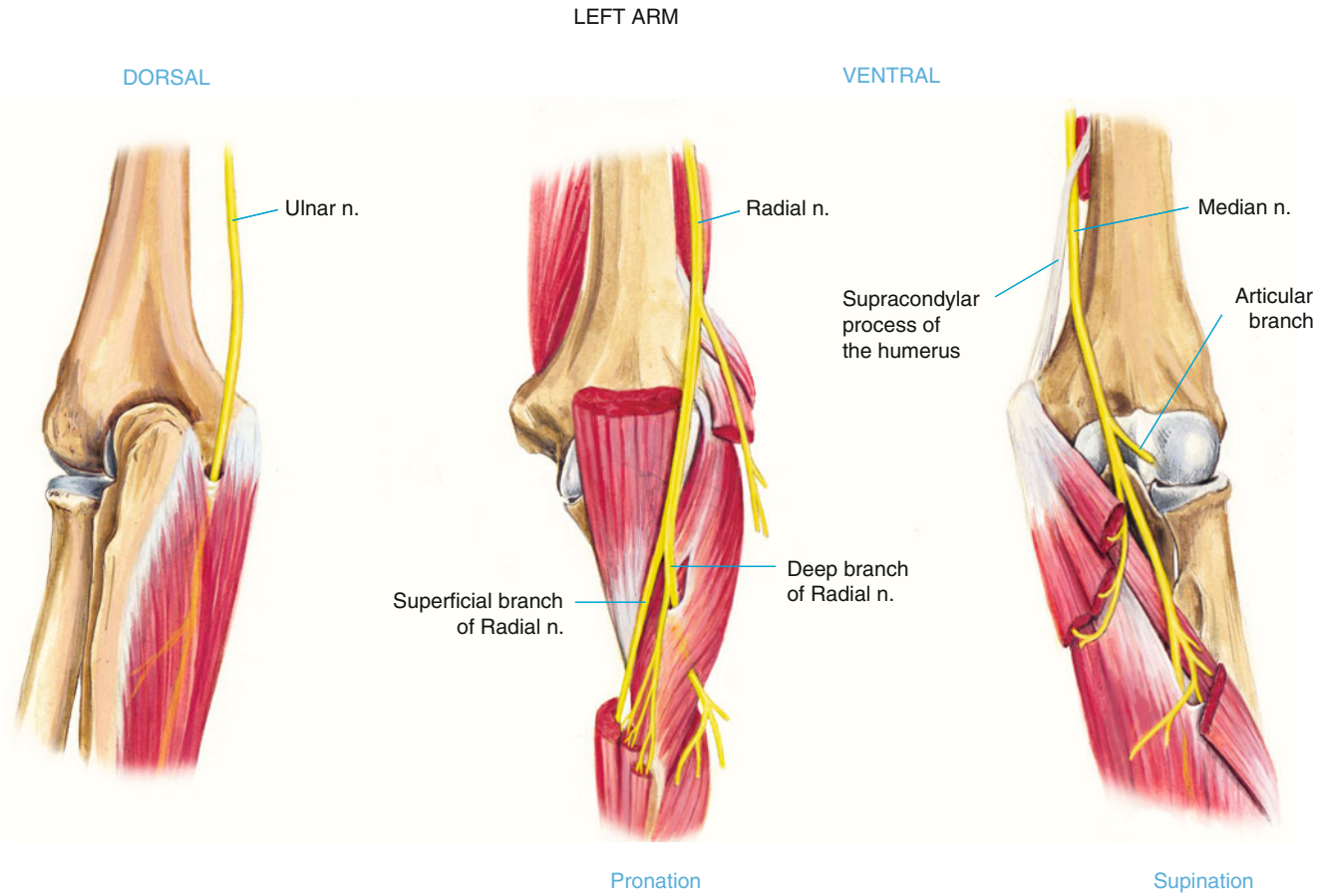


Fig. 8.6 Anatomy of the elbow. Demonstrating the position of the ulnar, radial and median nerve in relation to the joint

The elbow joint provides flexion of the elbow and also the more complex supination/pronation function of the lower arm, which is strongly associated with hand function. It can be damaged by trauma, or inflammatory and degenerative diseases.

Nerves Traversing

The elbow is passed by the median and ulnar nerve, which arrive in the medial bicipital sulcus and pass traverse the elbow in two distinct locations: the median nerve at the medial side of the biceps and the ulnar nerve passes through the ulnar groove. The radial nerve is located at the dorsal side of the elbow crossing the elbow capsule. In addition, the medial antebrachial nerve of the forearm (from the brachial plexus) and the lateral cutaneous nerve of the forearm, pass the joint.

Muscles

Muscles for flexion and extension of the elbow.

Sensory Innervation

Skin Medial and lateral antebrachial nerves, posterior antebrachial nerve, medial brachial, intercostobrachial nerve.

Joint Innervation The joint is mainly innervated by the ulnar nerve with 1–2 large branches. A branch comes from the median nerve and the radial nerve via the posterior interosseus nerve.

Lesions at the Elbow

Neurological Conditions Sulcus ulnaris syndrome, injection trauma.

Trauma Fractures.

"**Tennis Elbow**" Pain is at the lateral condyle. Passively stretching the extensor muscle tendons intensifies the pain. Usually the posterior interosseous nerve is not involved.

8.2.4 Median Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+	?	++	

Anatomy

Fibers for the median nerve come from the lateral and medial cord of 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 brachii tendon. It passes the cubital fossa with a motor branch to the brachial muscle. In the forearm, it is located 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 (Figs. 8.7 and 8.8). 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 (Fig. 8.9). The mnemonic "LOAF": Lumbricals 1 and 2, Opponens pollicis, Abductor pollicis brevis and Flexor pollicis brevis can be used. The sensory digital cutaneous branches to the common palmar digital branch and the proper palar digital branch of the median nerve, supplies the lateral (radial) three and half digits on the palmar side and the index, middle and ring fingers on the dorsum of the hand. The palmar cutaneous branch arises in the distal part of the forearm, and innervates the skin on the

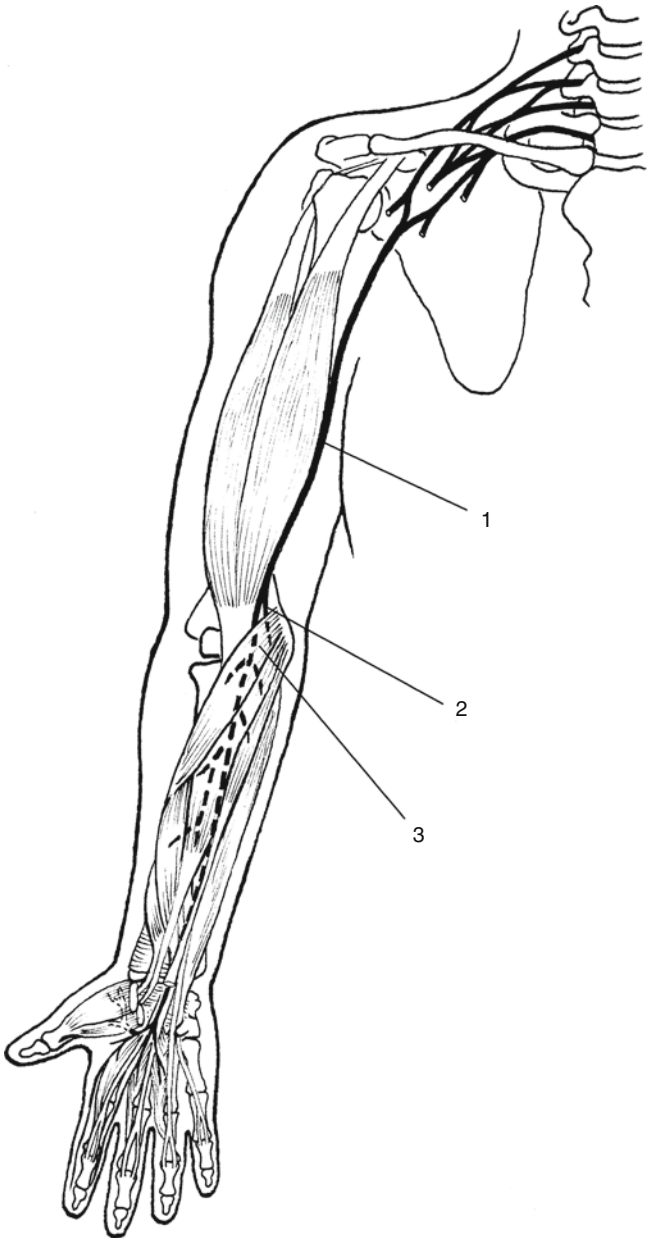


Fig. 8.7 *1* Median nerve. *2* Interosseus anterior nerve. *3* Pronator teres muscle

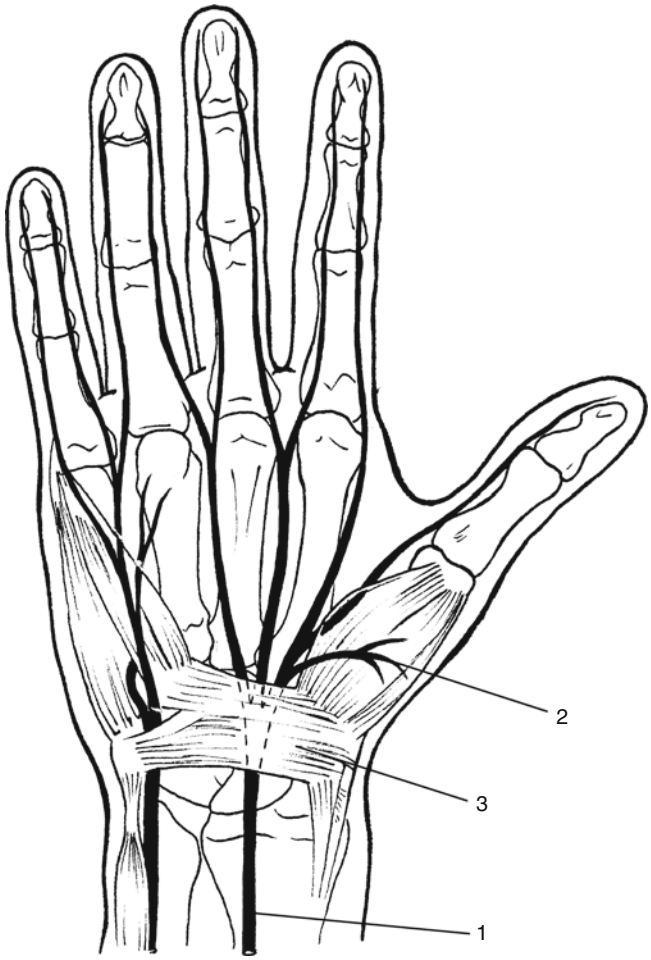


Fig. 8.8 *1* Median nerve. *2* Thenar branch. *3* Transversal carpal ligament

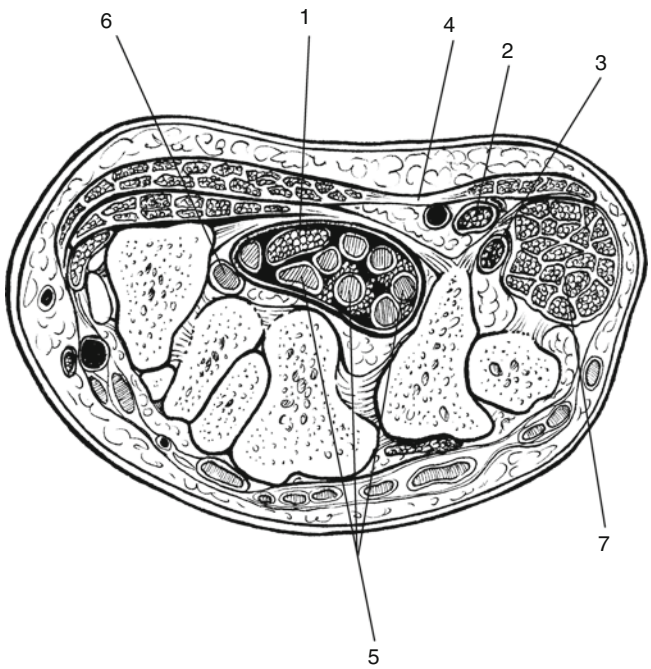


Fig. 8.9 Section at the distal end of the carpal tunnel. *1* Median nerve. *2* Ulnar nerve. *3* Deep ulnar nerve. *4* Flexor retinaculum. *5* Flexor tendons. *6* Flexor pollicis longus. *7* Abductor digiti minimi muscle

radial side of the palm (not the digits); it does not go through the carpal tunnel and can be used for electrophysiological tests.

Anomalies

Martin Gruber Anastomosis Nerve fibers cross from the median nerve to the ulnar nerve in the forearm. Variations include: median fibers crossing to the ulnar nerve; they then travel to the hand and supply muscles which are normally supplied by the median nerve. Similar to above, but the motor fibers supply both median and ulnar muscles. 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.

Ulnar-median Anastomosis Riche-Cannieu anastomosis, which is a sensory crossover of the palmar cutaneous branch.

Distal Nerve Bifurcation In a small number of individuals (5–10 %), the median nerve bifurcates in the forearm, proximal to the carpal tunnel.

Clinical Syndrome (Topographical Order)

Different levels of nerve lesions cause characteristic combinations of signs:

- Above the elbow: in addition to the core symptoms, also pronation and reduction of hand flexion at the wrist.
- Lesion of the anterior interosseus nerve causes the "anterior interosseus syndrome."
- The distal lesion in the carpal tunnel is listed below.
- A complete transsection of the nerve causes the median "claw hand" (Benedictine hand), due to paralysis of the median-innervated hand muscles, thumb and index finger.

Lesions in Shoulder, Axilla, Upper Arm Weakness in pronation (compensated partially by the brachioradialis muscle), wrist flexion (associated with ulnar deviation), reduced pronation, and loss of hand function (weak abduction and opposition of thumb, inability to flex distal interphalangeal joints of digits I-III, and of proximal joints of digits IV and V).

Elbow The nerve is rarely injured at this site. Venipuncture could be a cause.

Forearm Pronator teres syndrome: pain over the pronator teres, weakness of long flexor pollicis muscle, preservation of pronation, and sensory changes over the thenar eminence. Also, early fatigue of the forearm muscles is seen during enhanced motion. Positive Tinel's sign in forearm rather than at wrist. Anterior interosseus syndrome: synonymous with Kiloh-Nevin syndrome. Pain in the forearm, but normal sensation. Atrophy of forearm flexor muscles. Pinch sign: inability to form a circle with digits I and II. The flexor pollicis longus, flexor digitorum I and II, and the pronator quadratus muscle are involved. The "OK" sign cannot be made; patients make a triangle sign instead. Patients have difficulty

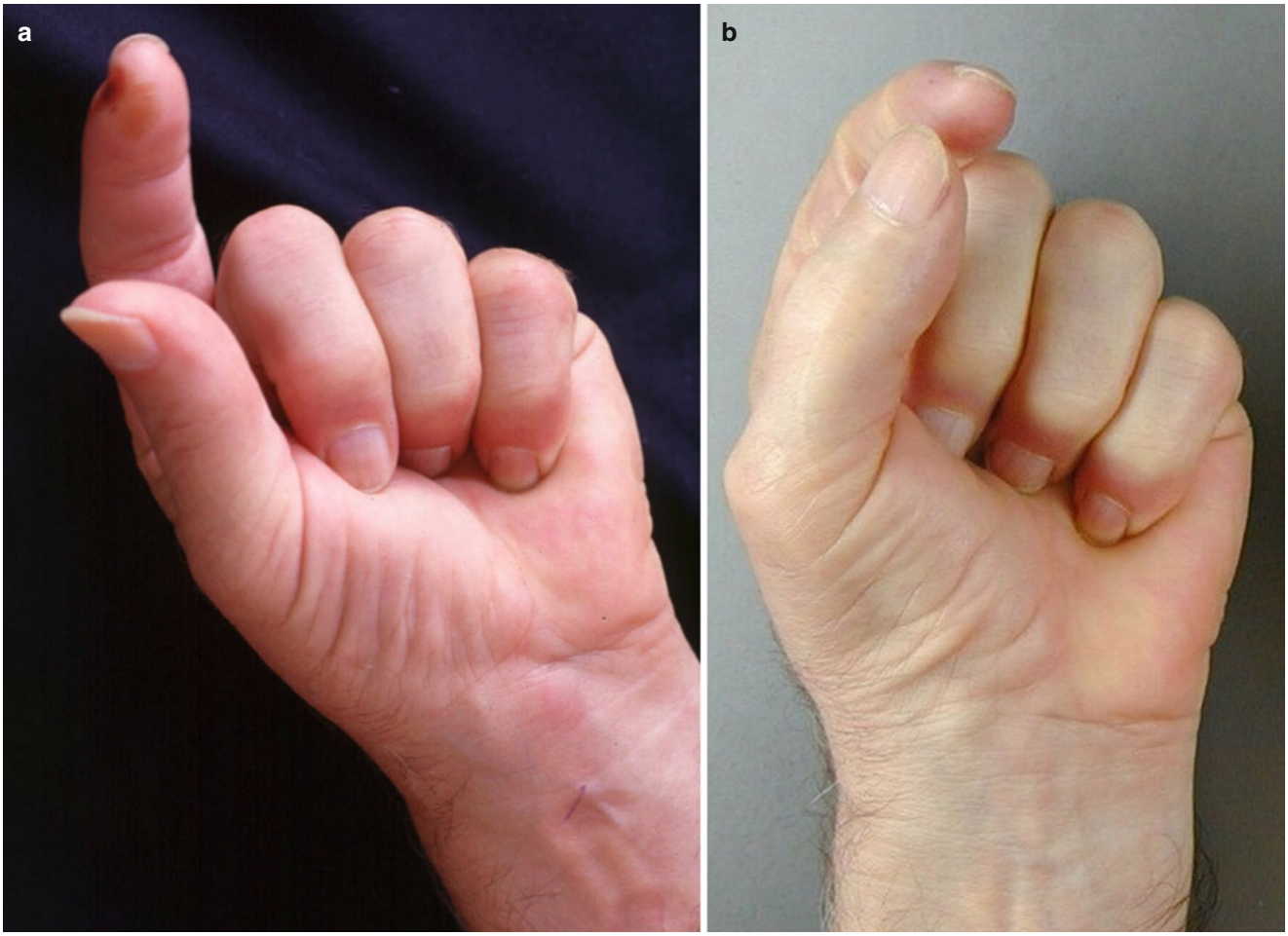


Fig. 8.10 Transsection of the median nerve and sural nerve interposition at a 24-month follow-up: (**a**) Orator's hand prior to surgery, (**b**) After 24 months, the long flexors of the thumb, and particularly the index finger, show increased mobility

picking up small items. Causes: (a) anterior intereosseus syndrome with forearm entrapment, (b) rarely part of "neuralgic amyotrophy."

Wrist Carpal tunnel syndrome (CTS): nocturnal paresthesias in the hand, may radiate up to shoulder. Paresthesias during daytime, particularly during the use of the hand with forced flexion 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 tip of the second and third fingers with a characteristic sparing of the palm (R. palm. of the median nerve). 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 or other nerve damage.

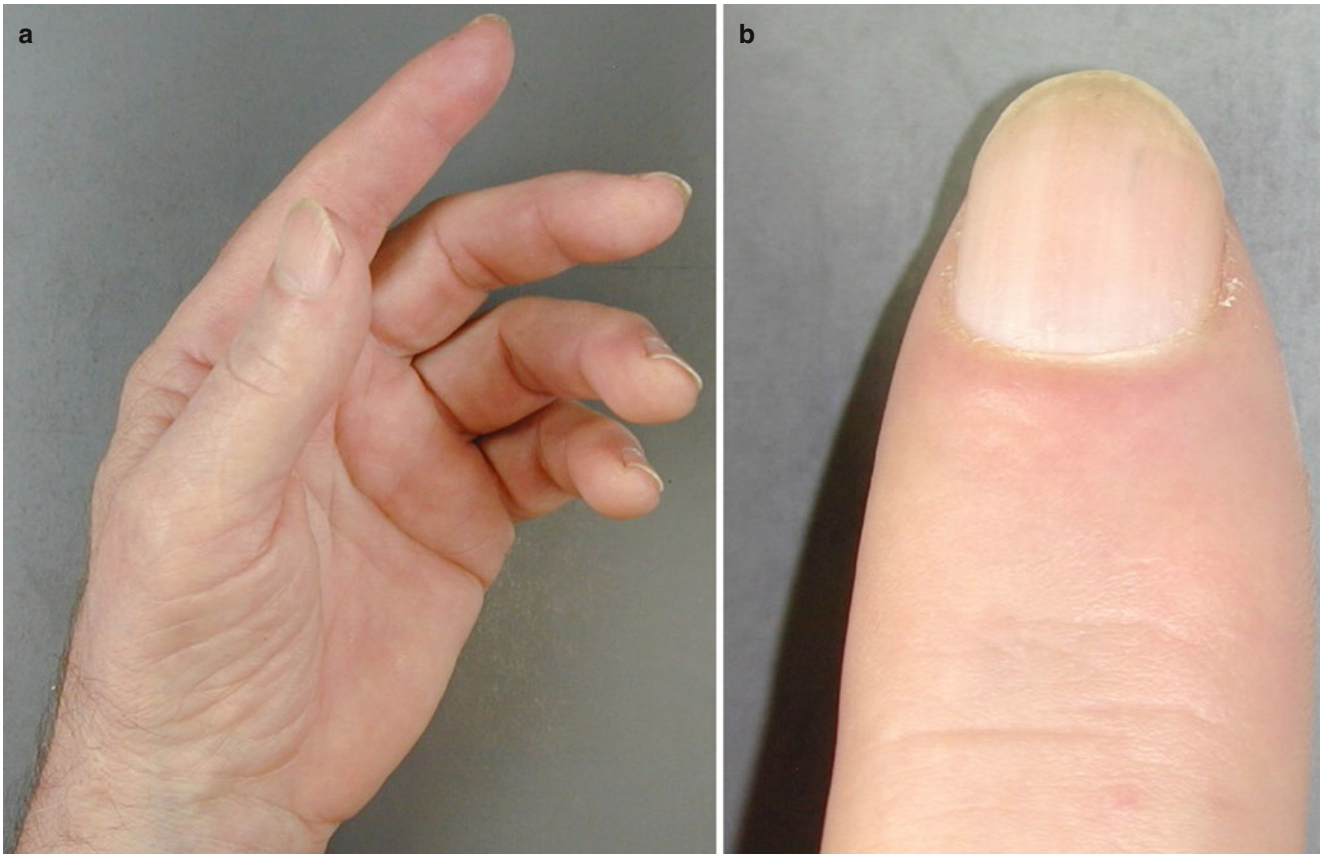


Fig. 8.11 Trophic changes after a median nerve transsection and nerve implantation. (**a**) Orator's hand, with thenar atrophy. (**b**) Glossy skin over index finger, and trophic changes of the nailbed

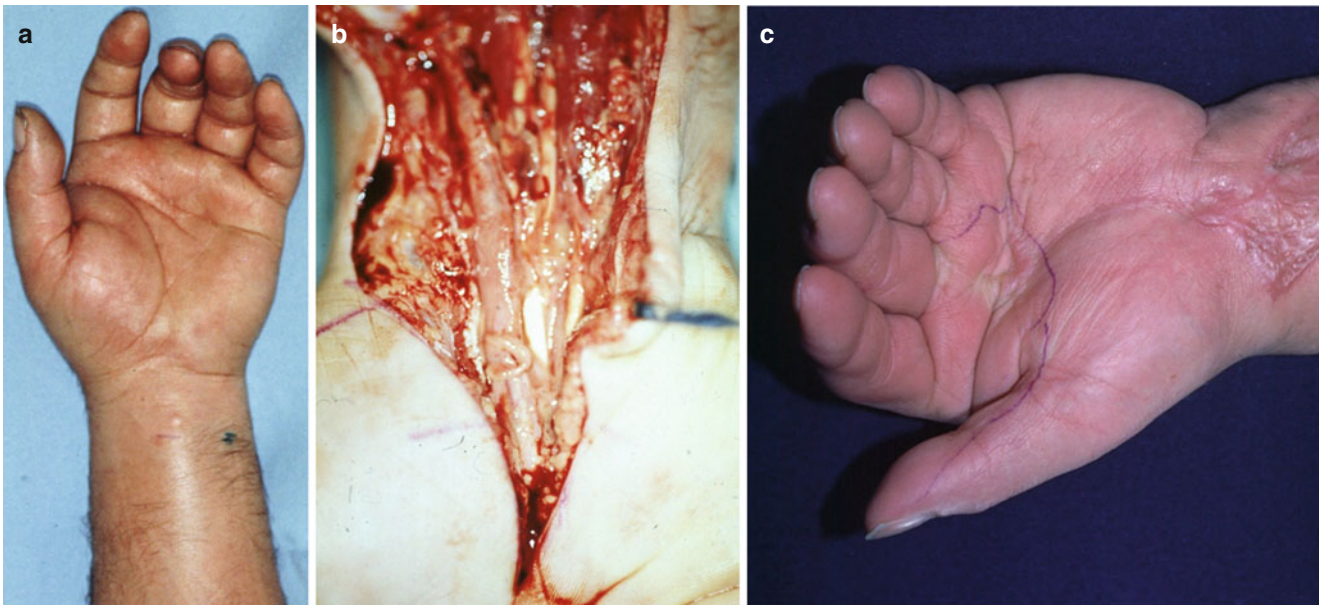


Fig. 8.12 Acute carpal tunnel syndrome: (**a**) Local painful swelling of the left volar wrist, sensory loss in median nerve distribution. (**b**) After confirmation with ultrasound, the median nerve was released. (**c**) Residual deficits were a sensory loss of the volar sides of the fingers (marked with a ball pen)

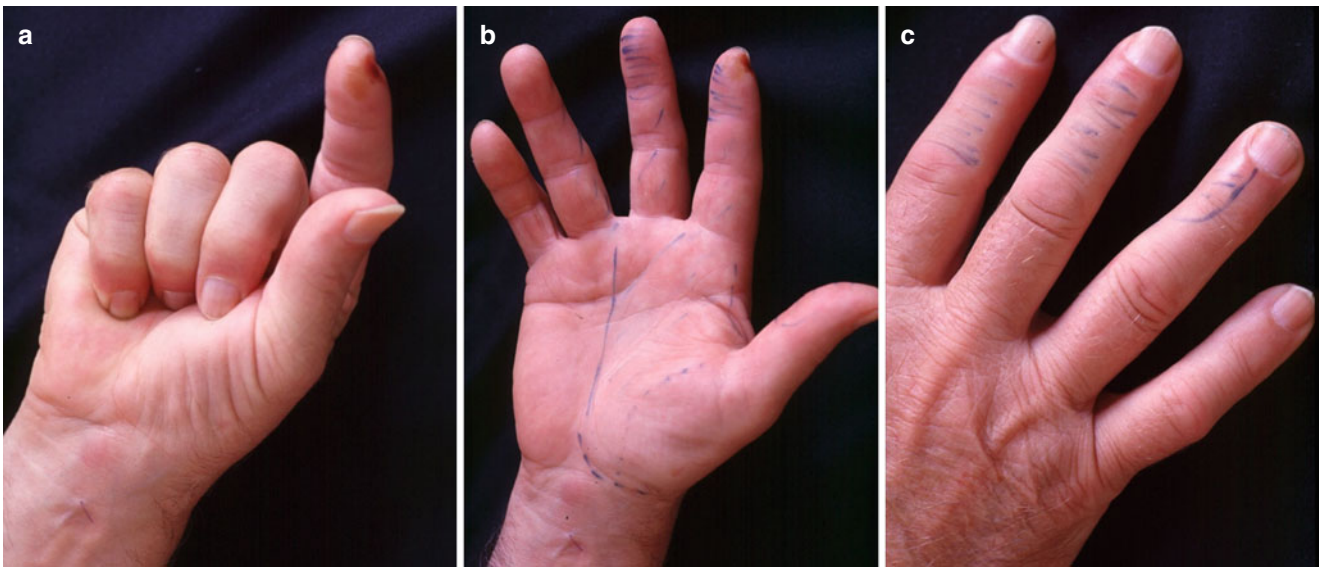


Fig. 8.13 Complete transsection of the median nerve at the upper arm: (**a**) Hand position trying to make a fist. Inability to flex index finger and thumb. Ulcer due to sensory loss at the tip of the index finger (orator's hand). (**b**) Sensory loss is accentuated at the tip of the fingers, but palm is also involved. (**c**) Dorsal view of the hand, delineating the sensory impairment

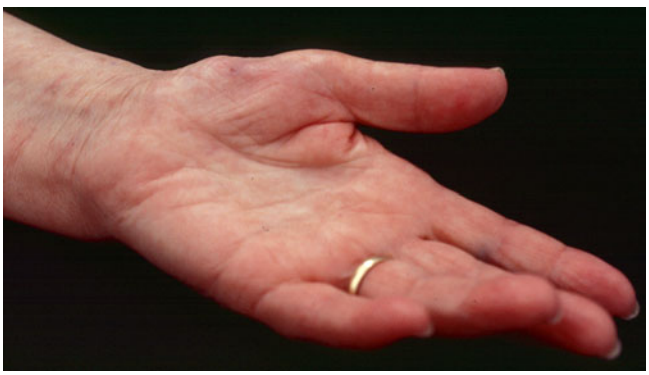


Fig. 8.14 Carpal tunnel syndrome: typical atrophy of the thenar eminence

Causes

Axillar Lesions Crutches, false aneurysm, missile injury, shoulder dislocation, sleep palsy, stab wounds

Upper Arm A-V fistula, compartment syndrome, fracture of the humerus, sleep, stab wounds, tourniquets

Elbow Angiography. Compression: bicipital aponeurosis, anomalous fibrous bands, pronator teres syndrome, elbow dislocations, humerus supracondylar fracture, medial epicondyle, supracondylar spurs, tumors and masses, IV injections. Pronator teres syndrome: anterior interosseus neuropathy, midshaft radius fractures, chronic compression, excessive muscular exercise

CTS Space reduction in carpal tunnel: exostoses, ganglia, gout, osteophytes, rheumatoid arthritis, tendons, thenar muscle hypertrophy, 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 condition): displaced physeal fractures of distal

Fig. 8.15 Neuropathic pain: This patient suffered from a complete median nerve transsection at the upper arm. Two years later his hand felt uncomfortably and painfully cold. Touch could elicit neuropathic pain. The patient wears a glove to avoid these sensations

radius and small bones of the carpus, decompression syndrome, hematoma, infection, RA exacerbation, wakeboard injury, wrist fracture and dislocation. Digital nerve entrapment: inflammation, trauma, tumor.

Diagnosis

Electrophysiology is the main tool for assessing CTS. In addition to the conventional motor and sensory NCV, several additional techniques, including measurements of other sensory nerves of the hand, inching, and mid-palmar sensory measurements, are performed by various laboratories. Practice guidelines have been published by the AANEM and the AAN. Imaging techniques, and in particular nerve ultrasound, are increasingly used. This is based on a direct measurement of the diameter of the nerve, and often also the swelling of the nerve proximally to the entrapment, as well as the mobility of the nerve and its relationship to the adjacent structures.

Laboratory: diabetes, hypothyroidism. Some types of paraproteinemia favor CTS; however, no standard routine tests are recommended.

Differential Diagnosis

Radicular lesions C6 and C7, thalamic infarcts, thoracic outlet syndrome.

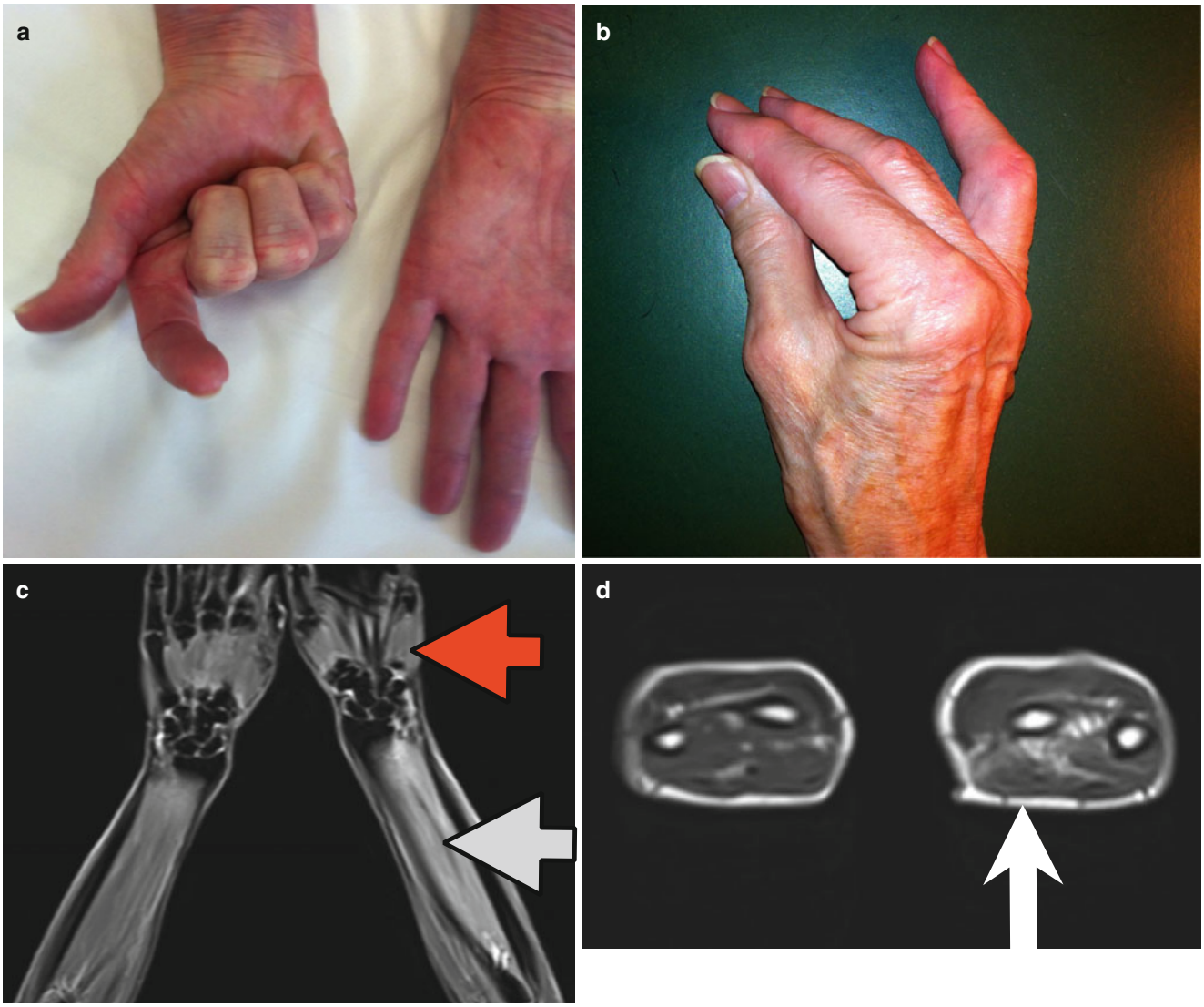


Fig. 8.16 Anterior interosseus syndrome. (**a**) Inability to flex digits I and II. (**b**) Inability to flex digits I and II as the patient attempts to pinch. (**c**) MR shows denervated muscles of forearm (*gray arrow*), with intact thenar muscles (*red arrow*). (**d**) MR cross section of forearm

Therapy

Depends on the etiology and electrophysiology, and is based on "conservative" treatment e.g., splinting at the wrist, "invasive treatment," e.g., local steroid applications, and surgical release.

Conservative Wrist splint (brace) at night. Note: ultrasound of the wrist, magnet therapy, laser acupuncture, exercise or chiropractic care and ergonomic positioning did not show symptom relief when compared to placebo or control.

Local Steroids Local steroid injections are considered effective in CTS, at least 1 month after the injection compared to placebo. Two local corticosteroid injections do not provide significant added clinical benefits compared to one injection.

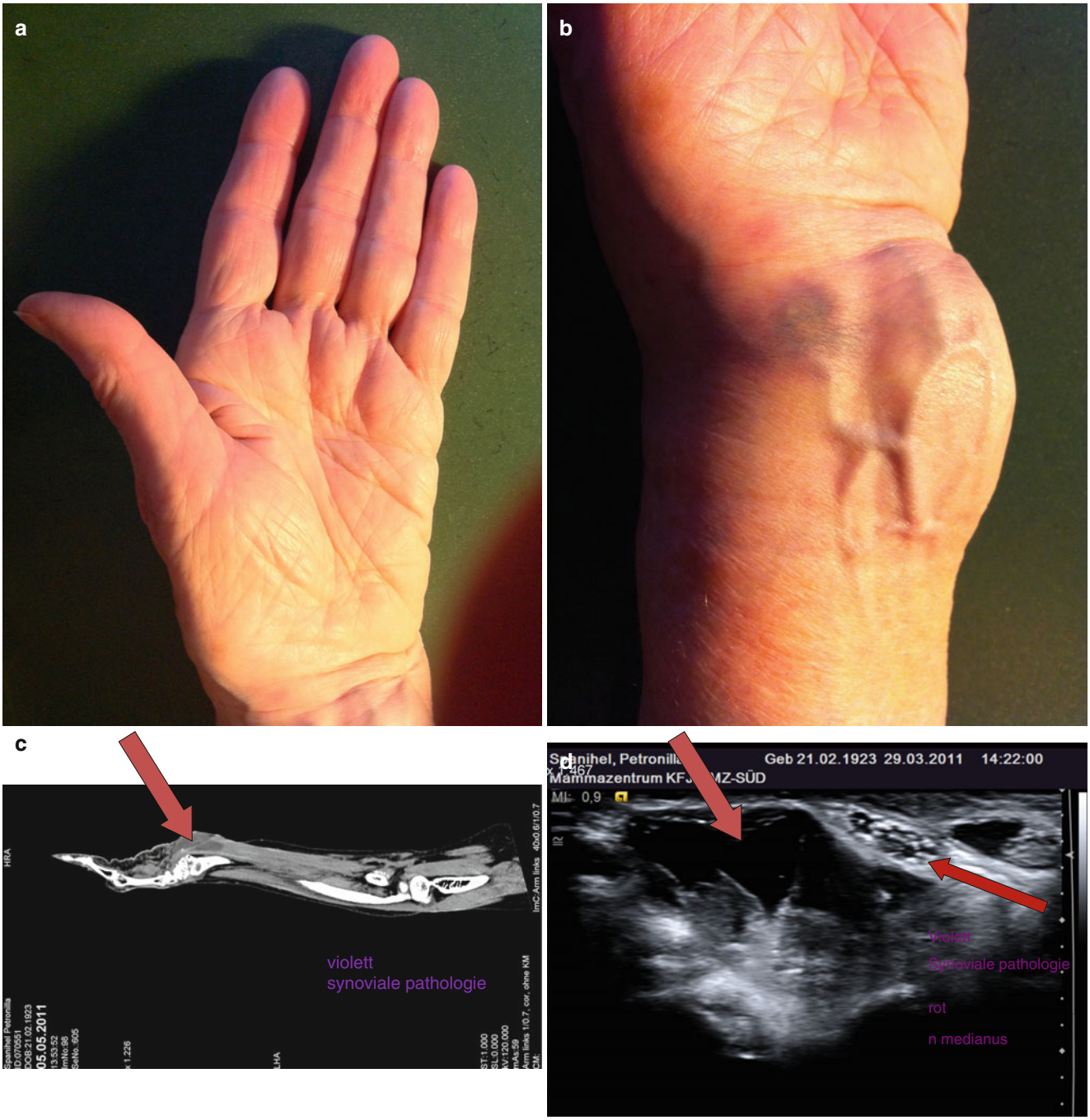


Fig. 8.17 Median nerve lesion mimicking carpal tunnel syndrome. The patient presented with symptoms of carpal tunnel syndrome; however, the sensibility of the palm was also affected. There was a marked atrophy of the thenar (**a**), proximal to the carpal tunnel, a large cystic non-pulsating tumor was found (**b**). CT reconstruction of the forearm and hand (MRI could not be done) showed a cystic lesion (**c**), which in US could show a compression of the median nerve by the cyst, proximal to the carpal tunnel (**d**), *red arrow*

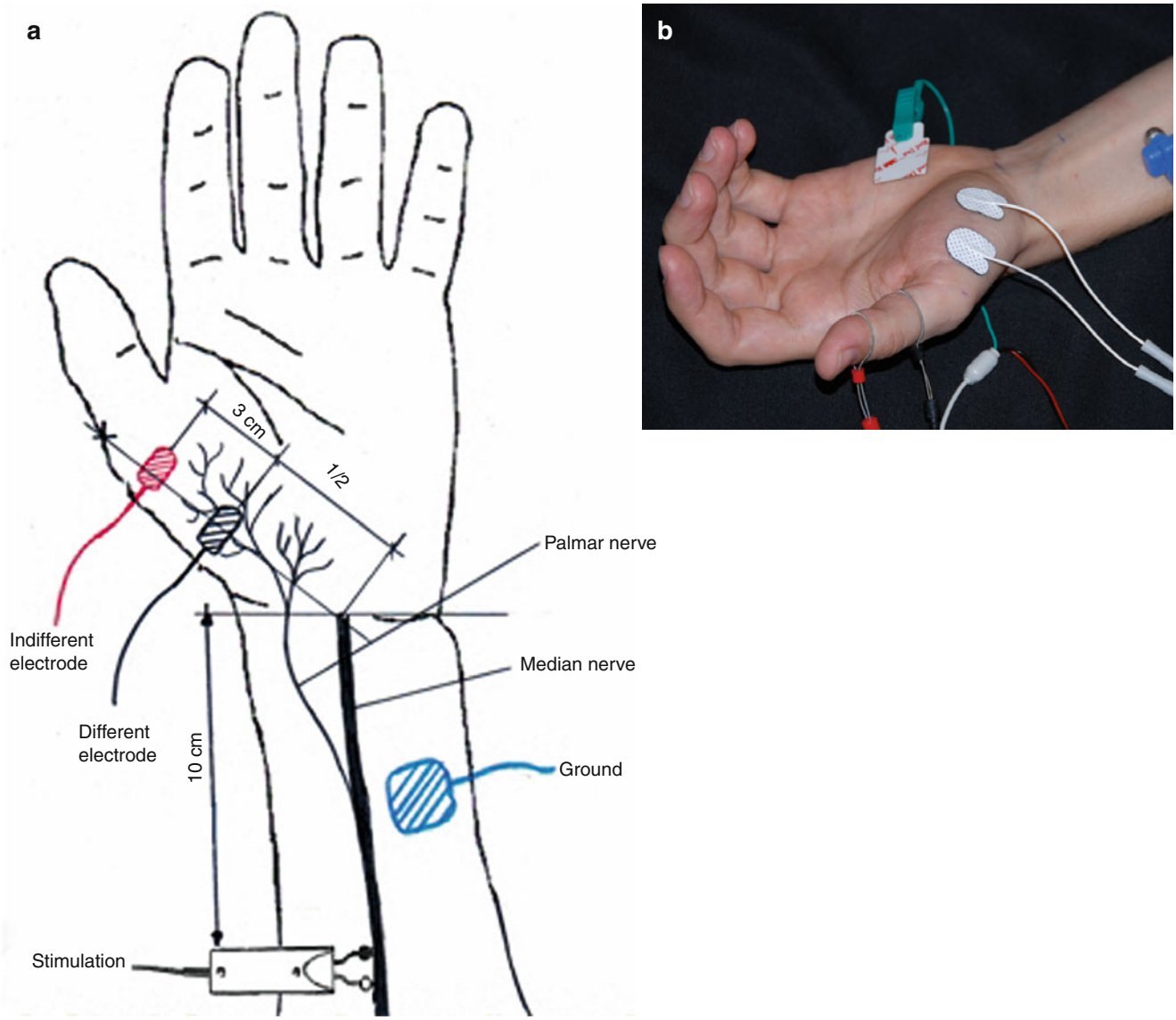


Fig. 8.18 Median nerve-palmar branch: This branch does not pass through the carpal tunnel and can be used in the diagnosis of carpal tunnel syndrome. (**a**) Cartoon shows the anatomical position of the nerve, and the position of electrodes. (**b**) The pick-up electrodes are placed over the thenar eminence

Median nerve changes following local steroid treatment have been described (Fig. 8.19).

Surgery Surgical treatment of carpal tunnel syndrome relieves symptoms significantly better than splinting. Further research is needed to discover whether this conclusion applies to people with mild symptoms and whether surgical treatment is better than steroid injections. However, the current practice of a trial of conservative management with surgical release for severe or persistent symptoms is evidence-based.

Acute CTS (**Rare**) In acute CTS, CTS with motor impairment, or persistent entrapment despite conservative therapy: operative split of carpi transverse, either via endoscopic or open technique.

8.2.5 Ulnar Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

Anatomy

The nerve fibers arise from C8 and T1, and pass through the lower trunk and medial cord of the brachial plexus (Fig. 8.20). The nerve continues along the humerus and the ulnar condylar groove (the humeroulnar arcade). The nerve enters the ventral compartment of the forearm between the two heads of the flexor carpi ulnaris (Fig. 8.21). Then the nerve continues with the ulnar artery and continues below the flexor carpi

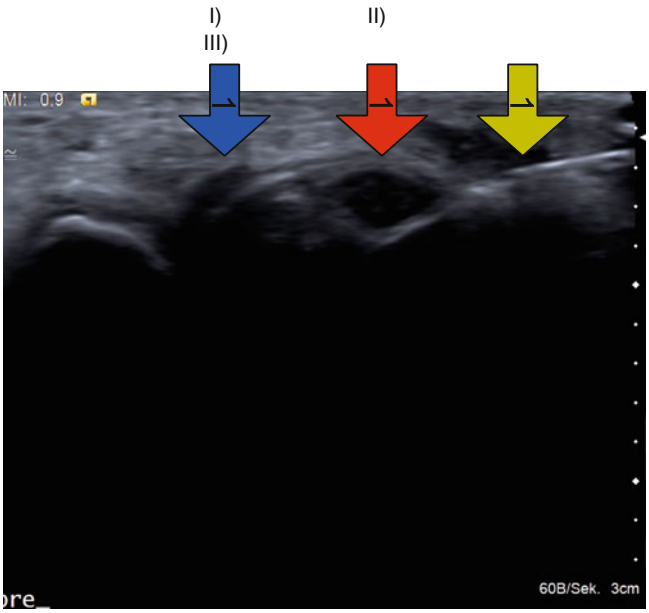


Fig. 8.19 Median nerve, local intervention: This image shows a local steroid application in a case of CTS recorded by ultrasound. *I* Retinaculum flexorum (*blue arrow*), *II* median nerve (*red arrow*), *III* intervention needle next to the median nerve (*yellow arrow*)

ulnaris muscle. Motor branches innervate the flexor carpi ulnaris, flexor digitorum profundus, most of the hand muscles (first dorsal interosseus, adductor pollicis, abductor digiti minimi, flexor pollicis brevis, and lumbricals 3–4). At the wrist, the nerve passes through Guyon's canal, then divides into superficial and deep terminal branches. The deep branch innervates the opponens digiti muscle and gives a branch to the remaining hypothenar muscles (Fig. 8.22). In the palm, it innervates all interossei and the third and fourth lumbrical muscles. In the thenar eminence, it supplies the adductor pollicis and parts of the flexor pollicis brevis. Sensory branches (superficial terminal, palmar cutaneous, dorsal cutaneous nerves) innervate the hand. The palmar branch of the ulnar nerve innervates the proximal part of the thenar eminence and leaves the nerve trunk in the midforearm (without passing through Guyon's canal). As a variation, an "all ulnar hand" has been described.

Symptoms

Lesions at the Elbow Medial elbow pain or aching is common at lesions at the elbow. Sometimes pain radiates along the medial forearm (numbness of the medial forearm; however, this indicates a more proximal lesion as C8/T1 or a lesion of the lower trunk of the brachial plexus). Numbness and tingling (exacerbated by arm use) in the fingers. Pain is restricted to the hypothenar region of the palm. Also loss of dexterity and control of the little finger. In comparison with median nerve lesions, hand function is less compromised.

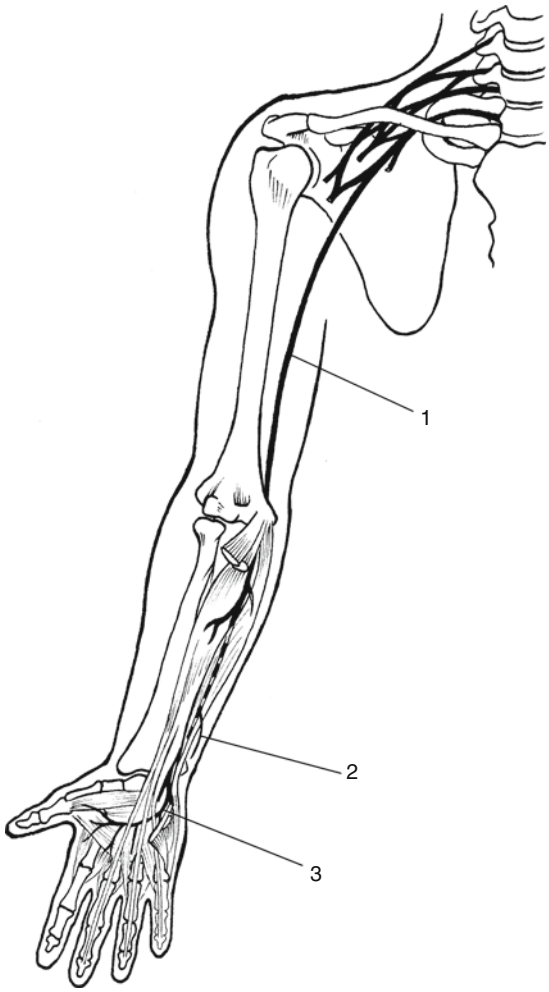


Fig. 8.20 *1* Ulnar nerve. *2* Dorsal cutaneous branch. *3* Deep motor branch

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 digits.

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), secondary to weakness of the ulnar innervated forearm muscles. Full-blown ulnar lesion results in claw deformity of the hand. Tinel's sign may be elicited by palpation of the ulnar nerve at the elbow. Rarely, nerve thickening can be palpated (Fig. 8.23).

Lesions at the Wrist Several classifications are available. Usually, four types are described:

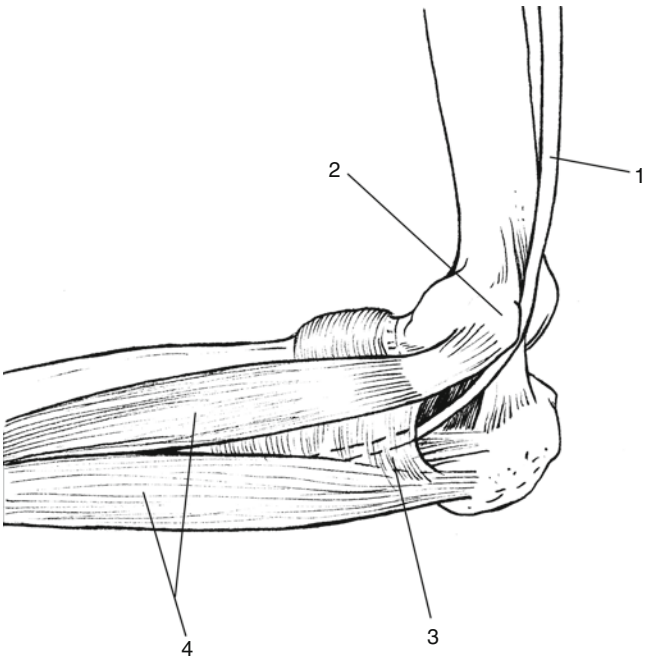


Fig. 8.21 Medial epicondyle and cubital tunnel. *1* Right ulnar nerve. *2* Medial epicondyle. *3* Aponeurosis. *4* Flexor carpi ulnaris

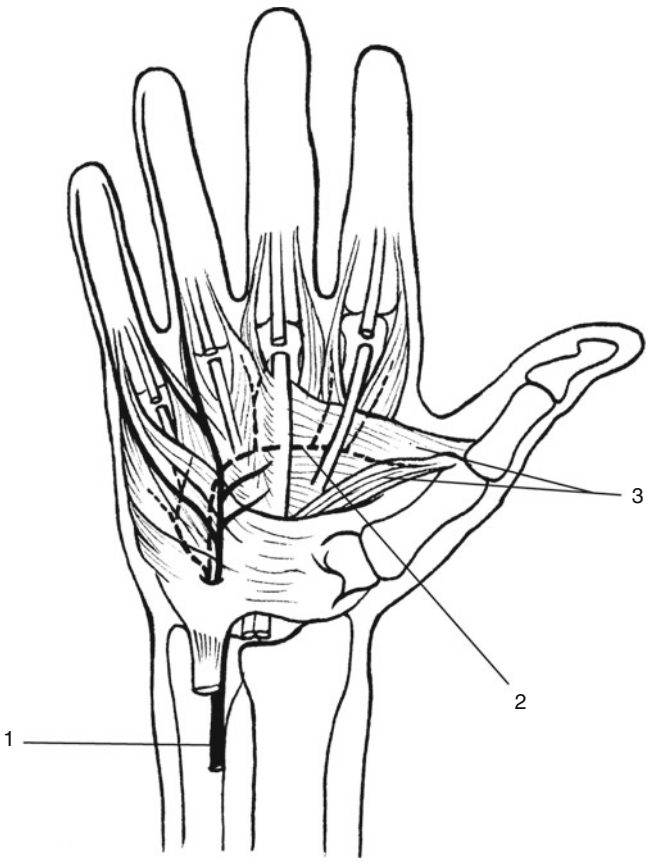


Fig. 8.22 *1* Ulnar nerve. *2* Deep terminal branch. *3* Hypothenar muscles

- Distal ulnar nerve lesion proximal to Guyon's canal: all small hand muscles are involved with sensory involvement of the terminal sensory branches, except for the dorsal ulnar cutaneous branch.
- Lesion of the deep terminal motor branch proximal to the branches supplying the hypothenar muscles.
- Injury of the deep motor branch distal to the hypothenar muscles (no sensory loss).
- Superficial terminal sensory branch results in sensory loss but preserved motor function.

Causes

Axilla and Upper Arm (**rare**) 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: ganglioid, sesamoid bone, recurrent subluxation, repetitive flexion, supracondylar spurs, trauma (Fig. 8.24).

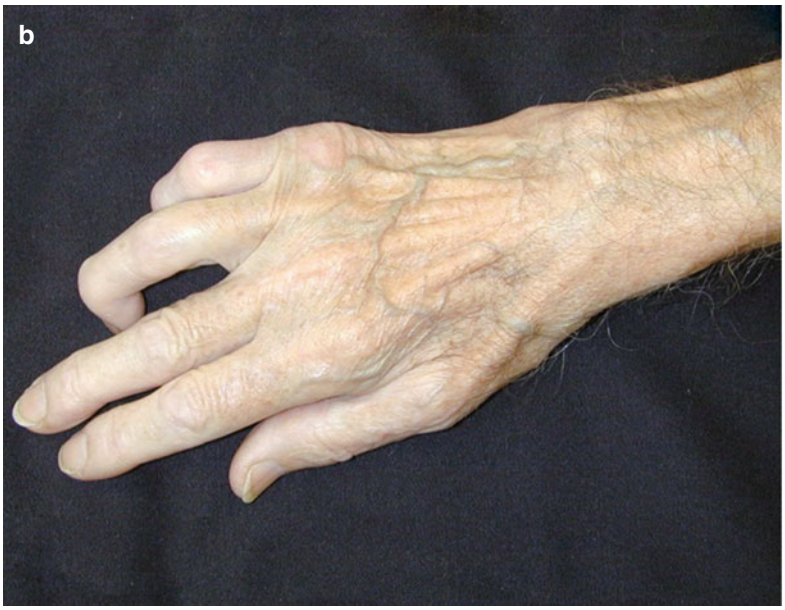
Forearm Hypertrophic flexor carpi ulnaris.

Wrist and Hand Forced use: bicycle (Loge de Guyon's canal). Pressure: ganglion, pisohamate ligament, injuries, lacerations. Double crush: also the double crush hypothesis has been applied in ulnar nerve damage, but is not universally accepted. Ulnar neuropathy at the elbow is the second most frequently diagnosed focal neuropathy in Europe.

Diagnosis

Clinical Tests Tinel's, elbow flexion, compression, combined elbow flexion and pressure, and palpation of thickened nerve are not very useful for diagnosis.

Nerve Conduction Studies Motor: fractionated measurements, lower arm and sulcus, where an "inching" technique is useful. Sensory: distal sensory NCV can indicate an ulnar nerve lesion albeit with an undetermined location. Direct sensory nerve conduction measurements in the sulcus region are time-consuming and potentially difficult to interpret, due to the short distances and the difficulty in measuring the length of the nerve across the sulcus. Measurement of the dorsal sensory ramus is helpful in distinguishing a proximal from a distal nerve lesion. Several additional techniques as a comparison of motor latency between the median and ulnar nerve to the 2nd and 3rd interosseus, or the sensory measurement to the 4th digit, can be easily applied. EMG: carpi flexor ulnaris muscle: EMG lesion indicates a proximal nerve lesion. EMG of the abductor digit V and interosseus I can indicate the stage of axonal lesion (normal in neurapraxia, denervating, reinnervating, chronic neurogenic).



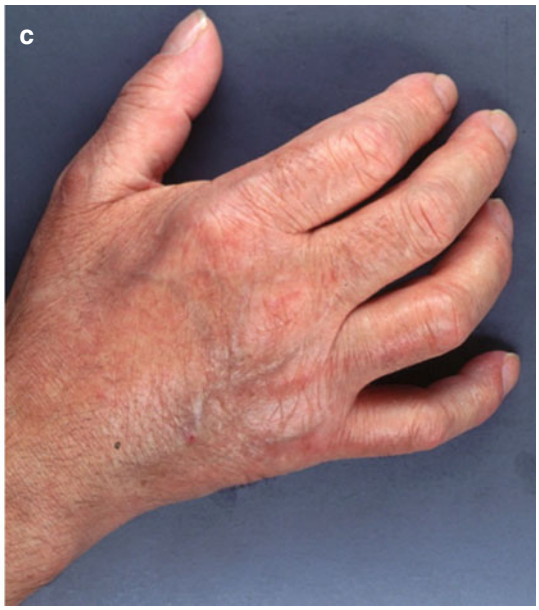


Fig. 8.23 (**a**) Ulnar nerve lesion: complete transsection at lower arm level by a glass pane. Note the typically flexed fourth and fifth fingers. (**b**) Distal ulnar nerve lesion with a 50-year duration. (**c**) Distal ulnar lesion, after the exit of the branch to the hypothenar. Note the atrophy of the interosseus I. (**d**) Long-lasting ulnar nerve palsy. Atrophy of interosseus I and other interossei

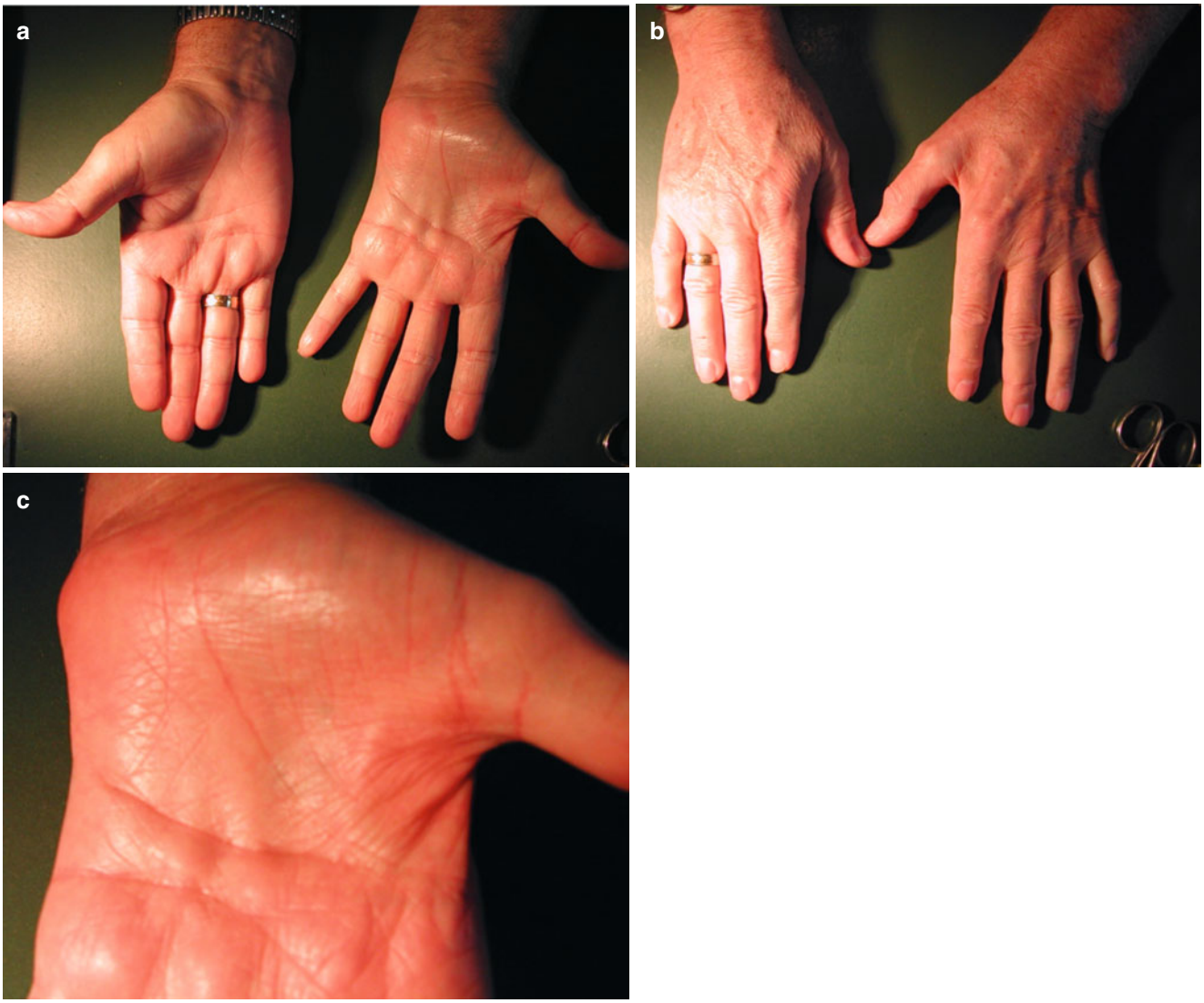


Fig. 8.24 Traumatic ulnar nerve lesion at the elbow, during intensive care treatment and malpositioning: (**a**) Atrophy of the small hand muscles with protruding flexor tendons and preserved thenar, and atrophied opponens muscles. (**b**) Dorsal view with interosseus atrophy. (**c**) Unusual atrophy of the opponens muscles, leaving a groove over the hypothenar

Imaging *US*: Ultrasound of the nerve at the elbow is a useful and simple-to-perform technique (Fig. 8.25). Compression of the nerve and proximal enlargement can be visualized. Distal ulnar nerve lesions are more difficult to detect with ultrasound, but can be identified with MR.

Differential Diagnosis

ALS, brachial plexus-lower trunk (additional involvement of N. antebrach. cut. med.), cervical myelopathy, monomelic atrophy, multifocal motor neuropathy, C8 lesion radiculopathy, split hand – indicating motor neuron disease (Fig. 8.26), syringomyelia (Fig. 8.27).

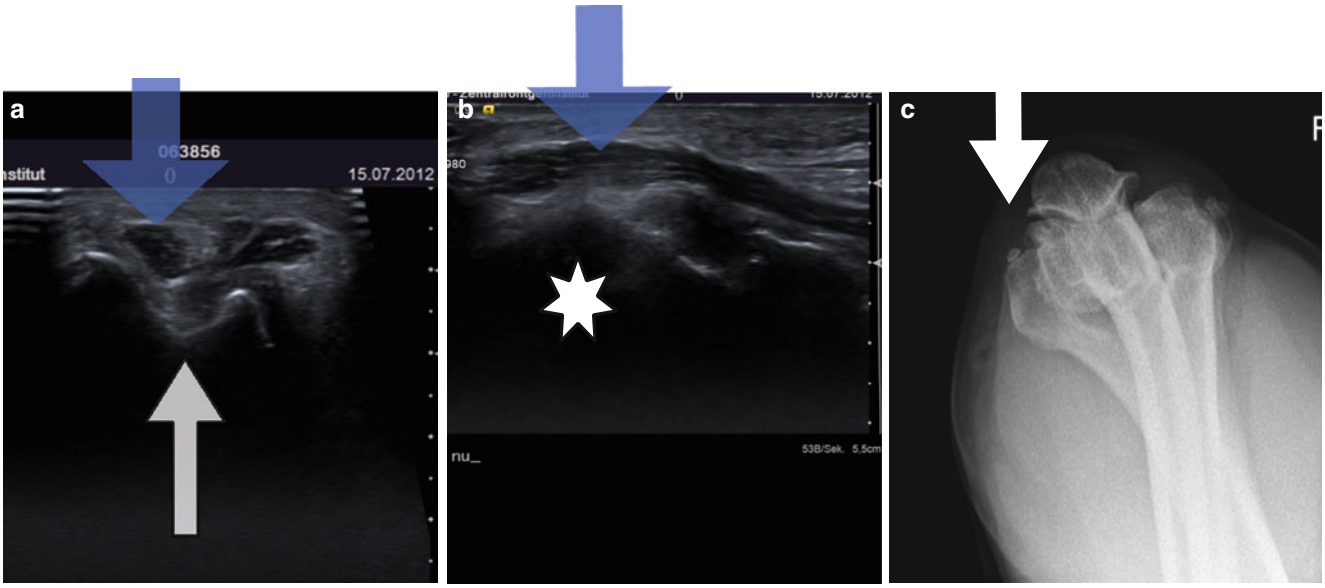


Fig. 8.25 Ulnar nerve in the sulcus ulnaris – ultrasound. The ulnar nerve can be seen in US in the ulnar sulcus, and can give additional information to NCV studies. The transverse section (**a**) shows the ulnar nerve (*blue arrow*) in relation to the ulnar sulcus (*white arrow*). (**b**) Longitudinal nerve section (*blue arrow*) and the humerus (*asterisk*). (**c**) A conventional x-ray shows the ulnar sulcus (*white arrow*)

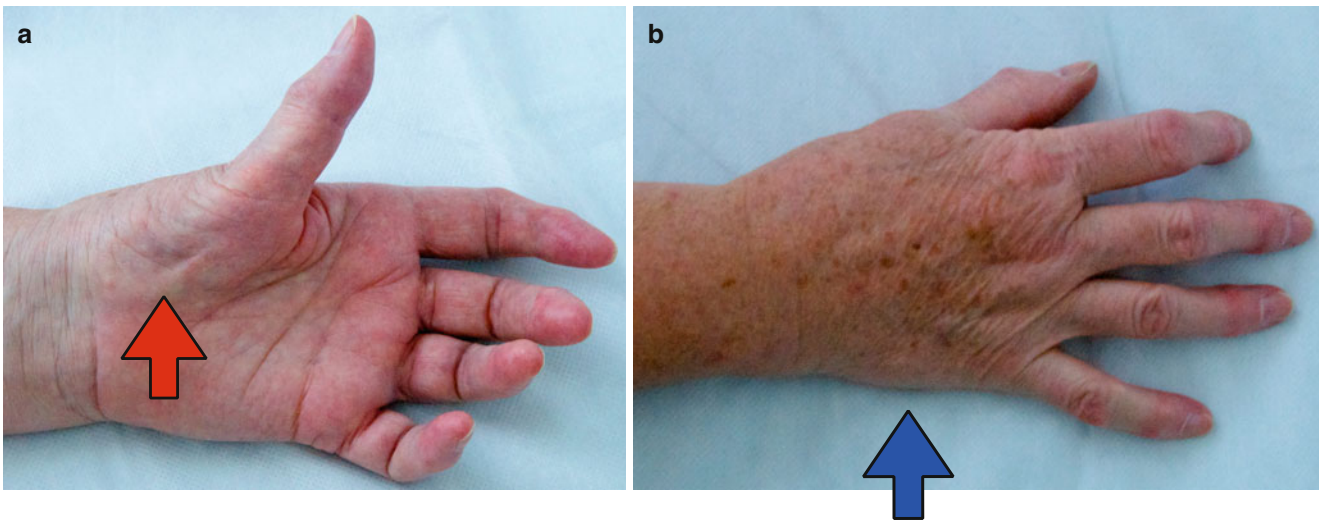


Fig. 8.26 Split hand. In motor neuron disease, (**a**) often a difference of atrophy (**b**) between thenar muscles, and relatively preserved hypothenar muscles is noted. This is called the "split hand" syndrome. *Red arrow*: thenar atrophy; *blue arrow*: relatively preserved hypothenar

Therapy

Therapy of ulnar nerve lesions is controversial. Conservative therapy is indicated if there is no detectable structural lesion and mild abnormality (clumsiness, no atrophy), or in some cases moderate abnormality (intermittent or constant paresthesias), mild atrophy, weakness (4+).

Conservative Therapy Elbow splint, physical therapy, rehabilitation. Specific conservative management also consists of avoiding leaning on or flexing the elbow.

Surgery: Indicated for severe abnormality (constant paresthesias, atrophy, weakness > 4). Severe weakness, persistent

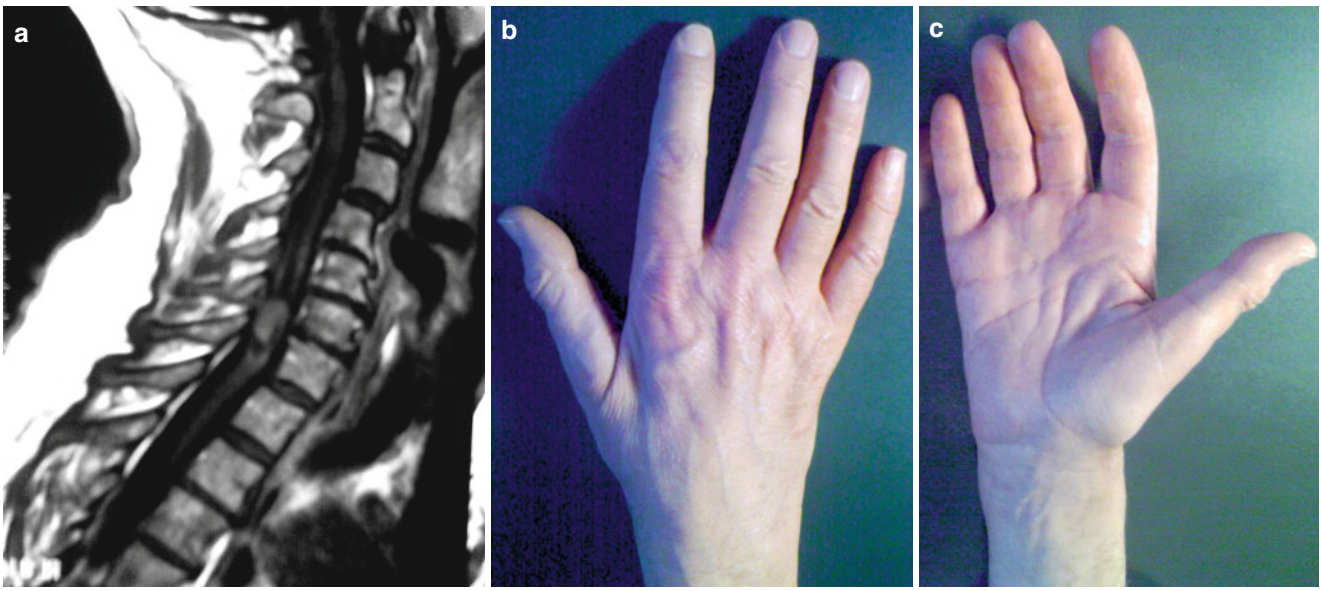


Fig. 8.27 (**a**) Spinal tumor causing hand atrophy. (**b**) Marked atrophy of the first interosseus and other interossei. (**c**) Volar aspect of the hand appears normal

sensory loss, often acute or subacute onset and evidence of axonal injury support. This may not be true for elderly patients as well as patients who had the lesion for 1–2 years. Simple decompression surgery and/or decompression with transposition. Decompression with transposition can result in more wound infections.

Prognosis

The natural history is not well known, which can be understood considering the complexity of different types of lesions and their severities. Milder forms often improve with conservative treatment. Patients with severe weakness, atrophy, or persistent sensory loss and axonal injury documented by NCV/EMG may benefit from surgery. Traumatic cases of ulnar nerve injury at the elbow, arm or hand, may be considered for surgery.

8.2.6 Radial Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		MRI, US	

Anatomy

Fibers from C5-T1 contribute to the radial nerve. They travel through the brachial plexus. The fibers from the posterior cord, which is formed from the three posterior divisions of the trunks (C5-T1), form the radial nerve (Fig. 8.28). The radial nerve travels though the brachio-axillary angle, then along the spiral groove of the humerus, continuing in the anterior compartment of the arm. At the elbow joint, it has two branches: the posterior interosseus nerve, which travels along the radius and innervates the supinator muscle; 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 nerve of the arm, which communicates with the intercostobrachial nerve. The other sensory branches are the posterior antebrachial cutaneous and superficial radial nerve.

Clinical Syndrome

Symptoms and causes (according to topographical aspects): the radial nerve can be damaged all the way from the axilla into its distal branch. One of the main clinical hallmarks of proximal lesions is wrist drop, which is caused by weakness of the extensor muscles (Figs. 8.29 and 8.30). However, when the wrist and metacarpophalangeal joints are passively extended, patients with radial neuropathy can activate median and ulnar-innervated lumbricals, thereby extending their interphalangeal joints. Wrist extension also improves interosseus muscle strength. This is practically applied in patients with radial nerve palsy when using splints.

Axilla

Radial nerve compression can occur proximally due to inappropriate crutch pressure at the axilla, prolonged tourniquet application, frequent automated blood pressure cuff inflation, or poor arm position during anesthesia. Radial nerve compression at the axilla or arm may be associated with

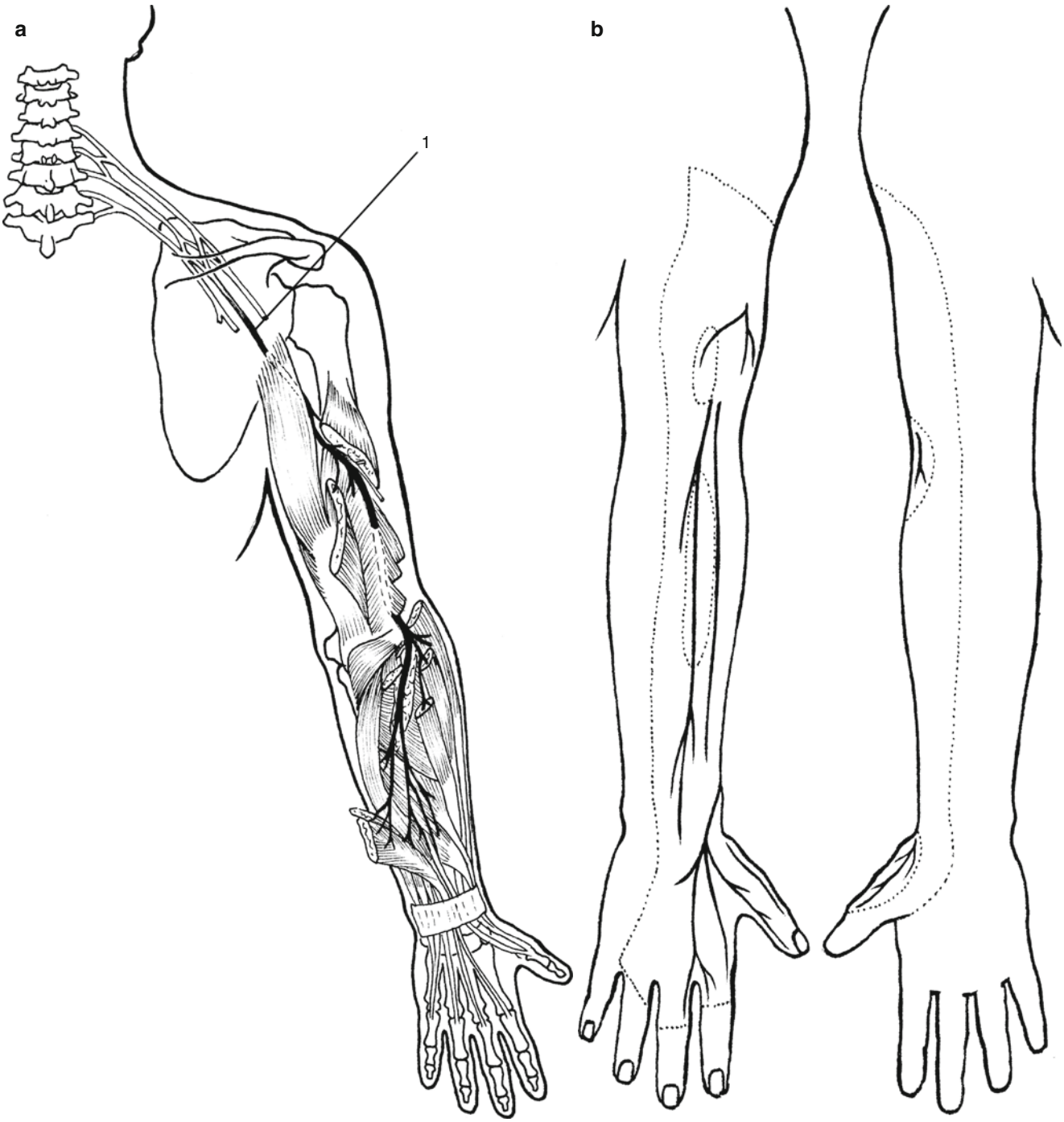


Fig. 8.28 (**a**) *1* Radial nerve. (**b**) Superficial radial nerve

additional ulnar or median nerve dysfunction. Windmill pitchers may develop radial neuropathy at variable sites proximal to the spiral groove.

Motor Lesions in the axilla cause weakness of the elbow extension, and wrist drop and reduced finger extension.

Sensory Sensory deficits occur in the dorsal upper arm and distal radial nerve distribution, depending on the site of the lesion (the dorsal cutaneous nerve of the arm leaves the main trunk in the axilla). Triceps tendon and radioperiosteal reflexes are absent.

Causes Compression by a fibrous arch of the triceps – slowly progressing, painful, sometimes bilateral. Crutch use (occasionally bilateral), false aneurysms, hyperabduction in surgery, missile injuries. Shoulder dislocation of humerus: with

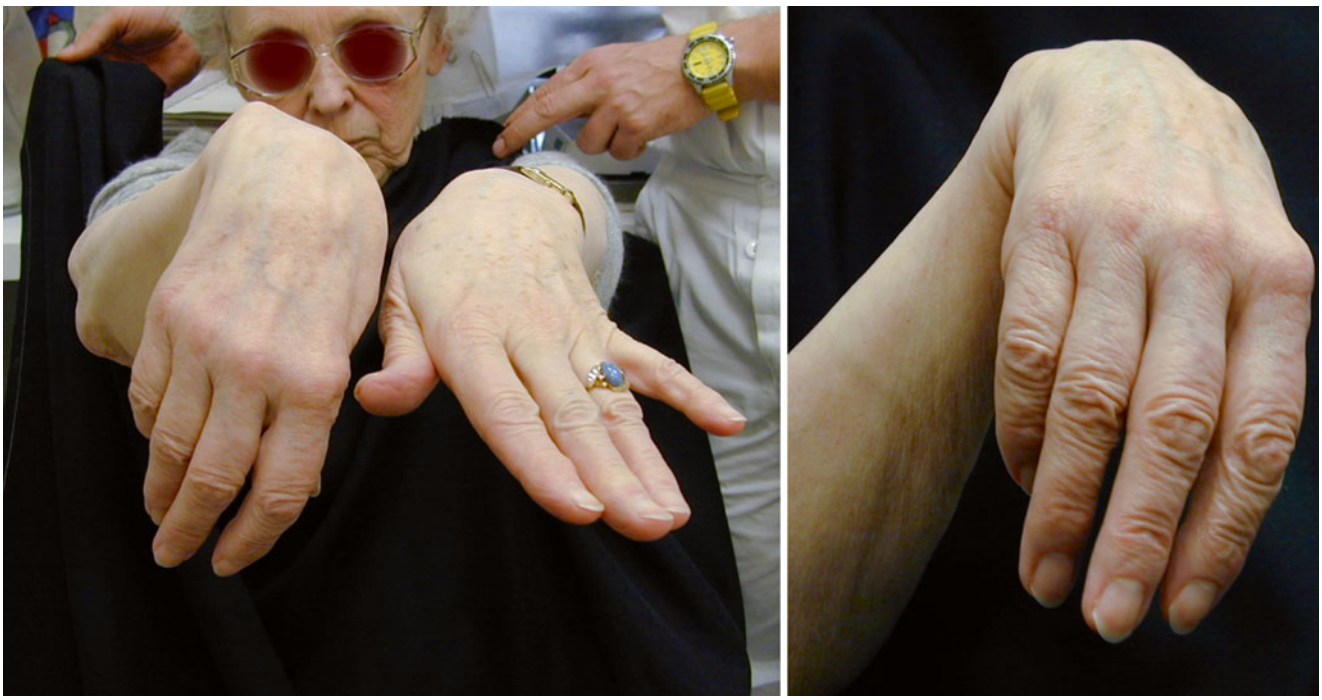


Fig. 8.29 Hand drop and wrist drop in a patient with residual symptoms of polyradiculitis

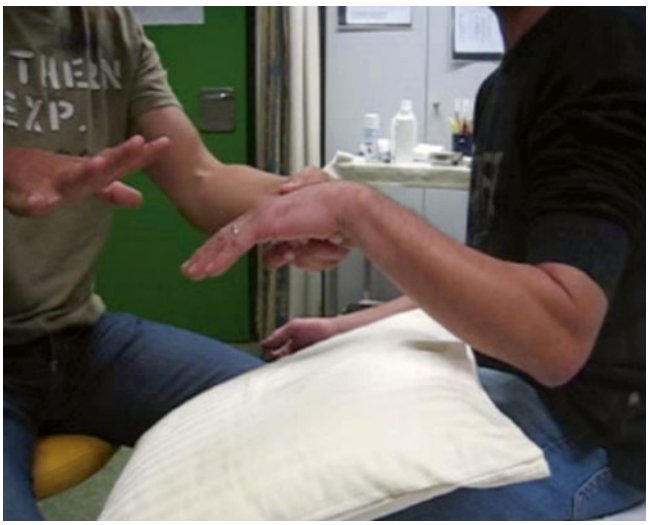


Fig. 8.30 Wrist drop. Typical wrist drop in radial nerve paralysis

significant displacement of mid- to distal humeral shaft fractures (median and ulnar nerve spared). Radial nerve lesion in about 20 % of midshaft fractures and more frequent in distal shaft fractures (60–70 % are neuraparaxia, resolving in 3 months). Strenuous muscular effort – acute onset, painless, trauma.

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 (about 11 % of cases). Onset is acute, and often from a traction injury. "Delayed" onset is rare, but can result from entrapment of nerve in fracture, callus or scar tissue. Secondary to osteosynthetic operations (nailing and plating). Compression at 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).

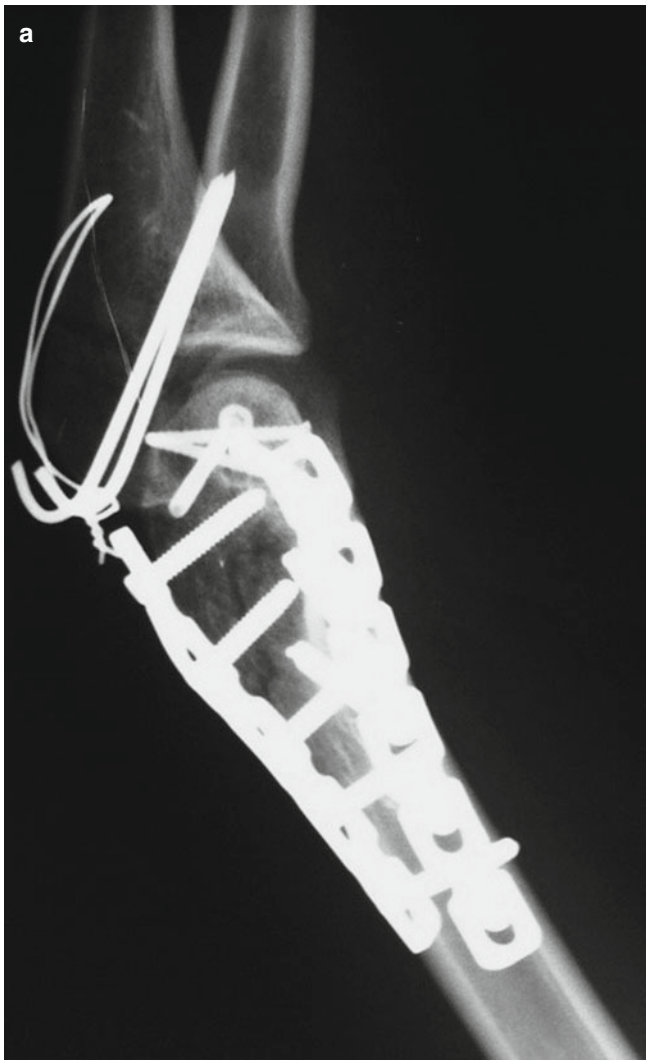
Injections, malpositioning, missile injury, neoplasms. *Trauma*: blunt trauma, neurapraxia, partial lesion.

Radial nerve lesions at the elbow: At the elbow, the radial nerve can be damaged by dislocation in extension trauma (Fig. 8.31). Surgical interventions, such as nailing and plating, as well as arthroplasty, can harm the nerve. Isolated dorsal cutaneous antebrachial lesions (see antebrachial nerves) can occur at the elbow during surgery. The radial nerve may be entrapped at the elbow at the proximal border of the supinator tendon, called the Arcade of Frohse.

Tennis elbow: is usually considered local pain at lateral elbow epicondyle, no direct involvement of the radial nerve.

Forearm

Posterior interosseus nerve (*PIN*): purely motor branch, supplies dorsiflexor muscles of the fingers. Dull pain in the deep



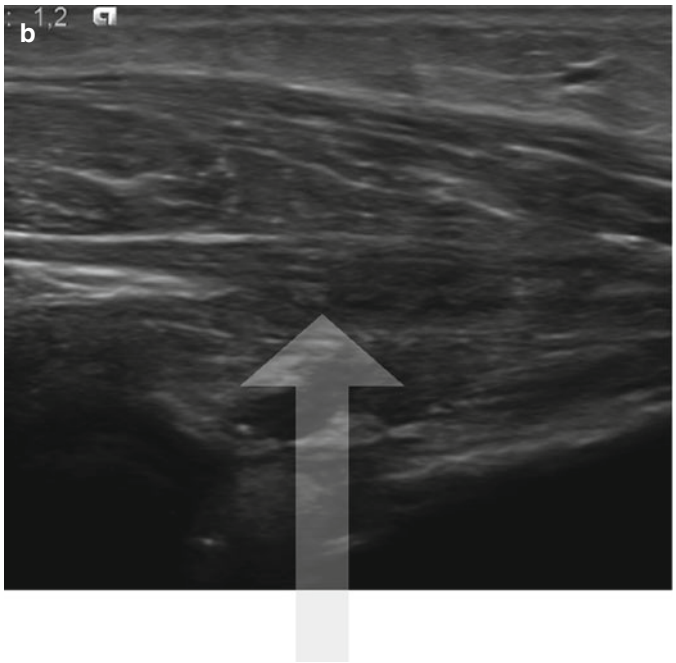


Fig. 8.31 (**a**) X-ray of an elbow after surgical repositioning. (**b**) The distal part of the radial nerve below the elbow had no motor or sensory conduction velocities. However, the radial nerve shows a swelling of the nerve (*arrow*) in the area, but no loss of continuity; thus, a conservative approach was chosen

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.

Radial tunnel syndrome: humeroradial joint to supinator muscle. Compression sites: similar to PIN syndrome. Clinically: pain at radial proximal forearm and lateral elbow. Worse with repetitive activity. Little or no motor weakness. Differential diagnosis: tennis elbow (lateral epicondylitis); lateral antebrachial cutaneous nerve compression.

Causes *Radius fracture*, *iatrogenic*: radial head resection, elbow arthroscopy, hemodialysis shunt, neuralgic amyotrophy isolated to PIN muscles. Overuse of musical instrument(s), rheumathoid arthritis, soft tissue mass, tumors, ganglions, lipomas. *Trauma*: missile injuries, laceration, fractures (Monteggia fracture – combination of fracture and dislocation).

Supinator Syndrome Entrapment/compression of nerve at the Arcade of Frohse, the tight pathway through the supinator tunnel (also called supinator channel syndrome, radial tunnel syndrome).

Posterior Cutaneous Nerve of Arm and Forearm Rarely affected in injuries and surgery (see cutaneous nerves of the forearm).

Distal Lesions *Distal posterior interosseus nerve syndrome*: persistent, dull, aching pain (aggravated by repetitive wrist dorsiflexion) on the dorsum of wrist.

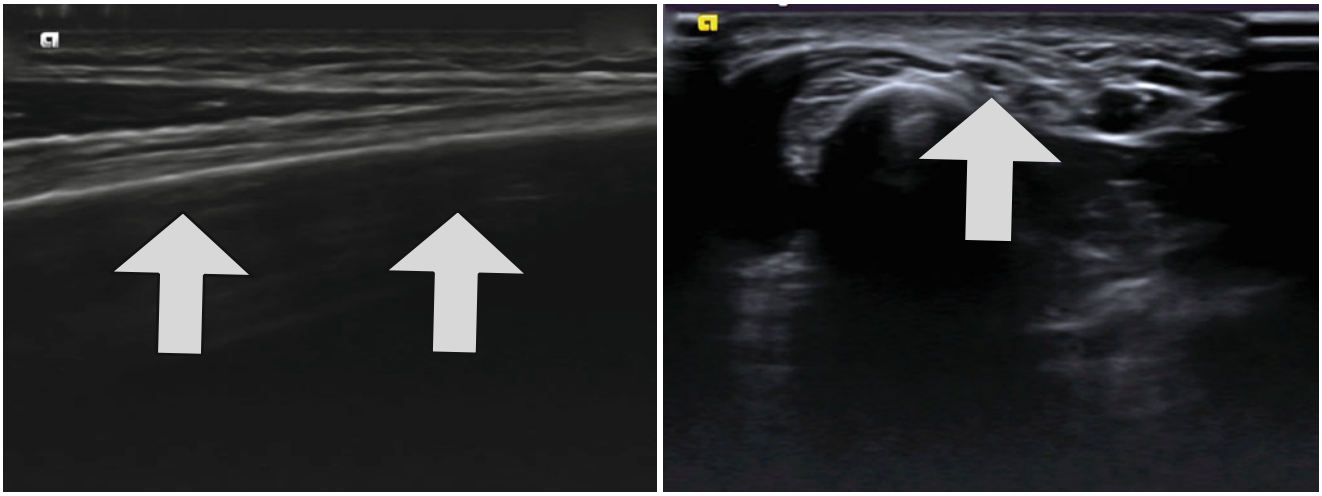


Fig. 8.32 Superficial radial nerve in ultrasound. This image shows the ultrasound finding of a normal radial superficial nerve: (**a**) longitudinal section and (**b**) transverse section

Other 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 dysesthesia (cheiralgia paresthetica). Pain and sensory loss at the dorsolateral hand, thumb and first, second or third digits.

Causes Compression: bracelets, ganglia, handcuffs, scaphoid exostosis. Occupational overuse. Iatrogenic: surgical procedures (e.g., tenosynovectomy, plating), vein puncture, tight casts. Trauma: lacerations (e.g., glasses, knives).

Diagnosis

Electrophysiology The NCV techniques are standard, and are subject to electrophysiological reviews. The EMG is useful in determining the affected muscles, and is indirectly precise in localizing the lesion.

US and MR The imaging techniques can be used for ultrasound following the nerve through its course, in particular at the radial groove. Also, the branching of the nerve in the forearm can be seen (Fig. 8.32). MR images are used for the proximal part, in particular the brachial plexus. In the arm and forearm, the distribution of muscle lesions can give important clues as to the site of the lesion.

Differential Diagnosis

Brachial plexus with lesions of the posterior cord, central paresis (pseudo-radial nerve paralysis). Radicular C7 lesion: radiating neck pain, weakness also affects median (pronator teres and flexor carpi radialis) and ulnar (flexor carpi ulnaris) muscles. Sensation is lost over dorsal and palmar surface of the middle finger.

Musculoskeletal Rupture of extensor tendon, tendinitis (e.g., rheumatoid arthritis), ischemic muscle necrosis.

Other Neuromuscular Disorders Hereditary neuropathy, lead neuropathy, migrant sensory neuritis ("Wartenberg" syndrome), multifocal motor neuropathy (MMN). Myopathies: (Gowers-Laing, congenital MG: slow-channel syndrome, nebulin myopathy and oculpharyngodistal myopathy, myotonic dystrophy, neuralgic amyotrophy, spinal muscular atrophy).

Therapy and Management

Conservative Bracing is useful to compensate for weakness.

Surgical Warranted for extrinsic space-occupying lesions, trauma. Scar, scarring, disruption of continuity. If no recovery is seen within 3 months, a surgical nerve exploration can be useful.

8.2.7 Cutaneous Forearm Nerves

The cutaneous nerves of the forearm can be damaged by injuries to the elbow and the forearm which include local lesions, traction, compression and local tumors. The anatomy and innervation pattern of the nerve involved determines the clinical characteristics of the mononeuropathy syndrome.

Nervus Cutaneus Antebrachii Lateralis

Anatomy The lateral cutaneous antebrachii nerve is the sensory branch of the musculocutaneous nerve. The nerve consists of a volar branch (radial border of forearm) and reaches the thumb. The dorsal branch innervates the dorsal side of the radial forearm and also reaches the wrist. It communi-

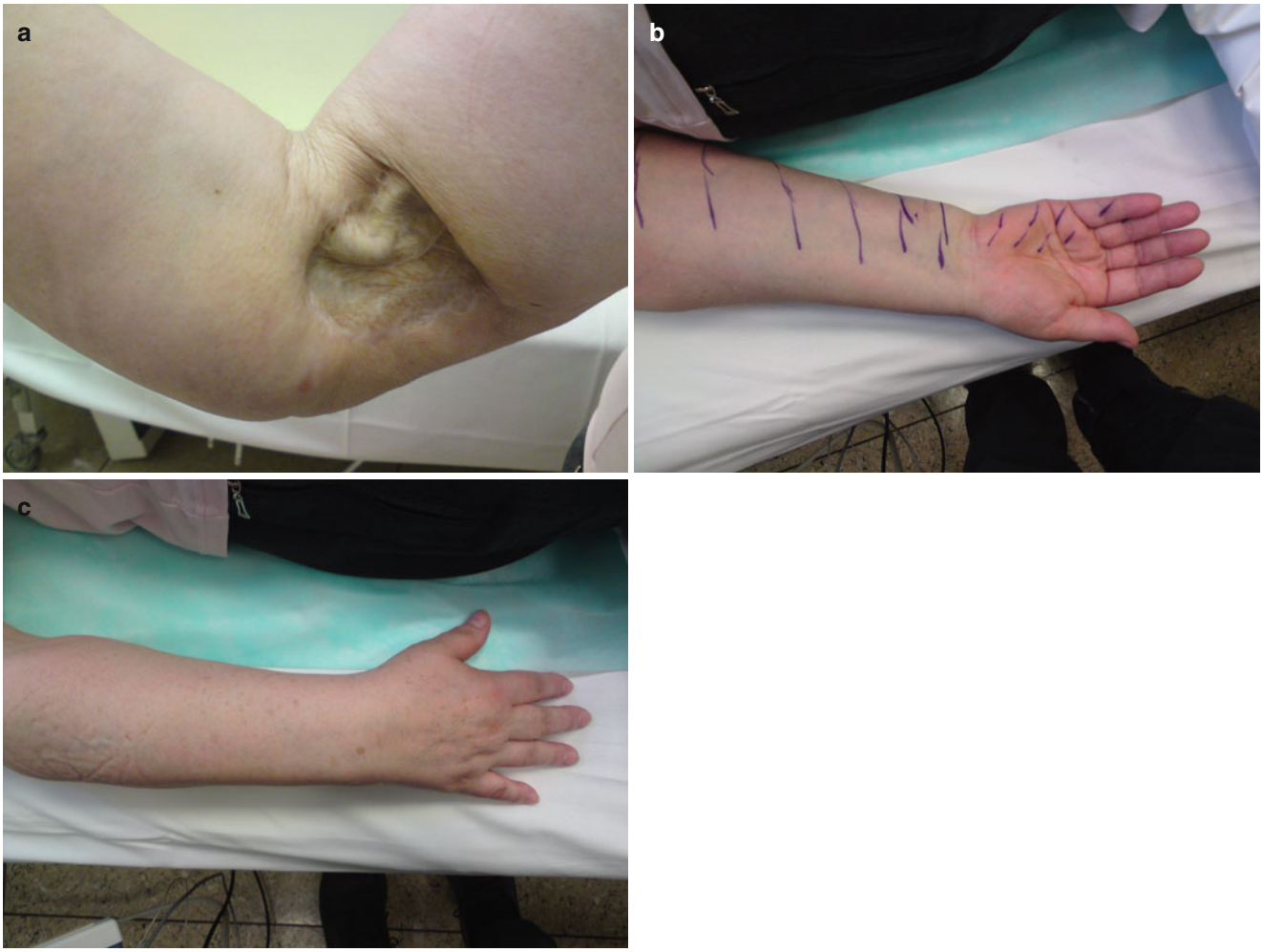


Fig. 8.33 Lesion of the medial cutaneous antebrachial nerve: (**a**) This patient was injected with an anti-cancer drug in the cubital vein. Despite pain, the injection was continued and caused a large skin necrosis. Subsequently, plastic surgery was required to cover the defect. In addition to the sensory impairment in the distribution of the medial cutaneous antebrachiin nerve (**b**)

cates with the superficial branch of the radial nerve and the dorsal antebrachial cutaneous branch of the radial nerve.

Symptoms Numbness in the distribution of the nerve. Also neuropathic pain and causalgia.

Signs Numbness or sensory loss.

Lesions The sensory nerve can be damaged in the axilla (also due to dislocation), and distally in antebrachial phlebotomy, and venipuncture and anesthesiologic procedures.

NCV Standard techniques available.

Nervus Cutaneus Antebrachii Medialis

Anatomy Arises from the medial cord of the brachial plexus (C8, T1). A small branch covers the skin over the biceps brachii. Travels along the ulnar side of the arm and divides in the middle of the forearm into a volar branch which innervates skin to the wrist and communicates with the palmar cutaneous nerve to the ulnar nerve, and an ulnar branch which descends on its ulnar side as far as the wrist, distributing filaments to the skin.

Symptoms Numbness, and occasionally neuropathic pain.

Signs Areas of numbness.

Causes Lesions of the lower brachial plexus, elbow surgery, direct nerve injury and also lipoma (Fig. 8.33).

NCV Standard techniques available.

EMG/NCV As the nerve stems directly from the brachial plexus, it can be used in electrodiagnostic studies to assess the function and integrity of the brachial plexus.

Posterior Cutaneous Nerve of Forearm

Anatomy Arises from the radial nerve in the posterior compartment of the arm. It passes the lateral side of the elbow, and innervates the dorsal side of the forearm to the wrist. In

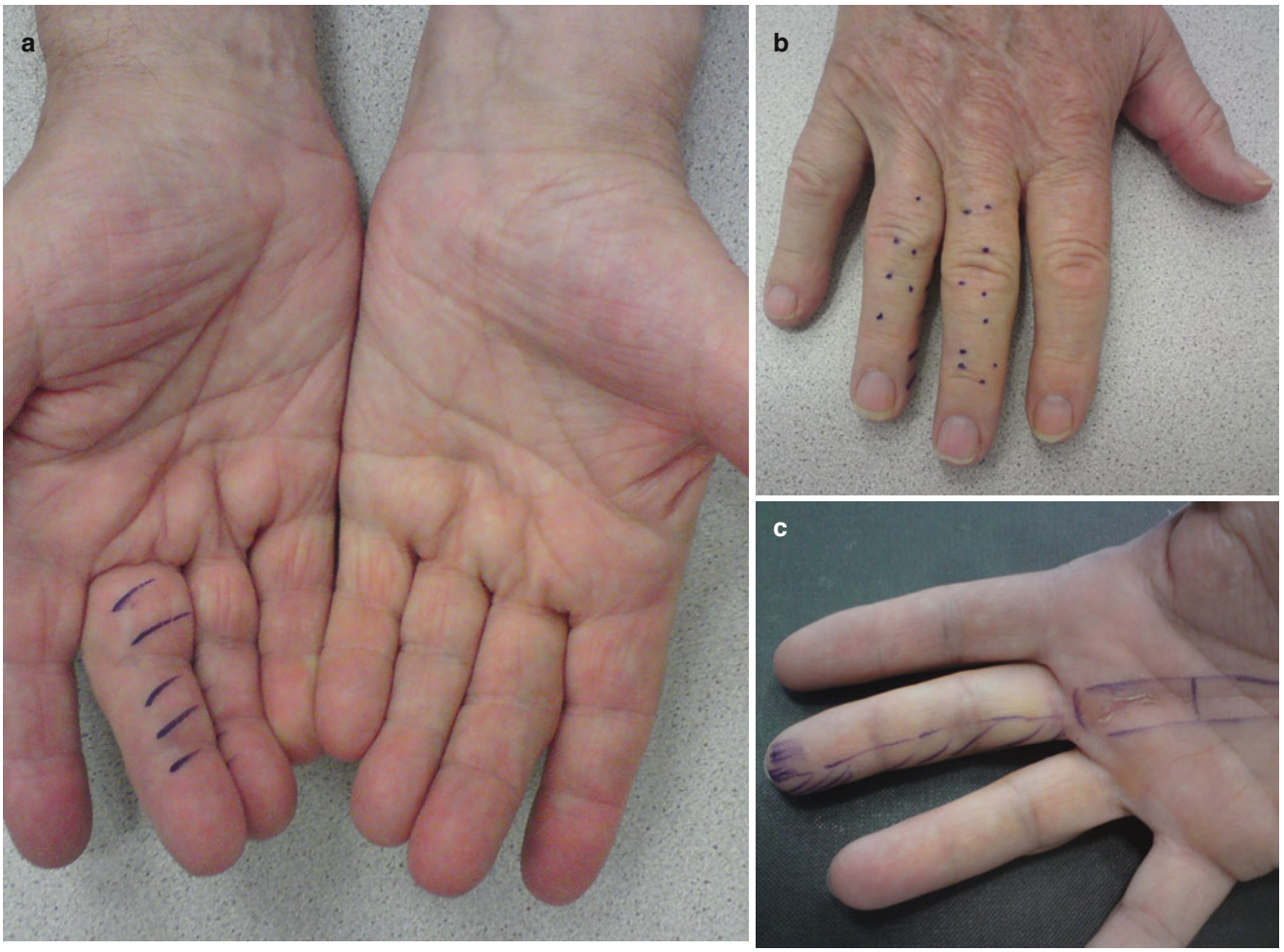


Fig. 8.34 Digital nerve lesions. Digital nerves: (**a**, **b**) Local digital nerve lesion. (**c**) Sensory loss of the lateral branch of the third digital nerve after an incision

the distal part, it communicates with the dorsal branch of the lateral cutaneous antebrachial nerve.

Symptoms Sensory loss, and also pain.

8.2.8 Digital Nerves of the Hand

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	(+)	(+)	+ (MR, US)	

Symptoms

Sensory loss in the fingers (Fig. 8.34), neuropathic pain (in neuroma formation).

Signs

Tinel's sign (focal, localizing neuroma), callus, local swelling.

Causes

Amputations (Fig. 8.35). Joint abnormalities: mucous cyst from arthritis, osteophytes. Miscellaneous: diabetes, leprosy. Rheumatoid arthritis: vasculitis. Musicians: bows, instruments. Nerve tumors, schwannoma. Tendon sheath pathology: cysts, giant cell tumors (Fig. 8.34), rheumatoid tenosynovitis. Trauma: blunt trauma digit and palm, chronic external compression, fractures, lacerations. Mechanical trauma: scissors, bowler's thumb, carrying nylon bags.

Diagnosis

NCV has only limited use. US: sonography of the volar digital nerves may be helpful.

Therapy

Conservative treatment, local anesthesia (batches), treatment of neuropathic pain. Surgical procedures (e.g., removal of neuroma).

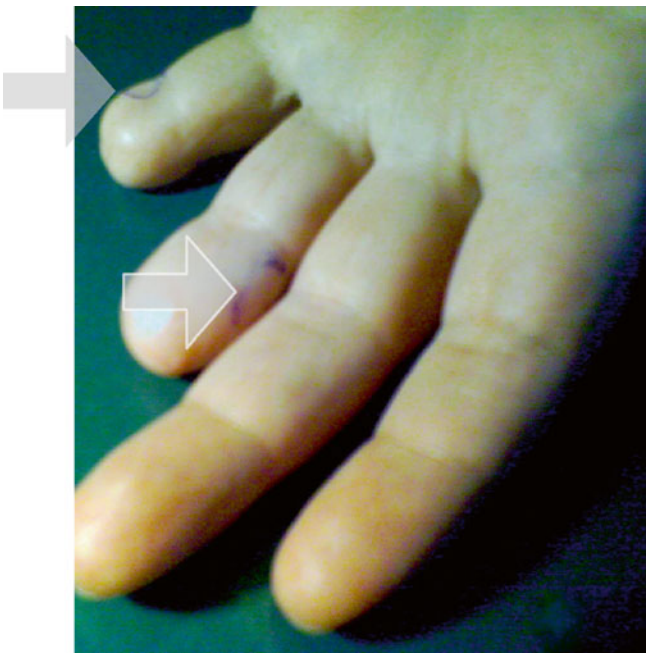


Fig. 8.35 Amputation neuroma: This patient had a traumatic finger amputation. Several months later, two local painful spots appeared (*arrows*). Upon palpitation, local swelling was noted, and Tinel's sign could be elicited

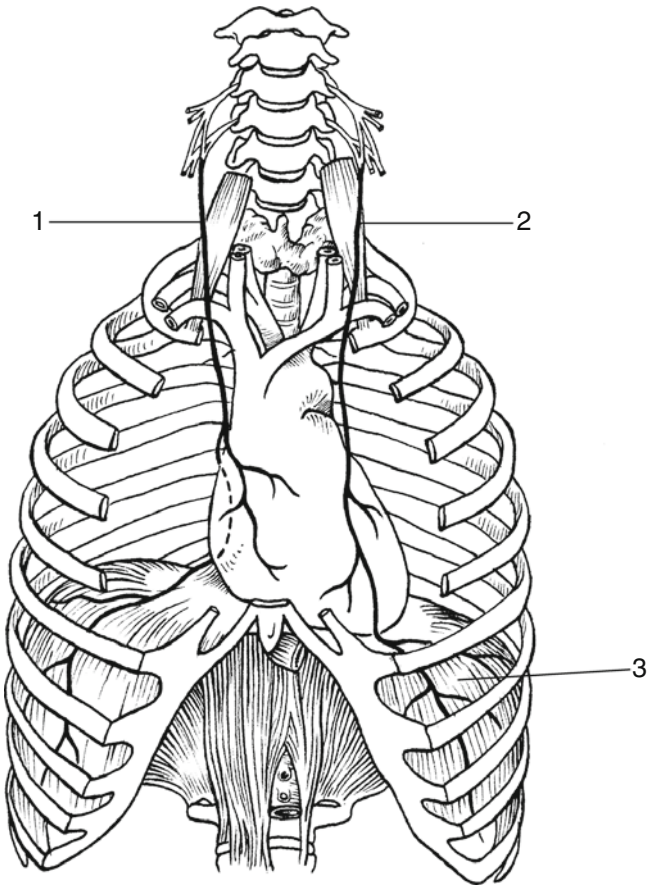


Fig. 8.36 Phrenic nerve shows vincinity to the pericardium. *1* Right phrenic nerve. *2* Left phrenic nerve. (**c**) Anterior portion of diaphragm

8.3 Truncal Mononeuropathies

8.3.1 Phrenic Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy Lung Function
	+	+		+

Anatomy

The phrenic nerve originates from C3, C4, and C5; variations occur in a prefixed bracial plexus. 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 phrenico-abdominal branches supply the peritoneum of the diaphragm, liver, gall bladder and pancreas. Terminal branches end in the celiac plexus (Fig. 8.36). The diaphragm consists of a costal (mainly for respiration) and a crural (closure of the esophagus) segment. The sensory feedback of the diaphragm is not well understood.

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.

Frequent Sites of Lesion

Neck: Neck wounds, traction, with upper trunk of brachial plexus damage, brachial plexus anesthesia, jugular and subclavian vein catheters. *Chest*: intrathoracic malignant tumors, chest surgery (intraoperative mechanical or local cooling), post-radiation, trauma to the thorax, rupture and tear of the diaphragm.

Causes

Acute brachial plexus neuropathy (idiopathic or hereditary), birth trauma (with associated brachial plexus lesions), idiopathies, neuropathies (GBS, critical illness, MMN), sarcoidosis, central paresis of the diaphragm that can occur in stroke.

Diagnosis

Chest radiograph, ultrasound. Clinically: respiration, ability to recline in a supine position, 8.38, 8.39 and 8.40).

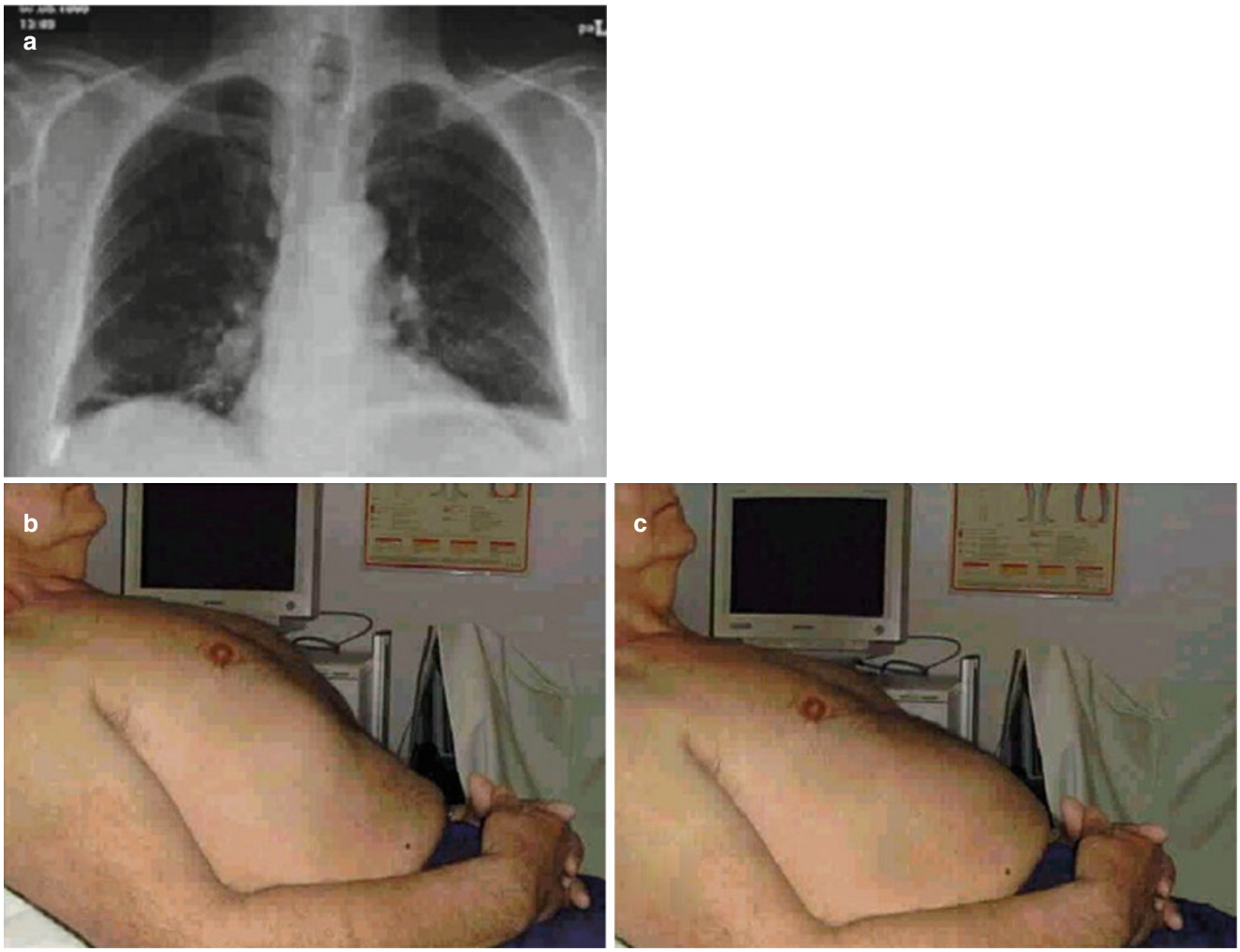


Fig. 8.37 (**a**) Diaphragmatic paralysis. (**b**) Inspiration. (**c**) Expiration

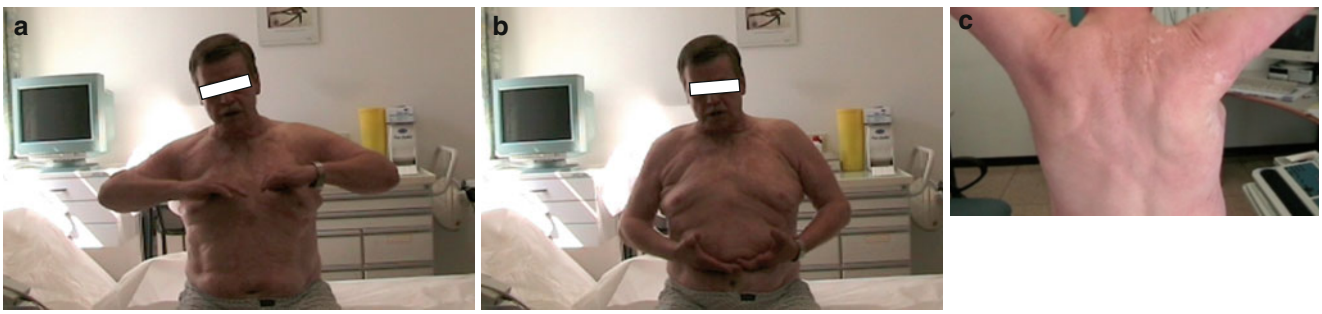


Fig. 8.38 "Swimming pool sign" in bilateral phrenic palsy: This gentleman suffered from a bilateral idiopathic phrenic palsy. He was used to going to a swimming pool once a week. After the onset of the palsy, he was uncomfortable breathing when the water level reached his abdomen (**a**), and was unable to breathe when the water level reached the T6/7 level (**b**). The innervation of the shoulder muscles was intact (**c**). The immersion of the body pressed the abdominal cavity upwards

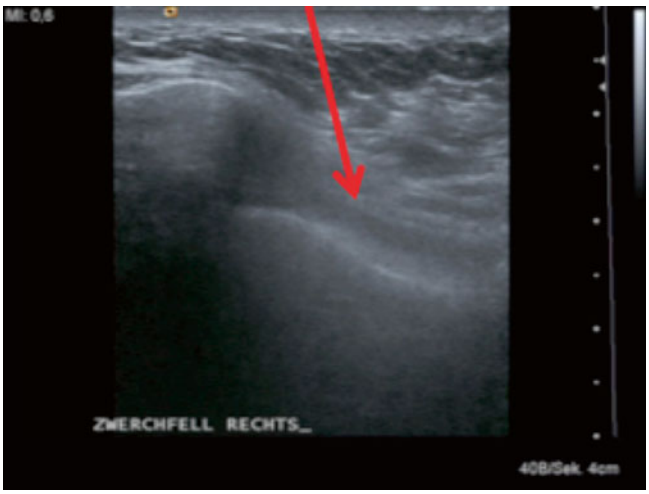


Fig. 8.39 Ultrasound of the diaphragm: ultrasound of the diaphragm, probe between the ribs. *Arrow* points to the diaphragm. Upon inhalation and exhalation, the movement of the diaphragm can be observed

Differential Diagnosis

Herpes zoster with motor involvement, motor neuron disease (ALS), myasthenia gravis, 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 night-time respiratory support.

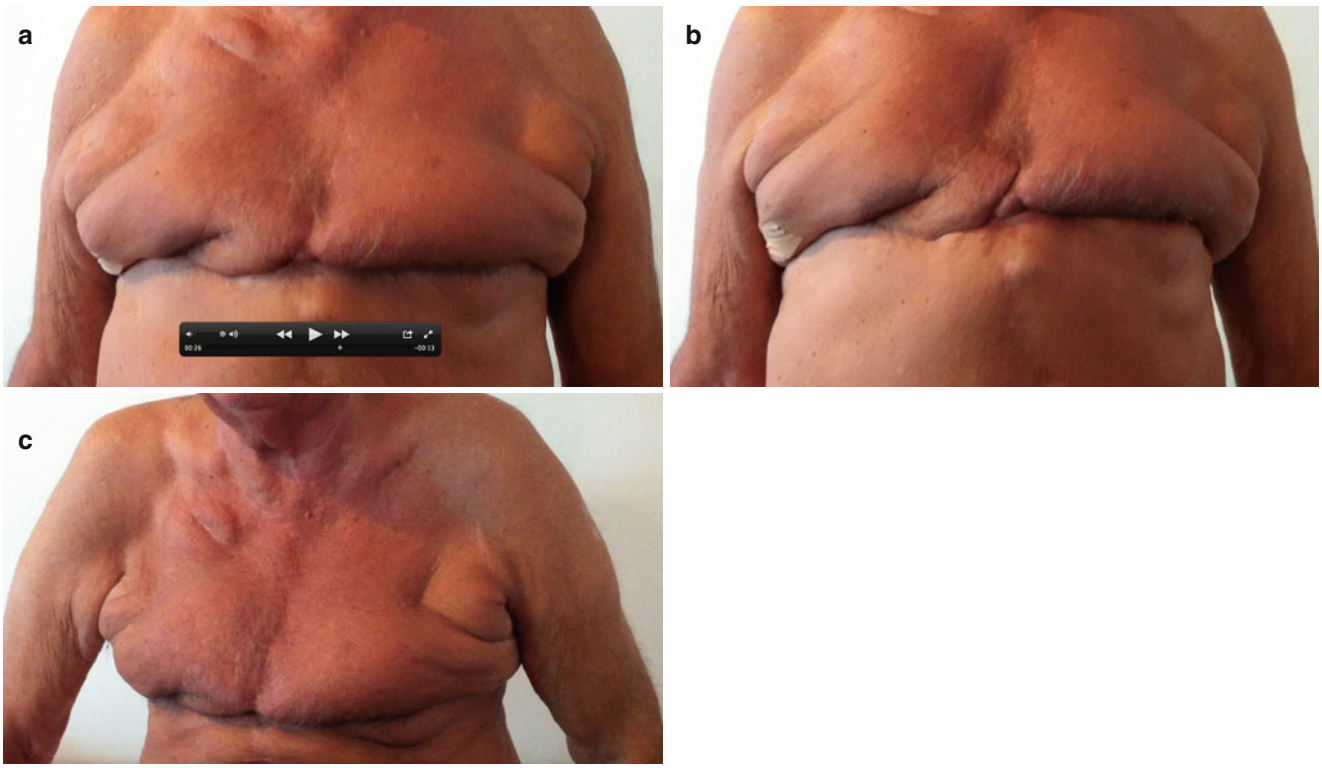


Fig. 8.40 Thoracic wall weakness (postoperatively): This patient had a thoracic operation with a remaining weakness of the thorax wall. Appearance of the thorax at rest (**a**), inhaling (**b**), and during forced exhalation, coughing (**c**) (images were saved from a movie documentation)

8.3.2 Dorsal Scapular Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+−		+	

Anatomy
The dorsal scapular nerve arises from fibers of C4 and C5 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. 8.41). *Function*: To elevate and adduct the medial border of the shoulder blade (together with rhomboid muscles).

Symptoms
Symptoms are rare, and only occur with forceful arm movements.

Signs
Atrophy of muscles cannot be seen. The scapula becomes slightly abducted from the thorax wall, with outward rotation of the inferior scapular angle (mild winging).

Pathogenesis
Iatrogenic – surgery; neuralgic shoulder amyotrophy; nerve can be used as a graft for nerve transplantation.

Diagnosis
EMG, MRI of the thorax can reveal atrophic rhomboid muscles.

Therapy
None.

Prognosis
Depends on etiology.

8.3.3 Suprascapular Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		MRI, US	

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 innervation (Fig. 8.42).

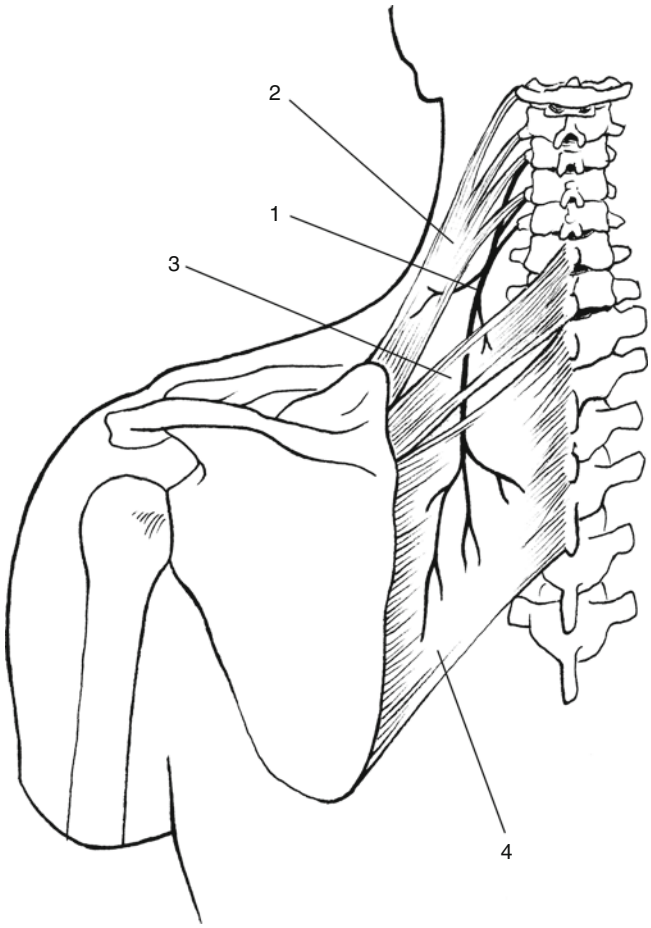


Fig. 8.41 *1* Dorsal scapular nerve. *2* Levator scapular muscle. *3* Minor rhomboid muscle. *4* Major rhomboid muscle

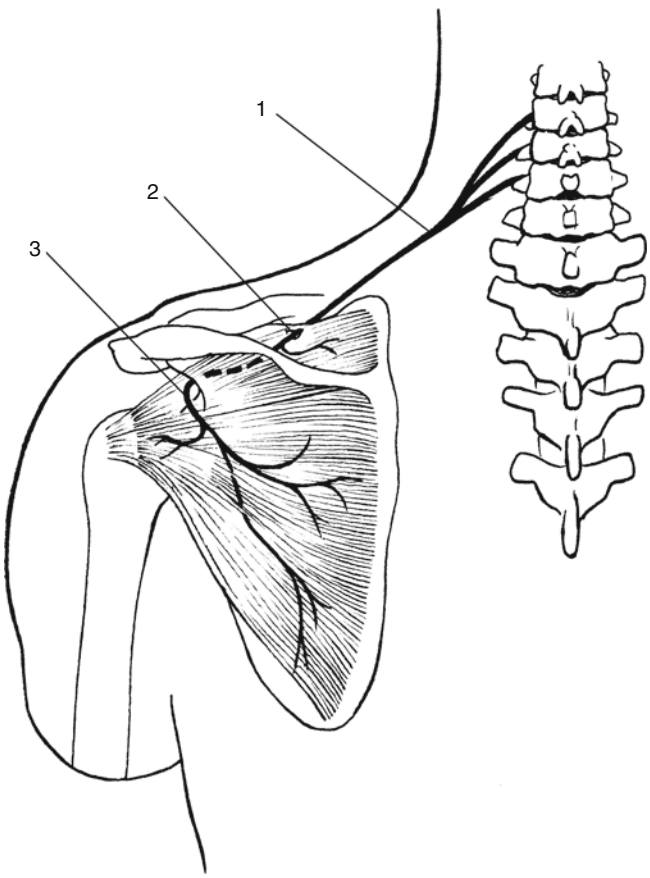


Fig. 8.42 *1* Suprascapular nerve. *2* Suprascapular notch/foramen. *3* Spinoglenoid notch

Symptoms
Dull, aching pain in the posterior aspect of the shoulder, which is aggravated by arm use – in particular, adduction of the extended arm. The patient is unable to lie on the 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. Weakness of arm abduction, elevation and external rotation.

Causes
Abnormal transverse scapular ligaments (occasionally bilateral). Arthroscopic shoulder surgery. Backpacking. Closed trauma: the most common cause. Entrapment by the transverse superior or inferior ligaments. Neuralgic shoulder amyotrophy. Overuse: athletic activities (basketball, volleyball, boxing) or construction trades (e.g., carpentry). Soft tissue masses: ganglion cysts. Trauma: hematoma and fracture. Tumors: ganglion, cyst, metastasis.

Diagnosis
Motor 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 brachial plexus lesions.

Therapy
Depends on the etiology and severity. Conservative: rest the limb, analgesics, activity modification, nerve block. Surgical: 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.

8.3.4 Subscapular Nerve (Inferior Scapular Nerve)

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+	?	+	

Anatomy
Nerve fibers arise from C5-C6, and travel through the upper trunk and posterior cord of the brachial plexus. It can be divided into an upper subscapular and lower subscapular nerve. The lower subscapular usually comes from the posterior cord, but may also originate from the axillary, radial or thoracodorsal nerves. The nerve innervates the subscapularis and teres major muscles to secure the shoulder joint and provide inward rotation of the shoulder. Some articular branches innervate the dorsal part of the shoulder joint (Fig. 8.43).

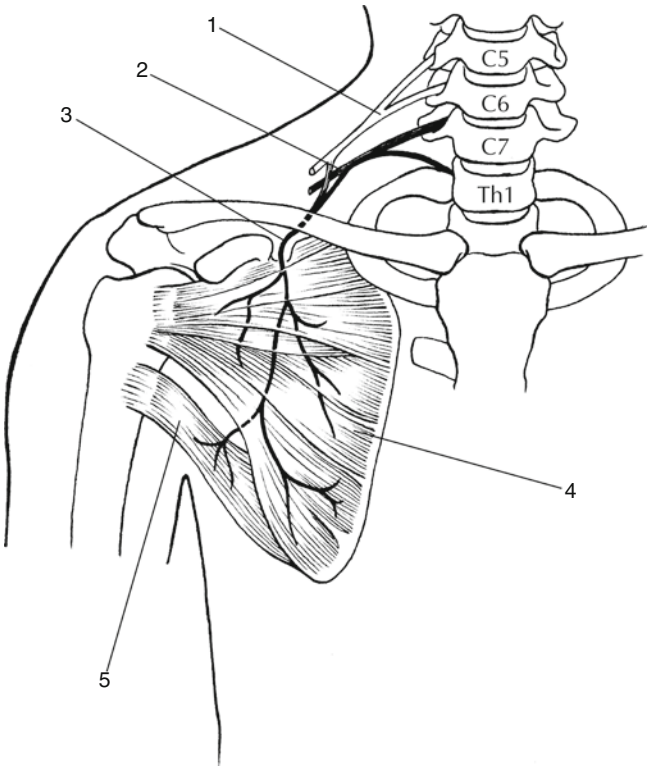


Fig. 8.43 *1* Upper trunk. *2* Posterior cord. *3* Subscapular nerve. *4* Subscapular muscle. *5* Teres major muscle

Symptoms
Reduction of inward rotation of the arm. Compensation for the function of both muscles is provided by the pectoralis major, latissimus dorsi, and anterior deltoid.

Signs
Secures shoulder joint and inward rotation of the upper arm. Atrophy is not visible, palpation of muscle contraction deep in the axilla may show differences with the contralateral side. There are no sensory findings.

Pathogenesis
Involvement either associated with radiculopathies or with posterior cord brachial plexus lesions. Impingement of the subscapular nerve has been described.

Diagnosis
EMG of the teres major muscle. MRI of muscle.

Differential Diagnosis
C5-C6 radiculopathy, posterior cord lesion of the brachial plexus.

Therapy
Conservative.

8.3.5 Long Thoracic Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
+	+		+	

Anatomy
Fibers originate from the ventral rami of C5-C7, and travel through the dorsal part of the brachial 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. 8.44).

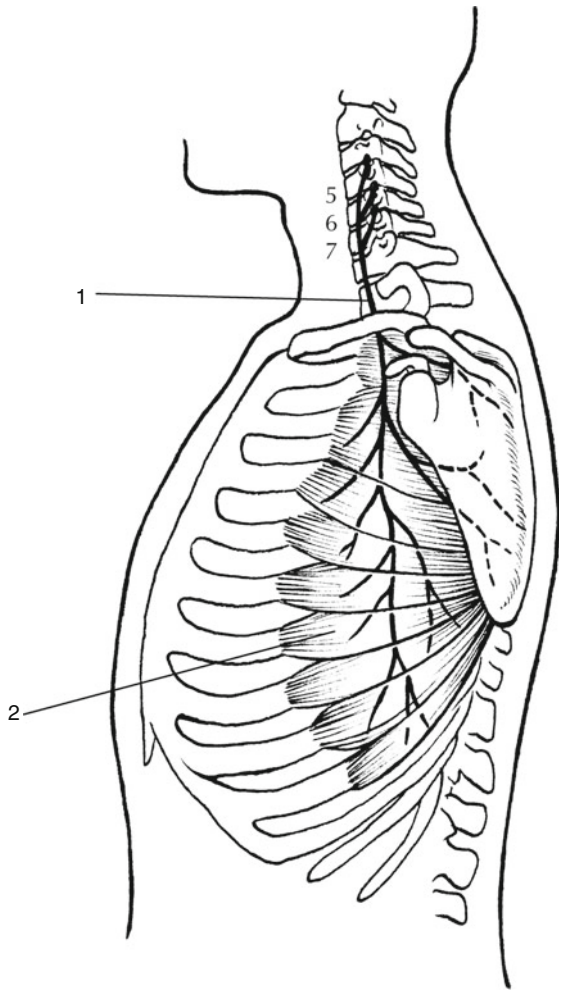


Fig. 8.44 Long thoracic nerve anatomy. *1* Long thoracic nerve, *2* Serratus anterior muscle (numbers stand for cervical vertebrae)

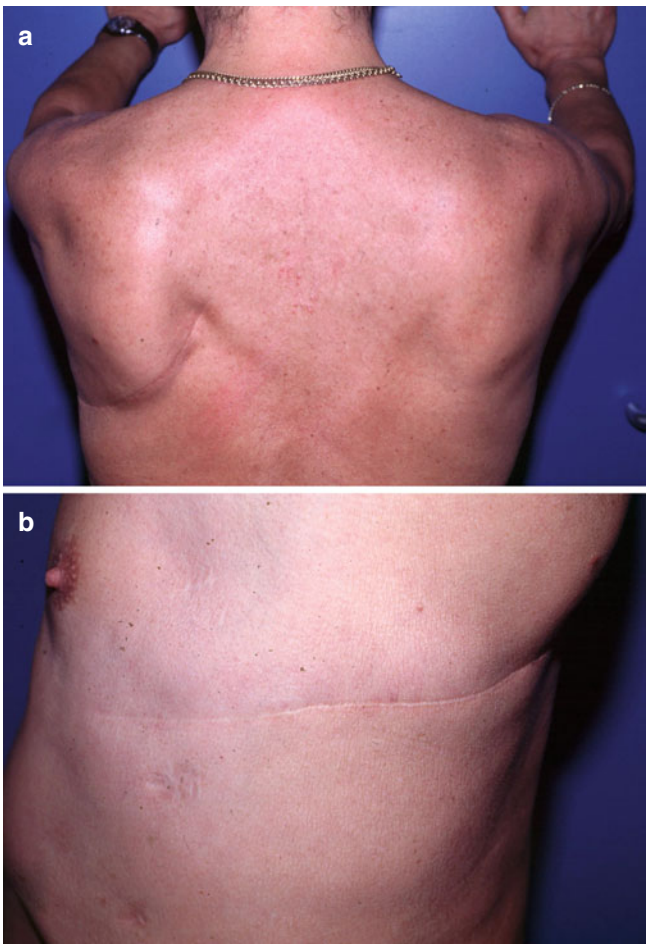


Fig. 8.45 (**a**) Long thoracic nerve palsy after thoracic surgery. Note winging of caudal edge of the scapula. (**b**) Scar after thoracic surgery

Symptoms
Dull ache in the shoulder, the affected shoulder seems lower, weakness of arm abduction, no sensory abnormalities.

Signs
Atrophy with scapular winging (Fig. 8.45) when arm is lifted forward or when the patient pushes the outstretched arm against resistance. Winging of the medial part of the scapula. Restriction of abduction and flexion of the arm above shoulder level.

Pathogenesis
Compressive Pressure – part of backpack paralysis.

Iatrogenic Intraoperative: thoracotomy, mastectomy, resection of the first rib, lymph node excision. Intraoperative positioning, malpositioning.

Infection Lyme disease, typhoid fever.

Inflammatory-Immune Mediated Neuralgic amyotrophy: seen mainly in association with other shoulder nerves, particularly with the suprascapular nerve. Rarely isolated.

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).

Diagnosis
Nerve conduction: recording either with needle or surface electrodes. EMG, MRI can show the atrophied muscle.

Differential Diagnosis
Acute brachial plexus neuropathy, multifocal motor neuropathy, muscle disease (usually bilateral), 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 (see around the shoulder).

Therapy
Conservative Physiotherapy, exercise.

Operative Trauma with severe axonotmesis, neurotmesis. Orthopedic surgery to correct non-reversible winging.

Prognosis
Generally good – partial lesions are common.

8.3.6 Thoracodorsal Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

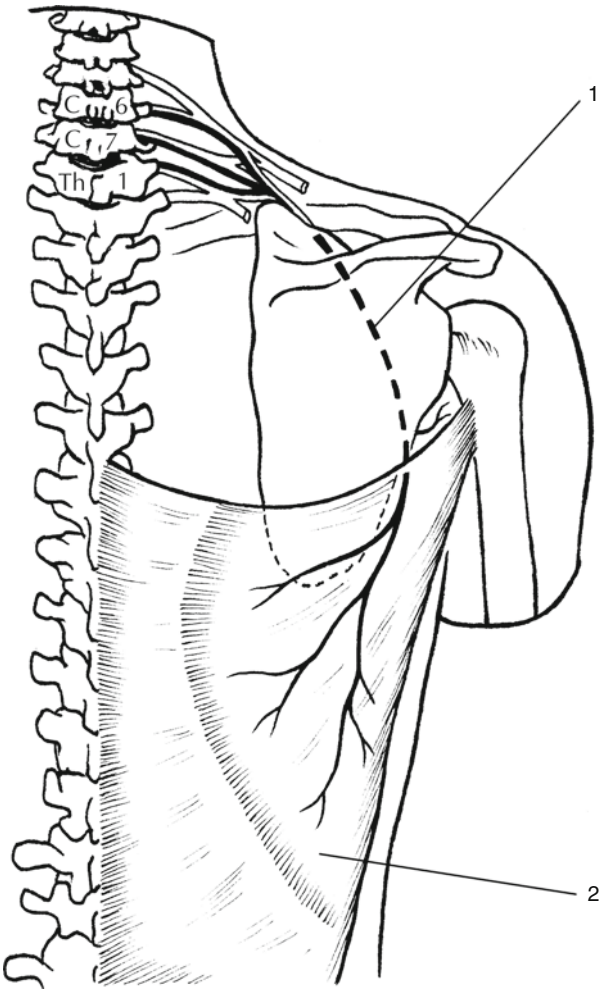


Fig. 8.46 *1* Thoracodorsal nerve. *2* Latissimus dorsi muscle

Anatomy
Fibers originate from C5-C7 roots (only 50 % of cases have fibers from C7 only). The fibers pass through the upper and middle trunks and the posterior cord, and continue with the lower subscapular nerve. Occasionally this nerve is a branch of the axillary and radial nerve. A motor branch innervates the latissimus dorsi muscle, and can 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 (Fig. 8.46).

Symptoms
Few clinical symptoms; the weakness is compensated in part by pectoralis major and teres major muscles.

Signs
Atrophy, and slight winging of the inferior margin of the scapula. Weakness in adduction and medial rotation of shoulder and arm.

Causes
Isolated lesion is uncommon. Neuralgic shoulder amyotrophy (rare). Plexus lesions: injury associated with posterior cord or more proximal brachial plexus lesions.

Diagnosis
EMG: the teres major muscle. MRI can show muscle atrophy.

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 the humeroscapular joint. Transplant: latissimus dorsi flap: is used to replace breast tissue after breast surgery.

Involuntary breast movements ("jumping breast") can occur via aberrant reinnervation. Other uses of muscle transplant are reconstruction of the chest wall, radial palsy, rotator cuff tearing and others.

Prognosis

Good.

8.3.7 Innervation of the Shoulder

Complex Structure and Function

The shoulder is a complex structure which contains several joints: glenohumeral, suprahumeral, scapulothoracic, acromioclavicular, sternoclavicular, sternocostal and costovertebral, and many ligaments and soft tissues as well as several nerves, muscles and their tendons. Basic examination of shoulder function consists of extension, abduction, rotation (external and internal), elevation and depression of the scapula and protraction of the scapula. Not all dysfunction is due to nerve, muscle or tendon lesions. Common shoulder problems include capsulitis ("frozen shoulder"), supraspinatus tendinitis, bicipital tendinitis, subdeltoid bursitis, subacromial bursitis, supraspinatus calcification, and triceps brachii calcification (Fig. 8.47).

Neuronal Structures Passing Through the Shoulder

The brachial plexus passes through the shoulder and is frequently damaged in trauma – in particular, dislocations of the shoulder. The large vessels, the lymph nodes, and the apex of the lung are close to the shoulder and can give rise to symptoms that may be perceived in the shoulder region.

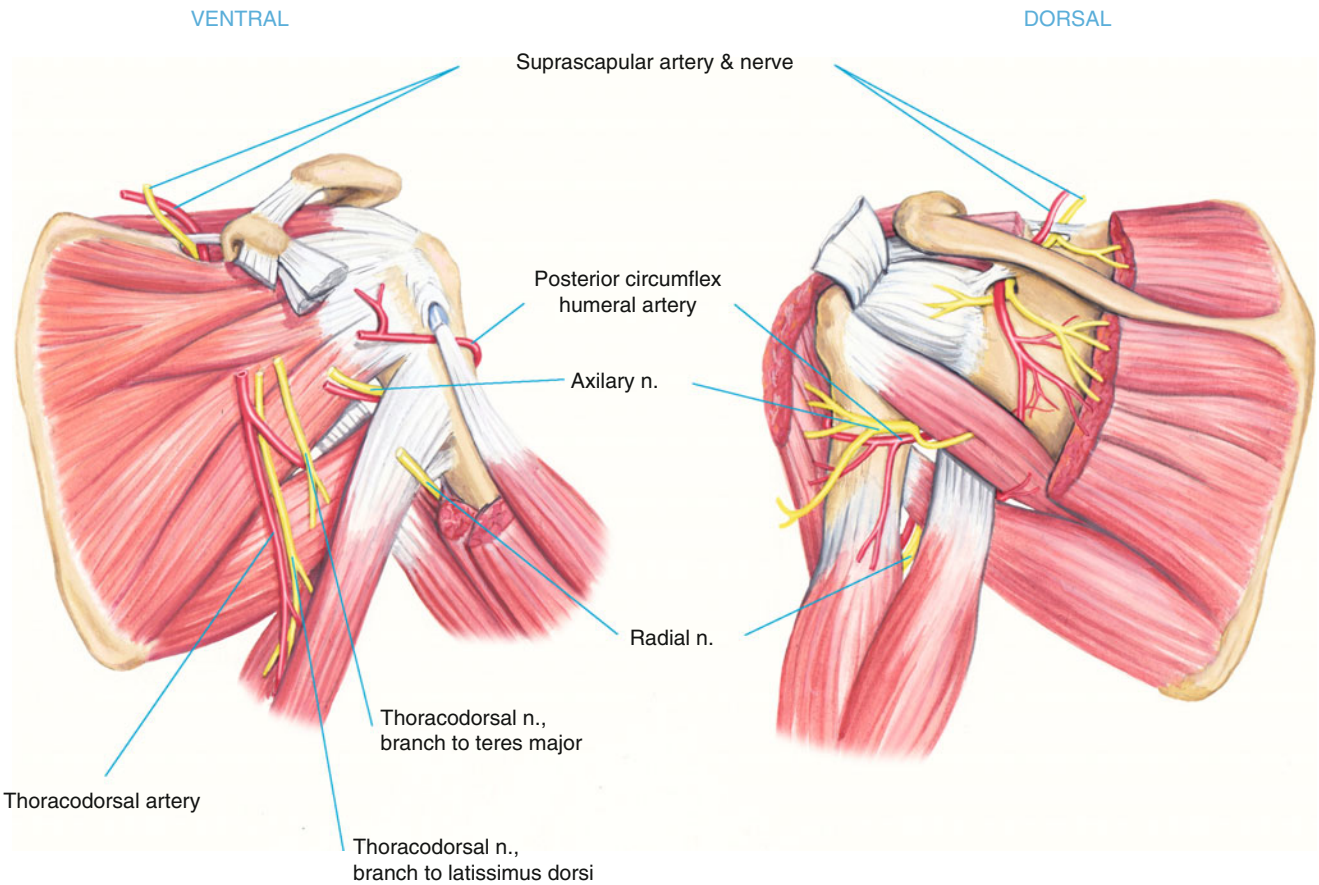


Fig. 8.47 Shoulder: The shoulder is surrounded by the rotator cuff. Atrophies and damage to muscle can be visualized in MR imaging. Images show normal site with intact muscles

Muscle

Several muscles are responsible for shoulder movement. These muscles are located in and around the shoulder and some have a "far-reaching" influence over the trunk (latissimus dorsi, serratus anterior), or extend over several joints (e.g., triceps brachii). They work as antagonists, rotators, and also fix the humerus to the glenoid surface.

Sensory Innervation Including the Joints

The sensory innervation has two main aspects: (a) innervation of the overlying skin (brachial lateral cutaneous nerve, axillary nerve, supraclavicular nerves, the upper intercostal nerves), including the axilla (medial brachial cutaneous nerve, intercostobrachial nerve), and (b) the innervation of the joints (e.g., acromioclavicular joint). Cadaver studies show that most of these structures have a double innervation by the suprascapular nerve and the lateral pectoral nerve.

The Quadrilateral Space Syndrome

This is a clinical syndrome resulting from compression of the axillary nerve and posterior circumflex humeral artery in the quadrilateral space. The quadrilateral space is an anatomic space in the upper arm defined by the long head of the triceps, the teres minor and teres major muscles, and the humeral shaft. Symptoms include vague shoulder pain, numbness or tingling in the arm and tenderness to pressure over the area of the quadrilateral space. A dull ache in the shoulder may worsen when the arm is repeatedly moved overhead. Causes are: shoulder dislocation, carrying heavy backpacks, repetitive stress, and overuse.

Nerve Entrapment Syndromes

The long thoracic nerve runs beneath the subscapularis muscle and terminates in the serratus anterior muscle. The compression syndrome occurs in soldiers carrying heavy packs and can also result from injury during a first rib resection for thoracic outlet syndrome. Heavy labor or sports can induce a stretch injury. The suprascapular nerve contains pain fibers from the glenohumeral and acromioclavicular joints, and provides motor supply to the supraspinatus and infraspinatus muscles. Nerve lesions can result in shoulder pain. Injury occurs from repetitive stretching as the nerve passes through the coracoid scapular notch (sports such as weightlifting, volleyball). Compression can also be caused by ganglia or tumors and scapular fractures with dislocation.

Rotator Cuff Tears and Nerve Injuries

Peripheral nerve lesions in the brachial plexus, the axillary nerve, suprascapular nerve, and cervical radiculopathy can result from rotator cuff tears. The rotator cuff muscles (supraspinatus, infraspinatus, teres minor and subscapularis muscle) are important in shoulder movements and in maintaining glenohumeral joint (shoulder joint) stabilization (Fig. 8.48). These muscles arise from the scapula and con-

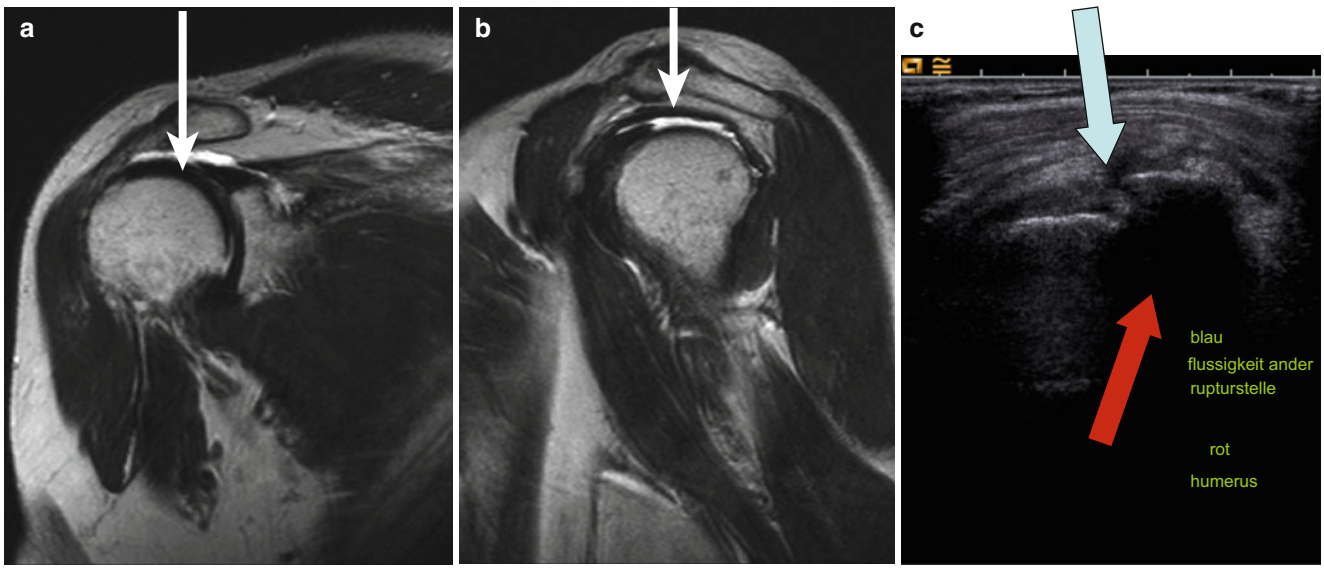


Fig. 8.48 Rotator cuff rupture: (**a**, **b**) MR of shoulder showing the site of tendon rupture (*white arrow*). (**c**) Ultrasound of the shoulder: *red arrow* humerus, *blue arrow* fluid extravasate at the site of the lesion

nect to the head of the humerus, forming a cuff at the shoulder joint. They hold the head of the humerus in the small and shallow glenoid fossa of the scapula. The rotator cuff may be injured by tearing, often resulting in a tendon rupture (most often supraspinatus).

Shoulder Impingement Syndrome

Occasionally, neurovascular compression beneath the coraco-acromial ligament will present with sensations of pain, swelling, and paresthesia in the arm. Tenderness and increased symptoms upon compression of the coracoacromial space will suggest the origin of symptoms.

Scapular Winging

Results from numerous causes:

- Nerve lesions: *Medial winging* is due to serratus anterior weakness, long thoracic nerve (Fig. 8.49a). Causes: compression and stretch, trauma, surgical, neuralgic amyotrophy, viral infections, immunizations, C7 radiculopathy. Examination: anterior abduction of arms followed by posterior and medial displacement of scapula. *Lateral winging* is due to trapezius and rhomboid weakness (Fig. 8.49b). Spinal accessory and dorsal scapular nerve lesions. Examination: lateral abduction of arms with lateral and upward displacement of scapula. Superior angle more laterally displaced. Lateral winging also occurs with rhomboid weakness with lateral abduction of arm and medial rotation of the lower scapular border. The inferior angle is more laterally displaced (Fig. 8.49).
- Myopathies and spinal muscular atrophies: muscle dystrophy, scapuloperoneal syndromes, centronuclear myopathy, FSH phenotype with ragged red fibers and cardiomyopathy, glycogen storage diseases, mitochondrial myopathy, spinal muscular atrophy (Fig. 8.50).
- Other causes: rotator cuff pathology, shoulder instability, acromial fractures, aseptic necrosis of the humeral head, fibrotic shortening of the middle and posterior deltoid, and acromegalic arthropathy of the shoulder.

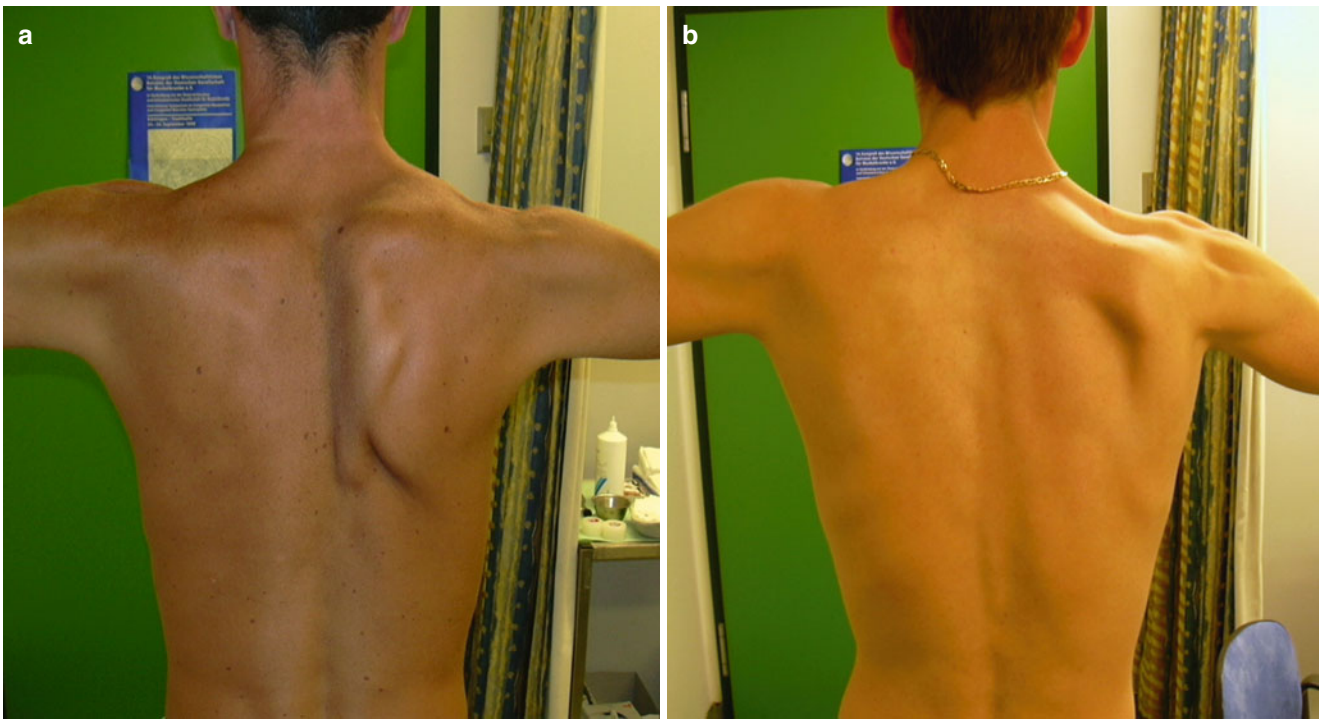


Fig. 8.49 (**a**) Nervus thoracicus longus lesions. (**b**) Lesions of the accessory nerve

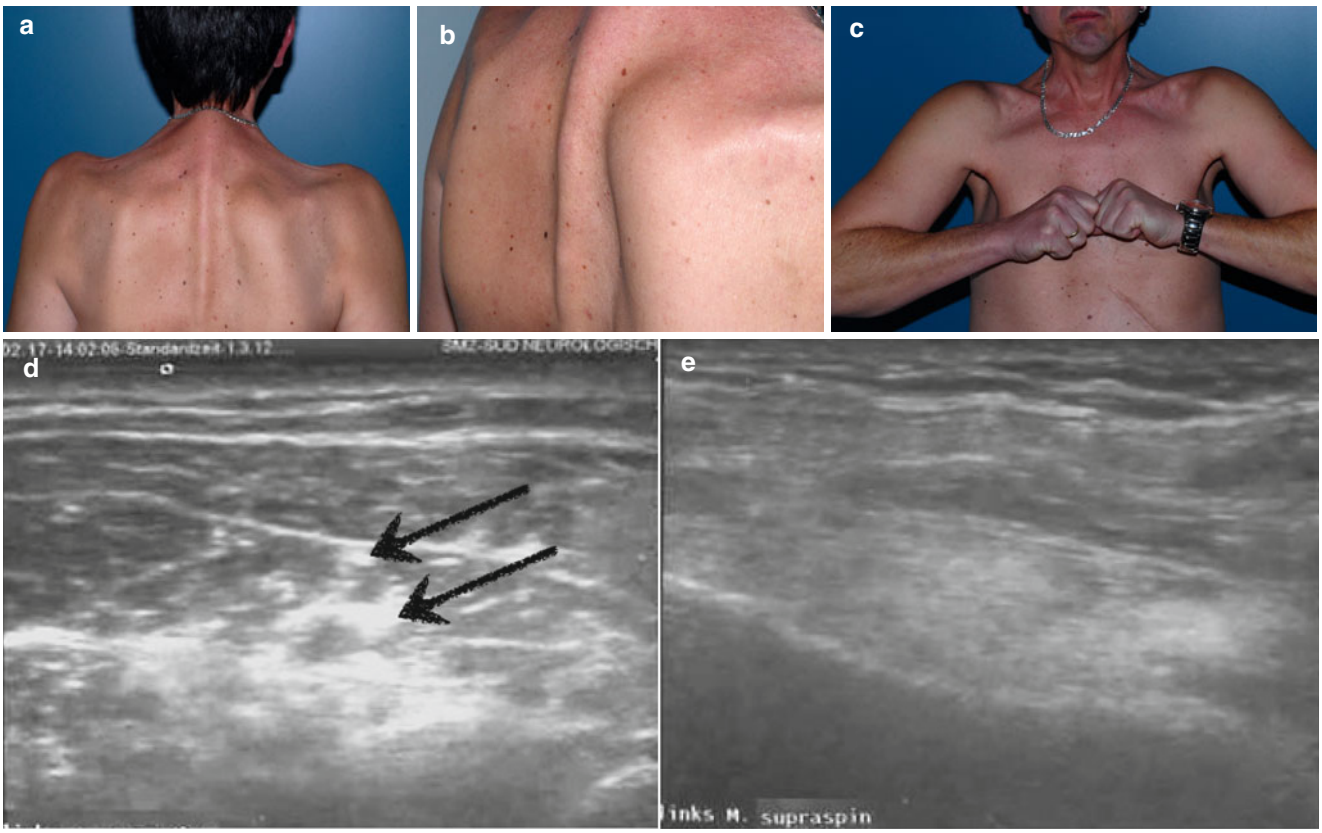


Fig. 8.50 Fibrosis of the shoulder muscles. Several years after RT for Hodgkin's disease, the patient experienced weakness and atrophy of the shoulder girdle. The inspection showed atrophy of the shoulder muscles (**a**–**c**) and fibrosis of the shoulder muscles (**d**, **e**)

8.3.8 Pectoral Nerve

Anatomy

Lateral pectoral nerve: receives fibers from C5-C7 and supplies the upper part of the pectoral muscle. Medial pectoral nerve: receives fibers from C8/T1 and supplies the lower part of the pectoral muscle.

Function

Purely motor nerve, some articular nerves to the shoulder joint. Pectoralis major: brings trunk to humerus (if humerus is fixed), adduction and medial rotation of humerus (medial and lateral pectoral nerves). Pectoralis minor: stabilizes the scapula by drawing it against the thoracic wall.

Symptoms

Reduction of arm adduction, usually not severe.

Signs

Muscle atrophy (Fig. 8.51).

Causes

The nerves are not infrequently damaged. Aplasia, entrapment in hypertrophies of minor pectoral muscle, brachial plexus lesions, neck dissection, radical mastectomy, weightlifting, seatbelt injury.

Therapy

Range of motion and strength training.

Table 8.1 Innervation and function of nerves in the shoulder girdle

Nerve	Root, Plexus	Muscle	Function	Sensory
Accessory nerve	CN XI, and spinal roots (C2-4)	Trapezoid	Side bends the head and neck to the same side, elevation of scapula, rotates glenoid fossa upwards.	
			Upper fibers: flex the head to the same side	
			Middle fibers: adduction of scapula	
			Lower fibers: adduct scapula, depress scapula	
Axillary nerve	Brachial plexus, C5-6	Deltoid	Anterior deltoid: flexion of humerus, adduction of flexed humerus	+
		Teres minor	Lateral: abduction of humerus	
			Posterior: extension of humerus	
			Lateral rotation of humerus	
Dorsal rami of middle and lower cervical nerves	C1-6	Splenii	Extension of head and neck, ipsilateral rotation and flexion	
	C2-T10	Spinalis capitis and cervicis		
Dorsal rami		Longissimus capitis	Flexion of spine laterally	
			Rotates head laterally	
Dorsal rami		Longissimus cervicis	Lateral flexion and rotation of the head	
		Other cervical spine:		
		Iliocostalis cervicis		
		Multifidi		
		Rotatores longus and brevis		
		Interspinales		
		intertransversarii		
Dorsal scapular nerve	C5	Levator scapulae	Elevation of scapula, rotates scapula medially	
Spinal nerves C3-4				
Dorsal scapular nerve	C4-5	Rhomboid major and minor	Adducts and elevates the scapula, medial rotation	
Supraspinatus	C5-6	Supraspinatus infraspinatus		
Subscapular nerve	C5-7	Teres major	Medial rotation of humerus	
Radial nerve	C6-C8	Triceps brachii		+
		Anconeus		
Thoracodorsal nerve	C6-8	Latissimus dorsi	Medial rotation when arm abducted, extension and adduction of humerus	
Long thoracic nerve	C5-7	Serratus anterior	Stabilizes scapula during flexion and abduction of arm, rotates scapula laterally, presses scapula against thorax, counteracts "winging"	
			Breathing assistance	
Superior and inferior subscapular nerve	C5-6	Subscapularis	Medial rotation and adduction of humerus	
Medial and lateral pectoral nerves	C5-T1	Pectoralis major	Adduction and medial rotation of humerus, flexion of humerus, inspiration remains (deep)	
		Pectoralis minor	Draws shoulder down and forward, lifts inferior angle of scapula away from ribs	
Subclavian nerve	C5-6	Subclavian muscle	Depresses shoulder	
Musculocutaneous nerve	C6-7	Coracobrachial muscle	Flexes arm forward, and adduction	+
	C5-6	Biceps brachii	Elbow flexion, supination of forearm, stabilizes humeral head	

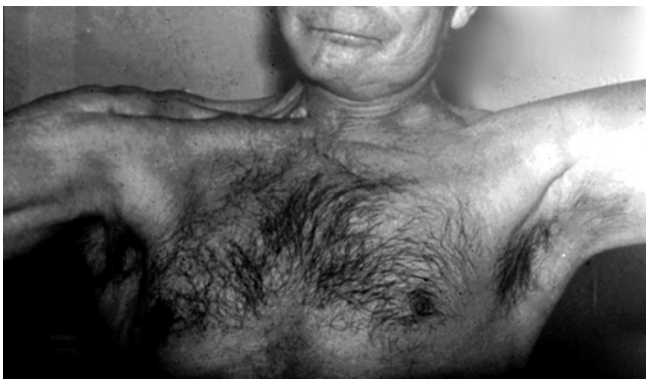


Fig. 8.51 The pectoral muscle can be damaged in neck dissection, resulting in atrophy of the pectoral muscle and severe reduction of shoulder movement

Muscle Transfer

The muscle is also used for muscle transfer in rotator cuff tears, or brachial plexus lesions.

8.3.9 Thoracic Spinal Nerves

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

Anatomy

Twelve pairs of thoracic spinal nerves innervate all muscles of the trunk and surrounding skin (except the lumbar paraspinals), and the corresponding overlying skin. Dorsal and ventral rami can be affected. Each nerve is connected with the sympathetic trunk. The dorsal rami are smaller and contain visceral motor, somatic motor, and sensory fibers to the skin and motor fibers to the muscles of the back. The thoracoabdominal nerves (T7-T11) innervate the intercostal (externals – inhalation; internals: exhalation), the subcostal, the levatores costarum, the serratus posterior superior, and the transversus thoracis. The last three send branches to the serratus posterior inferior. About mid-way in their course they give off lateral cutaneous branches. The thoracal nerves are divided into three groups: T1, T2-T6 and T7-T12:

- T1 and C8 form the first intercostal nerve;
- T2-T6 innervate the chest wall and T2 is the intercostobrachial nerve;
- T7-T11 are the thoracoabdominal nerves, and T12 is the subcostal nerve.

Symptoms

Pain, sensory symptoms, depending on whether the dorsal or ventral ramus is affected.

Signs

Muscle weakness is difficult to assess in the intercostal muscles. Weakness of abdominal muscles can be seen as muscles that bulge and increase with coughing. Tinel's sign on the ribs is suggestive of a neuroma.

Pathogenesis

Compressive Thoracic disc disease (rare, in T8-T12), nerve root compression (tumors), compression of the "notalgia paresthetica" dorsal branch. Ventral branch: abdominal cutaneous nerve entrapment when piercing through the rectus abdominis muscle and sheath.

Iatrogenic Postoperative (abdominal surgery, thoracotomy, lung biopsy).

Infectious Herpes (also preherpetic neuralgia), herpetic neuralgia, postherpetic neuralgia.

Metabolic Diabetic truncal neuropathy.

Neoplastic Lung tumors, schwannomas, vertebral metastasis (local vertebral pain is common).

Pregnancy Throraconeuralgia gravidarum (pain and sensory symptoms in upper abdomen).

Diagnosis

Laboratory: fasting glucose, serology (e.g., herpes). *CSF*: meningeal involvement in Lyme disease, neoplastic cells. *NCV/EMG*: NCV of intercostal muscles not routinely available. EMG of intercostals, abdominal wall muscles and paraspinal muscles.

Differential Diagnosis

"Intercostal neuralgia," hernia (bulging due to abdominal weakness), painful condition of the vertebral column radiating into the trunk (spondylodiscitis, metastasis), slipping rib (Cyriax syndrome).

Therapy

Depends on cause.

8.3.10 Intercostal Nerves

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+/–	+	Vertebral column ribs	

Anatomy

The intercostal nerves are the ventral rami of the thoracic spinal nerves (T1-T11). They innervate the intercostal (first 6) and abdominal muscles (lower 6), as well as the skin (via

anterior and lateral branches). The first ventral ramus is part of the brachial plexus; a smaller branch is the first anterior cutaneous branch of the thorax. Each nerve is connected with the sympathetic trunk. The dorsal rami are smaller and carry visceral motor, somatic motor, and sensory information to the skin and muscles of the back. 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 the medial cord of the brachial plexus) (see intercostobrachial nerve).

Symptoms
Pain, in particular radicular pain (belt-like). Dorsalgia (notalgia paresthetica): sensory neuropathy affecting mostly the posterior rami from T2-T6. Results in itching, pruritus, paresthesia and pain.

Signs
No muscle weakness can be detected.

Site of the Lesion
Thoracic spinal nerve, medial cutaneous nerve entrapment, dorsal branch (notalgia paresthetica, T2-T6).

Pathogenesis
Diabetic truncal neuropathy, herpes zoster, neuropathy: sarcoidosis, Sjögren's, neurolymphomatosis, notalgia paresthetica (dorsal rami), post-operatively: abdominal, retroperitoneal, and renal surgery. Post-thoracotomy syndrome, traumatic lesions of the thoracic spine, thoracic disc trauma (rarely), vertebral metastasis.

Diagnosis
Laboratory: Diabetes, paraproteinemia, 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. Pain can be also caused by a compartment syndrome of the rectus abdominis muscle, costochondritis, hernia, "intercostal neuralgia," pseudoradicular pain, rupture of the rectus abdominis muscle, syringomyelia, or thoraconeuralgia gravidarum.

Therapy
Depending on the cause of the lesion.

Prognosis
Depending on the etiology.

8.3.11 Intercostobrachial Nerve

Anatomy
Originates from the lateral cutaneous nerve of the second and third intercostal nerves to innervate the posterior part of the axilla and upper half of the medial and posterior arm. The nerve often anastomizes with the medial cutaneous nerve of the upper arm (from the medial cord of the brachial plexus). A second intercostobrachial nerve frequently branches off the lateral cutaneous branch of the third intercostal nerve to innervate the axilla and medial side of the arm.

Symptoms
Neuropathic pain in the axilla, chest wall or thorax combined with numbness in the nerve distribution. Often occurs 1–2 months after mastectomy. Reduced movement of the shoulder enhances pain, and can influence posture.

Signs
Sensation is impaired in the axilla, chest wall, and proximal medial and posterior upper arm. Neuralgic pain can restrict shoulder movement (Fig. 8.52).

Causes
Axillary adenectomy, malignant invasion (lung tumors), post mastectomy.

Diagnosis
Clinical: history and sensory loss.

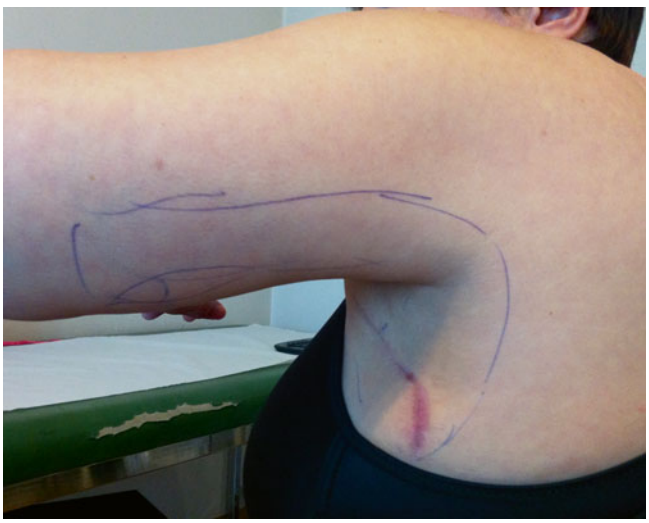


Fig. 8.52 After breast surgery with removal of axillary lymph nodes, the patient had a sensory loss in the axilla and upper arm, corresponding to the area of the intercostobrachial nerve. In addition to numbness, the patient experienced neuropathic pain, limiting shoulder movement

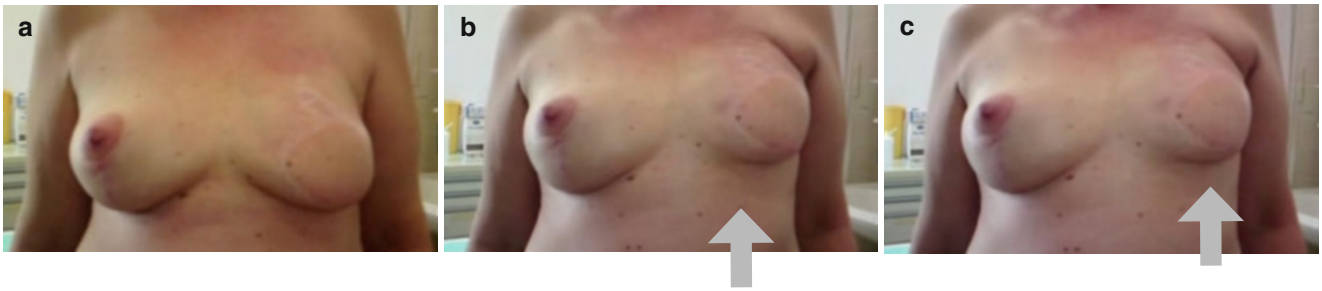


Fig. 8.53 Breast reconstruction with a latissimus dorsi flap. (**a**) Normal position. (**b**, **c**) Involuntary contractions of the transpositioned muscle lead to involuntary movements and elevation of the breast (*arrows*: direction of movements) (photos from a video documentation)

Differential Diagnosis

Intercostal neuromas, lung tumors, operations in the axilla (removal of lymph nodes, breast surgery) and for thoracic outlet syndrome.

8.3.12 Around the Breast

The breast can be a source of pain, usually in cancer patients following breast surgery. The term postmastectomy syndrome comprises a variety of pain syndromes following surgery of the breast. In addition, surgical procedures such as the latissimus dorsi flap can cause discomfort, as can hormone therapies resulting in painful gynecomastia.

Postmastectomy Syndrome (PMS)

Describes chronic pain syndromes following surgery for breast cancer. It can develop in 20–60 % of patients. Neuropathic pain occurs secondary to lesions of nerves in the breast and axilla. The prevalence of PMS is higher after lumpectomy than after mastectomy. Pain is often of neuralgic quality, and is located in the axilla (80 %), shoulder, arm or chest wall, or at the scar.

Intercostobrachial Nerve

The intercostobrachial nerve is described separately in this book (see above). Operations in the axilla and removal of lymph nodes can damage the nerve, which often has extensive branches in the axilla. Patients report sensory loss at the dorsal arm after surgery. Movement of the arm and shoulder can result in neuropathic pain radiating in the arm. Often the post-surgical symptoms are attributed to local scars and infections.

Scar Pain and Neuroma

Neuroma scar pain: can follow surgery in the breast and axilla, and is usually associated with neuropathic pain. Other causes for chronic pain after treatment for breast cancer include intercostal neuromas. Other types of nerve injury pain may result from damage or traction to the medial and lateral pectoral, long thoracic, or thoracodorsal nerves.

Phantom Pain

In the "phantom breast syndrome" (PBS) patients have a sensation of residual breast tissue and experience both non-painful sensations as well as phantom breast pain. Patients experience pain and discomfort, itching, pins and needles sensations, tingling, pressure, burning, and throbbing. The syndrome can begin even one year after surgery. The incidence varies.

Latissimus Dorsi Flap

The latissimus dorsi flap is an established method to use part of the latissimus dorsi to replace breast tissue for reconstruction. Two aspects deserve attention: the surgery site at the back where the muscle is harvested, and pathological co-innervation, which can induce unwanted movement of the breast (Fig. 8.53).

Male Gynecomastia

Painful gynecomastia is observed in elderly males who receive hormone therapy.

8.3.13 Abdominal Walls and Their Innervation

Muscular Innervation of the Abdominal Cavity

The abdominal cavity is a cylindrical space which has two cupula-like tops/bottoms (diaphragm and pelvic floor), a rigid posterior face with the spine and ribs, and a multilayer ventral soft abdominal wall which is formed by several layers of muscle and fascia. The evolutionary structure of the abdominal cavity is similar in amphibians, birds and humans. The inner surface is the mesothelium, which is pain-sensitive and involved in several abdominal diseases. The contents of the cavity, inner organs and the intestine, are innervated by the autonomic system and will not be discussed here. This summary focuses on the muscular and sensory innervation and does not discuss the complex autonomic innervation of the

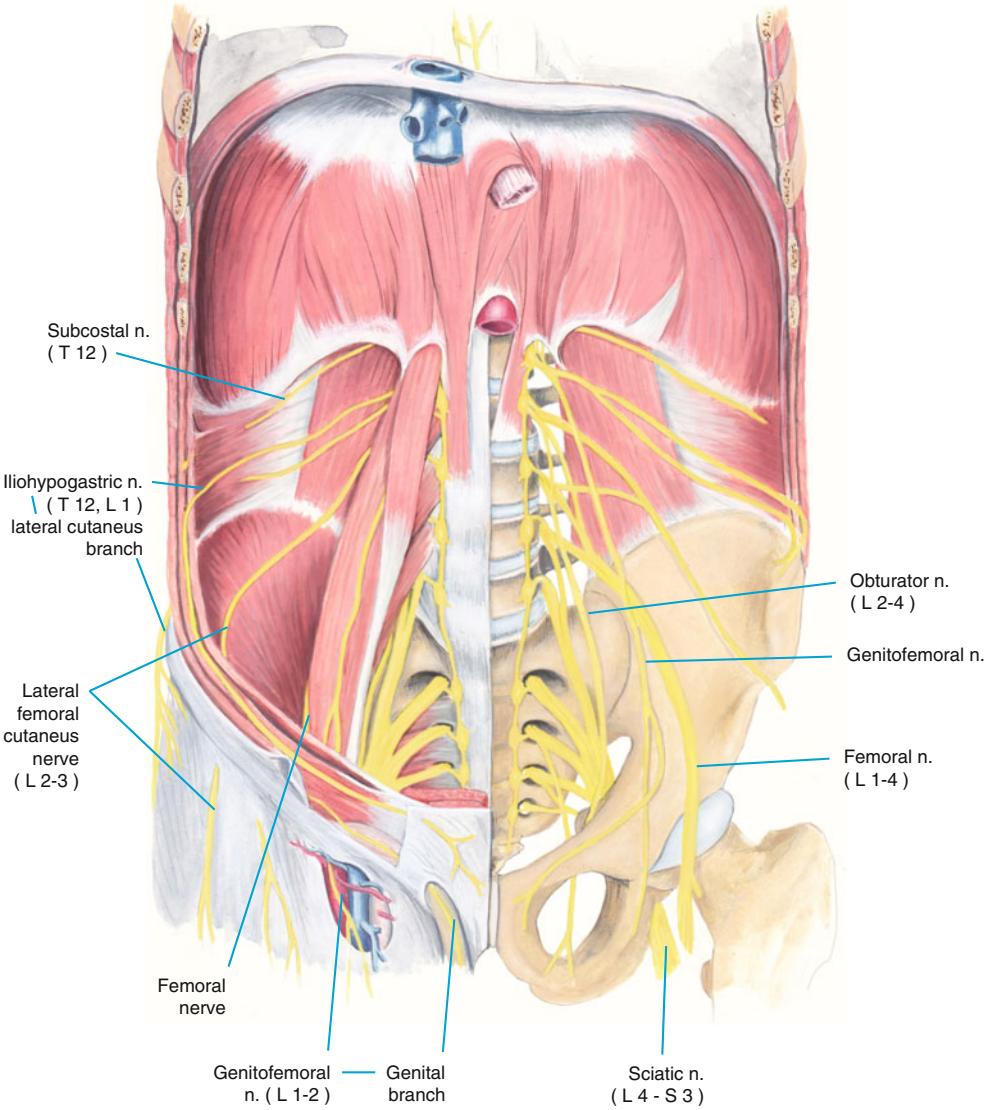


Fig. 8.54 Abdominal wall muscles

abdominal cavity, as well as the autonomic innervation that comes from both the vagus nerve and sacral plexus and the sympathetic nervous system. Clinical symptoms are variable and consist of weakness-related syndromes, resulting in hernia, breathing abnormalities and also disturbed posture and gait.

Anterior Abdominal Wall Muscles and Innervation

The layers of the abdominal wall are (from superficial to deep) formed thusly: the outer surface is formed by skin and fascia below. The muscles of the anterior wall are the rectus abdominis muscle, the external oblique muscles (innervated by the 6 intercostal-thoracoabdominal nerves and the subcostal nerve, the internal oblique muscles (innervated by the lower costal nerves), and the transverse abdominal muscle, which is innervated by the lower intercostal nerves (thoracoabdominal nerves), and also by the iliohypogastric and ilioinguinal nerves. They constitute the ventral wall of the abdominal cavity (Fig. 8.54). Clinical scenarios of damage are focal abdominal wall weakness either due to hernia or muscle weakness as seen in truncal neuropathy in diabetes, or as a result of abdominal surgery (Fig. 8.55). Also, myopathies can be associated with a weakness of abdominal wall muscles (see Beevor's sign). Fascia serve as soft tissue for muscle attachments. The fascia of psoas major forms the medial arcuate ligament associated with the diaphragm; inferiorly, the fascia extends to the thigh and contributes to the structure of the abdominal wall. Fascia of the quadratus lumborum (forming superiorly the lateral arcuate ligament of the diaphragm) and the thoracolumbar fascia anchored on the erector spinae, transverse processes, and the quadratus lumborum also contribute to abdominal wall structure.

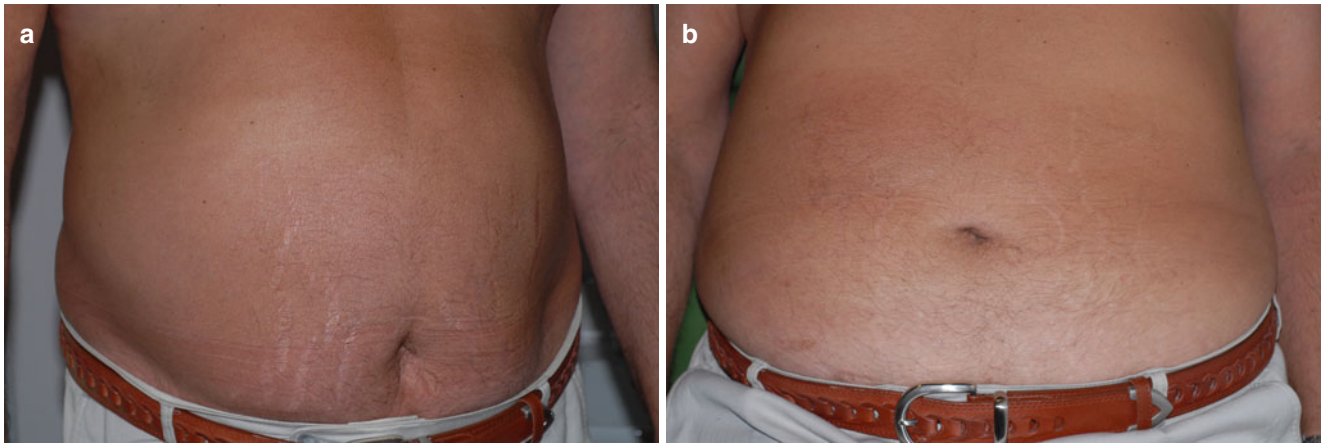


Fig. 8.55 Abdominal wall weakness: In a patient with diabetes, weakness of the abdominal muscles causes bulging of the abdominal wall. Sit-ups are difficult. The bulging is often mistakenly thought to be a hernia

Posterior Wall

The posterior wall of the abdominal cavity is formed by the vertebral column, the ribs and the retroperitoneal space. Rarely posterior hernias in particular after trauma (e.g., fracture of the pelvis) can occur, into the lumbar triangles, the lumbar muscles and the obturator foramen, compressing the obturator nerve (causing pain radiating to the knee). Also, sciatic and perineal hernias have been described. They occur at areas of weakness in the urogenital diaphragm, elevator ani muscle or coccygeal muscle.

Upper Cupula: Diaphragm

The upper cupula is formed by the diaphragm, which is innervated by the phrenic nerve. Unilateral dysfunction or plegia causes specific respiratory symptoms. In addition to the diaphragm, simultaneous contraction of accessory muscles of respiration (scalene, parasternal portion of the internal and external intercostal muscles, sternocleidomastoid, trapezius) are affected. Also, general muscle weakness, permanent, transient or fluctuating in nature, affect diaphragmatic function. The diaphragm is a boundary between the negative pressure thoracic cavity and the positive pressure abdominal cavity. The elevation of intra-abdominal pressure – for example, during defecation – is produced by a co-contraction of the diaphragm and pelvic floor in addition to the abdominal muscles. Rarely also hernia (hiatal and lateral) occur, and can cause local pain syndromes. Diaphragmatic injury is graded according to a severity scale (Grade I contusion thru Grade V laceration and tissue loss). In addition to blunt trauma, penetrating injuries (stab and gunshot wounds) can occur. Abdominal contents can herniate into the chest. The phrenic nerve can also be damaged by diaphragmatic tears.

Lower Cupula

The pelvic floor is a bowl-shaped structure whose rim is formed by the pelvic girdle (sacrum, ileum, ischium and pubis). Striated muscle is provided by the ileococcygeus and pubococcygeus muscles, as well as the coccygeus and puborectal muscle. The bone and muscle are interconnected with connective tissue and support the pelvic viscera (vagina, rectum, bladder). These structures are functionally involved in excretory functions. The anorectal angle can be seen in dynamic MR images upon defecation (Fig. 8.56). The levator ani nerve originates from the S3-S5 sacral spinal roots and innervates the levator ani muscle. The pudendal nerve innervates the sphincters of the urethra, the rectum, bulbocaverosus and ischiocavernosus muscles. The caudal extension of the smooth muscles from the rectum into the anal canal constitutes the internal anal sphincter.

Rectus Abdominis

Innervated by the thoracoabdominal nerves, run from the xyphoid to the symphysis and are contained in a sheath.

External Oblique Muscle

Innervated by ventral branches of the lower 6 intercostal (thoracoabdominal) nerves and the subcostal nerve on each side.

Internal Oblique Muscle

Innervated by lower intercostal nerves, as well as the iliohypogastric nerve and the ilioinguinal nerve. In men, the cremaster muscle is attached to the muscle.

Transverse Abdominal Muscle

Innervated by the lower intercostal nerves (thoracoabdominal, nerve root T7-T11), as well as the iliohypogastric nerve and the ilioinguinal nerve.

Posterior Abdominal Wall

The posterior abdominal wall is composed of bones (L1-L5), the ala of the sacrum and ala of the ilium, the anterior

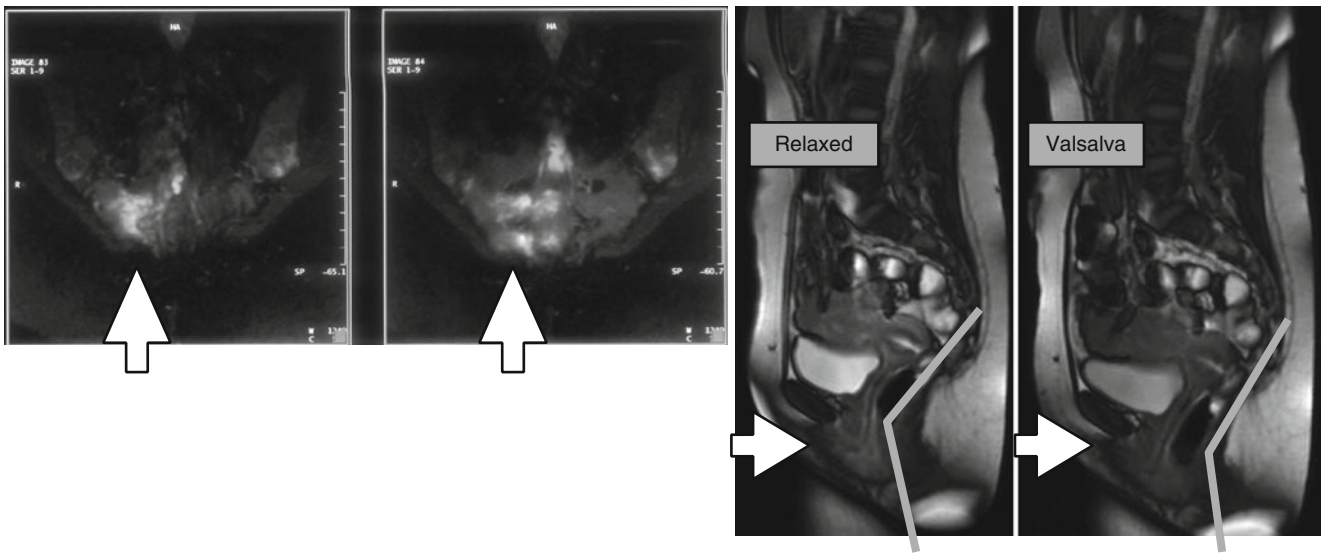


Fig. 8.56 Pelvic floor and muscle imaging. This patient had an iatrogenic lesion of the sacral plexus after a bone marrow harvest. The puncture was via the sacrum and can be seen in MR as edema (**a**). She could control her anal sphincter, but had difficulties in defecation. The functional MR revealed that the anorectal angle (*arrow*), remained unchanged during defacation. (**b**) There was no change in the anorectal angle (*white bars*) during Valsalva, indicating no contraction of the pelvic floor muscles

sacral-iliac ligaments and the iliac fossa on the anterior surface of the ala of the ilium.

Rostral Cupula

The superior cupula is the diaphragm (phrenic nerve). The muscles are the quadratus lumborum subcostalis and plexus lumbalis, the psoas major, and the iliacus muscle covered by fascia.

Nerves Involved

Subcostal nerve (T12), iliohypogastric nerve (L1), ilioinguinal nerve (L1), genitofemoral (L1-L2), lateral femoral cutaneous (L2-L3), femoral nerve (L2-L4), obturator nerve (L2-L4), lumbosacral trunk (L4-L5). The nerves of the posterior abdominal wall include the subcostal nerve (T12) and the lumbar plexus (L1-L5).

Subcostal nerve (T12): runs under the 12th rib and travels between the internal oblique and transverse abdominus, giving off cutaneous branches. Iliohypogastric (L1): anterior to the quadradus lumborum. It supplies the muscles of the lower abdominal wall as well as the skin over the pubic region. Ilioinguinal (L1): travels through the inguinal ring and into the scrotum/labia majora. Genitofemoral (L1-L2): on the anterior surface of psoas major. It travels toward the anterior part of the pelvis and branches into the femoral branch to the anterior surface of the thigh, and the genital branch to the cremaster muscle. Lateral femoral cutaneous (L2-L3): travels more laterally on the surface of the iliacus muscle and passes under the inguinal ligament. It supplies the lateral aspect of the thigh. Femoral (L2-L4): the largest nerve in the lumbar plexus travels under psoas major and supplies the extensors of the knee. Obturator (L2-L4): found on the medial aspect of psoas major and drops into the true pelvis through the operator canal. It supplies the main adductor muscles on the medial aspect of the thigh. Lumbosacral trunk (L4-L5): it is the most medial nerve of the plexus and runs over the ala of the sacrum. It contributes to the sacral plexus.

Muscular Components

Quadratus lumborum: a square muscle in the lumbar region that attaches to the 12th rib superiorly, transverse processes of L1-L4 medially, the iliolumbar ligament (transverse process running from L5 to ala of ilium) inferiorly, and the iliac crest laterally. Bilateral contraction extends to the back with erector spinae muscles. Unilateral contraction causes unilateral bending. The muscles are innervated by the ventral rami of T12-L4. Psoas major: Attaches to the transverse processes of L1-L4 superiorly, bodies and intervertebral disks medially, the lesser trocanter inferiorly. To reach the lesser trocanter, it passes the pelvis under the inguinal ligament. Contraction flexes the hip joint. It is innervated by L2-L4 ventral rami. Iliacus muscle: attaches to the superior two-thirds of the iliac fossa superiorly, the ala of sacrum medially (anterior to the anterior sacro-iliac ligament), and the lesser trocanter inferiorly. Combined with psoas major, the iliopsoas muscle is the primary flexor of the thigh. It is innervated by the L2-L4 ventral rami as the rami form the femoral nerve.

Fasica

Psoas: Superiorly, the fascia of psoas major forms the medial arcuate ligament associated with the diaphragm. Inferiorly, the fascia extends to the thigh. Quadratus lumborum: superiorly, the fascia forms the lateral arcuate ligament of the diaphragm. The quadratus lumborum fascia is located latero-posteriorly to the psoas. *Thoracolumbar*: dascia is anchored on the erector spinae, transverse processes, and the quadratus lumborum.

8.3.14 Iliohypogastric Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
			+	

Anatomy

Fibers originate at L1, then emerge from the lateral border of the psoas, crossing the lower border of the kidney, then reach the lateral abdominal wall. The nerve crosses the transverse abdominal muscle above the iliac crest and passes between the transverse and oblique internal abdominal muscles supplying them with motor branches. Finally, two branches are given off: the lateral cutaneous (gluteal region posterior of lateral cutaneous branch of T 12) and anterior cutaneous nerves (hypogastric region; Fig. 8.57).

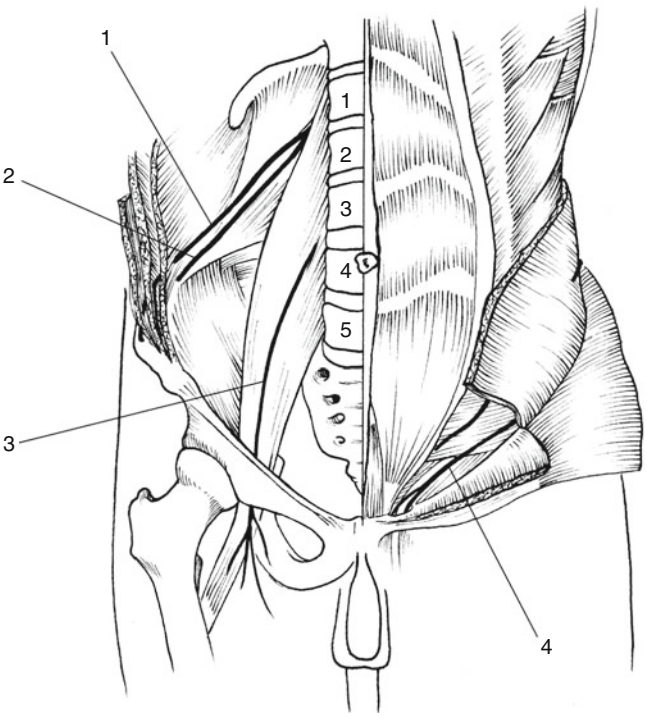


Fig. 8.57 *1* Iliohypogastric nerve. *2* Ilioinguinal nerve. *3* Obturator nerve. *4* Genitofemoral nerve

Symptoms

Burning and stabbing pain in the ilioinguinal region, which may radiate towards the genital area or hip. Occasionally neuralgia. Minor sensory loss. Symptoms increase when walking.

Signs

Difficult to examine in isolation. Spontaneous bulging of the abdominal wall (usually minor and only present if combined with a lesion of the ilioinguinal nerve). Minor sensory deficit may be present in the iliac crest and inguinal region. Tinel's sign can be present over a surgical scar. Sit-ups may enhance protrusion of the abdominal wall. The distinction between ilioinguinal and genitofemoral nerve lesions can be difficult due to variable sensory innervation.

Sites of Lesion

Retroperitoneal. Lower abdominal quadrant, inguinal canal.

Causes

Abdominal laparoscopy with large abdominal scars, appendectomy, hysterectomy; childbirth, inguinal herniorraphy, isolated lesion of the lateral branch secondary to compression over the iliac crest, postoperative scarring, renal surgery, tumor: retroperitoneal, lipoma.

Diagnosis

Electrophysiology not reliable. Nerve ultrasound.

Differential Diagnosis

Spontaneous entrapment in the abdominal wall, surgery, herniorraphy, appendectomy, abdominoplasty, nephrectomy, endometriosis, postherniorraphy pain.

Therapy

Steroids locally, scar removal, neurolysis.

8.3.15 Ilioinguinal Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
			+	

Anatomy

The ilioinguinal nerve originates from T12 and L1 and runs caudally from the iliohypogastric nerve. It pierces the transverse abdominis muscle near the anterior part of the iliac crest. The motor component innervates the internal and external oblique muscles, and the transverse abdominal muscle. It communicates with the iliohypogastric nerve. The sensory component (ramus cutaneous anterior) covers the skin overlying the pubic symphysis, the superomedial

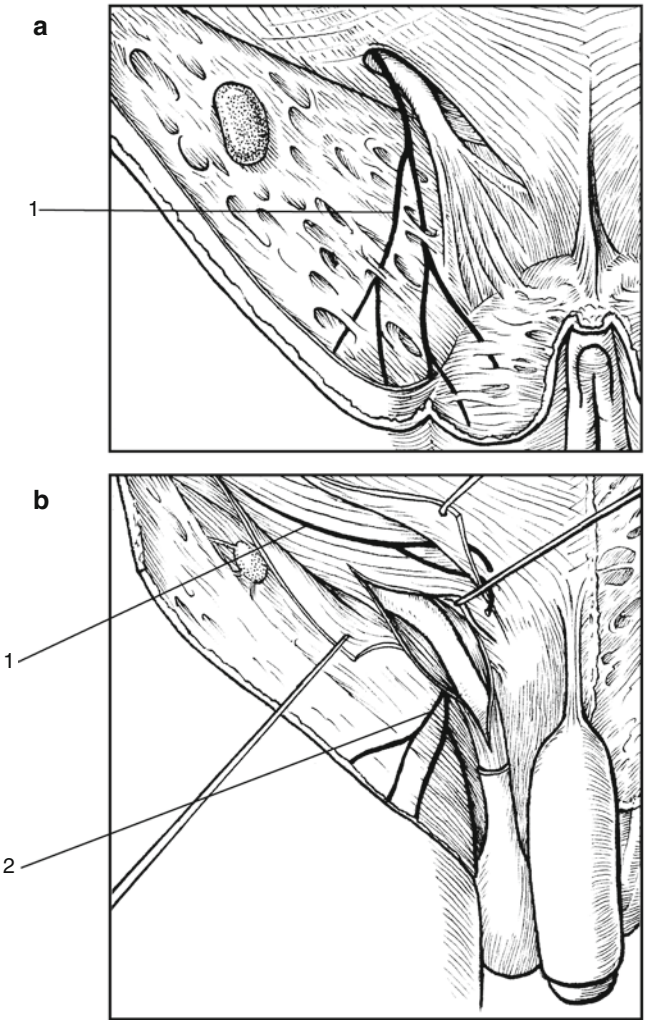


Fig. 8.58 (**a**) Female. *1* Ilioinguinal nerve. (**b**) Male. *1* Iliohypogastric nerve. *2* Ilioinguinal nerve

aspect of the femoral triangle, the anterior scrotal surface, and the root of the penis/labia majora and mons pubis (Fig. 8.58).

Clinical Syndrome

Hyperesthesia, sometimes with significant pain over the lower abdominal quadrant and the inguinal region and genitalia. Weakness of lower abdominal muscles, hernia (Fig. 8.59).

Signs

Sensory abnormalities in the groin, scrotum or labia, proximal inner thigh, sometimes groin pain and neuralgia.

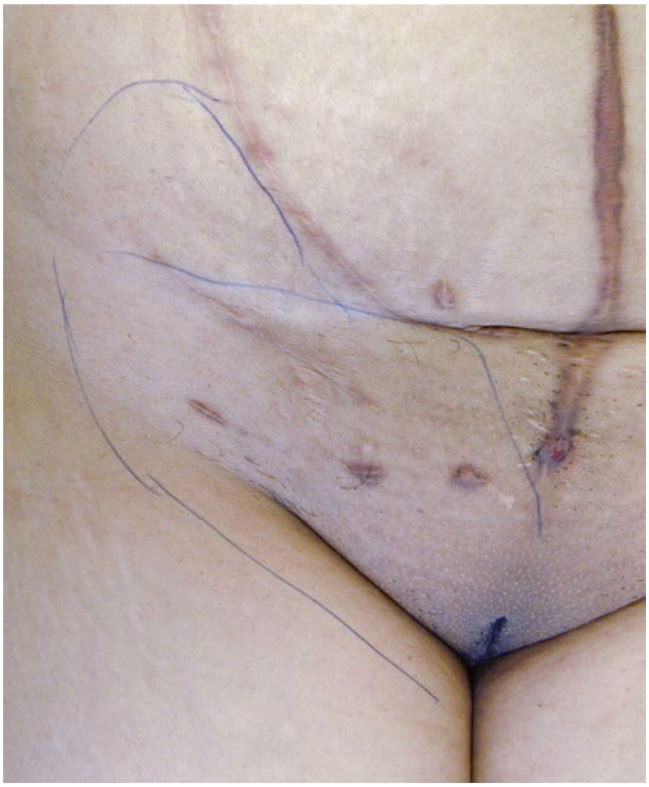


Fig. 8.59 Ilioinguinal nerve lesion after gynecological surgery. The sensory loss (marked with a ball pen) reached almost the labia

Causes

Abdominal surgery with a laterally placed incision, biopsy, endometriosis, leiomyoma, lipoma, entrapment syndrome, herniotomy (and postherniotomy pain), iliac bone harvesting, pregnancy, childbirth, retroperitoneal: surgery, tumors, spontaneous entrapment – "inguinal neuralgia" (Fig. 8.60).

Diagnosis

Studies: no standard electrophysiological techniques are available, US: can be an option, MRI.

Therapy

Local anesthetic infiltration, surgical exploration and resection of the nerve.

Differential Diagnosis

Genitofemoral neuropathy, inguinal pain syndrome, iliohypogastric neuropathy, L1 radiculopathy (very rare).

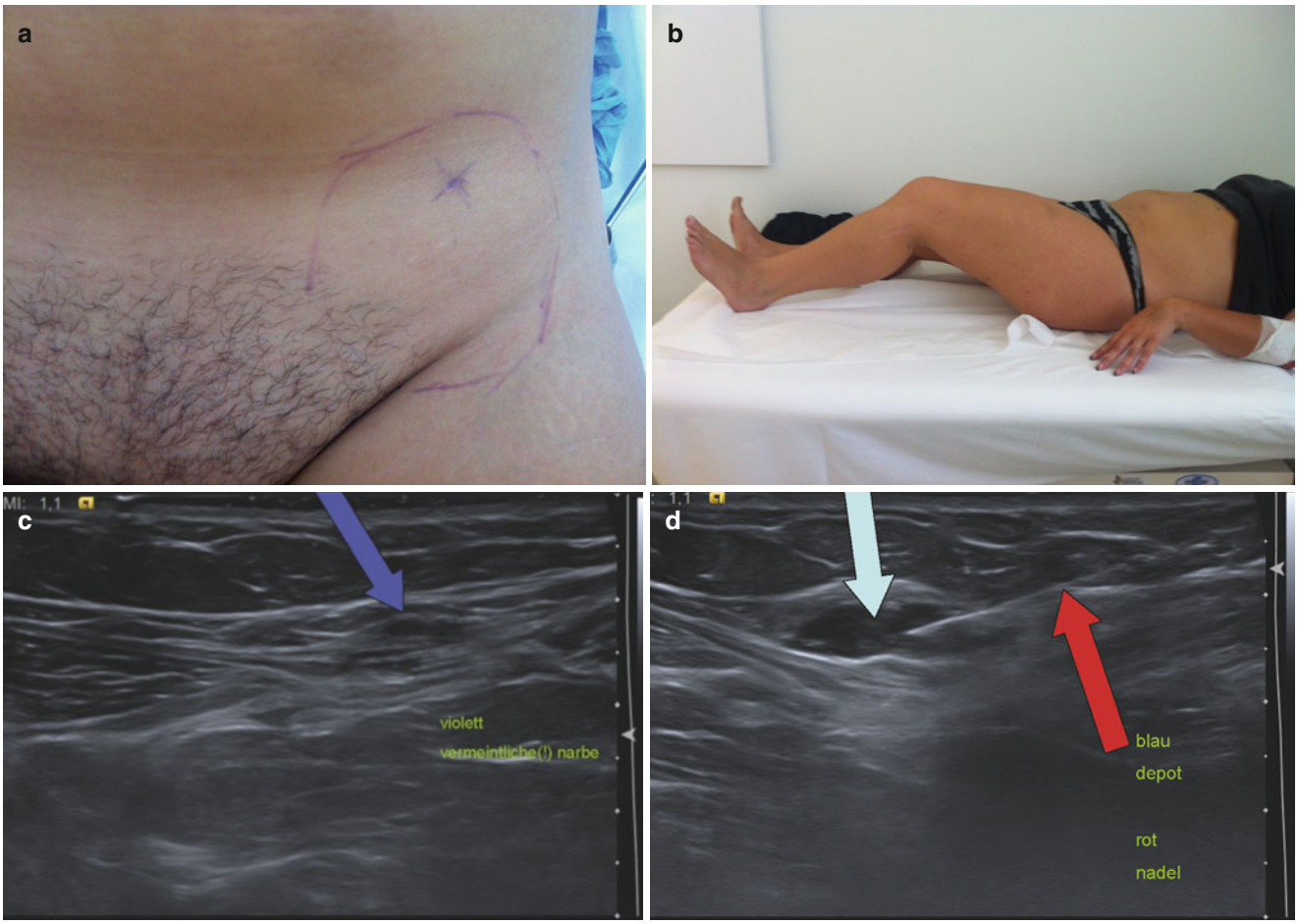


Fig. 8.60 Painful lesion of the ilioinguinal nerve after an endoscopic intervention. The cross marks the scar of the site of endoscopy; percussion of the scar elicited a Tinel's sign (**a**). Lying in a supine position, the patient could not stretch leg due to pain (**b**). Ultrasound of the area of the scar showed a focally enlarged iniinguinal nerve (**c**: *violet arrow*), the application of a local anesthetic is shown in (**d**) (*red arrow* needle, *blue arrow* local fluid deposit)

8.3.16 Genitofemoral Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
			+	

Anatomy

The nerve originates from the ventral primary rami of L1 and L2, then courses adjacent to 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 innervates the cremaster muscle, while the femoral branch innervates the proximal anterior thigh. Genitofemoral nerve lesions are rare.

Symptoms

Groin pain. Paresthesias (may be painful) of the medial inguinal region, upper thigh, side of scrotum and labium majora. Pain, sometimes called "spermatic and inguinal neuralgia" can be constant.

Signs

Tenderness in the inguinal canal. Cremaster reflex is unreliable but can be absent.

Causes
Appendectomy, bone graft removal, herniorraphy, nephrectomy, trauma, tumors (uncommon), tuberculosis, varicocele testis.

Diagnosis
No electrophysiological studies are available, diagnostic anesthetic blockade, US.

Differential Diagnosis
Spectrum of lesions of the iliohypogastric and ilioinguinal nerve and L1-L2 radiculopathy (rare) are similar.

Therapy
Neuropathic pain medications (gabapentin), topical treatment (lidocaine), anesthetic blockade, operative neurolysis.

Prognosis
Good.

8.3.17 Superior and Inferior Gluteal Nerves

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

Anatomy
The *superior gluteal nerve* originates with the posterior branches from ventral rami of L4-S1, to innervate the gluteus medius and minimus and tensor fasciae latae muscles. The *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 (Fig. 8.61).

Symptoms and Signs
Superior: Causes a gait disorder: Trendelenburg's gait. Excessive drop of the non-weight-bearing limb and a steppage gait on the unaffected side. Hip adduction is weak, but sensation is normal. *Inferior*: causes buttock pain and weak hip extension (weakness arising from a sitting position; Fig. 8.62).

Pathogenesis
Superior: misplaced injection, trauma (fractures), hemorrhage, arthroplasty, aneurysm, penetrating wounds, nerve ischemia, IV drug abuse. *Inferior*: rarely isolated, often associated with the sciatic nerve, occasionally with the pudendal nerve. Colorectal carcinoma, injections, trauma.

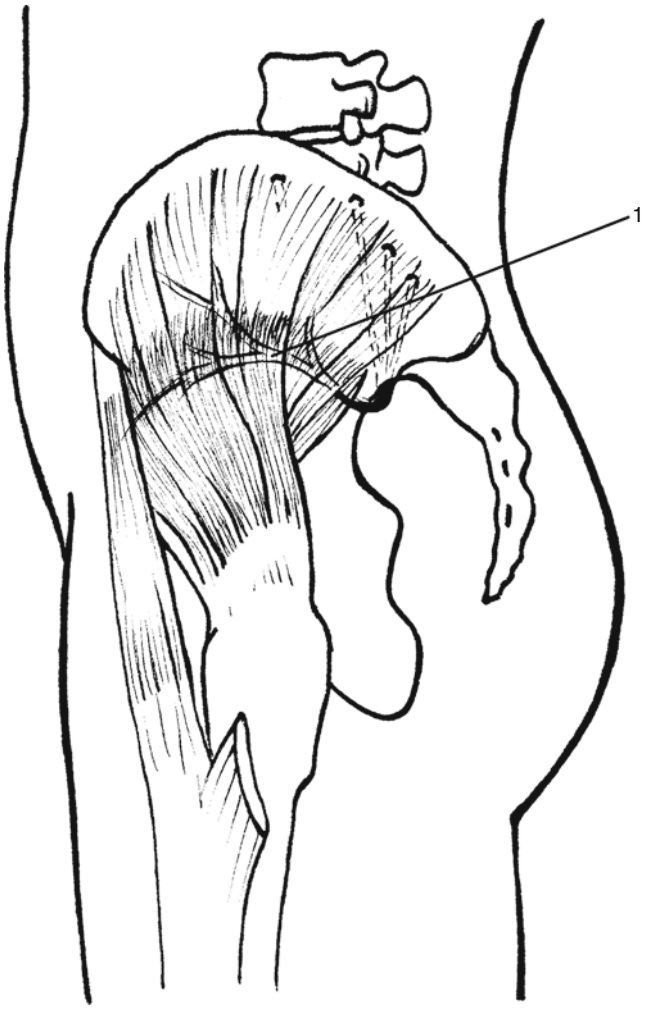


Fig. 8.61 *1* Gluteal superior nerve

Diagnosis
EMG, MRI transverse sections through the pelvis.

Differential Diagnosis
Sacral plexus lesion. Hip and pelvic pathology.

Therapy/Prognosis
Permanent lesions require physiotherapy and orthopedic interventions.

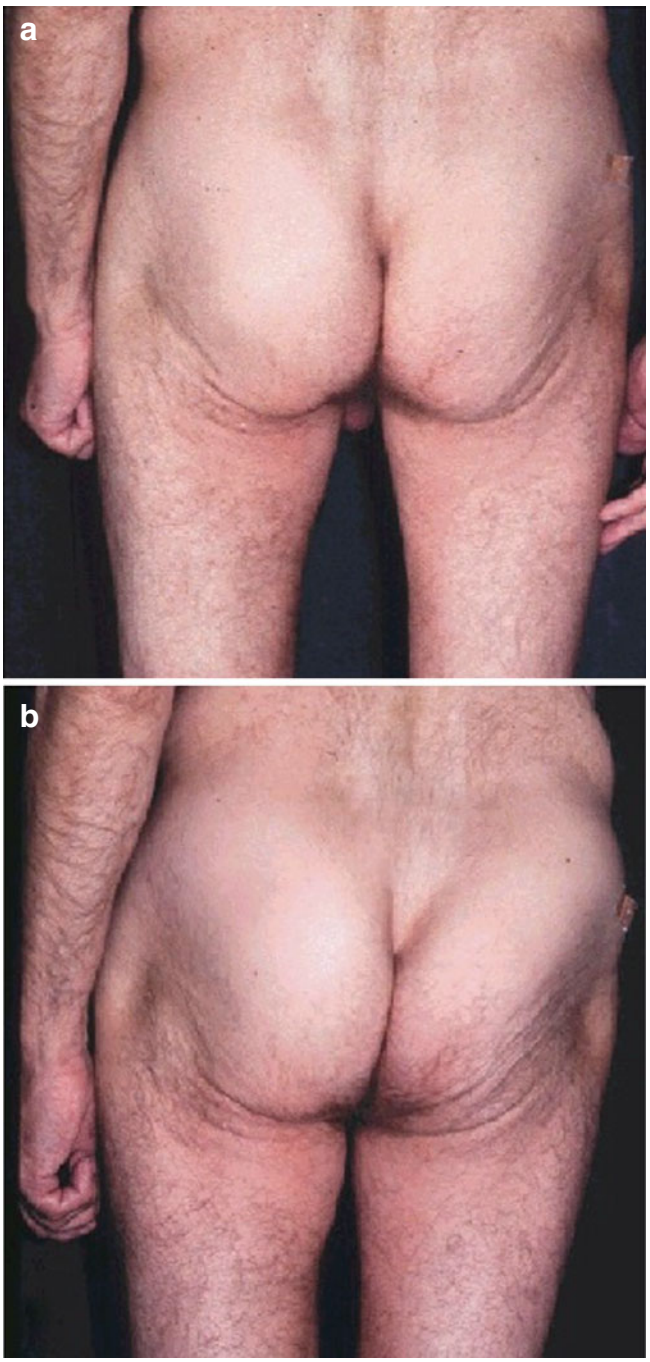


Fig. 8.62 Trendelenburg's sign, indicating weakness of the hip abductors (gluteus medius muscle). (**a**) Standing on both feet, the pelvis remains in horizontal position. (**b**) When the patient stands on his left leg, his pelvis tilts to the right. This patient had a left gluteus medius nerve lesion caused by an iliac aneurysm. Note that the greater gluteal muscles are not affected

8.3.18 Pudendal Nerve

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

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; Figs. 8.63, 8.64 and 8.65).

Symptoms and Signs

Perineal sensory symptoms, sexual and sphincter dysfunctions. One-sided lesions may cause urinary or fecal incontinence, impotence/anorgasmy, and sensory disturbances. Injuries are not common, as the nerve is deeply positioned and well protected. A possible entrapment site is the Alcock canal. Sphincter reflexes (anal, bulbocavernosus reflex) absent.

Causes

Entrapment: Alcock canal. External compression: perineal, postoperatively after hip fractures, long bicycle rides, suturing through sacrospinal ligament during colposcopy. Intrapelvic lesions: metastasis, postoperative, endometriosis, bone marrow harvest. Nerve stretch: childbirth, straining during defecation. Trauma: pelvic fracture, pelvic surgery, hip dislocation, intra-articular foreign body.

Differential Diagnosis

Radicular lesion (S2-S4), sacral plexus lesions, structural abnormalities of the pelvic floor or viscera.

Diagnosis

EMG of external anal or uretheric sphincter, pudendal SEP, anorectal manometry, urodynamic examinations. Functional MRI of pelvic floor.

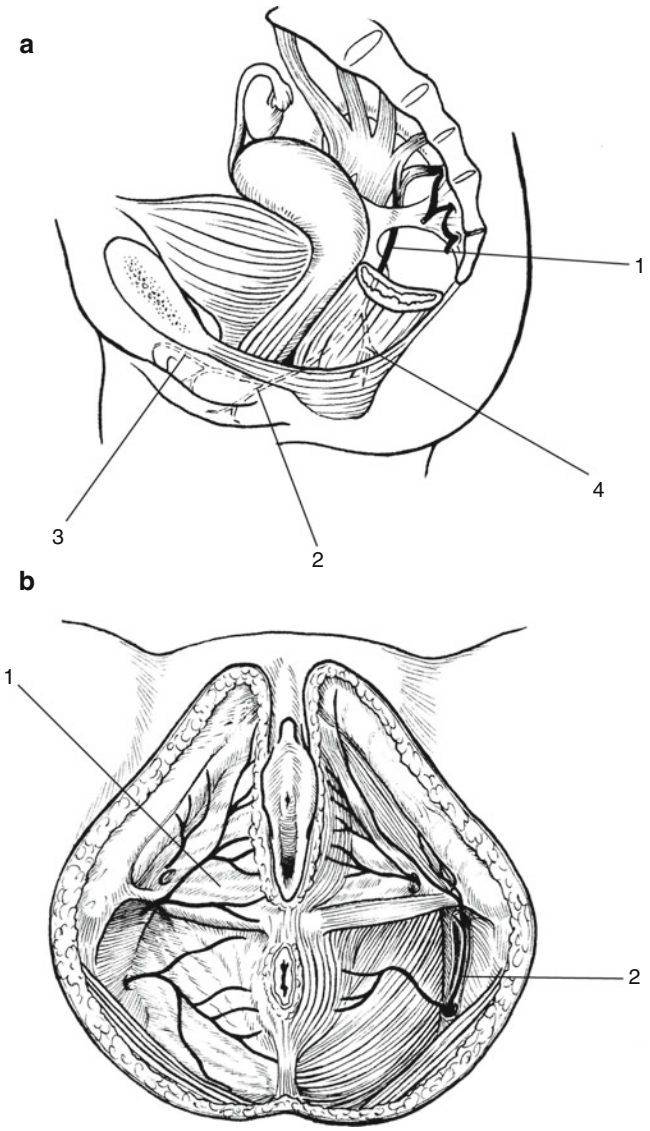


Fig. 8.63 (**a**) *1* Pudendal nerve. *2* Perineal nerves. *3* Dorsal nerve of clitoris. *4* Inferior rectal nerves. (**b**) *1* Perineal nerves. *2* Pudendal nerves

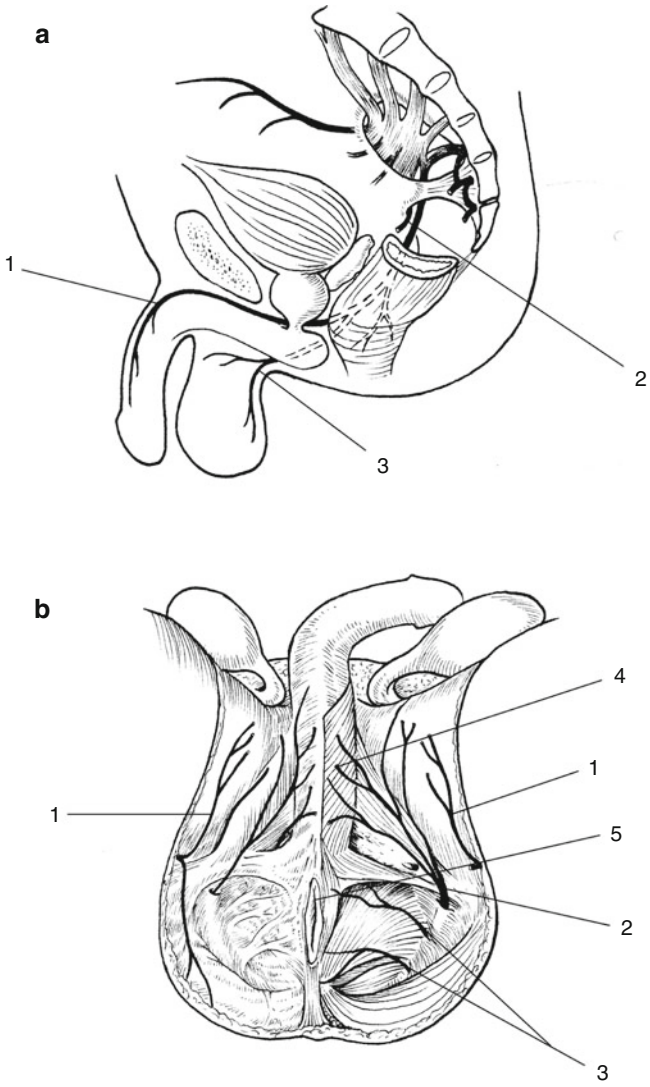


Fig. 8.64 (**a**) *1* Dorsal nerve of penis. *2* Pudendal nerve. *3* Perineal nerves. (**b**) *1* Perineal branch of cutaneous femoral nerve. *2* Pudendal nerve. *3* Rectal inferior nerves. *4* Bulbo spongiosus muscle. *5* Extemal anal sphincter muscle

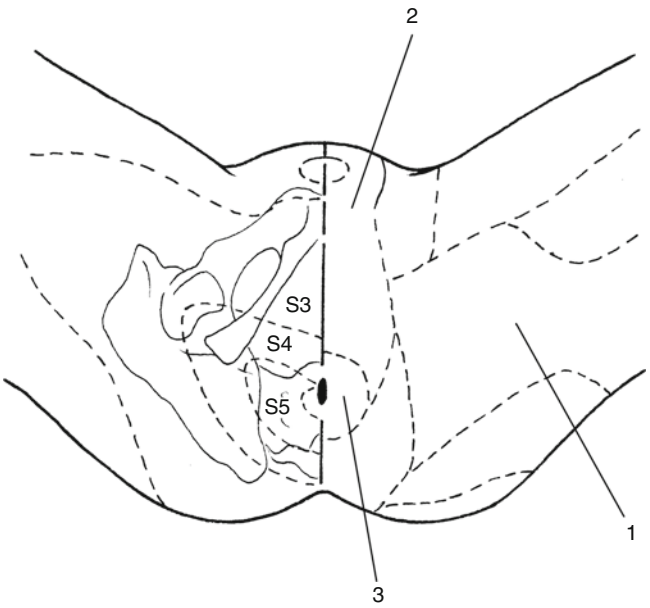


Fig. 8.65 *1* Cutaneous femoris posterior nerve. *2* Labial/scrotal nerves. *3* Anococcygeal nerve

8.4 Mononeuropathies: Lower Extremities

8.4.1 Obturator Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

Anatomy

The obturator nerve derives from the ventral division of L2-L4 and courses within the belly of the psoas muscle, emerging on the medial side of the psoas, then passing over the sacroilical joint, and continuing along the wall of the pelvis to the obturator canal. There it divides into an anterior and posterior branch (with variability in the site of branching). The anterior branch descends ventrally off the adductor brevis and behind the adductor longus, then descends upon the femoral artery. An articular branch goes to the hip joint. The posterior branch passes behind the adductor brevis and reaches the adductor magnus. A branch innervates the knee joint. The obturator nerve innervates the skin on the medial aspect of the thigh (Fig. 8.66).

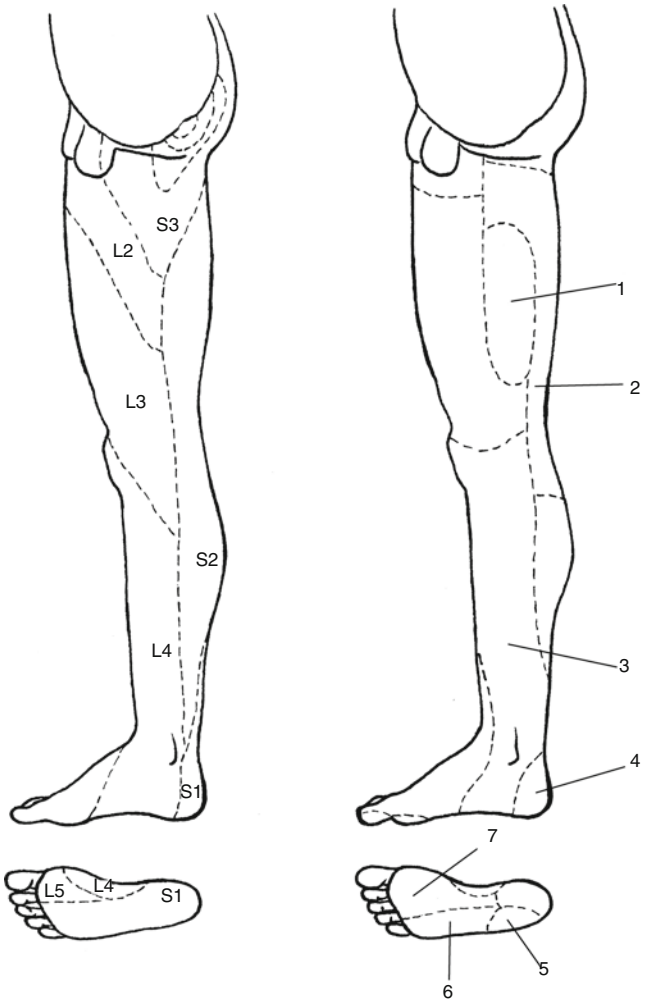


Fig. 8.66 *Right 1* Obturator nerve. *2* Cutaneous femoris posterior nerve. *3* Sapheneous nerve. *4* Calcaneal nerve. *5* Sural nerve. *6* Lateral plantar nerve. *7* Medial plantar nerve. *Left* shows the radicular innervation

Symptoms

Sensory loss, paresthesias, or radiating pain in the medial thigh. Gait disability secondary to impaired stabilization of the hip joint. The adductor magnus is a strong adductor. The obturator externus, the pectineus and the adductor brevis muscle support outward rotation. In obturator nerve lesions, the leg is held in an abducted position, leading to a wide-based gait. The adductor tendon reflex can be absent. Neuropathic pain may be confused with osteitis. An entrapment neuropathy rarely causes idiopathic obturator neuralgia.

Signs
Adductor weakness, with or without sensory deficits. Adductor reflex can be absent.

Causes
Compression: obturator hernia, scar in the thigh, labor (peripartum), endometriosis, lithotomy position, retroperitoneal schwannoma, aneurysm of the hypogastric artery. Iatrogenic: hip surgery, fixation of acetabular fracture, intrapelvic surgery, laparoscopic dissection of pelvic nodes, gracilis flap, pudendal nerve block, radical prostatectomy.

Myositis ossificans Trauma: pelvic fractures, gunshot wounds, retroperitoneal hematoma. Tumors: metastatic cancer, nerve sheath tumors, intraneuronal ganglia. Obturator nerve injury occurs commonly with a femoral nerve lesion. Causes include retroperitoneal hematoma, cancer, hip arthroplasty, lymphoma.

Diagnosis
EMG, imaging (MR, US).

Differential Diagnosis
L2-L4 radiculopathy, lumbar plexus lesions.

Therapy
Depends on etiology and type of nerve injury. Nerve blocks can be performed with ultrasound guidance.

Prognosis
Depends on etiology and type of nerve injury.

8.4.2 Neurology and the Hip

Hip and Neuromuscular Disease
Increased and decreased muscle tone: The hip is affected in several neuromuscular diseases, either by increased muscle tone (e.g., spasticity) or decreased muscle tone, as in any type of flaccid paresis. In particular, dysplasia, subluxation and degenerative changes occur in children (Fig. 8.67).

Conditions with increased muscle tone: in children, predominantly cerebral palsy; in adults, spasticity (e.g., secondary to stroke, spinal cord injury).

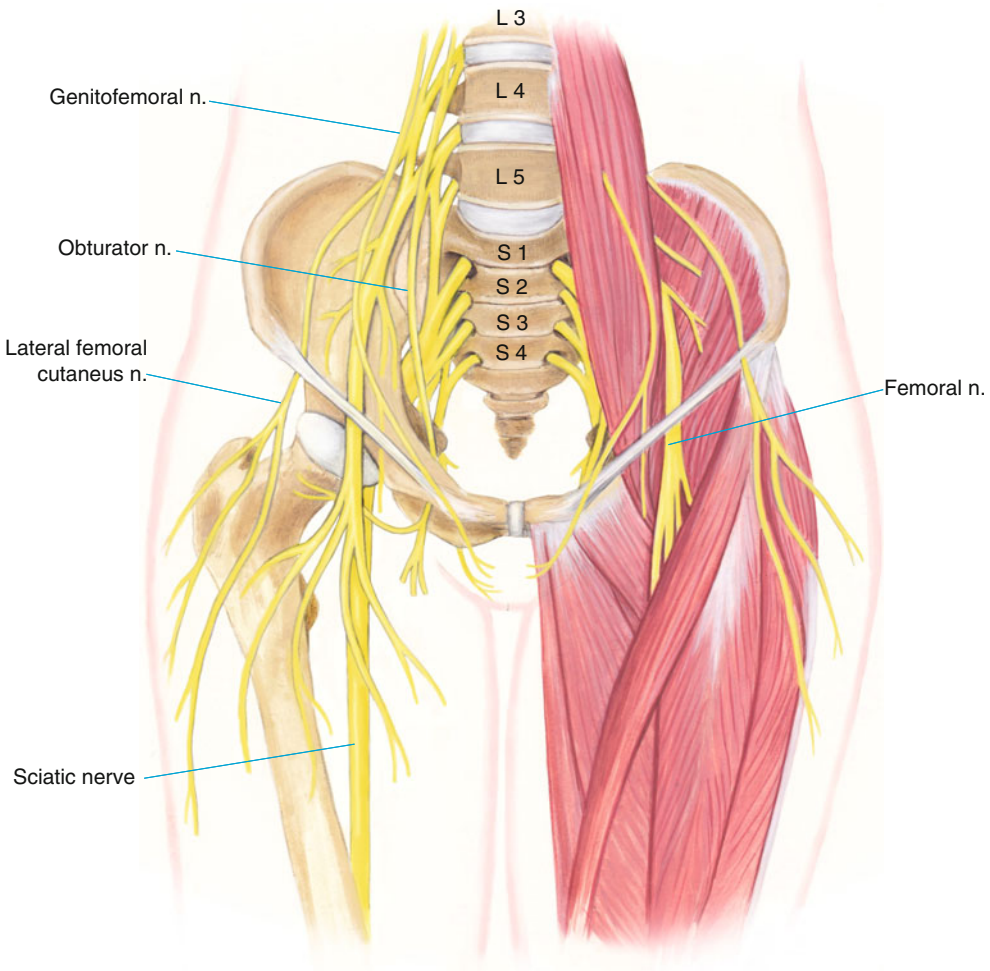


Fig. 8.67 Anatomy around the hip

Conditions with flaccid paresis: although poliomyelitis is now rarely seen, affected individuals have hip dysfunction either due to flaccid paresis, or residual paresis resulting in imbalance and hip deformities.

Hip Trauma

The sciatic nerve can be damaged in hip trauma or dislocation. Usually the peroneal division is more susceptible. The highest incidence is due to dislocation and fractures of the posterior wall and or acetabulum.

Hip Arthroplasty

Nerve injuries occur in 1–2 % of total hip arthroplasty, usually affecting the sciatic nerve, but also the obturator, superior gluteal and femoral nerves. The mechanisms are diverse and include mechanical (retractors, cautery), excessive limb lengthening, cement extrusion and heating, and local or regional anesthesia.

Hip Arthroscopy

The complication rate is low and nerve lesions are infrequent. They can be caused by traction of the joint (to gain access). Perineal and pudendal nerves are most commonly injured, but usually by neurapraxia.

Local Pain Syndromes

Other local pain syndromes are the femoral acetabular impingement (differential diagnosis includes ilioinguinal neuropathy, obturator neuropathy), sports hernia (differential diagnosis includes ilioinguinal neuropathy, genitofemoral neuropathy, obturator neuropathy) and greater trochanter bursitis (differential diagnosis includes L5-S1 radiculopathy, spinal stenosis, piriformis syndrome). Post-hernia pain syndrome with chronic groin pain needs to be considered.

8.4.3 Femoral Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

Anatomy

The femoral nerve is derived from the lumbar plexus (L2-L4). Proximal (intrapelvic) branches go to the psoas major and iliacus muscle passing through the inguinal ligament. Motor branches innervate the pectineus, sartorius and quadriceps muscles. Sensory branches innervate the medial aspect of the thigh (intermediate and medial cutaneous nerves), the anterior medial knee, and lower leg (saphenous nerve). The intermediate cutaneous branch descends along the anterior thigh and anastomoses with the patellar plexus. The saphenous nerve innervates the skin over the shin and ends distally at the medial malleolus (Fig. 8.68).

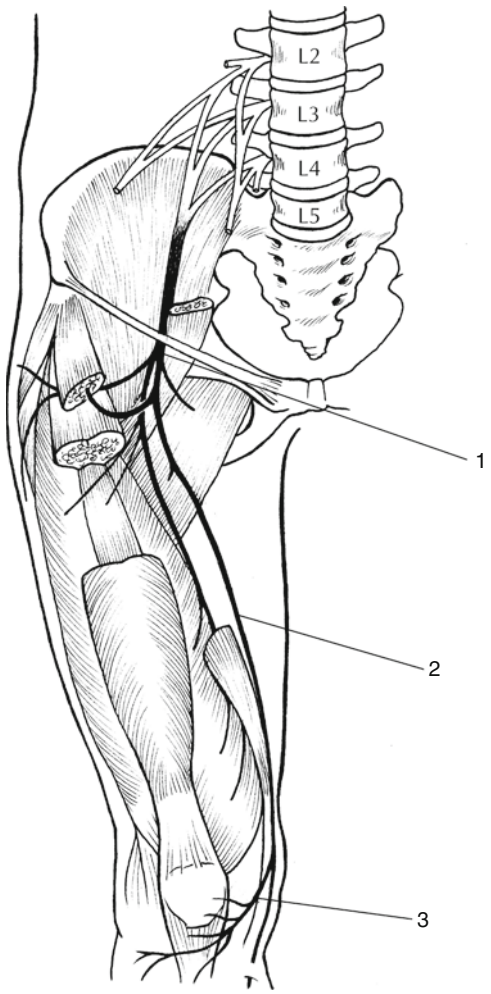


Fig. 8.68 *1* Femoral nerve. *2* Sapheneal nerve. *3* Patellar branch

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).

Signs

Atrophy and weakness of quadriceps muscles with a lower position of the patella when standing. Weakness of the psoas and quadriceps muscles only occurs with proximal lesions (the psoas muscle also receives direct branches from L2-L3 and has some preserved function – also the sartorius, tensor fasciae latae and rectus femoris contribute to hip flexion). Decreased or absent knee-jerk. Sensory loss over the anterior

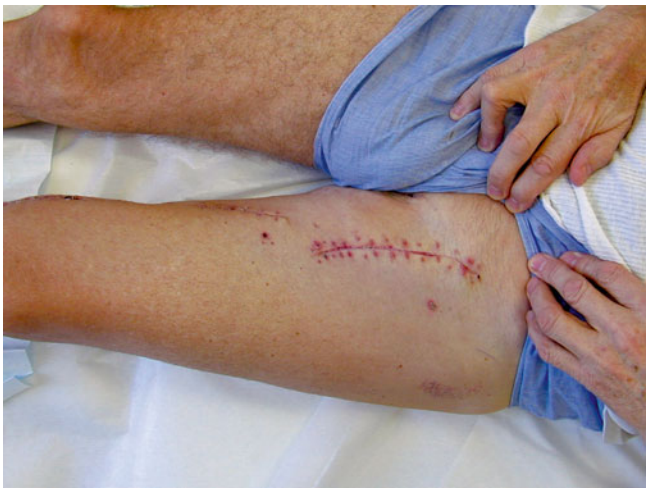


Fig. 8.69 Femoral nerve lesion after vascular surgery

aspect of the thigh and the medial side of the lower leg. Examination of the ilipsoas and hip adductors helps to pinpoint the site of the lesion. Climbing stairs with the affected leg is impossible, walking on a flat surface requires hyperextension of the knee. Partial lesions can spare sensory dysfunction, despite weakness (Fig. 8.69).

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, laparoscopic hernia repair, kidney transplantation, abdominal hysterectomy, vaginal delivery. Synovial cyst of hip. Iatrogenic: inguinal surgery, abdominal hysterectomy, hip surgery, renal transplantation, inguinal lymph node resection, femoral arterial puncture, femoral catheterization, inadvertent suturing, local infusions of chemotherapeutic agents, local anesthetic injections. Lithotomy positions. Lumbar spinal surgery (rare). Prolonged pressure: marked extension or flexion of the hip in unconscious patients, pregnancy.

Infection Inflammatory: heterotopic ossification, bursitis of iliopsoas muscle, lymph nodes in ilioinguinal region, hip abscess, iliacus abscess.

Metabolic Diabetic femoral neuropathy is a misnomer; it should be called diabetic lumbosacral plexopathy.

Neoplastic Local tumors, perineuroma, malignant invasion, perineuroma.

Neuropathy Multiplex type (vasculitis).

Radiotherapy After RT at the inguinal region.

Surgery Appendectomy, prostatectomy, rectopexy after prolapse of rectum, hip endoprosthesis, hysterectomy, delivery, lithotomy position, spinal surgery.

Traumatic Penetrating injury, stretch, hip and pelvic fracture.

Vascular Anticoagulant therapy (warfarin, heparin). Hematoma: psoas, iliacus. Hematoma in psoas or iliacus muscle can be caused by rupture of an abdominal aortic aneurysm; swelling in the iliac fossa and inguinally. It can be associated with pain, in particular flank pain (anemia and shock can develop). Spine surgery (lumbar artery L1).

Trauma The "iliacus hematoma syndrome," occurs by spontaneous bleeding, bleeding into the peritoneum and fascia transversalis – then dissection into the iliac fossa, hemorrhage into the rectus abdominis space with dissection into the retroperitoneal space, bleeding into the fascia lata and cephalead into the retroperitoneal area, spontaneous bleeding in the retroperitoneal space.

Diagnosis

NCV: femoral nerve latencies and CMAPs. Sensory nerve conduction of the main trunk within the abdominal cavity is difficult. Sensory nerve conduction of saphenal nerve. Saphenous SEP (stimulation inferomedial to patella) more reliable. NCV: medial femoral cutaneous nerve. EMG: quadriceps and iliopsoas muscle. Neuroimaging: CT scan for psoas hematoma (has to be done urgently if hematoma is suspected) or tumor infiltration of the psoas muscle. MRI – femoral nerve tumors. Ultrasound of the nerve inguinally. Laboratory tests: oral glucose tolerance test, serologies for vasculitis.

Differential Diagnosis

Aneurysm of iliac artery, irradiation of the inguinal area, L2-L4 radiculopathy, mononeuropathy multiplex, muscle infarct, quadriceps myopathy (rare), rupture of the quadriceps tendon.

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. Permanent femoral lesions need orthotic devices.

Prognosis

Generally good, depending on the cause of the lesion.

The Hip

The hip is a complex structure and a central point in movement and gait.

- **Nerve structures**: Nerve roots emerge from the lower lumbar vertebrae and the sacrum, forming the sacral and coccygeal plexus, which is usually well protected from mechanical injury. Several nerves emerge from the sacral plexus; the largest traversing near the hip into the thigh is

the sciatic nerve. The ventral compartment is composed of the lumbar plexus innervating the ventral pelvis, groin and thigh. The major nerves are the femoral and obturator nerves. Within the pelvis, the pudendal nerve innervates the urogenital area and the external sphincters. In addition, several autonomic nerves serve the sphincters and the sexual organs.

- **Muscle innervation**: The pelvic floor is the bottom of the abdominal cavity (caudal cupula of the abdominal cavity) and is comprised of the muscles required for sexual function, bladder control and defecation. Several muscles serve as flexors and extensors, abductors, adductors and rotators of the hip. Some are termed pelvic intrinsic muscles as the gluteal medial as the piriform and the obturator muscle. In a cross- section at the level of the femoral head, the dorsal muscles consist of the gluteus maximus muscle, more laterally the gluteus medius, and ventrally, the iliopsoas, rectus femoris, pectineus, and ventrally the rectus abdominis muscle.
- **Sensory innervation**:
  - The skin of the hip and pelvis are innervated by nerves from the lumbar and sacral plexus. The ventral nerves are the subcostal (last thoracic), iliohypogastric, ilioinguinal, genitofemoral, superior, medial and inferior cluneal nerves, perforating cutaneous nerves, and the pudendal nerve in the urogenital area. In the proximal part of the thigh there is an overlap with the lateral femoral cutaneous nerve and the anterior femoral cutaneous nerve.
  - Hip joint innervation: The sensory innervation of the hip capsule is important in pain relief strategies such as nerve blocks. The anterior medial innervation comes from articular branches of the obturator nerve and some fibers from the femoral nerve. The posterior part is innervated by the sciatic nerve, which innervates the posteromedial section of the hip capsule. In addition, the articular branches of the superior gluteal nerve innervate the posterolateral section of the hip joint capsule.

8.4.4 Saphenous Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

Anatomy

The saphenous nerve is one of three sensory branches of the femoral nerve. (The other two branches are the medial and intermediate femoral cutaneous nerves.) It has a long course through the adductor canal (Hunter's canal), penetrating the fascia above the knee, giving off an infrapatellar branch, and supplying the medial calf, medial malleolus, a small portion of the medial arch of the foot and skin on the medial and dorsal side of the foot. The nerve can be damaged as a result of a femoral nerve lesion, or during its course in the lower leg.

Symptoms

Numbness, also dysesthesias or severe neuropathic pain may occur.

Signs

Sensory loss on the medial side of the calf, Tinel's sign, loss of sudomotor function.

Anatomical Sites

Entrapment at Hunter's canal causes pain in the lower thigh and leg. Diagnosis can be made by a trial of local anesthetics. Infrapatellar branch: lesion of the infrapatellar branch may cause a small sensory loss below the knee. Lesions are secondary to knee surgery, arthroscopy and local trauma. Painful neuromas can occur. Entrapment above the medial ankle (nerve anterior to the prominence of the medial malleolus) causes saphenous neuropathic pain. Lesions of the lower leg secondary to varicose vein stripping, vein harvesting, arthroscopy of the ankle joint.

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 musical instruments. Surgery: arterial reconstruction, venous grafting, varicose vein surgery, vein stripping. Transplantation: this nerve is often used for nerve transplantation.

Diagnosis

Sensory NCV: use standard methods. EMG to distinguish for an L3, L4 radiculopathy.

Differential Diagnosis

L4 radiculopathy, partial femoral neuropathy.

8.4.5 Lateral Femoral Cutaneous Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+−		+	

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,

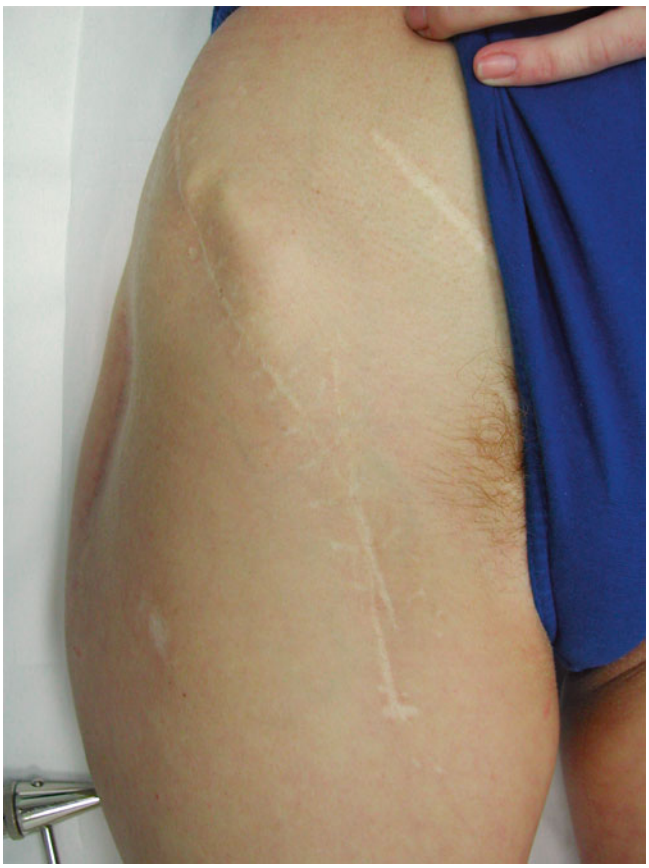


Fig. 8.70 Cutaneous femoris lateralis lesion after hip surgery. Note the postoperative scars in the vincinity of the nerve distribution.

exits the pelvis, dividing into an anterior and posterior branch. The nerve changes course from a horizontal to a vertical position. The distal branches communicate with the femoral nerve and saphenous nerve to create the patellar plexus. The occurrence of meralgia paresthetica is 32.6 per 100,000 patient years, with a higher incidence in overweight individuals, in the fourth to sixth decades. The diagnosis of meralgia paresthetica warrants a workup for diabetes (Fig. 8.70).

Symptoms

Pain, tingling or burning, or numbness of the skin territory. Symptoms do not extend to the knee. Sometimes highly irritable (can be irritated by clothes). Standing or walking (extending the hip) can aggravate, whereas hip flexion provides relief. Infrequently bilateral. Allodynia ("fear of putting hand in pocket") radiating into the lateral thigh (Fig. 8.71).

Signs

Deficits of superficial sensory sensation (numbness) in the center of the lateral cutaneous nerve's distribution. The pattern of distribution may be variable. Thermal perception is primarily affected, and in severe cases there is hypotrichosis and the appearance of "thinned" skin. Symptoms may be precipitated by hip extension, or pressure on an entrapment point. Tinel's sign can be elicited at the anterior superior iliac crest.

Pathogenesis

Exercise or postural, external compression, flaccid belly due to adiposity, hip extension, iatrogenic, pregnancy, (protuberant abdomen, with improvement after childbirth), psoas muscle, pelvic compartment syndrome, inguinal ligament, seat belts in motor vehicle accidents. Surgery: renal transplant, lower abdominal surgery, iliac bone for grafting, appendectomy, laparoscopic herniorraphias. Trauma: (fracture of the anterior superior iliac spine), tumors and masses, retroperitoneal malignancies. Unknown: idiopathic.

Upper thigh: blunt trauma, lacerations, misplaced injections, diabetes.

Diagnosis

EMG: Differential diagnosis is radiculopathy. NCV: Sensory NCV; several techniques are used, but are not reliable. Ultrasound: is useful (Fig. 8.72).

Differential Diagnosis

Coxarthrosis, L2 radiculopathy, neurinoma, pelvic neoplasm, Wartenberg's syndrome – "migrant sensory neuritis."

Therapy

Local anesthetic infiltration, steroids, spontaneous recovery, surgical intervention: only if pain persists.

Prognosis

Short-term: depending on etiology. Long-term: good.

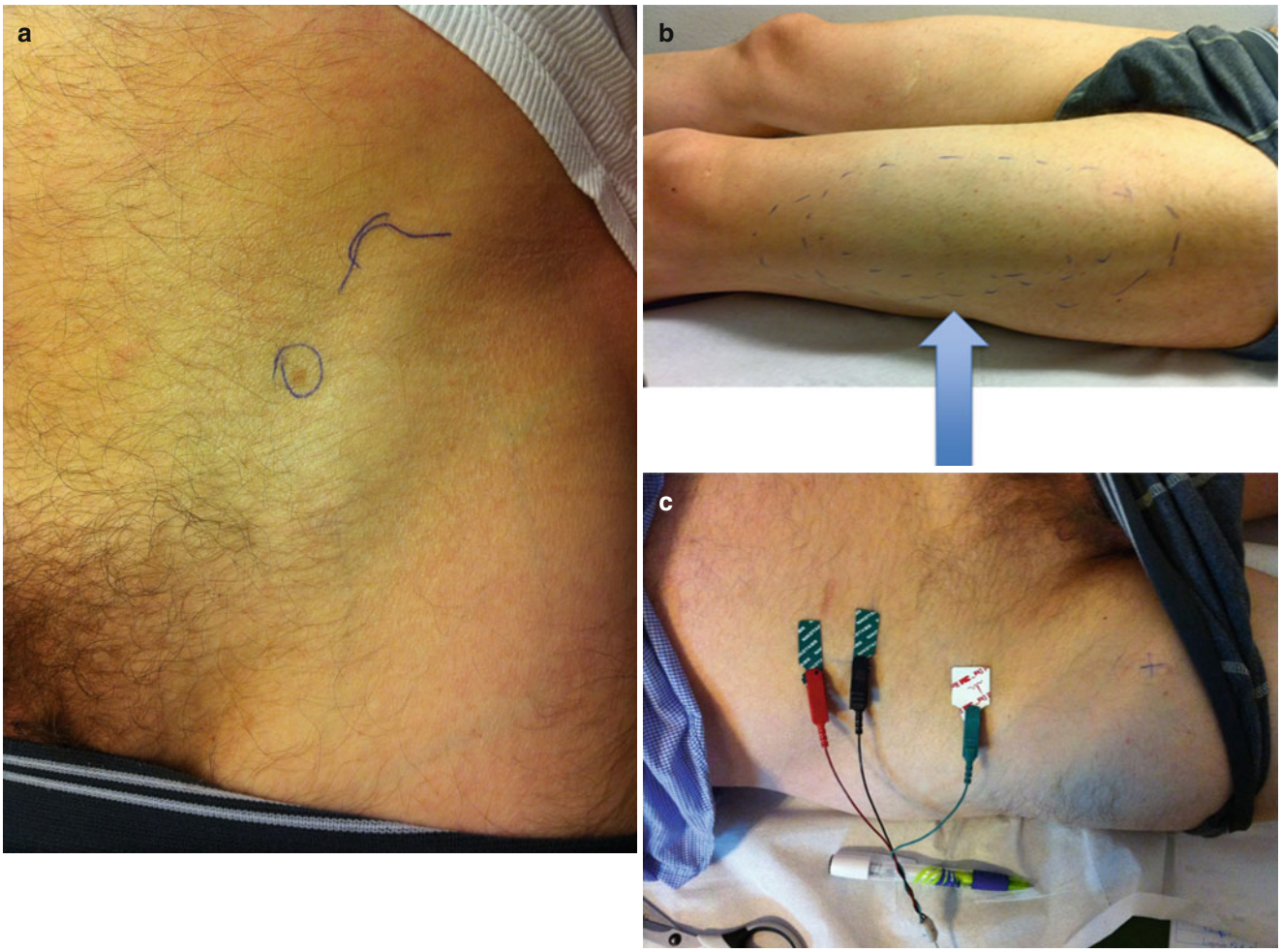


Fig. 8.71 Cutaneous femoral lateral nerve of the thigh: (**a**) A lesion occurred after a percutaneous hernia repair. Arrow points to the site of endoscope insertion. (**b**) Cutaneous field of the nerve. (**c**) Sensory conduction of the nerve. The nerve was stimulated at the thigh. The black electrode is the reference electrode

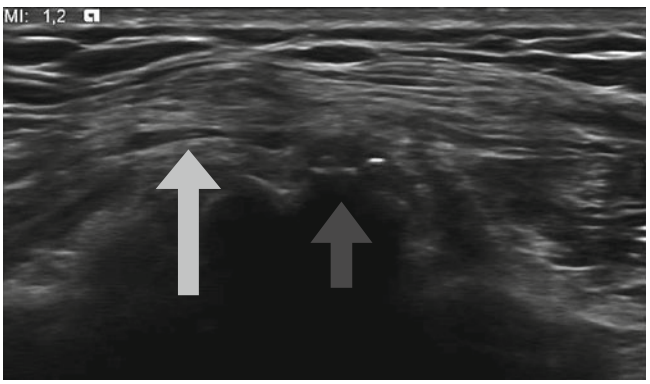


Fig. 8.72 Ultrasound of the lateral cutaneous nerve in a patient with meralgia paresthetica. *Left arrow* points to a "thickened" nerve, *right arrow* points to the anterior iliac crest (*black*)

8.4.6 Posterior Cutaneous Femoral Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		US	

Anatomy

Fibers come from the lower part of the lumbosacral plexus from the S1-S3 roots. The fibers descend together with the inferior gluteal nerve through the greater sciatic notch, below the piriform muscle. A branch leaves to the perineum and scrotum. The sensory area includes the lower buttock, parts of the labia or scrotum (cluneal and perineal nerves) and the dorsal side of the thigh and proximal third of the calf. The autonomic field is a small area above the popliteal fossa.

Symptoms
Paresthesia and numbness over the lower part of the buttock and posterior thigh.

Signs
Sensory loss.

Pathogenesis
Bicycle riding, buttocks trauma, colorectal tumors, hemangiopericytoma, iatrogenic injection in the buttock, ischemia of lower extremity, lacerations in the posterior thigh, sedentary occupation, venous malformation, wounds of the dorsal thigh.

Diagnosis
NCV: difficult technique, not very robust in this region.
EMG: may distinguish from sacral plexus lesion.

Differential Diagnosis
Sacral plexus or radicular lesion S2, S3, sciatic nerve lesion, S2 radiculopathy.

Therapy
Local infiltration, plastic and reconstructive surgery are rarely needed, spontaneous recovery.

Prognosis
Depending on etiology.

8.4.7 Sciatic Nerve

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

Anatomy
Fibers from L4 to 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 nerve vary, 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 injury and compression. From the tibial part of the sciatic nerve, the semimembranosus, semitendinosus muscle and the long head of the biceps femoris and adductor magnus arise from the peroneal part of the caput breve of the biceps femoris muscle and articular branches to the knee joint. The peroneal and tibial nerves include motor, sensory and autonomic fibers. The nerve provides motor innervation to the semitendinosus, the long head of the biceps femoris, the semimembranosus, part of the adductor magnus and all muscles innervated by the peroneal and tibial nerves (Fig. 8.73). The sensory innervation is the lower leg and foot with the exception of the saphenal nerve. Articular branches (rami articulares) arise from the upper part of the nerve and supply the posterior part of the hip capsule.

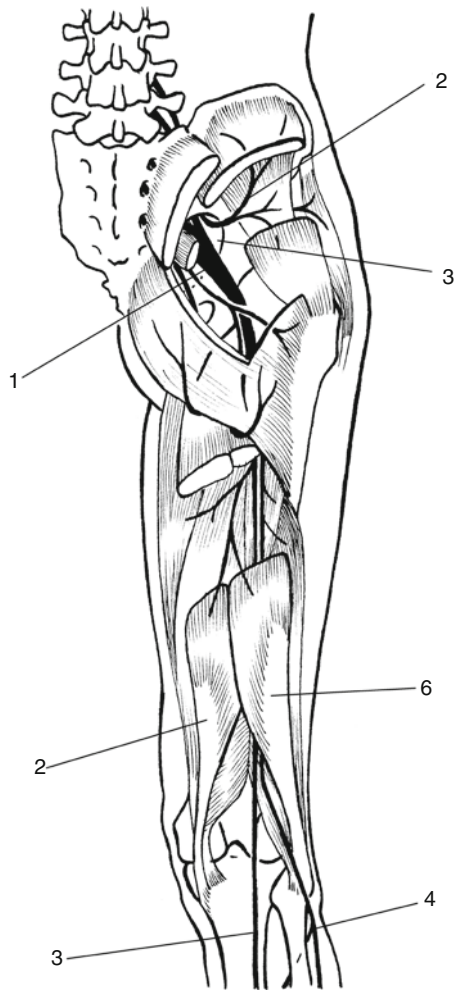


Fig. 8.73 Greater sciatic nerve. *1* Great sciatic nerve. *2* Gluteal superior nerve. *3* Infrapiriform foramen. *4* Peroneal nerve. *5* Tibial nerve. *6* Semitendinosus muscle. *7* Semimembranosus muscle

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 a

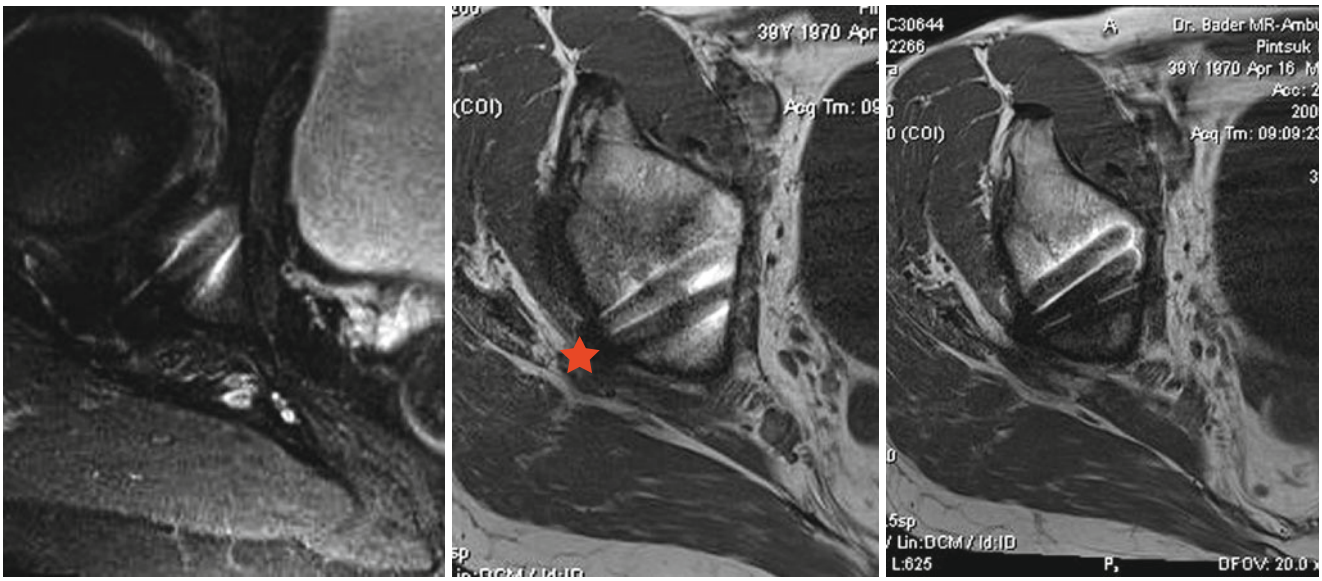


Fig. 8.74 Sciatic nerve lesion. Following hip surgery, a patient presented with pain in the distribution of the sciatic nerve. MR detected the tip of a screw, used for the hip operation, in close vincinity to the sciatic nerve (*star*)

peroneal nerve lesion, 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 areas except that 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.

Causes

In the Pelvis Aneurysm (hypogastric artery), AV malformation, bone marrow harvest, carcinoma, childbirth (by cesarean), common iliac artery aneurysm, endometriosis, ganglia (hip joint), gluteal compartment syndrome, hematoma, hip arthroplasty (traction, transection, thermal damage, wires and screws (Fig. 8.74), cement); delayed sciatic neuropathy (months to years), injection injuries (also delayed due to scar formation), lipoma, lithotomy (stretch), neonatal, operations in sitting positions. Trauma: (dislocation of the hip, posterior dislocation of the head of the femur, pelvis fractures, delayed in callus entrapment). Tumors: nerve sheath tumors, schwannomatosis, lipoma, lymphoma and neurolymphomatsosis, intraperineural neuromas, localized hypertrophic mononeuropathy, vascular malformations. Piriformis syndrome: is a matter of debate. Four different syndromes: proximal sciatic neuropathies, neurogenic piriformis syndrome, posttraumatic piriformis syndrome and nonspecific piriformis syndrome have been described. The mechanisms of spasm or muscle hypertrophy are speculative.

In the Thigh Aneurysm (persistent sciatic artery, popliteal artery), external compression, gunshot wound, stab wound, laceration, lipoma, neurofibroma, sarcoidosis, trauma. Tumors: nerve sheath, benign and malignant, schwannoma, intraneural ganglion cysts (Fig. 8.75).

Other Common Causes Acute compression (coma, drug overdose, intensive care unit, prolonged sitting, falls, hematoma), gluteal contusion or rhabdomyolysis gluteal compartment syndrome, gunshot or knife wound (Fig. 8.76), hip replacement, hip fracture or dislocation, or femur fracture, acetabular fracture, infarction (vasculitis, iliac artery occlusion, arterial bypass surgery), intramuscular gluteal injection.

Less Common Causes Tumor: carcinoma, lipoma, lymphoma, neurofibroma, schwannoma, perineurioma, AV malformations, ruptured aneurysm, false aneurysm of aorta, childbirth, infection, vasculitis, myositis ossificans, radiation injury (Fig. 8.77).

Diagnosis

Nerve conduction studies including F-wave, H-reflex (direct stimulation at thigh difficult). EMG: distinguishes from radiculopathy (paraspinals), or plexus lesions. Neuroimaging: MRI, ultrasound, CT.

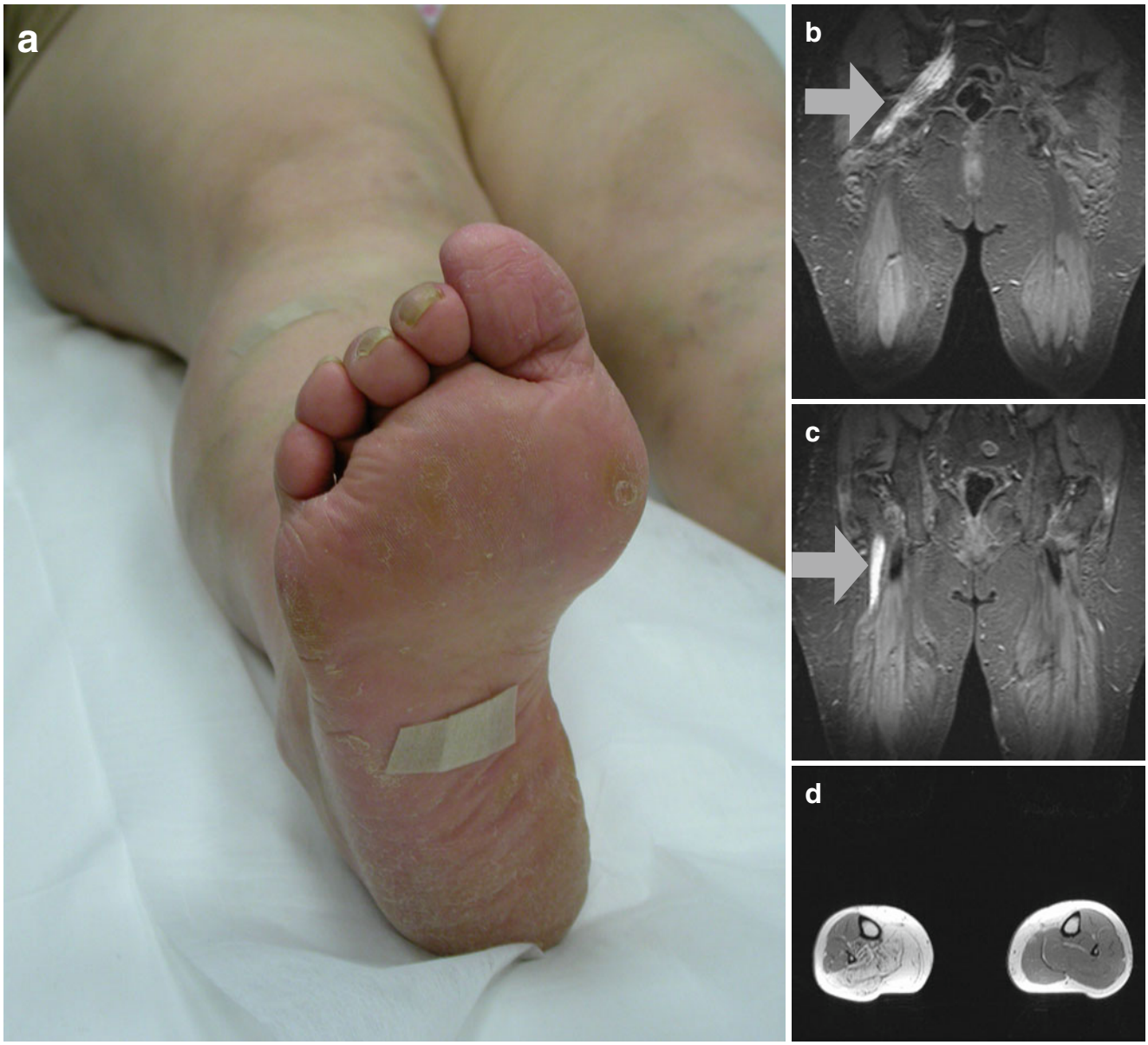


Fig. 8.75 Nerve tumor mimicking sciatica: This patient had been treated for "chronic sciatic" pain for several years. Atrophy of the intrinsic foot muscles and trophic changes of the skin (**a**) led to MR imaging which showed a nerve tumor (**b**, **c**). A transverse section of the thigh shows (**d**) the atrophy of the knee flexors (*arrow*)

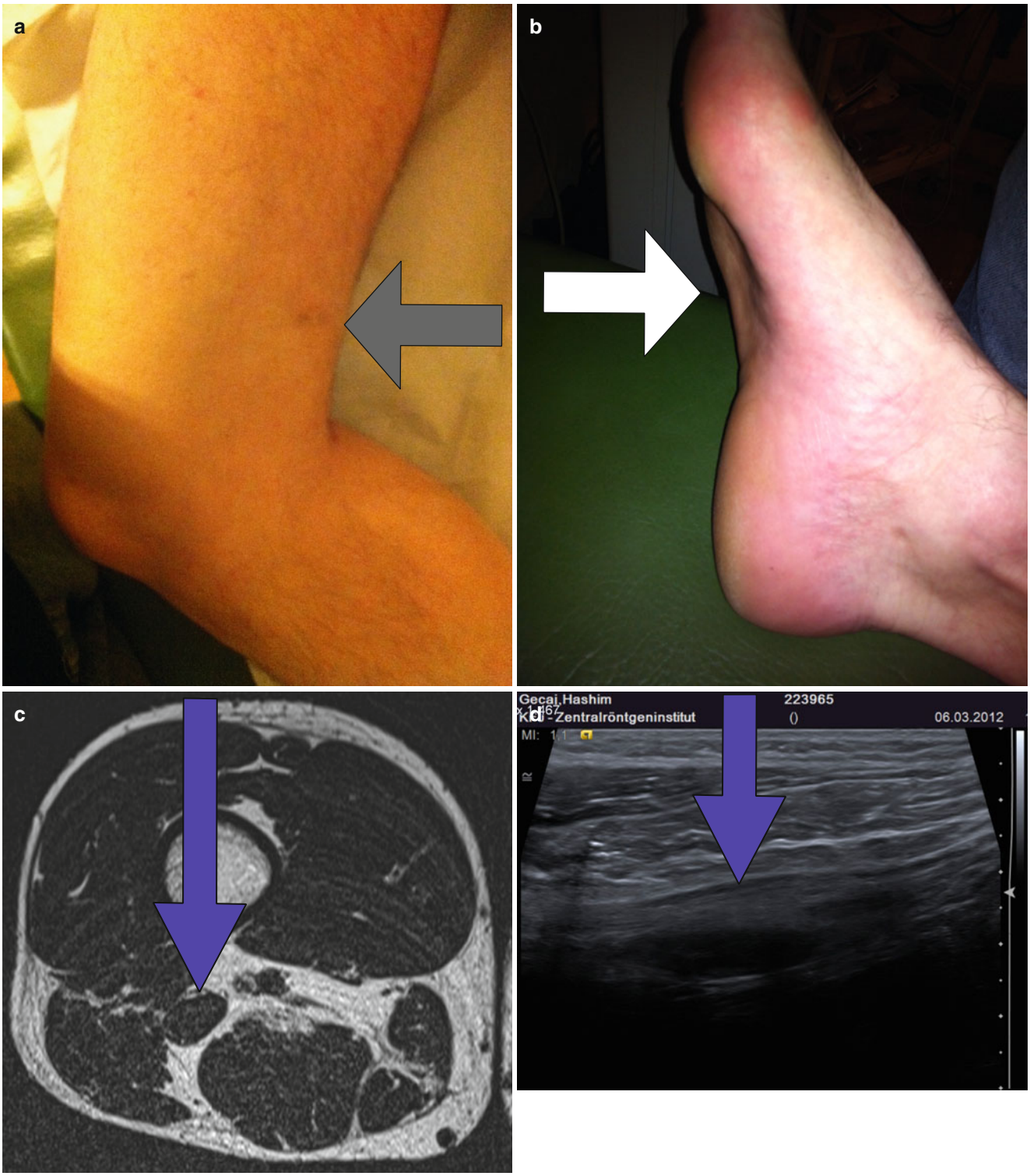


Fig. 8.76 Sciatic nerve lesion after a bullet injury. This patient suffered a bullet injury. He had neuropathic pain in his calf, radiating to the sole of his foot. Percussion of the scar was painful (**a**), the only sign was mild atrophy of the intrinsic muscles of the foot (**b**) (*dark arrows*). MR showed swelling of the sciatic nerve just above the ramification into the peroneal and tibial nerves (**c**), ultrasound confirmed the nerve swelling (**d**) (*violet arrows*)

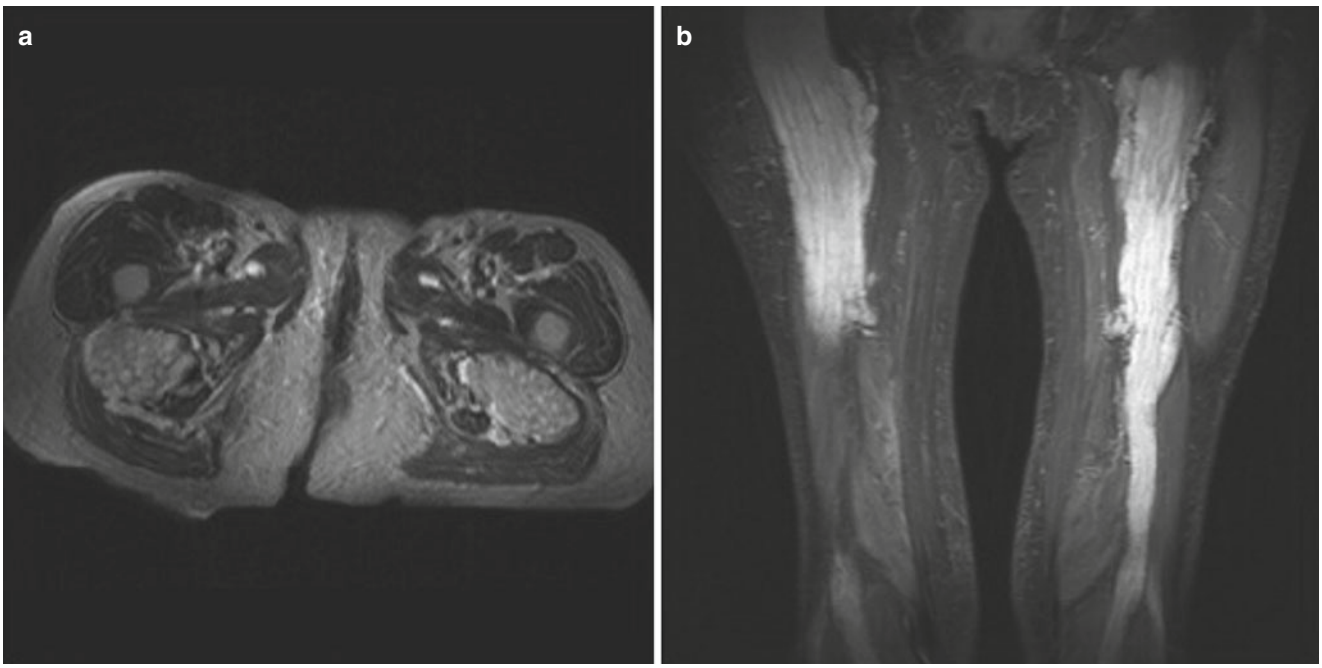


Fig. 8.77 Neurofibromatosis: bilateral enlargement of the sciatic nerve in transverse (**a**) and longitudinal section (**b**)

Differential Diagnosis

Benign monomelic atrophy, cauda equina syndrome, meningeal carcinomatosis, polyradiculopathy in Lyme disease, vasculitis, multifocal motor neuropathy, radiculopathies, sacral plexopathy.

Therapy and Prognosis

Depending on etiology: traumatic sciatic nerve lesions 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.

8.4.8 Around the Knee

The knee is a complex joint.

- Several nerves pass the knee on their way to the lower leg and foot: the sciatic nerve, or its divisions – the peroneal, tibial and saphenal nerves. Also, the posterior cutaneus nerve of the thigh reaches the popliteal fossa. The popliteal fossa is a flat surface whose medial borders are the semitendineus and semimembranosus muscle, the lateral border the biceps femoris muscle, and the caudal border by the two heads of the gastrognemius muscle. The bottom consists of the popliteal facies of the femur, the posterior part of the knee joint and the popliteal muscle.
- In addition to knee flexors and extensors, the outward and inward rotators of the knee are functionally important. The popliteus muscle is used to unlock the knee during walking/running by laterally rotating the femur on the tibia (or medially rotating the tibia) during a closed chain movement (such as one with the foot in contact with the ground). The inward rotation is performed by the semimembranosus, semitendinosus gracilis, sartorius and popliteus muscle.
- The sensory innervation of the knee has two main aspects: the sensory innervation of the skin and the innervation of the joint, which are both important for endoscopic or surgical intervention.
  - Sensory innervation of the skin: the skin is innervated by the anterior and lateral branches of the femoral nerve, the cutaneous femoral lateral, the saphenal and the posterior cutaneus femoris nerve. The medial and lateral patellar nerves are distal branches of the femoral nerve. The skin of the popliteal fossa is innervated by the posterior cutaneous femoral nerve, and on the lateral border from the cutaneus surae lateral nerve, and branches from the obturator nerve.
  - Innervation of the knee joint: the knee joint is innervated by branches of the posterior articular (from the tibial nerve), by the lateral articular nerve (common peroneal nerve) and the medial articular nerve (saphenal nerve).

Pathology Gonyalgia, lesions of the ramus patellaris (see saphenal nerve), knee dislocation: anterior, posterior, medial, lateral, and rotary, knee and/or hip replacements, patellofemoral pain, stretch injury, tabes dorsalis (Charcot joints), venous stripping: knee surgery (Fig. 8.78).

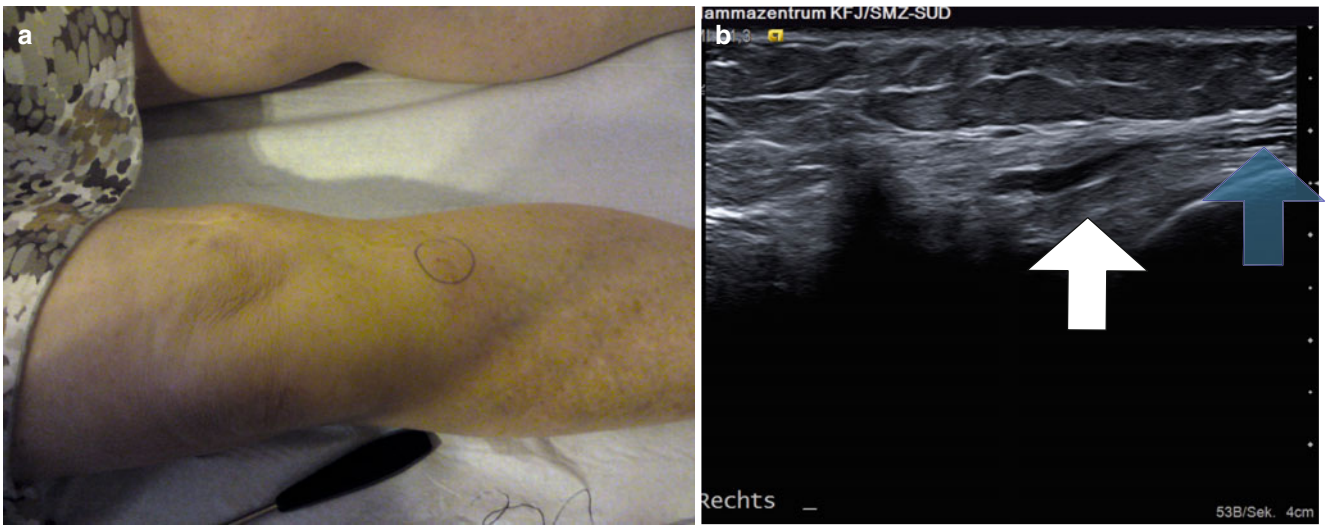


Fig. 8.78 Neuroma of the infrapatellar nerve: (**a**) After venous stripping, the patient experienced neuropathic pain in the distribution of the infrapatellar nerve. (**b**) Ultrasound showed a small neuroma (*white arrow*; the *blue arrow* shows the saphenous nerve)

8.4.9 Peroneal Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
+	+		+	

Anatomy

The peroneal nerve is the lateral trunk of the sciatic nerve, separating from the sciatic nerve in the upper popliteal fossa or above. The nerve originates from the posterior divisions of the ventral rami of L4, L5, S1, and S2. The nerve has 3 articular branches to innervate the knee joint and the recurrent articular nerve ascends to the front of the knee. The lateral sural cutaneous nerve supplies the skin on the lateral and posterior surface of the leg. 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 lateral compartment of the lower leg. In 28 % of people, this nerve also innervates the digitorum brevis medial extensor (the accessory deep peroneal nerve). The superficial peronal nerve provides superficial sensory innervation to the anterolateral lower leg and the dorsum of the foot (except between toes 1 and 2) (Fig. 8.79a). The deep branch runs between the tibialis anterior and extensor hallucis longus muscles to innervate these muscles as well as the extensor digitorum longus and peroneal muscles (Fig. 8.80). The terminal portion of the deep branch reaches the foot and passes the extensor retinaculum. The lateral terminal branch innervates the extensor digitorum brevis muscle. The medial sensory branch forms the digitales dorsales pedis, innervating the adjacent sides of toes 1 and 2. The accessory deep peroneal nerve arises from the deep peroneal nerve proximally at the fibular neck and descends to the lateral malleolus to innervate the extensor digitorum brevis muscle (completely or partially). This variation is important for the interpretation of peroneal nerve studies.

Symptoms

Most frequently, mononeuropathy of the lower extremity. Acute, or insidiously developing foot drop (depending on the cause) and loss of extension of toes. Rarely, the extensor hallucis longus may be disproportionately affected. Pain is usually not a feature; also, sensory symptoms are minor. Incomplete weakness may manifest itself only in tripping over their toes and leading to falls. Eversion deficits may be the cause of ankle sprains or fractures.

Signs

Foot drop or deficit of ankle dorsiflexion weakness is the hallmark of common peroneal nerve dysfunction. Varying degrees of foot dorsiflexion deficit to maximally complete foot drop. Steppage gait is the clinical sign of peroneal weakness. 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 the first and second toes. Eversion remains intact. Superficial peroneal nerve lesions depend on the site of the lesion; pain and paresthesias occur over the dorsum of the foot. Bilateral lesions are rare, and usually the sign of polyneuropathy.

Causes

Proximal lesions of the sciatic nerve by different mechanisms are prone to damage the peroneal fibers more than the tibial fibers. Compartment syndrome of the anterior lower

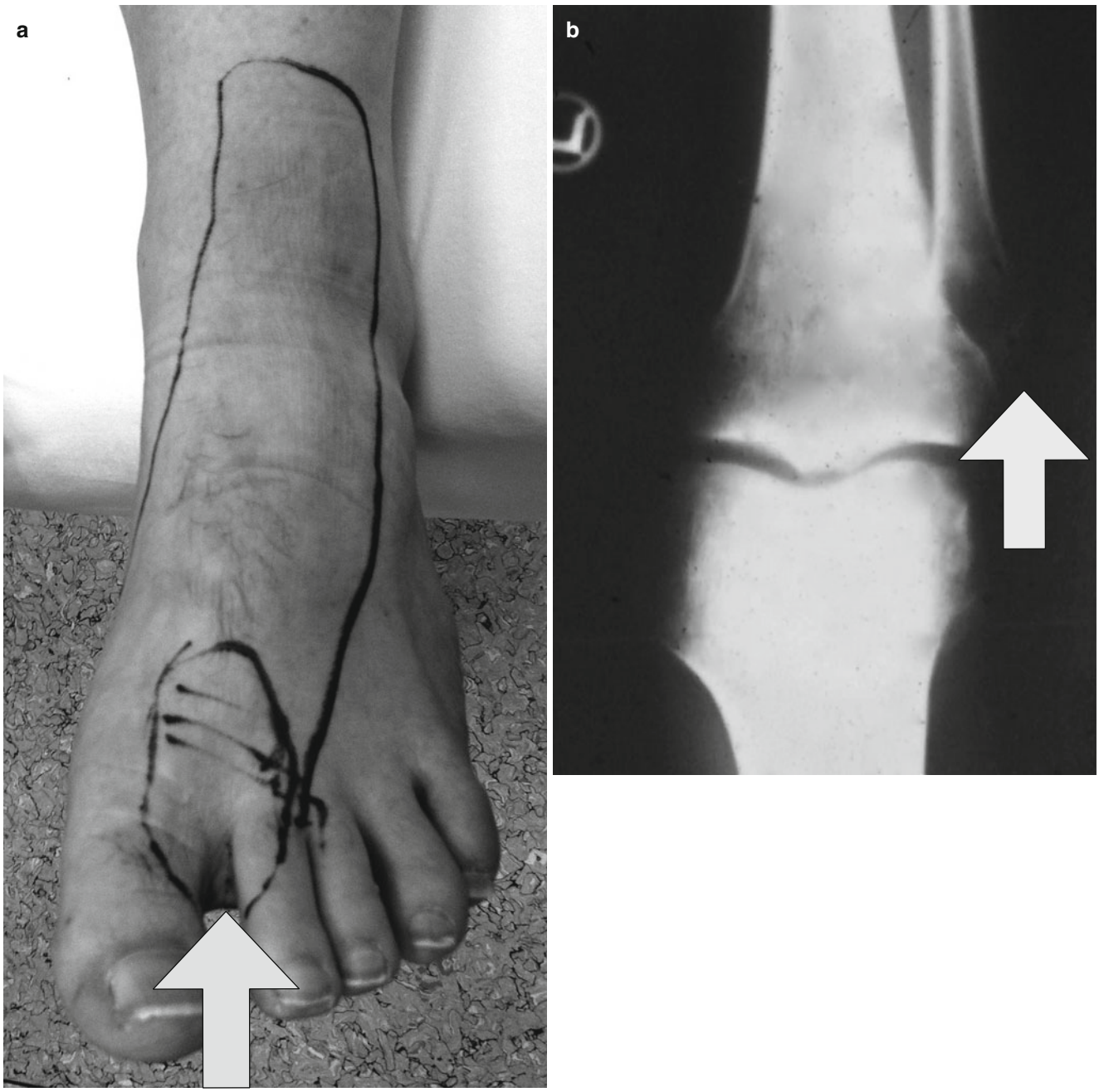


Fig. 8.79 Peroneal nerve: (**a**) Sensory innervation of the peroneus profundus nerve. (**b**) Metastasis of a lung cancer into the capitulum fibulae (*arrow*) presenting as a painful peroneal nerve palsy

leg: affects the deep peroneal nerve. Cuff or swelling of lower extremity (coagulation disorders).

Direct Trauma Adduction injury, knee dislocation, arthroscopy, fibular fracture, injury, knee surgery, laceration.

Entrapment Fibular tunnel (tendineous arch over the nerve, nerve curses under the peroneus longus muscle). Anterior compartment syndrome.

External Compression Anesthesia, coma, sleep, prolonged bed rest, habitual leg crossing, malpositioning, plaster cast, prolonged squatting.

Masses Aneurysm, Baker's cyst of gastrocnemius or semimembranosus, callus after fractures, hematomas (anticoagulant therapy, hemophiliacs), lipoma, nerve sheath tumors, nerve sheath ganglia. Most common: ganglia from the tibio-fibular

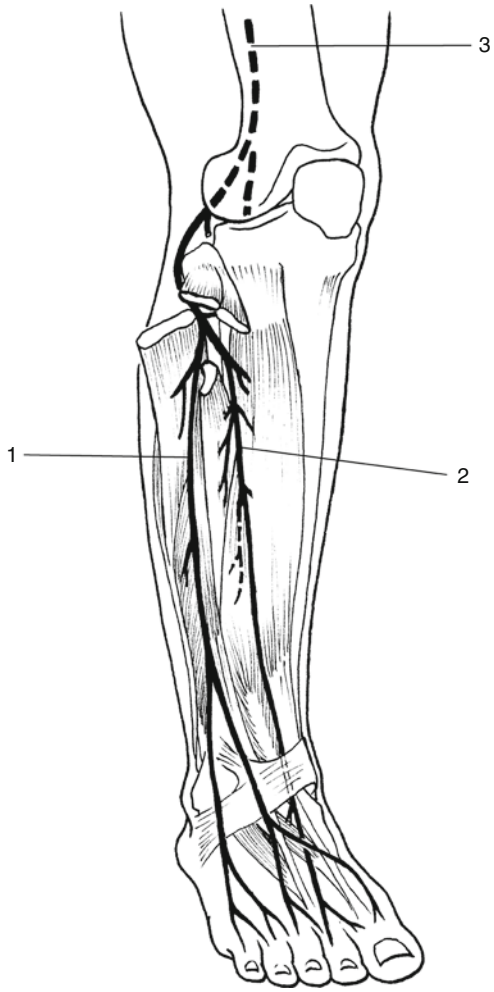


Fig. 8.80 Peroneal nerve. *1* Superficial peroneal nerve. *2* Deep peroneal nerve. *3* Sciatic nerve

joint. Benign, but may invade popliteal fossa and peroneus longus muscle and then invade or compress the nerve. Schwannomas, neurofibromas, osteomas (Fig. 8.79b).

Polyneuropathies Diabetic neuropathy, hereditary neuropathies, multifocal motor neuropathy, mononeuritis multiplex.

Traction Injury Acute ankle injury (inversion), knee injury with dislocation.

Trauma Knee dislocation, knee operations, perioperative, tibial osteotomies.

Others Idiopathic, leprosy, thrombosis or embolism (femoral or popliteal arteries), vasculitis, weight loss.

Common Peroneal Neuropathies and Partial Lesions The clinical picture of common peroneal lesions is not uniform, and can consist of a mix of sensory and motor patterns. This can be explained by the anatomy of the nerve, which consists of various fascicles that can be differentially damaged at multiple sites.

Branch Lesions Deep peroneal lesions: anterior tarsal tunnel syndrome, branch to the extensor hallucis longus: "big toe drop." Distal lesions: external compression, ganglion, injury, external compression at the ankle, mass lesions, trauma (fractures of tibia and fibula). Superficial peroneal nerve lesions: compression of sensory branch when traversing deep fascia of lower leg (N. dorsalis cutaneus intermedius), fibular fracture, peroneal (lateral compartment) compartment syndrome. Trauma: ankle surgery, arthroscopy. 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/EMG: conventional motor NCV examination should routinely stimulate the nerve below and above the fibular head. Usually the inching method is used. If distal CMAP is absent, the latency to the anterior tibial and long peroneal nerves are helpful. An accessory-deep peroneal nerve can be misleading and should be excluded. EMG is useful to help distinguish the stage of muscle involvement (normal, denervation, reinnervation). The distribution of affected muscles in EMG helps to distinguish peroneal neuropathy from an L5 radiculopathy. The short head of the biceps femoris is the only muscle supplied by the lateral trunk (useful in differentiation between a lateral sciatic nerve and a common peroneal nerve lesion). Imaging: knee: MR, ultrasound to look for a Baker's cyst. MR transverse section of the lower leg can show the involved muscle groups, and the distribution can distinguish between a peroneal nerve lesion and L5 lesion (Table 8.2).

Differential Diagnosis

Distal myopathies, hereditary neuropathies, lesions of L5, lumbosacral trunk, or plexus, multiplex neuropathies, radiculopathy (inflammatory, neoplastic), sciatic nerve lateral trunk, postpartum L5 lesions.

Therapy

Acute trauma/transsection: nerve repair, or interposition. Incomplete/blunt trauma: wait for spontaneous recovery. Compressive episode: decrease pressure, re-assess. Progressive: exclude mass, metastasis, fibular tunnel.

Prognosis

Depending on the cause, and on the site of the lesion. Lesions of the common peroneal nerve (with transsection, or severe axonal damage) have a poor prognosis. Tibialis posterior transfer is one method to overcome this weakness (Fig. 8.81).

Table 8.2 Causes of foot drop

Common peroneal nerve lesion	History of nerve compression, trauma	Tibialis ant., ext. hallucis, peroneal muscles
L5 radiculopathy	Low back pain	Tibialis ant., ext. hallucis, peroneal muscles, tibialis posterior, medial gluteal
Sciatic nerve	Hip surgery, trauma	Distribution like peroneal nerve, short head of biceps included
Lumbosacral plexopathy	Pelvic mass	Tibialis ant., ext. halluces muscles, peroneal muscles, tibialis posterior, gluteal muscles, sweating impaired (hot and dry foot)
Neuropathy	HNPP	Recurrent mononeuropathies
	Some types of CMT	CMT: usually bilateral
Distal myopathy	Insidious onset	Distal myopathies with anterior compartment involvement

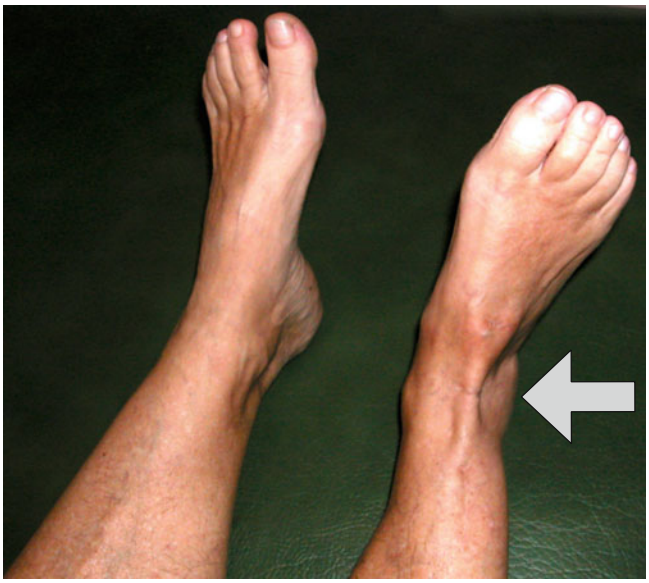


Fig. 8.81 Tibialis posterior tendon transfer. Foot drop is sometimes treated with posterior tibial nerve tendon transfer. The image shows the typical appearance of the tendon (*arrow*)

8.4.10 Tibial Nerve (Posterior Tibial Nerve)

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

Anatomy

Fibers for the tibial nerve stem from L3-S4. The nerve originates from the ventral part of the sciatic nerve. It has a protected position in the thigh and popliteal fossa and articular branches serve the knee joint. The medial cutaneous sural nerve leaves the main trunk in the 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. The calcaneal nerve innervates the medial heel and adjacent part of the sole. 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 big toe) and the lateral plantar proper digital nerve (to the little toe). Four terminal branches are called interdigital nerves (they divide into two digital nerves after the distal ends of metatarsal bones). In the popliteal fossa, the medial cutaneous sural nerve arises from the tibial nerve. This nerve unites with the lateral cutaneous sural 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) (Fig. 8.82).

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. Ankle: trauma, in particular fractures of the

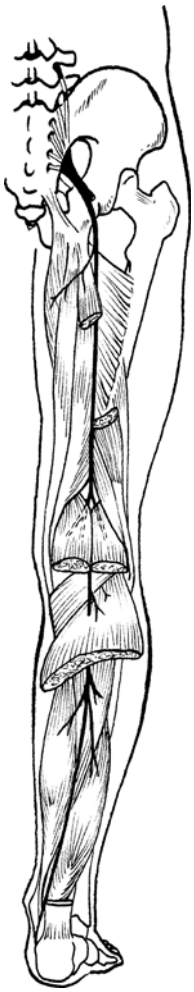


Fig. 8.82 The tibial nerve originates from sciatic nerve above the knee at varying sites

ankles, especially the medial malleolus, contusions, lacerations and other types of trauma. Tarsal tunnel syndrome: presents with ankle pain, foot pain and numbness or paresthesias of the soles of the feet. 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 in various areas on the sole of the foot, depending on the particular terminal nerve involved. Medial plantar nerve lesions are more frequent than lateral plantar neuropathies. The nerve passes under the abductor hallucis muscle, then through a fibro-osseus space formed by the flexor halluces brevis, to reach the tarsal bones. The lateral plantar nerve has its course under the abductor hallucis, then passes under the flexor digitorum and quadratus plantae muscle. Both nerves end after their division into digital nerves. The most medial terminal branch of the fibro-osseus medial plantar nerve is the medial plantar proper digital nerve. All intrinsic foot muscles are innervated by the plantar nerves. The medial plantar nerve innervates the abductor hallucis, flexor digitorum brevis and flexor hallucis brevis. The lateral plantar nerve innervates the abductor minimi, flexor digiti minimi, adductor hallucis and interossei muscles.

Signs

Atrophy of the calf muscles, weakness and atrophy of intrinsic foot muscles (atrophy and wrinkling of the skin in the arch of the foot). 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 (regardless of sural nerve involvement). Absent ankle jerk.

Autonomic: autonomic fibers travel with the tibial nerve. Lesions of the tibial nerve produce trophic skin changes and hyperkeratosis.

Causes

Pathogenesis of Proximal Tibial Nerve Lesions in the Popliteal Fossa Baker's cyst: arises from the knee joint and can compress the tibial and also peroneal nerves. Extravasation of joint fluids can also cause cysts. Hemorrhages into the popliteal fossa (Fig. 8.83). Iatrogenic: orthopedic surgery, injections into the knee. Trauma: femur fractures, knee dislocations, blunt injury, stab wounds, gunshot wounds, superior tibio-fibular joint injuries. Tumors: nerve sheath (neurofibroma, schwannoma).

Pathogenesis of Tibial Nerve Lesions in the Calf Compartment syndromes, entrapment by soleus or popliteus muscle, hematoma (muscle rupture), stretch from ankle sprain.

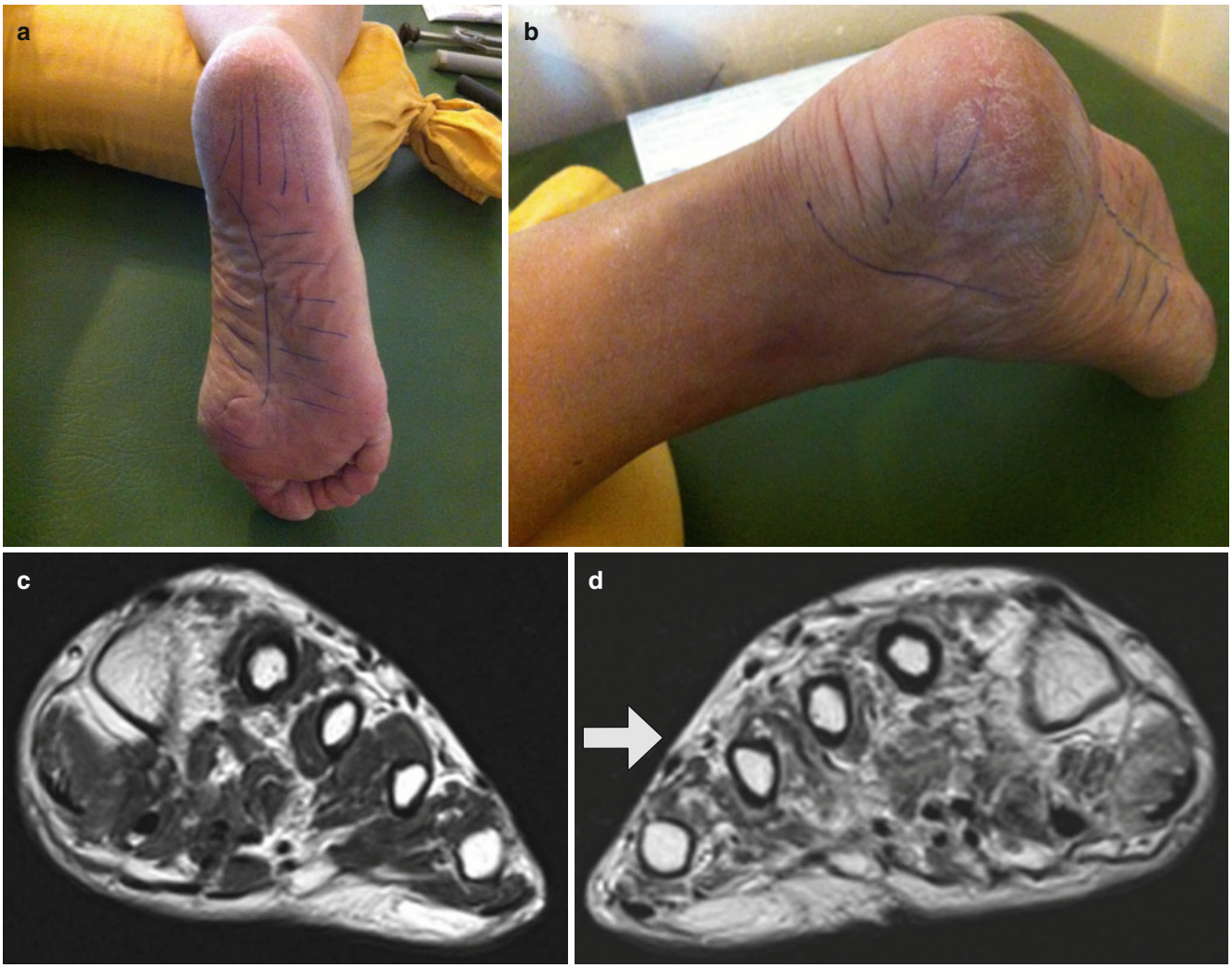


Fig. 8.83 (**a**) Sensory loss in an incomplete tibial nerve lesion (after a knee operation). (**b**) Involvement of the calcaneal nerve. (**c**) MRI of the foot muscles of the left (healthy) foot. (**d**) Damaged muscles in the right foot due to denervation

Pathogenesis of Distal Tibial Nerve Lesions Tarsal tunnel: see tarsal tunnel section.

Lesions of the Medial and Lateral Plantar Nerve Medial plantar: fractures of the foot, cysts, schwannomas, hypertrophy of abductor hallucis muscle. Lateral plantar: fractures, trauma, schwannomas, compression by foot muscles (Figs. 8.84 and 8.85).

Diagnosis

Electrophysiology: NCV can be obtained from the tibial nerve by stimulation in the popliteal fossa and distally proximal to the tarsal tunnel recording at the abductor halluces. In tarsal tunnel syndrome, the latencies between the medial plantar and lateral plantar nerve are compared. Sensory NCVs can be obtained by stimulating the toes, or the sole. EMG differentiates the site of the lesion. In the foot, usually the abductor

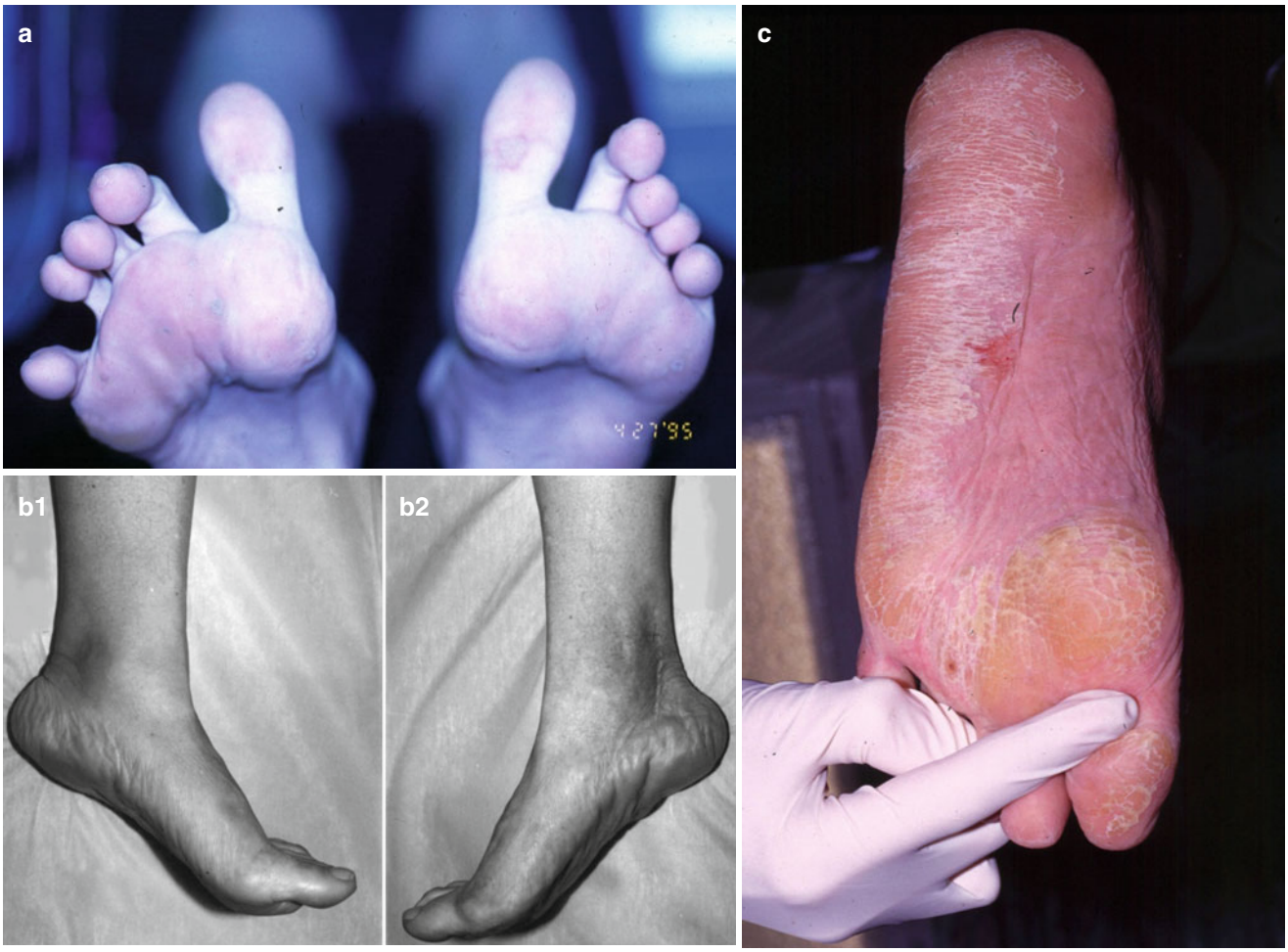


Fig. 8.84 Tibial nerve lesions: (**a**) Tibial nerve on the left leg. Note that the patient is unable to spread the toes. (**b**) Distal tibial nerve lesion: *B-1* normal, *B-2* atrophy and wrinkling of the skin of the plantar pedis. (**c**) Complete tibial nerve lesion; note the discoloration of the skin and hyperkeratosis

hallucis and the abductor digitii quinti are examined, although neurogenic lesions can also come from local damage (shoes, compression). Imaging: MR studies are useful for the whole course of the nerve, in particular the popliteal fossa, the tarsal tunnel and Morton's neuroma. The distribution of the affected muscles in the calf and foot are helpful for localizing the lesion. Sweat test: e.g., the ninhydrin test is useful to show involvement of peripheral autonomic fibers.

Differential Diagnosis

Sciatic nerve lesion, radicular lesion. Fasciitis: burning feet in neuropathies, such as in diabetes.

Therapy

Conservative: for pain, gabapentin. Physical therapy: orthotic devices. Surgical: removal of Baker's cysts and nerve sheath tumors.

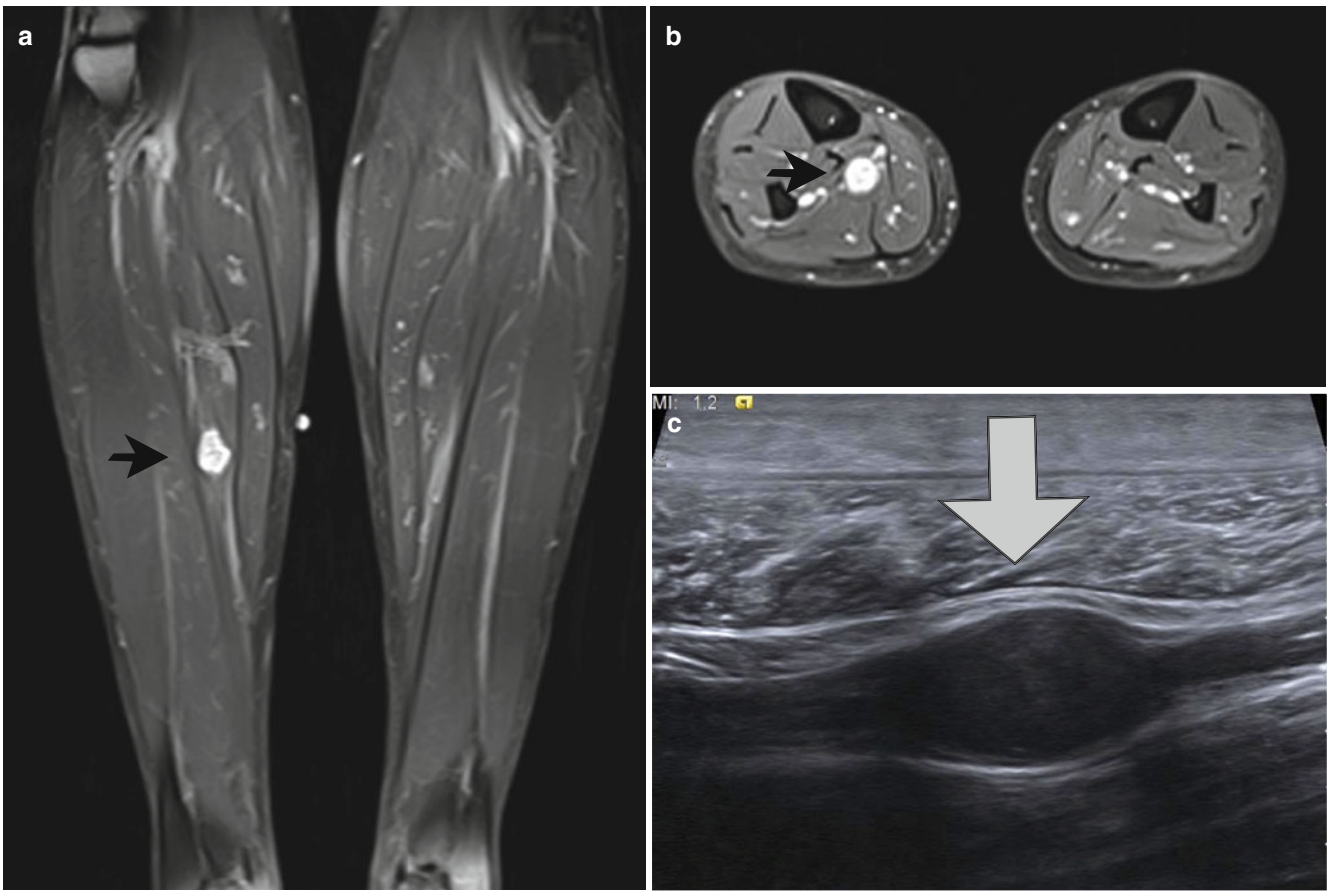


Fig. 8.85 Tibial nerve: schwannoma (*arrow*). Case: 50-year-old man complained of electric pain radiating from his lower leg into his foot. The clinical examination was normal, except a Tinel's sign was elicited with percussion of the lower leg. MRI (**a**, **b**) and ultrasound (**c**) showed a nerve tumor, which was identified to be a schwannoma

Prognosis

Depends on the etiology.

8.4.11 Sural Nerve

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

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 fifth 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 aspect of the foot.

Symptoms after sural nerve biopsy: dysesthesias occur in 40–50 % of cases with rare neuroma formation. Postoperative scarring may result in dysesthesias, postoperative pain. Rarely, wound infections occur. There is no difference between whole nerve biopsy or fascicular biopsy with regard to complications.

Signs

Tinel's sign may indicate the site of the lesion, sensory loss or dysesthesias in the distribution of the nerve.

Pathogenesis of Sural Nerve Lesions

Most common: biopsy or nerve grafting. Popliteal fossa: Baker's cyst, arthroscopy, surgery for varicose veins. Calf: calf muscle biopsies, elastic socks, footwear, tight lacing. Ankle

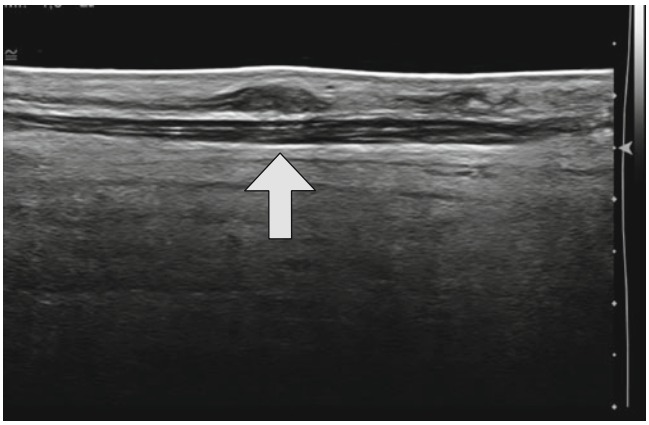


Fig. 8.86 Sural neuroma. The patient had a nerve biopsy and several years later developed pain and allodynia in his foot. There was a pronounced Tinel's sign in the area of the scar. Ultrasound showed the neuroma (*arrow*)

and foot: acute or chronic ankle sprain, avulsion fracture at the base of the fifth 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

Electrophysiology, imaging (US), biopsy, sensory NCV (Fig. 8.86).

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 radiculopathy.

Therapy

Padding of shoes, massage, steroid injections, excision and transposition of the nerve stump.

Prognosis

Depends on the etiology.

8.4.12 Posterior Tarsal Tunnel Syndrome

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy Hematology
	+		+	

Anatomy/Distribution

See also tibial nerve. The borders of the tarsal tunnel are the calcaneus, malleolus medialis, talus, flexor retinaculum and

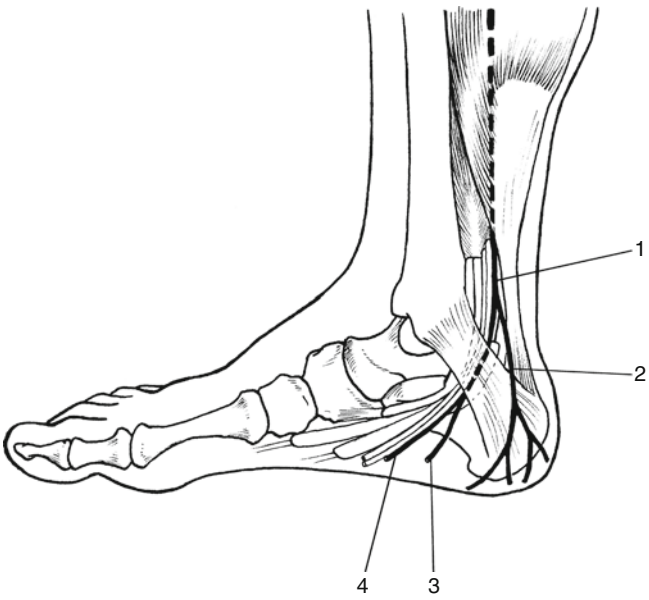


Fig. 8.87 Tarsal tunnel. *1* Tibial nerve. *2* Calcanear branch. *3* Lateral branch. *4* Medial branch

the tendons of the posterior tibialis muscle and the extensor hallucis longus muscle, the posterior tibial artery and the tibial nerve. Lesions may involve the complete nerve, or in a more distal lesion either the medial or lateral plantar nerves. Where the lateral and medial plantar nerves separate, the medial calcaneal nerve also leaves the trunk, which is purely sensory and innervates the heel. The calcaneal nerve can be involved in the tarsal tunnel syndrome. The inferior calcaneal nerve is the first branch of the plantar lateral nerve and innervates the abductor digiti quinti muscle and at times also the quadratus plantae muscle, and the periostal innervation of the anterior calcaneal bone (Fig. 8.87).

Symptoms

Local pain at the medial malleolus, sensory symptoms at the medial or plantar aspect of the foot. A Hoffmann-Tinel's sign can often be elicited; also, forced eversion or dorsiflexion of the foot can increase symptoms.

Signs

Tinel's sign, weakness of the small foot muscles (difficult to assess, difficult to spread toes). Tenderness of the nerve along its course is termed the Valleix phenomenon.

Pathogenesis

Acute tarsal tunnel syndrome is extremely rare and can occur with unusual mechanical stress and trauma. Chronic tarsal tunnel syndrome is more frequent in diabetes mellitus, hypothyroidism, gout, inflammatory conditions such as rheumatoid arthritis, unspecific tendosynovitis and adjacent osteomyelitis (Fig. 8.88).

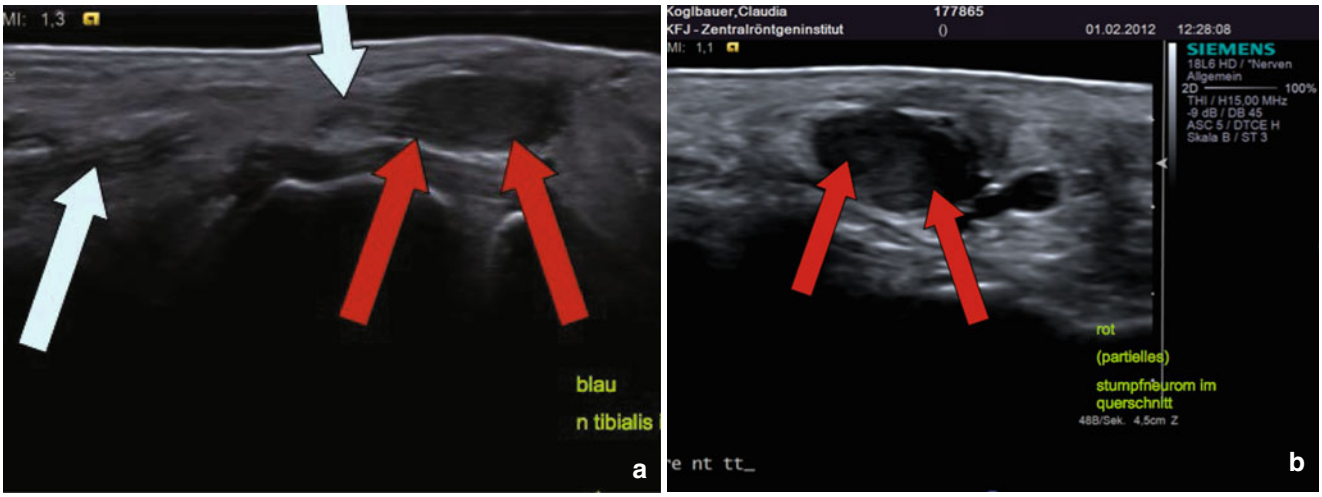


Fig. 8.88 Tibial nerve neuroma in ultrasound: (**a**) Tibial nerve in the tarsal tunnel (*blue arrows*). *Red arrows* (**a**, **b**) reveal neuroma of the tibial nerve distal to the tarsal tunnel

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, neurilemmoma, lipoma.

Others Dilated veins, varicosity, rarely hypertrophic or accessory muscles (e.g., abductor hallucis longus) or tendons (e.g., flexor digitorum longus) can compress the nerve in the tarsal tunnel.

Differential Diagnosis

Arthritis, "burning feet," bursitis, circulation disorders, compression of plantar nerve against tuberosities of the navicular bone, foot pain of other causes, orthopedic conditions, pes planus and hyperpronation, plantar fasciitis, plantar callosities, polyneuropathy.

Diagnosis

NCV: motor medial and lateral branch of the tibial nerve. Sensory: NCV of medial and lateral plantar nerve, stimulation either on the sole of the foot, or the first or fifth toes. EMG – small foot muscles often have neurogenic changes secondary to shoe wear and are less reliable.

Neuroimaging: ultrasound and MRI of tarsal tunnel and small foot muscles (may show atrophy).

Therapy

Anti-inflammatory drugs, arch supports and orthotics, local injections, neurolysis of the tibial nerve, neurovascular decompression, steroids, surgery.

Complications: new neurological deficits can arise as a complication in patients with any type of neuropathy, which makes the nerves vulnerable. Complex regional pain syndrome (CRPS) is a rare sequel of surgery; lesions of the calcaneal branches can produce causalgia in the heel. Postoperative complications include impaired wound healing and infection.

8.4.13 Anterior Tarsal Tunnel Syndrome

Terminal branch of the deep peroneal nerve. It passes under the pars cruciforme vaginae fibrosae. The anterior tarsal tunnel is formed by the fascia lining the inferior extensor retinaculum and talus as well as the navicular bone (Fig. 8.89).

Symptoms

Pain and burning pain at the dorsum of the foot. Sensory loss over the first interosseus space.

Signs

Atrophy of the extensor digitorum brevis muscle (often asymptomatic). Positive Tinel's sign.

Causes

Contusion of the dorsum of the foot, tight shoelaces, talonavicular osteophytosis, ganglion, and pes cavus, local compression, talus fractures.

Therapy

Local steroid injections, orthotics, splints, surgery.

Electrophysiology

NCV and EMG.

Differential Diagnosis

Local arthritis, osseous changes.

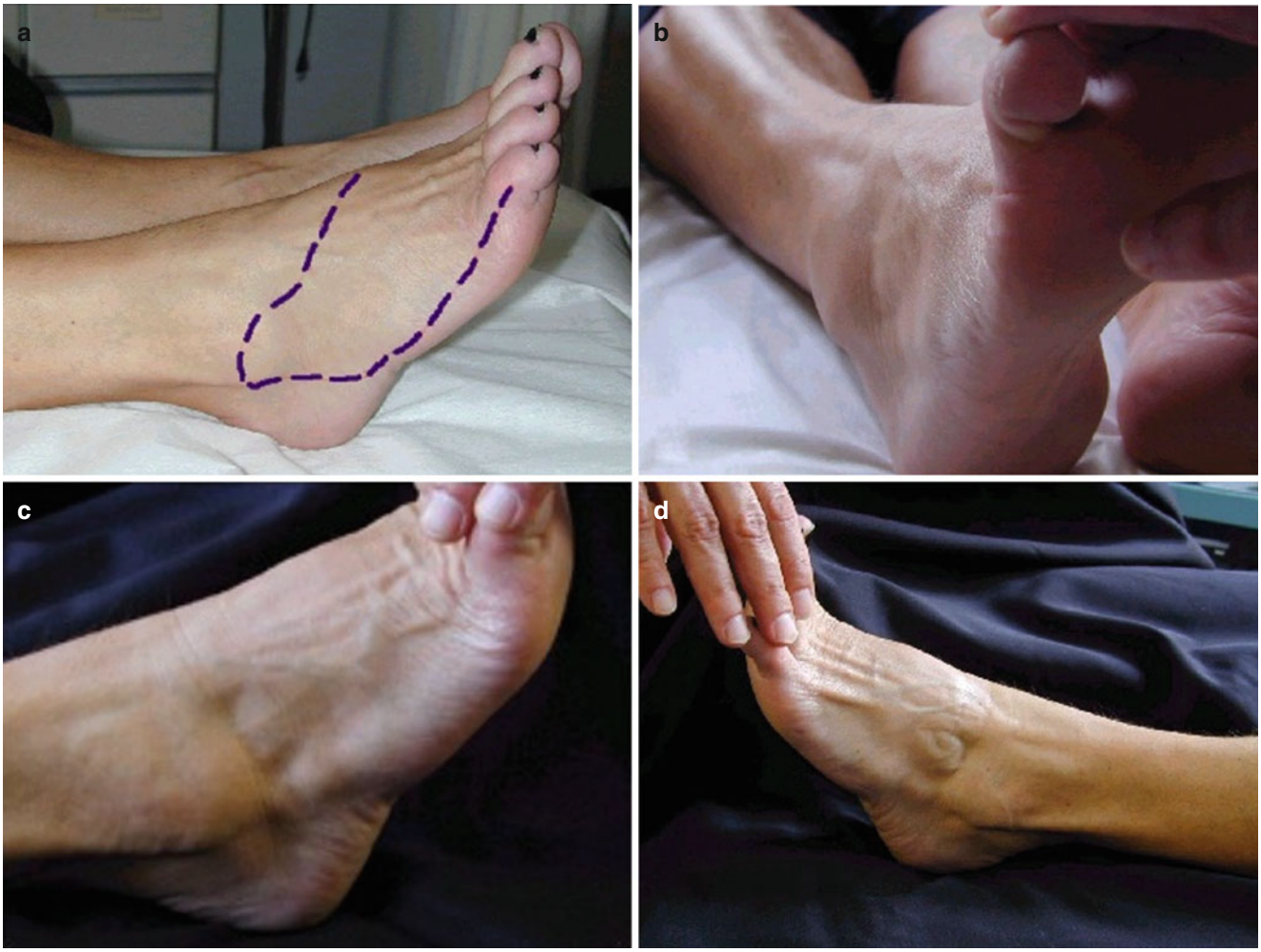


Fig. 8.89 Anterior tarsal tunnel syndrome: (**a**, **b**) Sensory loss in a case of anterior tarsal tunnel syndrome, atrophy of extensor digitorum brevis muscle. (**c**) Atrophy of the extensor digitorum brevis muscle. (**d**) Opposite foot with a normal muscle

8.4.14 Interdigital Neuroma and Neuritis

Genetic Testing	NCV/EMG	Laboratory	Imaging	Biopsy
	+		+	

Anatomy

Terminal branch of tibial nerve at the head of the third and fourth metatarsal bones, and toes.

Symptoms

Pain in the forefoot, localized to the second and third interdigital spaces. 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 the third and fourth or third and fifth metatarsals.

Clinical Syndrome

Interdigital tenderness. Pain might be elicited by adduction of metatarsals and metatarsal compression. Pain and paresthesias of adjacent toes, forefoot pain and numbness may also occur.

Causes

Mechanical irritation of the nerve can cause swelling and neuritis.

Plantar extension can elicit pain: lateral pressure from adjacent metatarsal heads results in nerve irritation and neuroma formation.

Diagnosis

NCV is not routinely used. Ultrasound and MRI are useful (Fig. 8.90). Diagnostic approach by local injection of anesthetic.

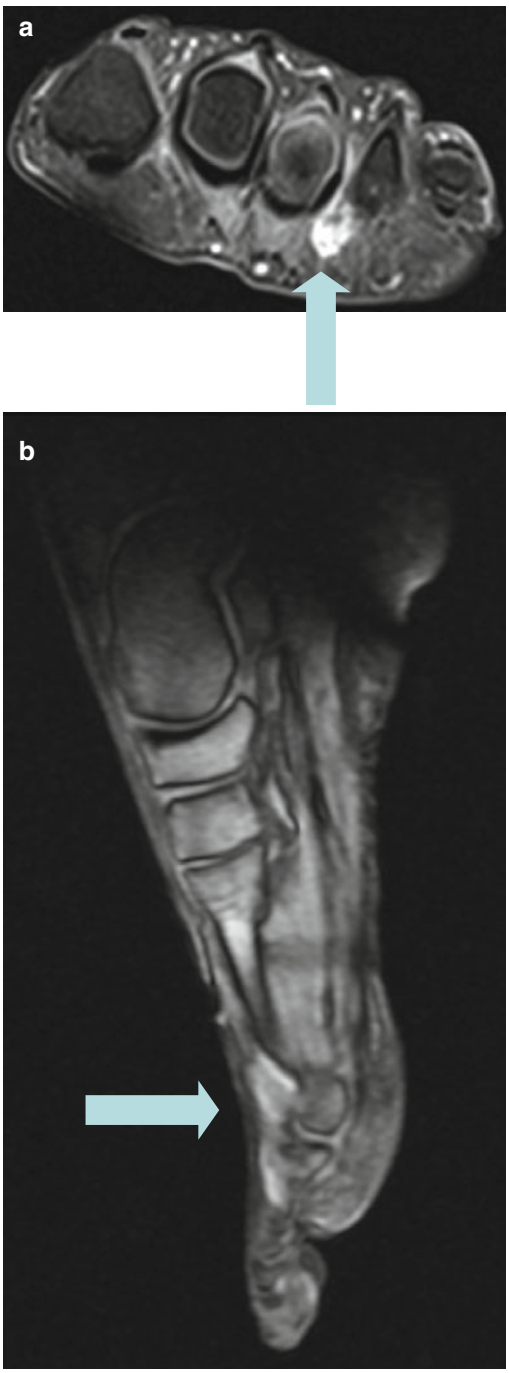


Fig. 8.90 Morton's neuroma. MR scan of a normal foot (**a**) and a foot with neuroma (**b**) (*arrow*)

Differential Diagnosis
Freiberg's infraction, metatarsophalangeal pathology (instability, synovitis), metatarsal stress fracture, plantar keratosis.

Therapy
Avoidance of high-heeled shoes, anti-inflammatory agents, and pain therapy. Steroid or local anesthetic agent injection, surgery.

Prognosis
Depends on etiology.

8.4.15 Nerves of the Foot

Joplin's Neuroma or Medial Plantar Proper Digital Nerve Syndrome

Anatomy
This nerve crosses the first metatarsophalangeal joint and runs on the medial side of the big toe.

Symptoms
Paresthesias and pain on medial side of the big toe when walking. Both sides can be involved.

Signs
Tender and thickened nerve; Tinel's sign may be positive.

Causes
Blows, lacerations, often chronic irritation (shoes) (Fig. 8.91).

Diagnosis
Clinical diagnosis, NCV (difficult to assess).

Differential Diagnosis
Arthritis of the first metatarsophalangeal joint.

Therapy
Appropriate footwear. Surgery: nerve excision.

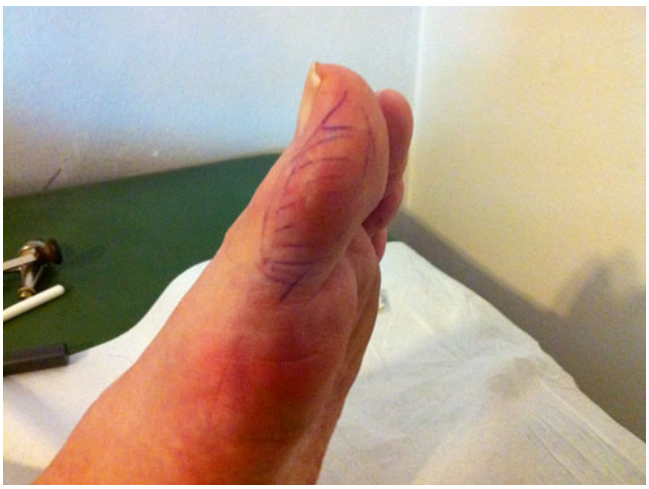


Fig. 8.91 Medial plantar proper digital nerve. A 50-year-old patient developed bilateral sensory loss on the medial side of the big toes. This occurred after a strenuous hike and is secondary to ill-fitting shoes

Calcaneal Nerves

Anatomy

The medial calcaneus nerve originates from the tibial nerve (at the point of the tarsal tunnel), and the lateral calcaneal nerve is a branch of the sural nerve.

Symptoms

Numbness, pain, and stabbing pain at the heel.

Causes

Medial calcanear neuropathy: damage and lesion of the medial calcaneal nerve in the tarsal tunnel. Numbness in the medial heel. Lateral calcaneal neuropathy: Local nerve lesion. Pain radiates to the lateral foot. Inferior calcaneal neuropathy: Baxter's neuropathy is a lesion of the first branch of the lateral branch of the tibial nerve. It is caused by a calcaneal spur or foot derangement. Symptoms include heel pain with symptoms similar to plantar fasciitis.

Differential Diagnosis

Plantar fasciitis.

Plantar Nerves (Medial and Lateral)

Both nerves pass through the tarsal tunnel, through the arch and sole of the foot (Fig. 8.92).

Medial Plantar Nerve

Is the larger of the two terminal divisions of the tibial nerve. It has sensory branches (skin of the sole of the foot, proper digital nerve to the medial side of the big toe). Muscular branches are: abductor hallucis, flexor digitorum brevis, flexor halluces brevis and the first lumbricals. Articular branches innervate the tarsus and metatarsus.

Proper Digital Nerve of the Great Toe

The proper digital nerve of the great toe supplies the flexor hallucis brevis and the skin on the medial side of the great 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 (Fig. 8.91).

Symptoms Pain or paresthesias on the medial side of the big toe, especially when walking. Often mild, but may also be disabling.

Medial Plantar Proper Digital Nerve (Joplin's Neuroma)

Differential Diagnosis Arthritis of the big toe: see chapter on Tarsal Tunnel.

Symptoms Sensory loss at the medial side of the toe. Tinel's sign at base of the big toe, sensory loss.

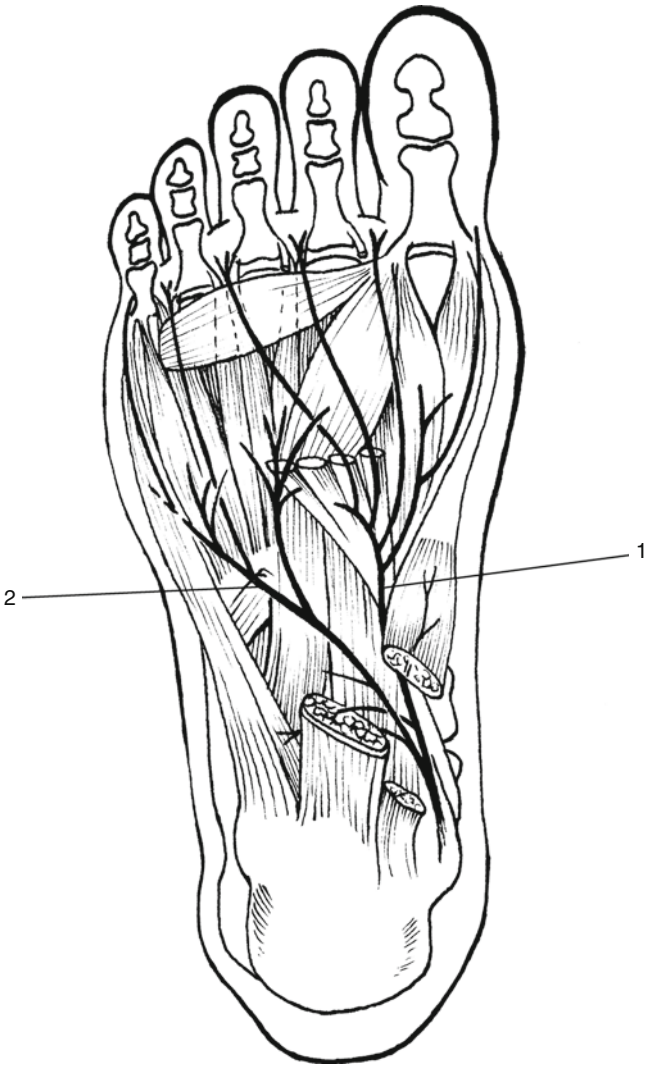


Fig. 8.92 Foot nerves. *1* Medial plantar branch. *2* Lateral plantar branch

Causes Acute blunt blows, lacerations, blunt trauma, poorly fitting shoes, scars.

Three Common Digital Nerves

Pass between the divisions of the plantar aponeurosis, and split into two proper digital nerves. The third common digital nerve receives a communicating branch from the lateral plantar nerve. Each proper digital nerve gives off cutaneous and articular branches. Opposite the last phalanx it projects a dorsal branch, which supplies the structures around the nail. The terminal part of the nerve supplies the ball of the toes.

Lateral Plantar Nerve (External Plantar Nerve) (Fig. 8.93)

This is a branch of the tibial nerve, and supplies the skin of the fifth toe and lateral half of the fourth, as well as most of

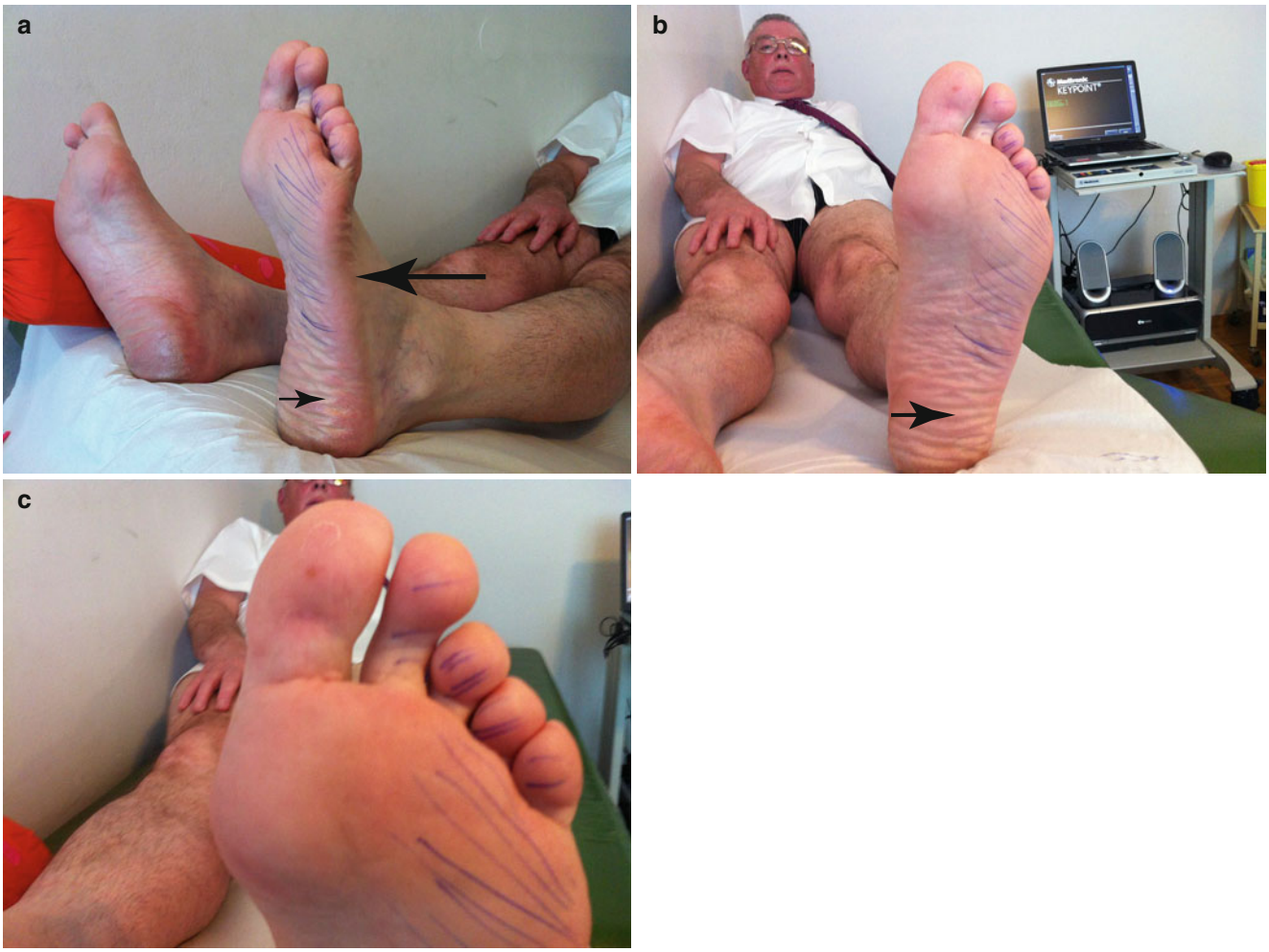


Fig. 8.93 Tibial lateral plantar nerve: Sensory loss in the distribution of the lateral plantar nerve. Note the sparing of the heel (calcaneal lateral nerve) and the lateral side of the foot (sural nerve)

the deep foot muscles (abductor digiti minimi, accessory flexor [quadratus plantae], adductor hallucis, flexor digiti minimi brevis, interossei, lumbrical muscles 3, 4, and 5). It divides into a superficial and a deep branch. Before its division, it supplies the plantae and abductor digiti minimi.

Causes Trauma, tendon sheath cysts, schwannomas, hypertrophy or fibrosis of abductor hallucis muscle, sometimes from a nondiscernible cause. Isolated lateral plantar nerve lesion: occurs less frequently, from foot fractures or ankle sprains. Entrapment of the first branch of the lateral plantar nerve has been described. This affects intrinsic foot muscles, and the calcaneal periosteum. Occurs in athletes and is associated with heel pain.

Interdigital Nerves (Morton's Metatarsalgia)

Occurs at adjacent metatarsal bones before the division into two digital nerves.

Dorsum of the Foot

The dorsum of the foot is mainly innervated by the superficial peroneal nerve, the space between digits 1 and 2 by the deep peroneal nerve. The lateral side of the foot is innervated by the sural nerve and the medial malleolus by the saphenal nerve.

Medial Malleolus

The skin of the medial malleolus is innervated by the saphenal nerve, which is the terminal branch of the femoral nerve. Acute ankle sprain and hematoma can cause acute compartment syndrome of the foot. Ultrasound can show the hematoma.

8.4.16 Peripheral Nerve Tumors

Peripheral nerve tumors usually present with a slowly progressing mononeuropathy or plexopathy. Initial paresthesia and pain are followed by motor and/or sensory loss. The tumors

Table 8.3 Peripheral nerve tumors

	Benign tumors	Malignant tumors
Nerve sheath	Schwannoma (neurolemmoma, neurinoma)	Malignant schwannoma
	Neurofibroma (solitary, plexiform)	Neurofibrosarcoma
	Fibrolipoma	
Neuronal tumors	Ganglioneuroma	Ganglioneuroblastoma
		Neuroblastoma
Tumor-like conditions	Amputation neuroma	
	Ganglionic cysts	
	Giant proximal nerve hypertrophy	
	Lipoma	
	Morton's neuroma	
	Nerve sheath cysts	
	Hamartoma	
	Neurothekoma	
	Pallisaded encapsulated neuroma	
	Perineuroma	

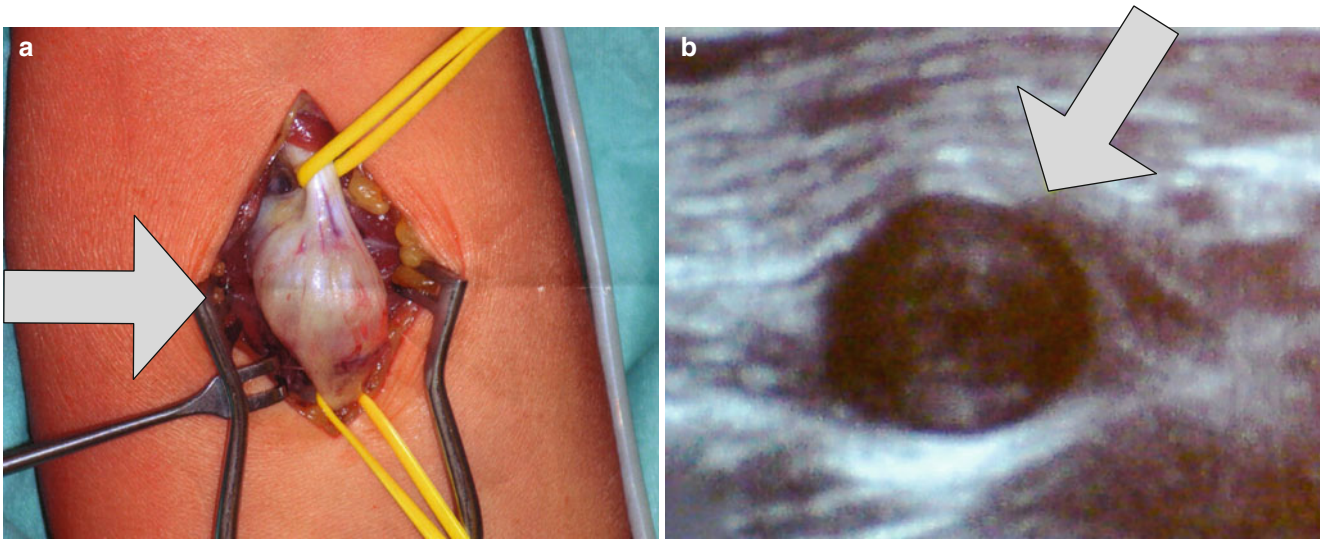


Fig. 8.94 Schwannoma. This patient presented with a mass in her forearm. There was no sensory or motor loss and the NCVs were normal. The surgical excision shows the intraneural position of the tumor (**a**); the ultrasound image preoperatively (**b**)

may be grossly visible, palpable, or detected by CT, MR, or ultrasound. Mechanical factors (e.g.. sitting, stretching the sciatic nerve, walking if tumor is on the foot) can exacerbate pain or paresthesias or induce a Tinel's sign. MRI or US can give a precise location and information on the size and structure of the tumor. Also, PET studies can be helpful to detect tumors. NCV and EMG can be used to assess the functional impairment caused by the nerve lesion. The final classification of the tumor relies on histological assessment. Peripheral nerve tumors can be benign and malignant. On rare occasions they may be the result of metastases from other tumors (Table 8.3).

Benign Tumors

Schwannoma is the most common peripheral nerve tumor in adults. The majority of schwannomas are spontaneous, and only 5 % stem from predispositions such as NF2 or schwannomatosis. Multiple schwannomas often occur in NF2. Paraspinal schwannomas often have both intradural and extradural parts ("dumbbell shape"). They are encapsulated and displace adjacent nerve fascicles. Schwannomas can present as a painless, palpable masses on upper or lower extremities, often of the flexor surfaces (Fig. 8.94). Sensory loss often dominates motor symptoms, and pain often occurs. A Tinel's sign can usually be elicited. Neurofibromas are benign tumors due to primary transformation of Schwann cells, although additional stromal cells can be found in the tumors. Neurofibromas can occur spontaneously or in association with NF1. Plexiform neurofibromas can arise in large and deep nerves and grow within the fascicles. Neurofibromas cause neurological symptoms and pain. Malignant transfor-

mation occurs in up to 5 %. Painful swelling associated with sensory and motor symptoms occur. Tinel's sign is rare.

Tumor-Like Disorders

Amputation neuromas 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 are characterized by disorganized growth of small fascicles from the proximal stump. Ganglionic cysts occur near joints or tendon sheaths and may cause compression of adjacent nerves. The main sites are the median and ulnar nerves at the wrist, the posterior interosseus nerve at the elbow, and the common peroneal nerve at the knee. Giant proximal nerve hypertrophy occurs in CMT. Lipoma originates from fibro-fatty tissue. It is a benign tumor and can be intrinsic or extrinsic to peripheral nerves, but may infiltrate the nerves. Localized hypertrophic mononeuropathy is a slowly progressing mononeuropathy with little pain or numbness that may occur isolated or with NF1. It is composed of perineurial and Schwann cells. Any nerve or nerve root can be affected, with upper and lower extremities equally affected. MR shows nerve enlargement. Morton's neuroma is a frequent condition occurring with advanced age. It is localized between the 3rd and 4th metatarsal bone. Often numbness between the two adjacent toes can be noted. Nerve sheath ganglia (or cysts) are mucin-filled cysts in the perineurium which occur most often in the common peroneal nerve. Neuromuscular hamartoma (benign triton tumor) is a mosaic tumor with striated muscle within nerve fascicles. Neurothekoma is a myxomatous tumor of Schwann cell origin occurring in the neck, face, and shoulder region. Palisaded encapsulated neuroma is a benign tumor consisting of Schwann cells, perineural cells, and small axons. It occurs in middle age, predominantly in the face. Perineuromas occur typically in middle-aged persons and arise in the soft tissue of the extremities. They are not associated with NF1 or NF2. Imaging via MR or US shows focal enlargement of nerves. The most affected nerves are ulnar (17 %), median (11 %), common peroneal (9 %), posterior interosseus (9 %), and sciatic (8 %), but the radial and other nerves can have perineuromas. Other benign tumors include desmoid tumors, epidermoid cysts, hemangiomas, hemangiopericytomas, lipohamartomas, lymphangiomas, mucosal neuroma, and myoblastomas.

Malignant Peripheral Nerve Tumors

Malignant tumors of peripheral nerves can arise from primary malignant transformation of Schwann cells (MPNSTs), or secondary to infiltration or metastasis of lymphomas, carcinomas, or sarcomas. Malignant peripheral nerve sheath tumors often arise from the malignant transformation of plexiform neurofibromas, particularly those associated with NF1. Growth, pain, and increasing sensorimotor deficits suggest malignant transformation. Primary peripheral nerve lymphoma is rare. While it can present focally, it usually presents as multiple mononeuropathies (neurolymphomatosis). Cancers of various origins can affect peripheral nerve structures, in particular the nerve plexus or spinal nerve roots. Isolated mononeuropathies are caused in rare instances by cancer infiltration or metastasis (Fig. 8.95). Retrograde peripheral nerve infiltration has also been observed in nerves of the face and occurs more frequently from ENT tumors in the lower cranial nerves. The different types of nerve infiltration have been described by Meller as compression, invasion, engulfment, diffuse infiltration, or metastasis. Cranial nerves, nerve roots, nerve plexuses, and single nerves can be affected in cancer patients by different mechanisms. Table 8.4 gives an overview of the most frequently affected nerves. Other malignant peripheral nerve tumors arising from soft tissue sarcoma or the neural crest include neuroblastoma, ganglioneuroblastoma, ganglioneuroma, paraganglioma, and pheochromocytoma.

Involvement of Peripheral Nerves in Cancer

In patients with cancer, direct cancer effects, therapy-related, and other causes must be considered in peripheral nerve lesions.

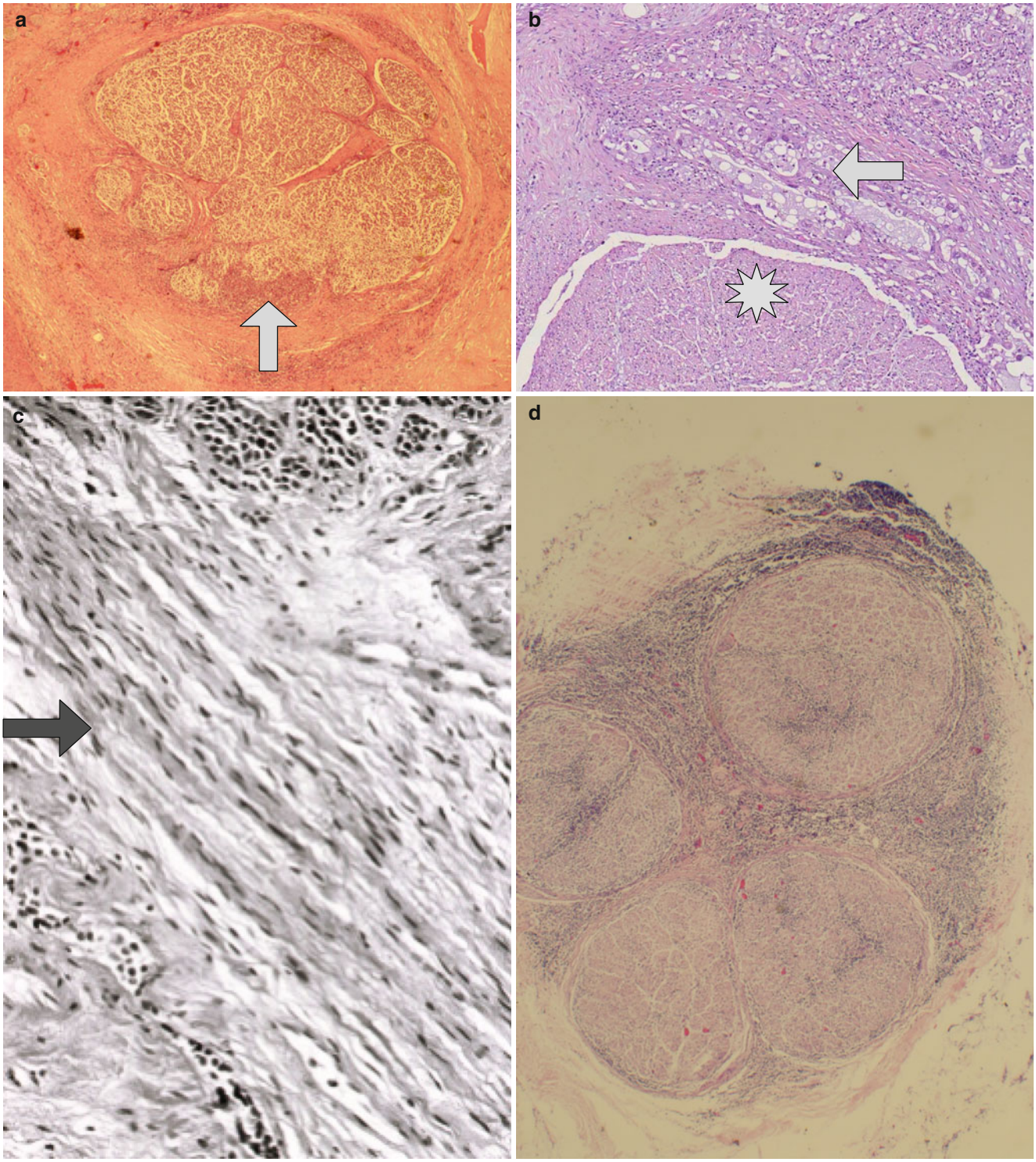


Fig. 8.95 Nerve infiltration: Peripheral nerves can be infiltrated by adjacent tumors or cancer. (**a**) Infiltration of the oculomotor nerve in the cavernous sinus. Tumor formation see arrow. (**b**) Brachial plexus infiltration by carcinoma formations (*arrow*). Adjacent nerve (*asterisk*). (**c**) Peripheral nerve (*arrow*), *asterisk*: cancer metastasis, tumor cells. (**d**) Diffuse patchy infiltration in and in between fascicles in a median nerve in neurolymphomastosis (autopsy)

Table 8.4 Involvement of peripheral nerves in cancer patients (direct cancer effect, therapy-related, and other causes)

Nerve	Neoplastic lesion	Therapy-related	Other causes
Cranial nerves	Base of the skull metastasis, leptomeningeal carcinomatosis, retrograde spread along cranial nerves	Local RT therapy, surgery, chemotherapy (vincristine, rarely)	Infections
Cervical plexus	Lymph node metastasis, ENT tumors	Effect of local RT, surgical effects	
Brachial plexus	Lower brachial plexus: tumors in the apex of lung or lymph nodes affected by breast cancer Panplexopathies and retrograde spread	RT, affects upper plexus more often	Infectious and immunological causes
Axillary nerve		Surgery, mastectomy	
Pectoral nerves	Local spread of breast cancer	Thoracic surgery	
Musculo-cutaneous nerve	Nerve metastasis		
Anterior cutaneous antebrachial nerve	Can be a sign of lower brachial plexus lesion	Paravenous injection	
Median nerve	Neurolymphomatosis	Paravenous injection	Amyloid deposition, paraproteinemia
Ulnar nerve	C8 lesions and Pancoast tumors can resemble ulnar nerve lesions	Radiotherapy, malpositioning	
Radial nerve		Malpositioning, neurotoxicity (vinca alkaloids)	
Truncal nerves	Local metastasis, vertebral column collapse	Surgery, long-term steroid treatment with osteoporotic changes	Herpes zoster
Long thoracic nerve		Surgery, mastectomy	Infection, idiopathic causes
Thoracodorsal nerve		Latissimus dorsi flap	
Phrenic nerve	Local metastasis, intrathoracal tumor spread, thymoma	Surgery, thymectomy	Idiopathic, critical illness neuropathy (ICU treatment)
Iliohypogastric nerve Ilioinguinal nerve Genitofemoral nerve		Renal or abdominal surgery, endoscopic procedure	
Cutaneous femoral lateral nerve		Surgery, RT, bone marrow harvest	
Femoral nerve	Local pelvic tumor, inguinal tumor, or lymph nodes	Surgery, coagulation disorders, radiotherapy	Angiography
Obturator nerve	Metastasis to the obturator foramen	Pelvic or prostate cancer surgery	
Gluteus medius nerve	Local tumor recurrence		Aneurysm
Sciatic nerve	Metastasis to the foramen piriforme	Intra-arterial 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 cause discussed. Cachexia. Peroneal lesion may be part of sciatic nerve lesion

Any nerve that is surgically damaged can develop a painful neuroma. Rarely, radiation can induce malignant nerve sheath tumors

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Polyneuropathies

9

Eva L. Feldman

9.1 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 the 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 the 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 a 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 9.1 provides a more complete list of disorders that lead to polyneuropathy. Multiple isolated peripheral nerve injuries, known as multiple mononeuropathies or mononeuritis multiplex, are also usually due to systemic disease. It can be difficult 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 a separate chapter.

9.1.1 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. 9.1). 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 and Tangier's disease. 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.

9.1.2 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 the 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

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Table 9.1 Differential diagnosis of polyneuropathy

Metabolic disease	Diabetes
	Renal failure
Systemic disease	Amyloid
	Paraproteinemia
	Vasculitis
	Critical illness
Infectious	Human immunodeficiency virus (HIV)
	Herpes zoster neuropathy
	Lyme
	Leprosy
Inflammatory	Acute inflammatory demyelinating polyradiculoneuropathy
	Acute motor axonal neuropathy
	Acute motor and sensory axonal neuropathy
	Miller Fisher syndrome
	Chronic inflammatory demyelinating polyradiculoneuropathy
	Demyelinating neuropathy with MAG antibodies
	Multifocal motor neuropathy with conduction block
Nutritional neuropathies	Cobalamin
	Post-gastroplasty
	Pyridoxine
	Strachan's syndrome
	Thiamine
	Tocopherol
Industrial agents, metals and drugs	Industrial agents
	Acrylamide
	Carbon disulfide
	Hexacarbons
	Organophosphorus agents
	Drugs
	Alcohol
	Amiodarone
	Colchicine
	Dapsone
	Disulfiram
	Etanercept and infliximab
	Isoniazid
	Nitrofurantoin
	Nucleoside analogues
	Pyridoxine abuse
	Nitrous oxide
	Metals
	Arsenic
	Lead
	Mercury
	Thallium
Hereditary	Hereditary motor sensory neuropathy (Charcot–Marie–Tooth disease)
	Hereditary neuropathy with pressure palsies
	Hereditary autonomic and sensory neuropathy
	Hereditary sensory neuropathy
	Hereditary neuralgic amyotrophy
	Distal hereditary motor neuropathies
	Porphyria
Cancer and neuropathy	Paraneoplastic
	Neoplastic
	Chemotherapy-induced
	Neuropathies in lymphoma and leukemia

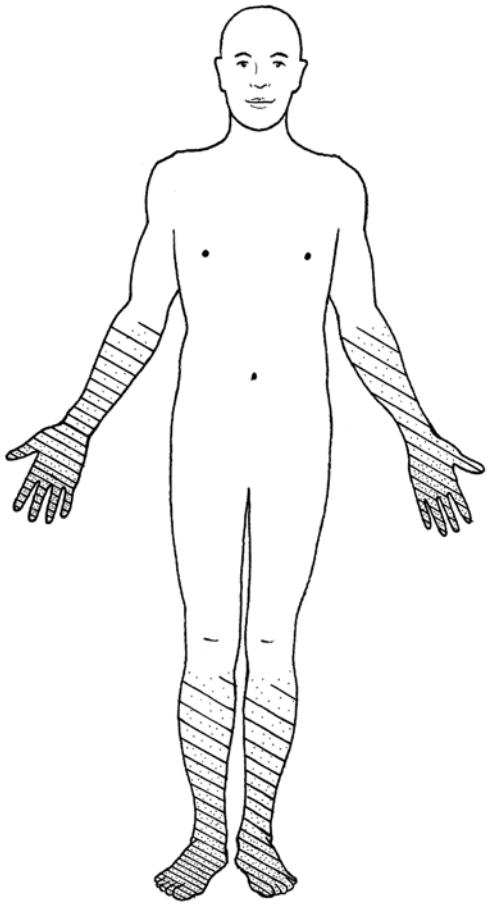

Fig. 9.1 Common stocking–glove distribution in polyneuropathies

absence or presence of external stimuli. At rest, patients can experience no painful paresthesias and/or frank pain. In response to normal stimulus 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 9.1.

9.2 Metabolic Diseases

Diabetes is the most common cause of neuropathy in the Western World. The four 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.

9.2.1 Diabetic Distal Symmetric Polyneuropathy

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

Distribution/Anatomy

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 and 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. 9.2). Commonly, all sensory modalities are decreased in a stocking–glove pattern with loss of ankle reflexes. Weakness is uncommon and presents distally in only the most severe cases. When sensation loss reaches the mid calf, early sensory loss is found in the fingers.

Pathogenesis

The Diabetes Control and Complications Trials (DCCT) confirmed that hyperglycemia underlies the development of DPN in type 1 patients. It is likely that the hyperglycemic state disrupts both the normal metabolism and the blood flow of peripheral nerves. Hyperlipidemia and hypertension along with hyperglycemia underlies DPN in type 2 diabetes.

Diagnosis

Laboratory HbA1C and lipid profiles are 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.

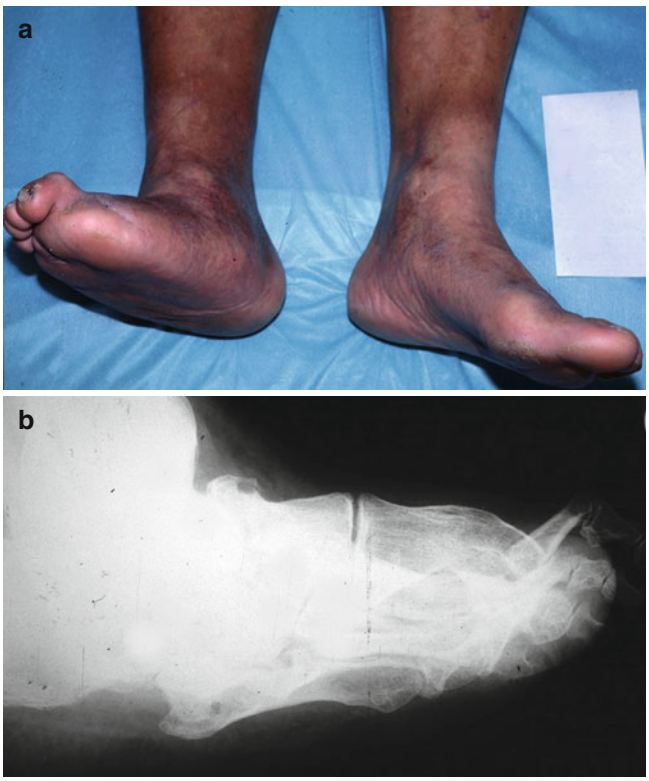

Fig. 9.2 Diabetic neuropathy and pes planus. (**a**) Sensory loss may induce osseous changes with collapse of the small bones of the foot. (**b**) X-ray showing the collapsed bones

Electrophysiology Early in neuropathy, NCV reveal low normal or absent sural sensory responses with mild decreases in peroneal motor conduction velocities. As the neuropathy progresses, sensory amplitudes in the hand decline, and there is evidence of denervation by EMG in distal foot muscles.

Imaging None.

Nerve Biopsy There is loss of large and small axons in the absence of inflammation with thickening of blood vessel basement membrane (Fig. 9.3). Nerve biopsy is usually not required for the diagnosis.

Differential Diagnosis

A systematic stepwise elimination of other common causes is required (see Table 9.1).

Therapy

DPN requires preventative and, in some cases, symptomatic therapy. Preventative therapy consists of optimal glycemic and lipid 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, pregabalin (150 mg TID), duloxetine (60 mg QD), and amitriptyline or nortriptyline (25–150 mg/QHS). Please see the recent review by Callaghan (2012) for a complete approach to the treatment of painful neuropathy.

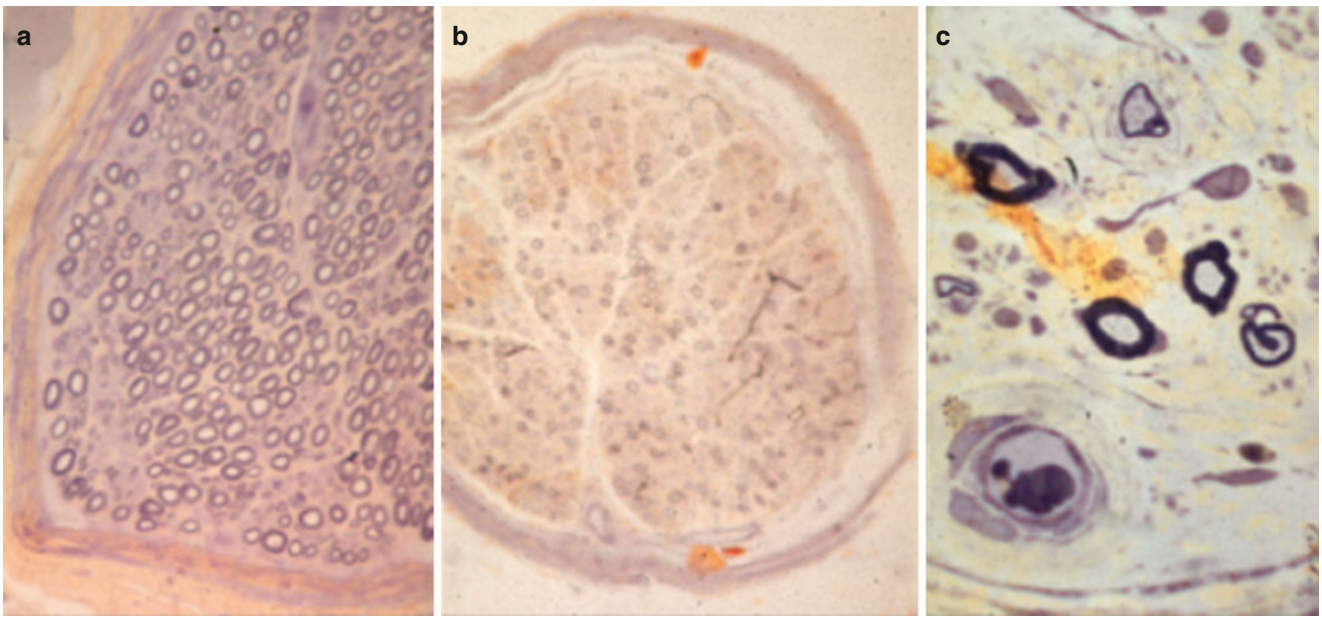

Fig. 9.3 Histology of sensory nerves in diabetic neuropathy. Sural nerve biopsies from an asymptomatic control subject (**a**) and a patient with diabetic neuropathy (**b**). (**a**) The control sural nerve shows abundant and normal distribution of myelinated fibers. (**b**) Sural nerve from a patient with diabetes, showing severe axonal loss and demyelination. (**c**) High-magnification view of (**b**) showing loss of myelinated fibers and splaying of myelin with early onion bulb formation

Prognosis

Fifteen percent of patients with neuropathy develop an ulcer in their lifetime. Prognosis is dependent on daily foot hygiene and care as well as metabolic control.

9.2.2 Diabetic Autonomic Neuropathy

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

Distribution/Anatomy

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, nighttime 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 anhidrosis 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 a supine position with the patient breathing at a fixed rate of six breaths per minute during a 6 min 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 lying to standing position. The shortest R-R interval around the 15th beat and the longest R-R interval around the 30th beat after starting to stand are 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.

Biopsy 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.

Prognosis

Like DPN, DAN usually progresses slowly over the 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.

9.2.3 Diabetic Mononeuritis Multiplex and Diabetic Polyradiculopathy (Amyotrophy)

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

Anatomy
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 nerves 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 is a rare complication of diabetes, sudden in onset, often self-limited, and occurs primarily in older, poorly controlled type 2 patients. 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. Involvement of thoracic nerve roots presents as band-like abdominal pain that is often misdiagnosed as an acute intra-abdominal emergency. L2–L4 diabetic polyradiculopathy is often confused with a pure femoral neuropathy; the former is common while the latter is rare. Patients have weakness 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. Epineurial vessels are inflamed with IgM and complement deposition.

Diagnosis
Laboratory It is essential to exclude vasculitis by appropriate serological screening.

Electrophysiology Loss of sensory nerve amplitudes (SNAPs) and in advanced cases compound motor action potentials (CMAPs) and mildly slowed motor and sensory 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 scan is routine to rule out intra-abdominal pathology in patients with diabetic thoracic radiculopathy and a mass lesion in the lumbosacral plexus in patients with diabetic lumbar polyradiculopathy.

Biopsy None.

Therapy
Patients usually 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 gamma globulin (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.

9.2.4 Distal Symmetric Polyneuropathy of Renal Disease

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

Anatomy
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, dysesthesias, 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 two 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 creatinin and 24 h urine collection all indicate renal failure.

Electrophysiology Early in neuropathy, there are prolonged distal latencies, slowed motor conduction velocities, and prolonged F waves. SNAPs and CMAPs are reduced 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.

9.3 Systemic Diseases

9.3.1 Amyloid Neuropathies

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
In familial amyloid neuropathy: *Transthyretin*	Motor and sensory nerve conduction studies can be normal or show sensory > motor axonal damage.	In acquired amyloidosis: monoclonal gammopathy	–	Amyloid in liver, nerve, abdominal fat, rectal mucosa, gingiva, or salivary gland biopsy
Rarely: *APOA1 gelsolin*	Absent sympathetic skin response			

Epidemiology

Familial amyloid polyneuropathy (FAP) due to transthyretin mutations is endemic in Portugal, Sweden, and Japan. Sporadic cases are rare but found worldwide. Apolipoprotein A-1 FAP is rare; gelsolin FAP is almost exclusively found in individuals of Finnish descent. Acquired amyloid neuropathy is found in about 20 % of patients with primary (light chain) amyloidosis (AL), 10 % of which can have multiple myeloma.

Anatomy and Pathophysiology

Congo red staining identifies amyloid deposition in various tissues (Fig. 9.4). Amyloid distribution is multifocal and is found in the endoneurium and in capillary walls. Amyloid can also be seen on electron microscopy. Laser microdissection mass spectroscopy can differentiate hereditary from acquired amyloidosis. Immunolabeling with anti-TTR antibodies suggests TTR amyloidosis.

Symptoms

In AL neuropathy, neuropathic pain in the lower legs is typical. Orthostatic symptoms, impotence, bladder dysfunction, and reduced sweating are reported. Weight loss occurs. In TTR-FAP, early-onset (third to fourth decade) patients report discomfort and neuropathic pain in the feet. Symptoms progress and extend more proximally within months and numbness and weakness develop. Postural hypotension, impotence, bladder dysfunction, weight loss, and gastrointestinal dysfunction are early symptoms. Late-onset (sixth to eighth decade) TTR-FAP is commonly less painful with mild autonomic symptoms and a slower progression.

Signs

Temperature and pain sensation is impaired early on. With disease progression, vibration and light touch perception are also impaired and distal weakness develops. Rare subtypes present with multifocal neuropathy of upper limbs or ataxia. Carpal tunnel syndrome is frequent. Weight loss, macroglossia, organomegaly, and cardiomyopathy are found in AL. Extra-neurological manifestations in TTR amyloidosis frequently include restrictive cardiomyopathy and ocular abnormalities, especially vitreous opacities. Neuropathy is not prominent in APOA1 amyloidosis. Gelsolin amyloidosis is characterized by cranial nerve involvement (facial,

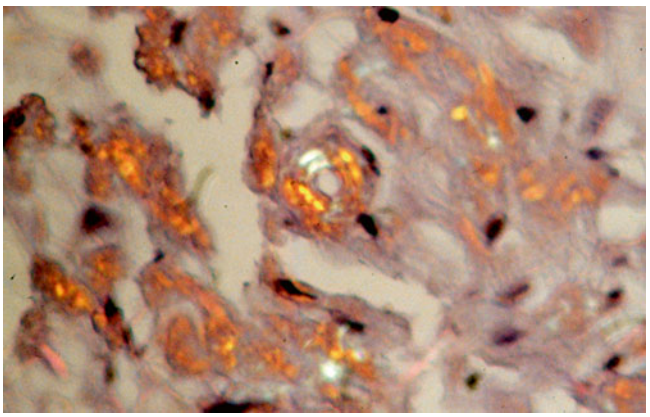

Fig. 9.4 Peripheral nerve amyloidosis. The biopsy shows a congo red-stained section with evidence of green birefringence in amyloid deposits within endoneurial vessels

hypoglossal, glossopharyngeal, and vagal nerves), dermatological (cutis laxa), and ophthalmological (corneal lattice dystrophy) manifestations.

Causes

Primary acquired amyloidosis is caused be overproduction of monoclonal immunoglobulin light chains. Transmission in FAP is autosomal dominant. The most common FAP is due to mutations in *transthyretin* (*TTR*) *gene*. Val30Met accounts for most mutations in Portugal and Sweden and for approximately 50 % of the mutations worldwide. Mutations in the *apolipoprotein A-1* (*APOA1*) *gene* are rare and mutations in the *gelsolin gene* are almost exclusively found in individuals of Finnish descent.

Diagnosis

Monoclonal gammopathy and demonstration of amyloid in liver, nerve, abdominal fat, rectal mucosa, gingival, or salivary gland biopsy suggests AL, although low-grade monoclonal gammopathy of unknown significance (MGUS) can also be found in FAP. Genetic analysis of the *TTR gene* is appropriate to diagnose most cases of FAP.

Electrophysiology At early stages in cases with pure small fiber neuropathy, nerve conduction studies can be normal. After a few months SNAPs are reduced or absent. CMAPs can also be reduced. Nerve conduction velocities are normal or slightly reduced. Carpal tunnel syndrome is frequently found.

Imaging None.

Laboratory Monoclonal light chain gammopathy is found in serum and urine. IgG is more frequent than IgA and IgM, and lambda light chains are more frequent than kappa light chains. CSF protein can be elevated.

Differential Diagnosis

Other causes of progressive axonal neuropathies with small fiber and autonomic involvement (See Table 9.1).

Therapy

AL is treated with chemotherapy and stem cell transplantation. TTR-FAP is treated with liver transplantation which improves survival. Recently, tafamidis, a TTR kinetic stabilizer, has been approved for the treatment of stage 1 (ambulatory) TTR-FAP to delay progression of neuropathy. Treatment of neuropathic pain follows the standard treatment guidelines.

9.4 Neuropathies Associated with Paraproteinemias

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

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	If CIDP like, treat CIDP
MGUS–MAG	Distal involvement, predominately large fibers with ataxia and pseudoathetoid movements	While various immunosuppressive therapies are described, none are effective
POEMS syndrome	CIDP like	Treatment of the myeloma; plasmapheresis; stem cell transplant
Waldenström's macroglobulinemia	Distal sensorimotor neuropathy, predilection for large fibers	Treatment of Waldenström's
Amyloidosis (AL type)	Polyneuropathy: autonomic involvement, involvement of skeletal muscle	Colchicine, steroids

9.4.1 Multiple Myeloma Neuropathy

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 (CTS), and autonomic signs.

Diagnosis
Nerve conduction velocities are slowed. Serum electrophoresis can show IgA or IgG monoclonal gammopathy. Bone marrow studies reveal myeloma, and a skeletal survey reveals lytic lesions.

Differential Diagnosis
Other types of polyneuropathy may be responsible for the clinical picture.

Therapy
The primary therapeutic goal is treatment of the myeloma and supportive care.

9.4.2 Monoclonal Gammopathy of Undetermined Significance (MGUS)

Symptoms
Symptoms may be motor, sensory, or sensorimotor depending on the associated paraproteinemia.

Clinical Syndrome/Signs
Motor or sensory signs present in a sensorimotor neuropathy or CIDP-like pattern.

Pathogenesis
Disease is associated with monoclonal gammopathy with IgM > IgG > IgA.

Diagnosis
Nerve conduction velocities may be slowed. Electrophoresis shows gammopathy. Myeloma should be excluded.

Differential Diagnosis
Other types of polyneuropathy, including myeloma-associated neuropathy.

Therapy
IgG monoclonal gammopathies associated with a CIDP-like picture frequently respond to immunosuppression and plasmapheresis. Other monoclonal gammopathies are less responsive, even in the presence of a CIDP-like pattern.

IgM Paraproteinemia with Anti-MAG Antibodies
Half of the patients with MGUS develop antibodies against MAG (myelin-associated glycoprotein).

9.4.3 Waldenström's Macroglobulinemia

Associated with chronic lymphocytic leukemia or lymphoma.

Symptoms
Large fiber sensory function is lost and there may be tremor.

Signs
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 Waldenström's over time.

Pathogenesis
There is likely an autoimmune attack against peripheral nerves.

Diagnosis
Skeletal survey is normal. Laboratory studies can show IgM monoclonal gammopathy, IgM antibodies to MAG, GMI, sulfatide, GD1a, or GD1b. Bone marrow and/or lymph node biopsy may be abnormal.

Therapy
Chemotherapy, IVIG, and plasmapheresis can be effective.

Prognosis
Neuropathy can often be arrested or improved with treatment.

9.4.4 Osteosclerotic Myeloma (POEMS Syndrome)

POEMS syndrome stands for polyneuropathy, organomegaly, endocrinopathy, M-component, and skin lesions (Fig. 9.5). POEMS syndrome is associated with osteosclerotic myeloma, located in the vertebral column and long bones, but not in the skull. A polyneuropathy resembling CIDP occurs, and papilledema has been described. Therapeutic efforts are directed against osteomyelosclerotic myeloma.

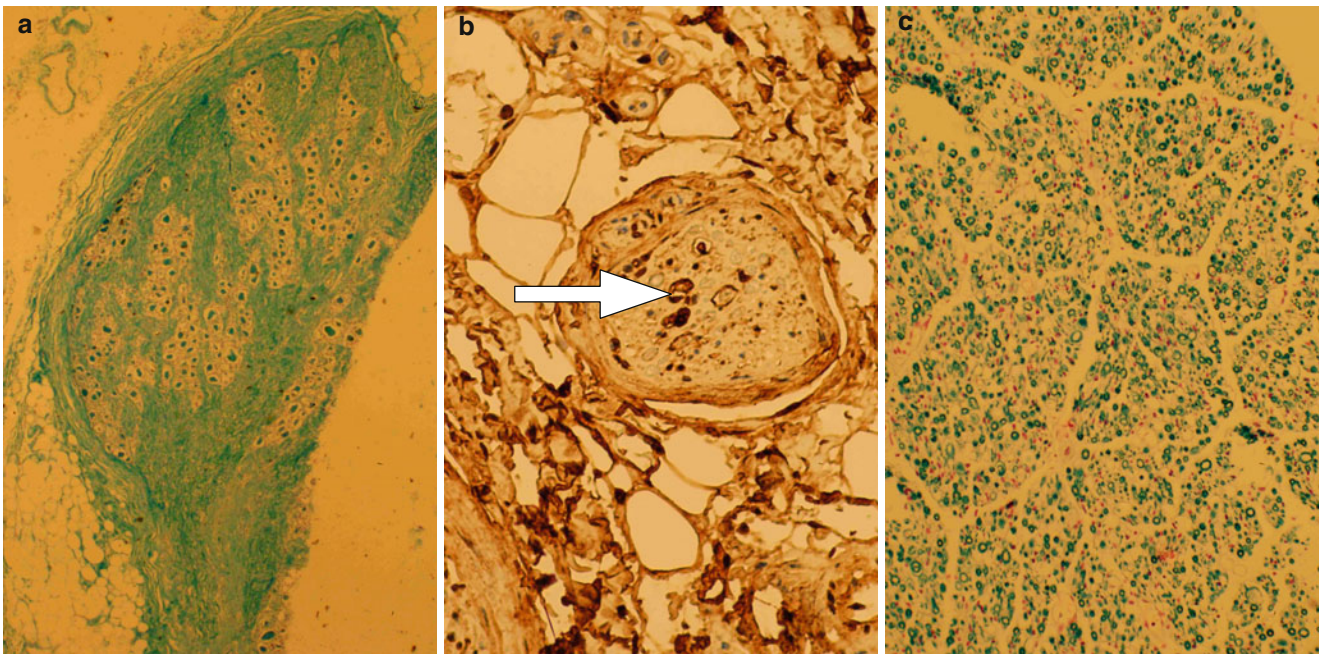

Fig. 9.5 An autopsy from a patient with POEMS syndrome. (**a**) A dorsal root ganglion, normal nerve cells. (**b**) Paravertebral small spinal nerve: loss of myelinated fibers with the remaining myelin sheath stained with anti-IgG (*arrow*). (**c**) Myelinated motor nerve roots

9.4.5 Vasculitic Neuropathy, Nonsystemic

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

Distribution/Anatomy

Both sensory and motor fibers are affected in individual peripheral and cranial nerves.

Symptoms

The symptoms in vasculitic 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). Fifteen percent of patients present with a symmetric polyneuropathy.

Clinical Syndrome/Signs

Pure peripheral nervous system vasculitic neuropathy is 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. CSF analysis is normal.

Electrophysiology Multiple axonal mononeuropathies with low or absent SNAPs and CMAPs and denervation in innervated myotomes.

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 vasculitis or infectious neuropathies, need to be excluded.

Therapy

Treatment consists of steroids combined with steroid-sparing immunosuppressive agents.

Prognosis

With treatment, the disorder frequently stabilizes yielding a good prognosis.

9.4.6 Vasculitic Neuropathy, Systemic

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

Distribution/Anatomy

Nerve and muscle pathology relates to the destruction of blood vessels.

Symptoms

Proximal and distal weakness, pain, and sensory loss occur in a multifocal distribution.

Clinical Syndrome/Signs

It 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 vasculitis (Fig. 9.6).

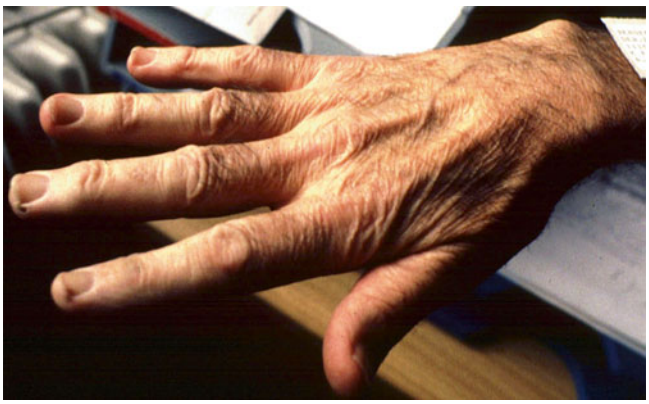

Fig. 9.6 Hand in a patient with vasculitis. There is atrophy of small hand muscles with vasculitic changes at the nail bed

Pathogenesis

Several immune-mediated mechanisms have been identified that lead to the destruction of vessel walls and subsequent ischemic necrosis of axons (Figs. 9.7 and 9.8). Systemic disease that can involve vasculitic neuropathy can be divided into the following categories:

Immune/Inflammatory Mediated Wegener's granulomatosis (Fig. 9.9), polyarteritis nodosa, Churg–Strauss syndrome, and 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.

Electrophysiology SNAPs and CMAPs are reduced in named nerves with denervation of corresponding myotomes.

Biopsy Muscle and nerve biopsies reveal T-cell and macrophage invasion, with necrosis of blood vessels.

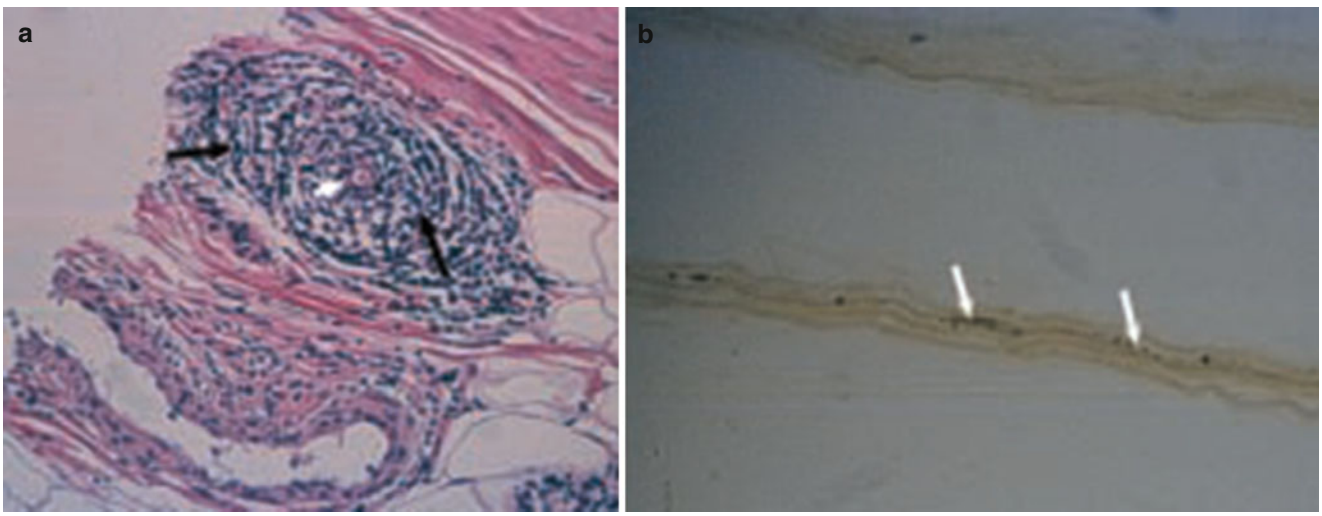

Fig. 9.7 Sural nerve biopsy from a patient with isolated peripheral nerve vasculitis. (**a**) Infiltration of a perineurial vessel wall by multiple inflammatory cells including lymphocytes and macrophages (*black arrows*). There is also evidence of pink fibrin deposits consistent with the presence of fibrinoid necrosis (*white arrows*). (**b**) Teased fiber preparation showing multiple axon balls (*white arrows*) and evidence of empty strands consistent with axonal degeneration

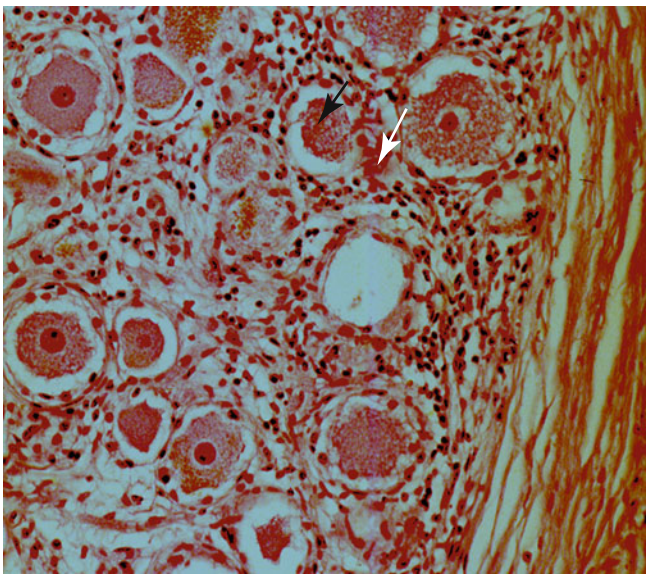

Fig. 9.8 Dorsal root ganglion biopsy from a patient with severe sensory ataxia due to dorsal root ganglionitis. There are clusters of inflammatory cells (*white arrow*) surrounding the dorsal root ganglion neurons (*black arrows*). Many of the neurons show evidence of degeneration

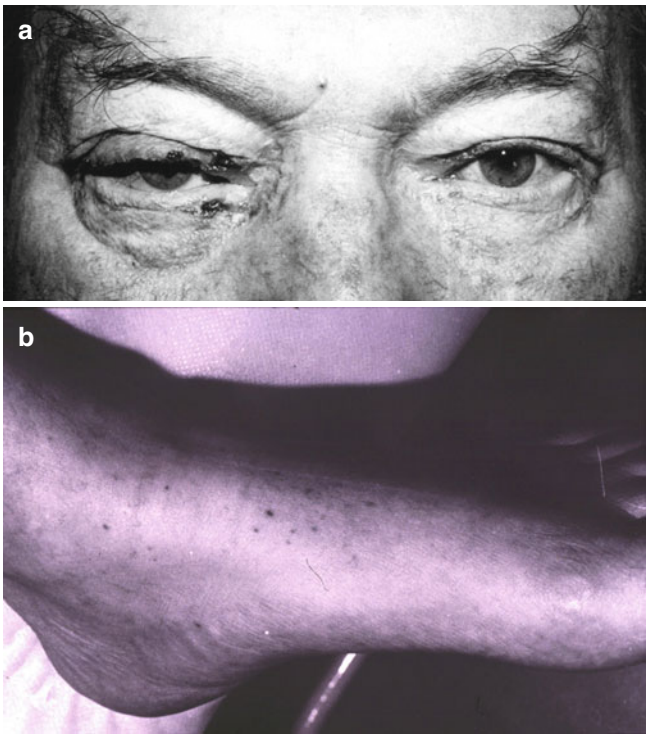

Fig. 9.9 Wegner's granulomatosis. (**a**) This patient had a right orbital involvement. (**b**) Vasculitic neuropathy was heralded by vasculitic skin changes

Differential Diagnosis

Diabetic neuropathy, HNPP, CIDP, multifocal neuropathy with conduction block, plexopathies, porphyria, multiple entrapment neuropathies, Lyme disease, and sarcoidosis.

Therapy

Aggressive treatment of systemic disease. Steroids and cyclophosphamide are frequently used in the treatment of systemic vasculitis. Aggressive pain management should be a special concern of the neurologist.

Prognosis

Therapy can lead to improvement, but there is usually a fixed deficit. Pain symptoms often respond quickly, but importantly this is not necessarily a marker for resolution of the disorder itself.

9.4.7 Critical Illness Neuropathy (CIP)

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

Anatomy/Distribution

Length-dependent axonal degeneration of motor and sensory nerves without signs of demyelination. In the majority of cases, concomitant damage to muscle is seen, and the terms CIMYN (critical illness myopathy and neuropathy) or critical illness neuromyopathy are frequently used.

Symptoms

Symmetric weakness and sensory loss in awake patients. Failure to wean from the ventilator in an ICU setting.

Clinical Syndrome/Signs

Exam reveals symmetric, distal > proximal weakness and atrophy, and large fiber sensory loss. Phrenic nerve frequently affected.

Pathogenesis

Steroid use with paralytics in a ventilator-dependent patient, sepsis, multiorgan failure, and the presence of a systemic inflammatory response syndrome (SIRS) are relevant risk factors for the development of CIN. Immune activation and increased vascular permeability, inflammation, edema, and hypoxia are thought to result in nerve damage.

Diagnosis

Laboratory CPK is usually normal or slightly elevated.

Electrophysiology Low-amplitude motor and sensory compound action potentials. NCVs are normal or slightly reduced. EMG shows widespread denervation. Direct muscle stimulation can differentiate between critical illness neuropathy and myopathy.

Biopsy Axonal degeneration of motor and sensory fibers and denervation atrophy. Myopathic changes are frequently seen in the muscle.

Differential Diagnosis

Other causes of ICU acquired weakness.

Therapy

No specific therapy. Prevention and early treatment of sepsis and strict glucose control might reduce the incidence and severity of CIP. Rehabilitation after ICU discharge is beneficial.

Prognosis

Functional outcome is generally good, although some weakness may persist.

9.5 Infectious Neuropathies

9.5.1 Human Immunodeficiency Virus-1 Neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
–	Motor and sensory nerve conduction studies EMG	Antibody and virus detection in peripheral blood	–	–

Epidemiology

Prevalence data about HIV-related neuropathies vary widely, but it is generally estimated that approximately 50 % of HIV-positive patients have evidence of distal symmetric polyneuropathy (DSP), the most common form, on clinical examination. Older age and severe disease increase the risk for DSP. Other forms are rare. The various types of neuropathy are linked to the stage of HIV infection: HIV-GBS and HIV-CIDP occur mainly in the early phase when patients are otherwise asymptomatic. Mononeuritis multiplex typically is a disease of the early symptomatic phase of HIV. DSP occurs in the late phase of HIV infection. Antiretroviral toxic neuropathy (ATN) begins within weeks to month after initiation of treatment with nucleoside analogue reverse transcriptase inhibitors (NTRIs). An autonomic neuropathy is more frequent in HIV patients at later stages of the disease.

Anatomy and Pathophysiology

DSP is a dying back axonopathy with the occasional presence of macrophage and lymphocytic infiltration; HIV-infected macrophages are reported in the dorsal root ganglia. Skin biopsies in DSP and ATN show reduced intraepidermal nerve fiber densities.

Symptoms

Painful burning dysesthesias in a stocking and later in a stocking–glove distribution are the leading symptoms in DSP and ATN. Lower extremity pain may be so severe that patients cannot walk or tolerate contact with bedding. Symptoms in GBS, CIDP, and mononeuritis multiplex in the setting of HIV infection are similar to the idiopathic syndromes. Orthostatic hypotension and diarrhea can result from autonomic neuropathy.

Signs

In DSP and ATN, allodynia and small > large fiber sensory loss are found on clinical examination together with absent ankle reflexes. Signs may seem mild compared to the pain experienced by the patient. Weakness is uncommon. GBS, CIDP, and mononeuritis multiplex present with typical signs.

Causes

The pathophysiology of HIV neuropathies is poorly understood but are likely immune-mediated. ATN is secondary to drug-induced mitochondrial dysfunction.

Diagnosis

The diagnosis rests upon the known diagnosis of HIV infection, its treatment, and the typical clinical picture.

Electrophysiology In DSP and ATN SNAPs are decreased or absent. Motor nerve conduction studies are generally normal with the exception of mildly prolonged F-wave latencies. GBS, CIDP, and mononeuritis multiplex present with typical electrophysiological findings.

Imaging None.

Laboratory No neuropathy-specific tests exist once HIV has been diagnosed. Other causes of neuropathy should be explored.

Differential Diagnosis

DSN and ATN are clinically similar. The only feature to differentiate ATN from DSN is the initiation of treatment with NTRIs weeks to a few months before symptom onset.

Therapy

Pain control is frequently required for DSN and ATN. If drug treatment is discontinued secondary to ATN, the symptoms can continue to worsen (known as coasting). HIV-GBS and CIDP are treated as non-HIV GBS and CIDP with immunomodulatory treatment with IVIG or plasmapheresis.

9.5.2 Herpes Zoster Neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
–	–	CSF mononuclear pleocytosis; in acute herpes PCR to detect virus	–	–

Epidemiology

The incidence of herpes zoster in the USA between 1945 and 2003 was between 1.2 and 6.5 cases/1,000 person years. Its incidence increases with increasing age. A large proportion of patients with herpes zoster (HZ) develop postherpetic neuralgia (PHN).

Anatomy and Pathophysiology

After infection with varicella zoster virus (VZV) in childhood, the neurotropic virus becomes latent in the dorsal root, cranial nerve, and autonomic ganglia. Virus reactivation causes shingles within one to three dermatomes. PHN may result from chronic ganglionitis.

Symptoms

Burning, stabbing neuropathic pain in a dermatomal distribution is the first symptom. Hypesthesia and allodynia develop and are followed by the typical rash. Weakness occurs in 1–30 %, more frequently if lumbosacral dermatomes are affected. The Ramsay Hunt syndrome, herpes oticus, is characterized by facial weakness, a painful ear, and vesicles in the ear.

Signs

Hypesthesia and allodynia are present in the affected dermatomes with weakness occurring in a radicular pattern with corresponding absent reflexes. PHN is characterized by allodynia, hyperalgesia, and hypesthesia in affected areas.

Causes

Reactivation of VZV causes acute herpes zoster and chronic vasculitis, and central reorganization is implicated in PHN.

Diagnosis

Skin rash in a dermatomal distribution and CSF findings define acute herpes zoster. PHN is diagnosed in the setting of previous herpes zoster and dermatomal neuropathic pain.

Electrophysiology Sensory nerve conduction studies are normal. In cases with weakness signs of de- and reinnervation can be found on EMG. QST reveals impaired small and large fiber function.

Imaging None.

Laboratory In acute herpes zoster, CSF shows a mononuclear pleocytosis and PCR confirms the VZV infection. In PHN affected areas of the skin have reduced intraepidermal nerve fiber densities.

Differential Diagnosis

Before the typical rash develops, other causes of radicular pain have to be considered. In patients with facial palsy, the pain and vesicles in the ear distinguish it from other causes of facial nerve palsy (idiopathic, Lyme's disease).

Therapy

Valacyclovir (1,000 mg tid for 7 days) and famciclovir (500 mg tid for 7 days) are used to treat acute herpes zoster. Topical high-concentration capsaicin patches are used to treat PHN. Vaccination with a live, attenuated zoster vaccine reduces the incidence of herpes zoster and PHN, although it is less effective with increasing age.

9.5.3 Lyme Disease (Neuroborreliosis)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
–	–	CSF mononuclear pleocytosis; PCR to detect Borrelia	–	–

Epidemiology

In the USA most cases of Lyme disease occur in northeastern and north-central states. In several European regions, Lyme disease is endemic. The epidemiology depends on the distribution of infection in vector ticks.

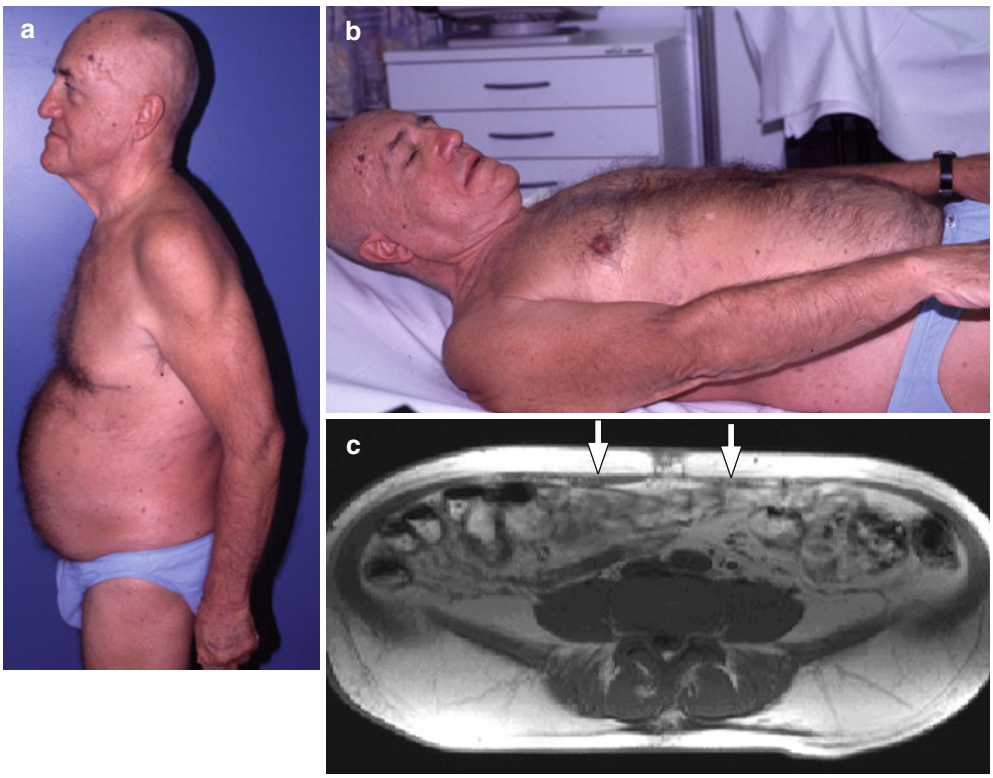

Fig. 9.10 Abdominal weakness in Lyme disease: This patient had a protruding abdomen due to abdominal weakness (**a**), he was unable to do sit ups (**b**), the MRI (**c**) showed atrophy of the rectus abdominis muscles (*arrows*). Lyme borreliosis with involvement of thoracic nerve roots was identified

Anatomy and Pathophysiology

Erythema migrans is caused by local spreading of Borrelia in the skin. An immune response is triggered which can result in neurological and systemic manifestations. Lymphocytic infiltration is present in affected tissue.

Symptoms

The earliest stage of Lyme disease (Stage 1) develops 7–10 days after a tick bite and is characterized by the unique skin rash (erythema migrans) and mild constitutional symptoms. 10–20 % of these patients develop neurological manifestations typically 4–6 weeks after the tick bite. This neuroborreliosis (Stage 2, Bannwarth syndrome) is characterized by radicular pain and weakness, headache, and cranial nerve palsies (Fig. 9.10). Some patients develop asymmetric oligoarthritis, cardiac impairment, and myositis alongside with CNS impairment 6 month after the tick bite (Stage 3).

Signs

The radiculitis frequently affects thoracolumbar spinal roots. Besides sensory symptoms in affected areas, weakness is seen in the form of bulging of the abdominal wall. Facial nerve palsy frequently is bilateral; other nerves, e.g., trigeminal, optic, vestibulocochlear, and oculomotor nerves, are less commonly affected. Profound CNS symptoms are probably rare, and the relationship to Lyme borreliosis has recently been questioned. Sensory neuropathies are found in acrodermatitis chronica atrophicans.

Causes

Lyme disease is caused by infection with the spirochete *Borrelia burgdorferi*. The infection is transmitted by bites from the *Ixodes dammini*, *scapularis*, *and pacificus* tick species. Three genospecies exist and their occurrence varies between US and Europe, which may account for the variation of clinical presentations between these countries.

Diagnosis

Clinical picture, CSF pleocytosis, and detection of intrathecal antibody production against Borrelia confirm the diagnosis. A history of tick bite and erythema migrans can be missing in up to 50 % of cases with confirmed neuroborreliosis.

Electrophysiology In radiculitis SNAPs are normal. In cases with weakness, signs of de- and reinnervation are present on EMG. In cases with neuropathy, SNAPs are reduced or absent.

Imaging None.

Laboratory CSF shows a mild lymphomonocytic pleocytosis in neuroborreliosis. Antibody detection in serum commonly leads to false positive results in up to 30 % of healthy individuals in endemic areas. Antibody detection in CSF is specific, and the combination of CSF and serum antibody titers is used to calculate an antibody index. PCR of blood and CSF can be used in difficult cases.

Differential Diagnosis
Unilateral facial nerve palsy needs to be distinguished from idiopathic Bell's palsy.

Therapy
Isolated facial nerve palsy can be treated with oral or intravenous antibiotics; meningitis, radiculitis and other neurological manifestations are treated with intravenous antibiotics. Oral doxycycline (200 mg daily) and intravenous ceftriaxone (2 g daily) are typically used for 2–3 weeks. Doxycycline is contraindicated in pregnancy and lactation and in children below 8 years of age. In these cases, amoxicillin is the drug of choice.

9.5.4 Leprosy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
–	–	No accepted serological tests to date	–	Acid fast bacilli in skin smears or infected tissue biopsies

Epidemiology
Leprosy is one of the most common treatable neuropathies in several Asian, South American, and African countries. Although the incidence of leprosy has decreased in the last decade, the WHO reported nearly a quarter of a million new cases in 2009.

Anatomy and Pathophysiology
Infection with *M. leprae* results in a destructive inflammatory immune response. Early lepromatous disease involves infection of Schwann cells with minimal inflammatory response. Later, increased inflammation may lead to axonal damage with episodes of demyelination and remyelination.

Based on the immunological status of the patient, leprosy is classified as tuberculoid, lepromatous, or borderline. In tuberculoid leprosy, the immune response is good and only a few lesions without mycobacteria are detectable. In lepromatous leprosy patients are anergic toward *M. leprae* and show multiple lesions containing bacteria.

Symptoms
Numbness and weakness affecting individual peripheral and cranial nerves.

Signs
Leprous neuropathy is characterized by sensory loss in a patchy distribution. Lepromatous disease is extensive, with loss of temperature and pain occurring in the forearms, legs, ears, and dorsum of the hands and feet (Fig. 9.11). Cranial nerve damage can lead to facial damage, including iritis, alopecia, and changes in eyelid and forehead skin. Tuberculoid leprosy involves only a few skin lesions with accompanying local sensory loss. Several nerves, typically the greater auricular and/or radial cutaneous, are enlarged.

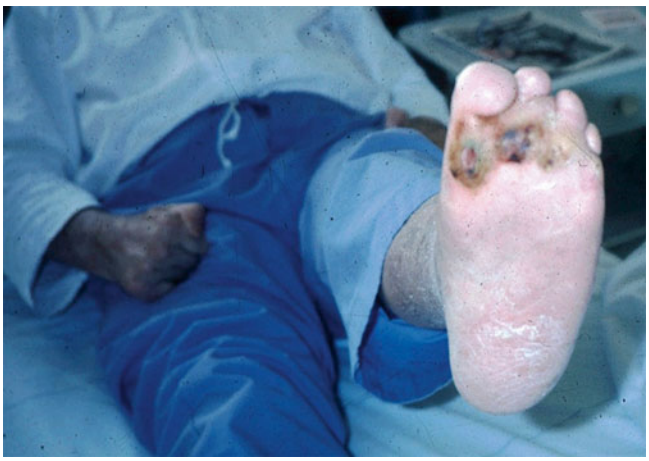

Fig. 9.11 Leprosy in a patient who served with the foreign legion in North Africa. He has mutilated hands and toes and an ulcer

Causes
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). The transmission of *M. Leprae* is not completely understood but person-to-person infections via airborne droplets are believed to be the main route of infection.

Diagnosis
Typical clinical picture and detection of acid fast bacilli in skin smears or biopsies secure the diagnosis. PCR can be used to detect *M. Leprae* DNA in biopsies.

Electrophysiology NCV and EMG show axonal damage of affected nerves with decreased or absent SNAPs and CMAPs; nerve conduction velocities can be mildly slowed.

Imaging None.

Laboratory No accepted serological test to diagnose or monitor leprosy is currently available. Promising are assays to detect antibodies to PGL-1.

Differential Diagnosis
Mononeuropathies and mononeuritis multiplex.

Therapy
The WHO recommends treating patients with paucibacillary disease (tuberculosis and borderline leprosy) with dapsone

and rifampicin (rifampin) for 6 months. Those with multibacillary disease (lepromatous leprosy) should be treated with dapsone, rifampicin, and clofazimine for 12 months. Cases of treatment-induced reactions require quick diagnosis and treatment with high-dose steroids until the reaction subsides.

9.6 Inflammatory Neuropathies

9.6.1 Acute Inflammatory Demyelinating Polyneuropathy (AIDP, Guillain–Barre Syndrome)

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

Distribution/Anatomy

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 predominate 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 the patients. One-third of patients need respiratory support. Numerous types of autonomic dysfunction are possible, but not typical (Figs. 9.12 and 9.13).

Pathogenesis

Eighty percent of patients have an antecedent event (infection, surgery, and 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 with AIDP. Research suggests a complex interaction of humoral and cell-mediated immunity events that lead 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 two or more motor nerves, with distal latency exceeding 130 % of the upper limit of normal in two 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 1 or more motor nerves and an F-response latency exceeding 130 % of the upper limit of normal in one 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 is usually required, along with the following treatments: (1) Total plasma exchange QOD×5. (2) As an alternative to plasma exchange, IVIG is administered at a rate of 0.2 g/kg I.V. daily for 5 days, followed by 1 g/kg weekly for 4 weeks. (3) General supportive management with physical/occupational therapy helps with 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.

9.6.2 Acute Motor Axonal Neuropathy

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.

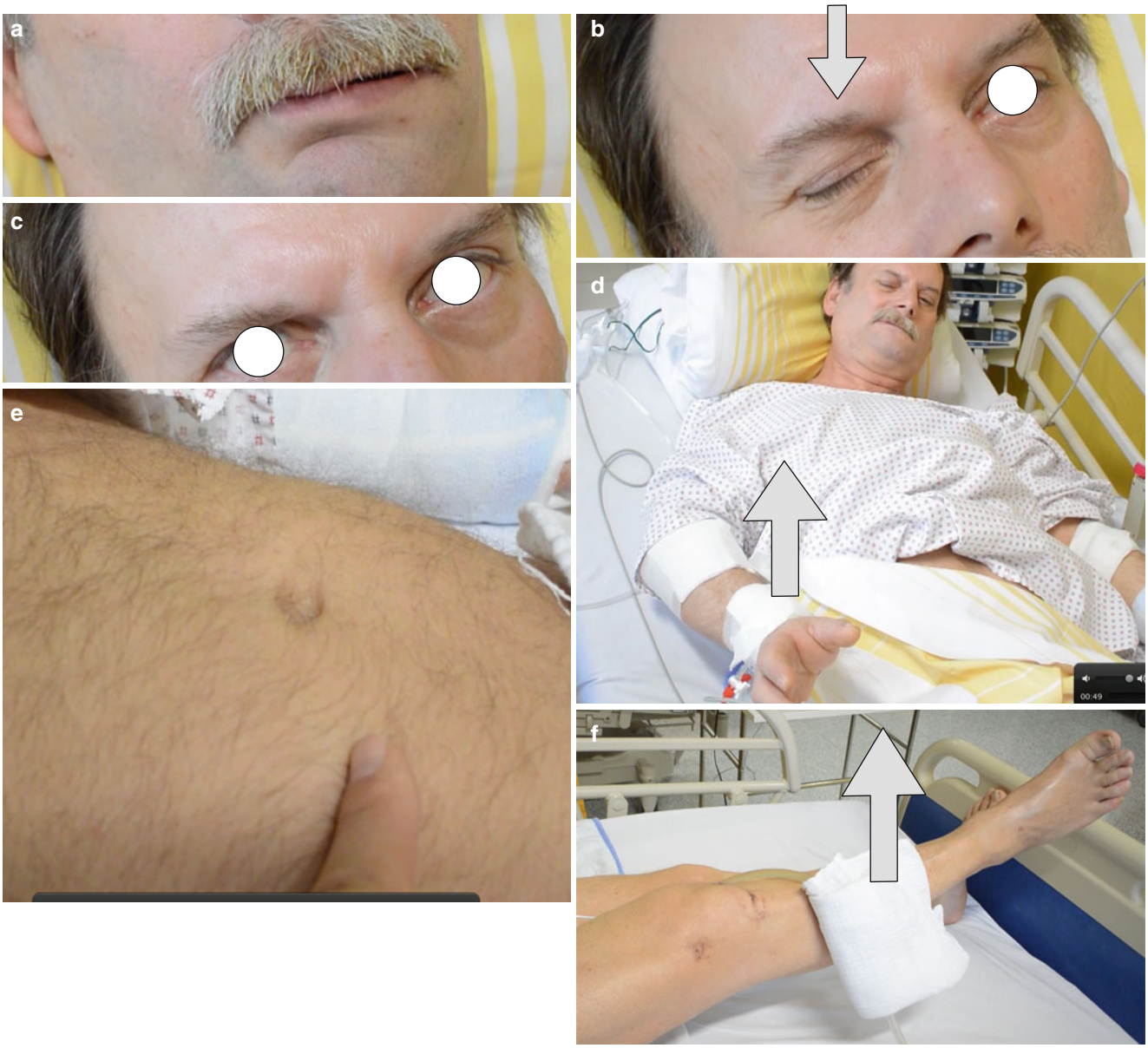

Fig. 9.12 Clinical findings in acute inflammatory demyelinating polyneuropathy (GBS). (**a**) Incomplete mouth closure due to a bilateral VII palsy. (**b**) Slightly asymmetric incomplete lid closure. (**c**) Right frontal muscle remains partially intact. (**d**) Arm raising with only mild elevation. (**e**) Positive Beevor's sign as a sign of abdominal muscle weakness. (**f**) Weakness of leg elevation (Images are adapted from a video)

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

AMAN may result from *Campylobacter jejuni* infection. Cases almost always occur in the summer months and are preceded by a gastrointestinal illness. Axons may be the specific target of autoimmune attack.

Diagnosis

Laboratory Protein is increased in the CSF. IgG anti-GMI or anti-GalNac-GD1a ganglioside antibodies are present. CMAPs are low or absent while SNAPs are normal.

Therapy

IVIG and supportive care are the only available treatments.

Prognosis

Younger patients recover better. Recovery is variable overall.

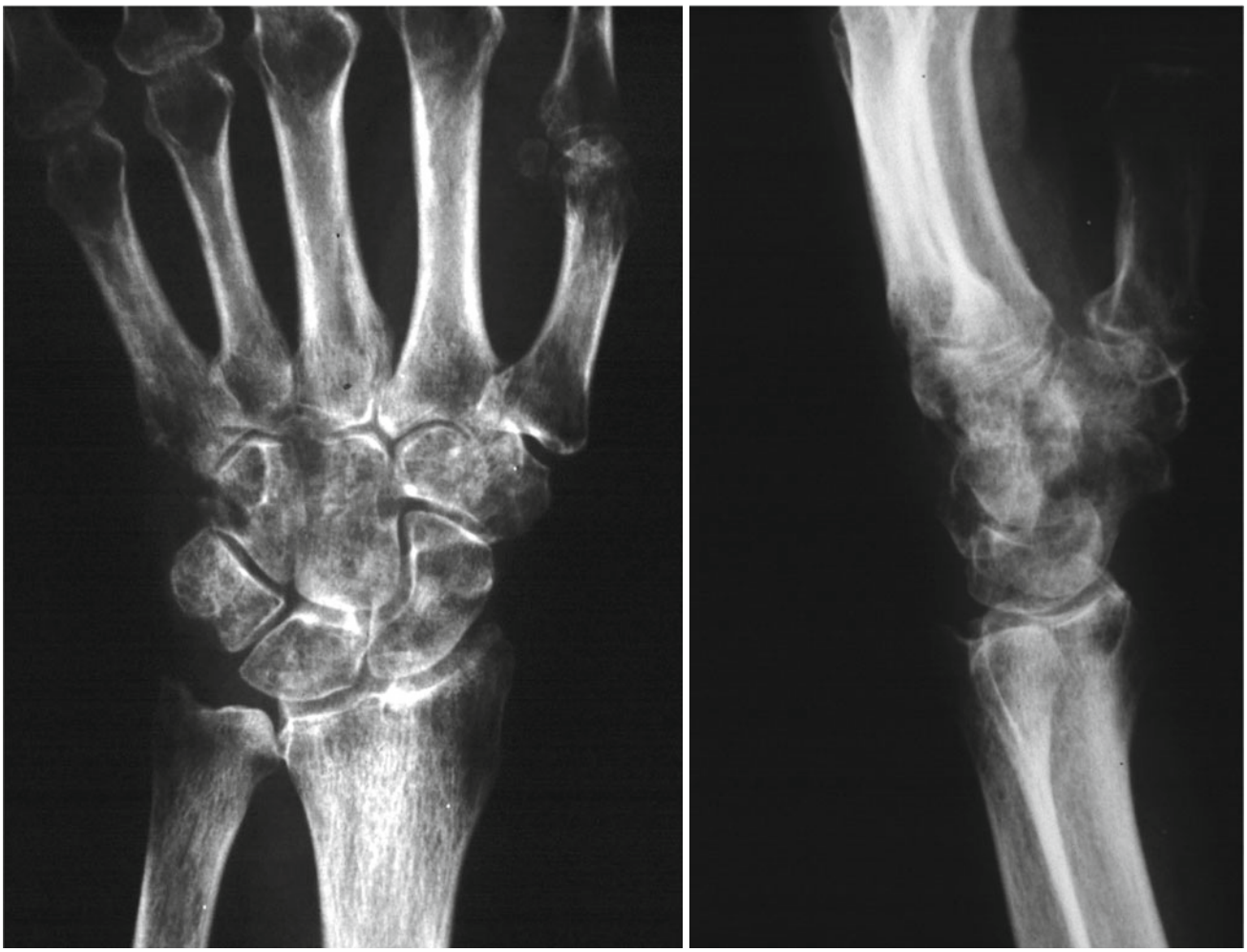

Fig. 9.13 X-ray of the hands of a patient with long-standing polyradiculitis and poor recovery. Note the severe changes of osteoporosis

9.6.3 Acute Motor and Sensory Axonal Neuropathy

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 with variable autonomic dysfunction.

Pathogenesis
Immune reactions are believed to be directed against axons.

Diagnosis
Laboratory Protein is increased in the CSF. SNAPs and CMAPs are reduced or absent.

Therapy
IVIG, plasma exchange, and supportive care are the only available treatments.

Prognosis
Chances for recovery are poor. Residual weakness usually remains, and some require ventilation for long periods of time.

9.6.4 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, myalgias, paresthesias, ataxia, and vertigo. In some cases, there is weakness of other motor cranial nerves and rarely limbs. Symptoms progress over days to weeks (Fig. 9.14).

Signs
MFS is characterized by the triad of extraocular muscle weakness, ataxia, and areflexia. Ptosis and mydriasis can be demonstrated with examination.

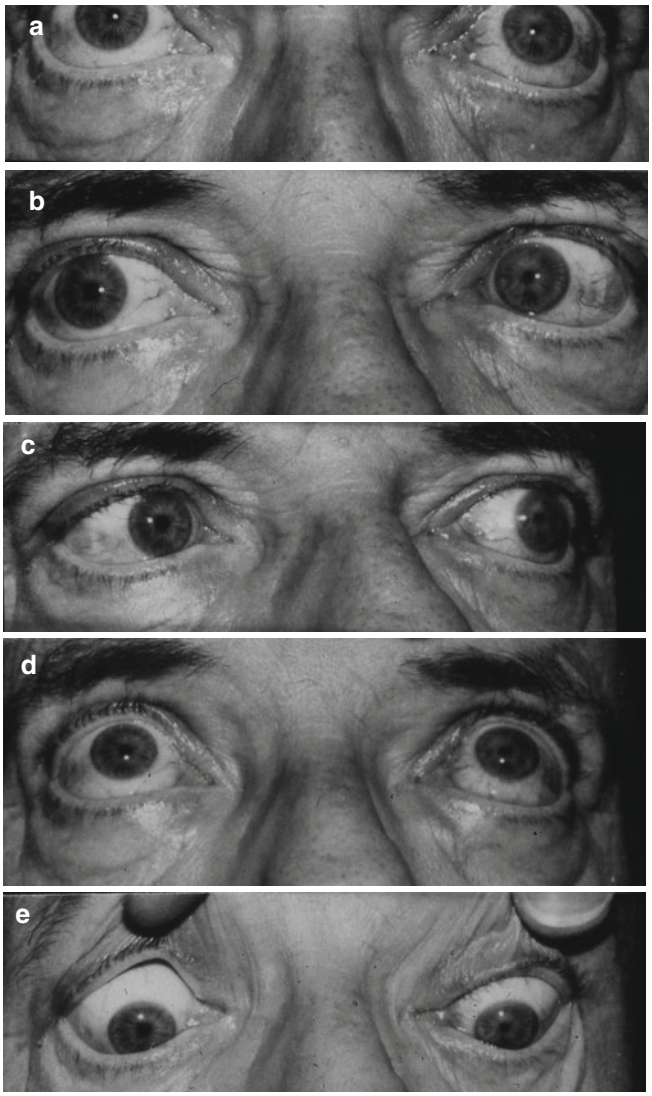

Fig. 9.14 Miller Fisher syndrome. (**a**) Patient with Miller Fisher syndrome and ophthalmoparesis with restricted horizontal gaze (**b**, **c**), and reduced upward and downward gaze (**d**, **e**)

Pathogenesis
MFS is considered a variant of AIDP, and cases initially appearing to fall in the classic MFS triad can progress to a syndrome 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 strokes. The absence of CNS specific signs and the presence of abnormal peripheral nerve studies would indicate MFS.

Therapy
IVIG, plasma exchange, and supportive care are the only available treatments.

Prognosis
Most patients will recover.

9.6.5 Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

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

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 can take up to 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

Thirty percent of patients have an antecedent event (viral infection, immunization, and surgery). CIDP is believed to be an autoimmune disorder, with elements of both cell-mediated and humoral immunity.

Diagnosis

Laboratory Cell count is elevated in the CSF 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 two or more motor nerves. Distal latency exceeds 130 % of the upper limit of normal in two 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. 9.15).

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.
- IVIG is given at a rate of 1 g/kg I.V. monthly.
- Azathioprine, at a dose of 2–3 mg/kg per day or mycophenolate mofetil (1 g BID), 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, especially for those patients on prednisone, includes dietary counseling, twice yearly eye evaluations for cataracts and glaucoma, elemental calcium 1,000 mg/day, a regular graded exercise program, and regular monitoring of serum electrolytes, liver function tests, and glucose.
- Once the patient is stable or improved, the prednisone is tapered to an every other day dosage by approximately 10 % at 4 weekly intervals. The dose should be maintained at a steady state if the patient relapses.

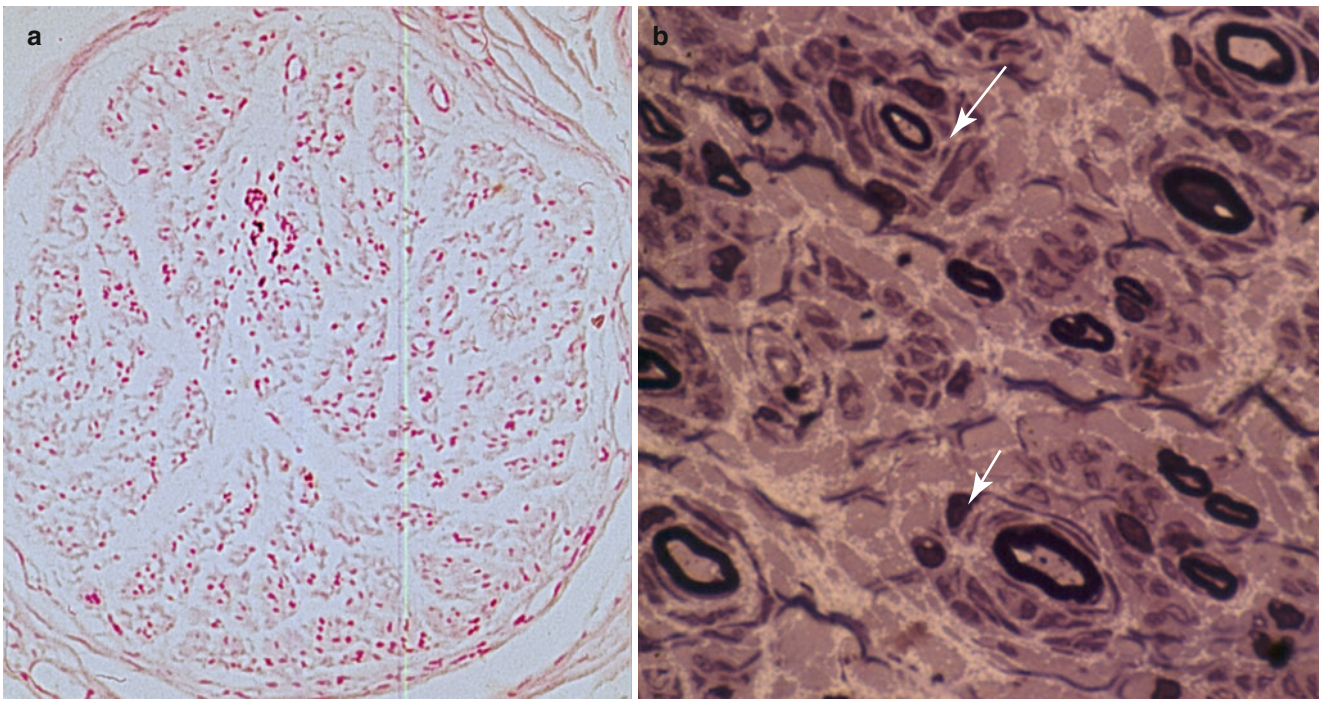

Fig. 9.15 Sural nerve biopsy from a patient with chronic inflammatory demyelinating polyneuropathy. (**a**) Multiple inflammatory cells in the endoneurium of the sural nerve. (**b**) Variation in myelin thickness in the presence of multiple onion bulbs (*white arrow*). This is consistent with chronic de- and remyelination

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.

9.6.6 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. Patients may have palpable peripheral nerves, suggesting bouts of demyelination and remyelination.

Pathogenesis
Anti-MAG IgM antibodies result in complement deposition on peripheral nerve myelin with minimal cellular infiltration compared to other inflammatory neuropathies.

Diagnosis
Laboratory Anti-MAG IgM antibody is positive and CSF protein is elevated.

Electrodiagnostic Studies Prolonged distal latencies, slowed sensory and motor NCVs without conduction block, and prolonged F waves. CMAPs and SNAPs are reduced or absent.

Therapy
IVIG and plasma exchange are not effective. Strong cytotoxic drugs (cyclophosphamide, fludarabine) along with rituximab are used but without strong evidence that treatment modifies the gradual progressive nature of the disease. Often, the patients that typically develop this neuropathy are elderly and cannot tolerate these therapies.

Prognosis
This is a progressive disorder that frequently results in falls in the elderly secondary to severe sensory loss; motor function remains much more intact than sensory function, which is the common underlying cause of physical disability.

9.6.7 Multifocal Motor Neuropathy (MMN)

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

Anatomy/Distribution
Paranodal demyelination and Wallerian degeneration of motor nerves.

Symptoms
MMN is characterized by asymmetric progressive weakness in the distribution of peripheral nerves without sensory symptoms. Weakness worsens in the cold.

Clinical Syndrome/Signs
Exam reveals asymmetric, predominantly distal weakness without sensory loss in the distribution of individual terminal nerve branches. Finger extensor weakness and wrist or foot drop are frequently initial signs. It starts in the legs in 20–30 % of cases. Weakness is greater than atrophy initially. The course typically is progressive. Over time muscle atrophy develops. Cranial nerve involvement is rare. The disease develops before the age of 50 years in approximately 80 % of patients and affects more men than women.

Pathogenesis
Dysfunction of the nodes of Ranvier leads to conduction failure and thus weakness. IgM antibodies against GM1 gangliosides are probably pathogenic and MMN is believed to be an autoimmune disorder.

Diagnosis
Laboratory IgM antibodies against GM1 gangliosides are present in 20–85 % and CSF protein is <1 g/l.

Electrophysiology Conduction block (CB) outside of common sites of entrapment is the hallmark of the disease. Extended NCV are necessary, but CB cannot always be found. Sensory NCV are normal.

Imaging MRI studies have shown increased signal intensity, and ultrasound reveals nerve enlargements at sites of conduction block.

Differential Diagnosis
Other pure motor disorders such as progressive muscular atrophy, spinal muscular atrophy, inclusion body myositis, and motor CIDP.

Therapy
IVIG is the treatment of choice. The patient is given a loading dose of 2 g/kg and treatment is then repeated monthly at 1 g/kg. Maintenance treatment should be tailored to the

individual patients needs. Subcutaneous immunoglobulin might be an alternative in selected patients. When IVIG fails there are case reports of successful treatment with cyclophosphamide and rituximab.

Prognosis
Over time treatment effects usually decline and a slowly progressive weakness and atrophy develops.

9.7 Nutritional Neuropathies

9.7.1 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.

Clinical Syndrome/Signs
Loss of vibratory and position sense with loss of ankle reflexes are common sensory signs. Neuropathy is difficult to separate from myelopathy, which involves spasticity, posterior column dysfunction, ataxia, along with CNS involvement, particularly memory loss, and confusion. 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 anesthetics. 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 velocities. Somatosensory and visual evoked potentials are often abnormal, but brainstem evoked potentials 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
Other causes of myelopathy should be considered including multiple sclerosis, tumors, compression, vascular abnormalities, and myelitis. Myelopathy and a sensorimotor polyneuropathy together should suggest vitamin B12 deficiency.

Therapy
One thousand micrograms crystalline vitamin B12 is injected intramuscularly (IM) daily for 5 days, then 500–1,000 μg is given IM once a month for life for maintenance. Oral B12 (1,000 μg daily) can also be considered for maintenance after the initial 5-day IM load depending on the etiology of the deficiency.

Prognosis
If treatment begins within 6 months of onset, the prognosis can be very good. More prolonged disease is more resistant to therapy.

9.7.2 Post-gastroplasty Neuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
		+		+

Anatomy/Distribution
Biopsy shows a severe axonal sensory and motor neuropathy.

Symptoms
Patients report distal paresthesias and leg weakness.

Clinical Syndrome/Signs
Exam can show loss of ankle reflexes, weakness, distal sensory dysfunction, and lumbar plexopathy. Wernicke-Korsakoff syndrome is also described.

Pathogenesis
Malabsorption of both vitamins and essential elements such as copper. Thiamine deficiency has also been suggested as the cause, but the symptoms are unlike beriberi. RBC transketolase may be elevated.

Therapy
TPN with multivitamins and 100 mg thiamine daily is required for patients experiencing frequent emesis; oral multivitamins with elemental supplementation can be given once the patient is stable.

Prognosis
Early recognition and treatment is essential for good long-term prognosis.

9.7.3 Pyridoxine Neuropathy

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

Anatomy/Distribution
Pyridoxine deficiency causes motor and sensory axonal injury, whereas overdose of pyridoxine causes a sensory neuropathy.

Symptoms
Distal burning paresthesias in hands and feet.

Clinical Syndrome/Signs
Pyridoxine (vitamin B6) 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, from 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. Electrophysiology shows predominately low or absent SNAPs in pyridoxine toxicity; in deficiency, there are low or absent SNAPs and CMAPs.

Differential Diagnosis
Pyridoxine deficiency looks like many other sensorimotor axonal neuropathies (see Table 9.1 for a differential diagnosis).

Therapy
One hundred to one thousand milligrams pyridoxine given daily is effective if the deficiency is secondary to isoniazid or hydralazine treatment. Deficiency caused by alcoholism or other states of malnutrition should also be treated with pyridoxine supplemented with multivitamins, since other deficiencies are likely concurrent.

Prognosis
The deficiency neuropathy may improve with B6 replacement or when isoniazid or hydralazine is stopped. The sensory neuropathy caused by overdose shows little improvement.

9.7.4 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 axonal loss 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, and POWs). The patients treated with vitamins during the Cuban outbreak responded well, and thus it is thought that the pathology is due to a poly-deficiency of thiamine, niacin, riboflavin, and pyridoxine.

Therapy
Multivitamin replacement with a balanced 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.

9.7.5 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 palsies, 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 is the likely 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 sensorimotor neuropathy caused by beriberi is similar to other causes of nonspecific sensorimotor neuropathy. Facial and tongue weakness and recurrent laryngeal nerve palsies are uncommon in other causes of sensorimotor 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 3 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 deficits.

9.7.6 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 atresia), or a familial defect of the tocopherol transport protein. Tocopherol is a free radical scavenger and 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 (see Table 9.1).

Therapy

Patients with isolated vitamin E deficiency can be treated by replacement with 1–4 g vitamin E daily. Patients with cystic fibrosis can be treated with 5–10 IU/kg. Abetalipoproteinemia patients can be treated with 100–200 mg/kg per day.

Prognosis

Progression of symptoms can be halted by vitamin E.

9.8 Drugs, Industrial Agents, and Metals

9.8.1 Alcohol Polyneuropathy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy	Associated Diseases
	+	+			Liver disease, vitamin deficiency

Symptoms
Distal sensory loss, paresthesias, and burning feet, with aching and pain in the lower extremities. In particular, patients experience painful calves, cramps, weakness, and sensory ataxia.

Signs
Exam shows sensory loss, motor weakness, distal areflexia, and orthostatic hypotension from autonomic involvement. In rare cases, foot ulcers develop.

Distal Symmetric Weakness Legs > hands. Tendon reflexes diminished or absent (hyporeflexia).

Sensory Pan-modal reduction, allodynia, pain (dull-lancinating).

Autonomic Hyperhidrosis, esophageal dysmotility.

Cranial Nerves Vagal involvement leading to a hoarse voice. The types of neuropathy include sensorimotor, sensory, motor, and multifocal.

Special Association Proximal neuropathy with cranial nerve involvement, including a toxic alcohol amblyopia.

Mononeuropathies Due to Pressure Palsies Radial nerve, peroneal nerve, sciatic nerve, brachial plexus lesions.

Causes
Difficult to separate from nutritional neuropathy. Incidence is 9–30 % of hospitalized alcoholics. Occurs after several years of consuming at least 100 mg alcohol daily. Women are more susceptible. Chronic alcohol intake leads to malnutrition and vitamin deficiencies.

Pathophysiology
Axonal degeneration with loss of large and small myelinated fibers in autonomic, sensory, and motor nerves. Pathophysiology is unknown but is often associated with nutritional deficiency.

Diagnosis
Electrophysiology, laboratory (liver, transketolase studies), SNAPs may be absent or reduced, variable involvement of motor nerves; distal degeneration on EMG.

Differential Diagnosis
Toxic neuropathies, other axonal neuropathies.

Therapy
Abstinence, multivitamin replacement, pain therapy, and 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.

9.8.2 Other Drug-Induced Neuropathies

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
–	Motor and sensory nerve conduction studies EMG	–	–	–

Epidemiology
A variety of drugs can cause neuropathies, some frequently and others rarely. The incidence of drug-induced neuropathies varies depending on the drug and dose used and also on patient characteristics such as underlying peripheral nerve disease and genetic polymorphisms.

Anatomy and Pathophysiology
Most drug-induced neuropathies affect peripheral nerve axons in a length-dependent pattern and cause a distal symmetric, axonal dying-back neuropathy. Sensory fibers are generally more vulnerable than motor fibers and thus sensory symptoms dominate. The "coasting" phenomenon – worsening of the neuropathy up to 1 year after the drug has been discontinued – has been described for chemotherapeutic agents.

Symptoms
Paresthesias and dysesthesias in the feet and later in the hands are present. Neuropathic pain is frequent. If the motor nerves are affected, foot drop and hand weakness can develop. The onset typically is gradual over weeks to months.

Signs
Distal large- and/or small-fiber sensory loss and areflexia are found in the majority of cases. Atrophy of intrinsic foot muscles and at later stages dorsiflexor weakness can occur. Signs of autonomic involvement can be found in some forms. See Table 9.2 listing features of selected or frequent drug-induced neuropathies.

Causes
See Table 9.3 for a list of drugs which cause neuropathies.

Diagnosis
The diagnosis rests upon a close proximity of symptoms to exposure, stabilization, or improvement after cessation of the drug and the exclusion of other causes. Nerve biopsies usually show nonspecific signs of axonal degeneration and occasionally disruption of myelin.

Electrophysiology In typical sensory dominant neuropathy routine motor nerve conduction studies are normal or show low

Table 9.2 Specific features or relevant drug-induced neuropathies (alphabetical order)

Drug	Features of neuropathy
Amiodarone	Variable incidence and poor correlation with dose; subacute to chronic sensorimotor distal symmetric neuropathy. Predominant motor and GBS-like presentations have been reported. Electrophysiology can show demyelinating or axonal features. Tremor, ataxia, and myopathy are rare additional features. The neuropathy is at least partially reversible after dose reduction or drug discontinuation
Colchicine	Usually in patients with at least mild chronic renal insufficiency; subacute to chronic progressive distal sensory neuropathy in combination with proximal myopathic weakness. Percussion and grip myotonia can occur. NCV show distal axonal sensory neuropathy and EMG of proximal muscles demonstrates myopathic features and occasionally myotonic discharges. CPK is mildly to significantly elevated. The myopathy resolves after drug withdrawal; symptoms and signs of the sensory neuropathy remain
Dapsone	Rare; occurs after long-term and high dose use. Predominantly distal motor neuropathy of lower and upper limbs. Reflexes are typically normal. NCV show low-amplitude CMAPs and normal SNAPs. Spontaneous activity and motor unit loss is seen on EMG. After dapsone discontinuation neuropathy dramatically improves within months to a year
Disulfiram	Dose-dependent neuropathy after several months of treatment. Distal symmetric large- and small-fiber sensory and later sensory and motor neuropathy of lower and at later stages upper extremities. NCV show axonal sensory and motor neuropathy. Recovery after drug withdrawal is slow and frequently incomplete
Etanercept and Infliximab	Tumor necrosis factor-α blockers can cause inflammatory demyelinating neuropathies. Cases with Guillain-Barre syndrome, Miller Fisher syndrome, and CIDP-like neuropathies are reported. The neuropathies develop after 6 months to 2 years after treatment. NCV show signs of acquired demyelination. Drug withdrawal only sometimes improves symptoms, but most patients respond to standard treatment
Isoniazid (INH)	Isoniazid treatment results in a pyridoxine deficiency which is responsible for a sensory predominant large- and small-fiber neuropathy. Burning feet are an early complaint. Weakness and atrophy can develop at later stages. The neuropathy is prevented by the intake of 10–50 mg pyridoxine/day. However, pyridoxine treatment does not affect the recovery once neuropathy has developed
Nitrofurantoin	Rare; higher risk in females, elderly and patients with renal dysfunction or diabetes mellitus. Distal symmetric sensory neuropathy; in some patients a rapidly progressive motor neuropathy can develop, suggesting Guillain-Barre syndrome. NCV show reduced motor and sensory potentials with normal or mildly decreased nerve conduction velocities. Recovery is poor in severe cases
Nucleoside analogues	Frequent and dose-dependent painful sensory neuropathy. Usually abrupt onset and more painful than HIV-related painful neuropathy. Weakness rarely develops at later stages. SNAPs are reduced or absent indicating an axonal neuropathy. Coasting can occur but usually is followed by at least some degree of recovery
Pyridoxine abuse	High-dose pyridoxine intake causes a pure sensory neuropathy; at 500 mg daily neuropathy develops after several years, at 1,000 mg/after several months. Distal symmetric numbness on the feet and gait ataxia can be followed by large-fiber sensory loss in the hands. NCV show a sensory axonal neuropathy, while motor studies are normal. Following drug withdrawal coasting can occur which is followed by a slow recovery

Table 9.3 Drugs associated with neuropathy (drugs which frequently cause neuropathies are in bold text)

Cardiovascular drugs	Central nervous system drugs	Antibiotics, antiviral drugs	Miscellaneous drugs
Amiodarone	Chlorprothixene	Chloroquine	**Allopurinol**
Clofibrate	Glutethimide	Chloramphenicol	**Colchicine**
Perhexiline	Phenelzine	**Dapsone**	**Cyclosporin A**
Propafenone	Phenytoin	Ethambutol	**Dichloroacetate**
Statins		Fluoroquinolones	**Disulfiram**
		Isoniazid	**Etanercept**
		Linezolid	**Gold**
		Metronidazole	**Hydralazine**
		Nitrofurantoin	**Infliximab**
		Nucleoside analogues	**Interferons alpha 2a and 2b**
		Sulfasalazine	**Leflunomide**
			Penicillamine
			Pyridoxine abuse
			Tacrolimus

CMAPs. SNAPs are reduced or absent. EMG can show polyphasic, medium- to high-amplitude, long-duration motor unit action potentials when motor fibers are involved. Demyelinating forms show nonuniform slowing of motor nerve conduction velocities, temporal dispersion, and conduction block.

Imaging None.

Laboratory CPK can be mildly elevated in all forms of neuropathies.

Differential Diagnosis

See Table 9.1.

Therapy

Discontinuation of the causative medication is the only known treatment. Symptomatic treatment for neuropathic pain and motor symptoms can be offered when necessary.

9.8.3 Toxic Neuropathies: Industrial Agents

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
–	Motor and sensory nerve conduction studies EMG	–	–	–

Epidemiology

Toxic neuropathies caused by industrial agents are rare in developed countries. A causal relationship has been established for some industrial agents (Table 9.4).

Anatomy and Pathophysiology

Toxic industrial agents usually affect nerve axons in a length-dependent pattern and cause a distal symmetric, axonal dying-back neuropathy. Sensory fibers are generally more

Table 9.4 Features of neuropathies caused by industrial agents

	Neuropathy	Other features	Morphology and neurophysiology	Source
Acrylamide	Distal symmetric sensory neuropathy; sensory ataxia	Dysarthria, hallucinations, weight loss, memory loss	Large fiber loss; Paranodal accumulation of neurofilaments EDX: axonal swelling. Low SNAPs and CMAPs	Monomeric acrylamide for production of polyacrylamide; Intoxication is via skin contact and to a lesser degree inhalation of the monomer
Carbon disulfide	Depending on exposure either mild sensory or progressive length-dependent sensorimotor neuropathy	Headache, depression, dizziness, memory impairment; Extrapyramidal signs in severe intoxication	In animals, CS2 causes axonal degeneration with giant fusiform axonal swellings and accumulation of 10 nm neurofilaments EDX: Distal slowing of sensory and later motor NCVs. Denervation on EMG in distal muscles	Used in the manufacture of viscose rayon, cellophane, pesticide production, and in chemical labs. Main route of intoxication is by inhalation
Hexacarbons	Distal symmetrical sensory neuropathy; prolonged exposure can result in weakness of hands and feet. Autonomic symptoms can occur. Coasting is typically seen and lasts from 1 to 4 months	Hyperhidrosis and blue discoloration of hands and feet can occur in glue sniffers. Spasticity and loss of color vision can be found	Focal axonal accumulation of 10 nm neurofilaments; Paranodal demyelination and myelin retraction EDX: In mild cases NCV can be normal but with clinical progression significant nerve conduction slowing occurs	Used in industrial solvents and cleansers and household glues. Commonly due to intentional inhalation of glues (glue sniffing)
Organophosphates	Initial symptoms are cramping and calf pain, numbness, burning, and tingling feet. Progressive distal weakness in legs more than arms develops and proximal muscles may become involved	After weeks to month signs of corticospinal tract dysfunction become evident in some patients	Dying-back axonal degeneration in both central and peripheral nerve fibers EDX: Low amplitude or absent SNAPs and CMAPs. EMG can initially show denervation	Common in insecticides, petroleum additives, plastic modifiers, fuel additives, lubricants. All are AchE inhibitors and cause organophosphate-induced delayed neurotoxicity (OPIDN) 7–21 days after exposure

affected than motor fibers and thus sensory symptoms dominate.

Symptoms
Numbness, paresthesias, and dysesthesias in a stocking or stocking-and-glove-like distribution are reported. Neuropathic pain can occur. Systemic symptoms are frequent (Table 9.4).

Signs
Distal large and/or small-fiber sensory loss and areflexia are found in the majority of cases. Atrophy of intrinsic foot muscles and dorsiflexion weakness can occur. Table 9.4 lists specific features of some agents.

Causes
See Table 9.4 for a list of industrial agents which cause neuropathies.

Diagnosis
The diagnosis rests upon known exposure to an industrial agent, which is known to cause peripheral neuropathy, and upon a typical clinical picture and specific systemic features.

Electrophysiology SNAPs are reduced or absent. Motor nerve conduction studies are normal or show low CMAPs. EMG can show polyphasic, medium- to high-amplitude, long-duration motor unit action potentials when motor fibers are involved. Demyelinating forms show nonuniform slowing of motor nerve conduction, temporal dispersion, and conduction block.

Imaging None.

Laboratory CPK can be mildly elevated in all forms of neuropathies.

Differential Diagnosis
Other causes of neuropathy (see Tables 9.1 and 9.2).

Therapy
Removal of the offending agent stops progression of neuropathy, and recovery depends on the extent of axonal damage. Symptomatic treatment for neuropathic pain and motor symptoms can be offered when necessary.

9.8.4 Toxic Neuropathies: Metals

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
–	Motor and sensory nerve conduction studies	Urine levels	–	–
	EMG	Serum levels for lead and mercury		

Epidemiology
Increased exposure to metals can be present in industrial and agricultural workers. Metal intoxications are seen in attempted suicide and homicide and rarely after consumption of contaminated traditional herbal medicine.

Anatomy and Pathophysiology
All metals cause widespread damage not only to the PNS. At the level of the human PNS, metals primarily result in axonal degeneration. The most common metals affect distinct anatomical structures (Table 9.5).

Symptoms
Symptoms depend on the disease-causing metal. Occasionally systemic symptoms predominate (see Table 9.5).

Signs
Signs depend on the disease-causing metal. Lead is commonly associated with an upper limb motor neuropathy, mercury with pure sensory features, and thallium and arsenic with sensorimotor neuropathies (Fig. 9.16). See Table 9.5 for associated symptoms.

Causes
See Table 9.5 for a list of relevant metals which cause neuropathies.

Diagnosis
The diagnosis rests upon known exposure to, a typical clinical picture, specific systemic features and evidence of increased body content of a given metal.

Electrophysiology Signs of axonal degeneration are found. Depending on the metal and the phenotype, CMAPs and/or SNAPs are reduced or absent. Conduction velocities can be mildly slowed. In motor predominant forms, EMG shows signs of denervation and reinnervation.

Imaging None.

Laboratory Heavy metals can be detected in urine but 24 h urine sampling may be necessary. Lead and mercury can be measured in serum, but mercury measurements are unreliable (see Table 9.5).

Differential Diagnosis
Other causes of neuropathy.

Therapy
Removal of the offending agent stops progression of neuropathy, and recovery depends on the extent of axonal damage. Chelating agents have been used in lead, arsenic, and mercury neuropathy to increase excretion. While this seems beneficial in lead and arsenic neuropathy, little is known

Table 9.5 Features of neuropathies caused by metals

	Neuropathy	Other features	Laboratory
Arsenic	5–30 days after exposure: distal symmetric sensory > motor; burning painful paresthesias in hand and feet. With high doses AIDP-like neuropathy	Acute gastrointestinal illness with abdominal pain and vomiting before neuropathy. Hypotension, renal failure, CNS symptoms. Chronic exposure: Mees lines and arsenic exfoliative dermatitis	Increased urine excretion; aplastic anemia, pancytopenia; increased arsenic in nail and hair; increased protein without pleocytosis in CSF
Lead	Motor neuropathy of arms > legs. Finger and wrist extensors preferentially affected. Asymmetry, atrophy, and fasciculations occur. Minimal sensory signs and symptoms. Tendon reflexes are reduced or absent	Anemia, abdominal pain, and constipation are typically present. Nephropathy and gout can be found. Children typically present with encephalopathy	Increased urine excretion; increased serum levels; microcytic and hypochromic anemia; red cells can show a basophilic stippling due to ribosomal clustering
Mercury	Mild distal sensory neuropathy with paresthesias. GBS-like neuropathies have been reported in children	Anorexia, gingivitis, hypersalivation. Personality change, ataxia, dysarthria, head and limb tremor	Increased urine excretion
Thallium	Painful distal symmetric sensory neuropathy. Severe cases show distal > proximal weakness. Proximal reflexes relatively preserved. Cranial nerve involvement and ptosis. Autonomic neuropathy can develop	Nausea, abdominal pain, and diarrhea within hours after acute intoxication. Neuropathy develops after 1–2 days. Alopecia develops 2 weeks after intoxication. With increased exposure: behavioral changes, anxiety, psychosis, tremor, and ataxia. Nephropathy, anemia, abnormal liver function tests	Increased urine excretion; increased protein without pleocytosis may be seen in CSF

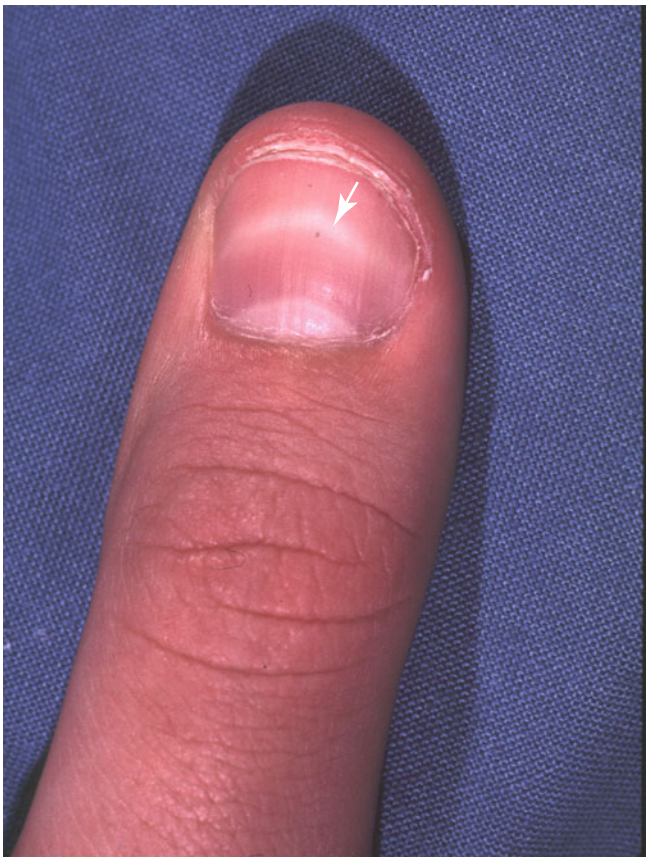

Fig. 9.16 Meese lines (*white arrow*) at the nail bed in case of arsenic poisoning and polyneuropathy (Courtesy Dr. Freymueller, Hermagor Austria)

about its efficacy in mercury neuropathy. Intravenous EDTA, penicillamine, British anti-Lewisite (BAL), and dimercaprol have been used. Symptomatic treatment for neuropathic pain and motor symptoms can be offered when necessary.

9.9 Hereditary Neuropathies

9.9.1 Hereditary Motor and Sensory Neuropathies: Charcot-Marie-Tooth Disease

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
+++	NCV of median nerve to define subtype	To exclude other disorders	CT/MRI: may show nerve enlargement	–

Epidemiology

Hereditary motor and sensory neuropathy (HMSN) or Charcot-Marie-Tooth disease (CMT) is the most common form of inherited neuropathy with an estimated prevalence of 1:2,500. The disease usually starts in the first or second decade of life, but severe early-onset and mild late-onset variants have been described. CMT may be inherited in an autosomal dominant, autosomal recessive, or X-linked trait but de novo mutations frequently occur. Demyelinating

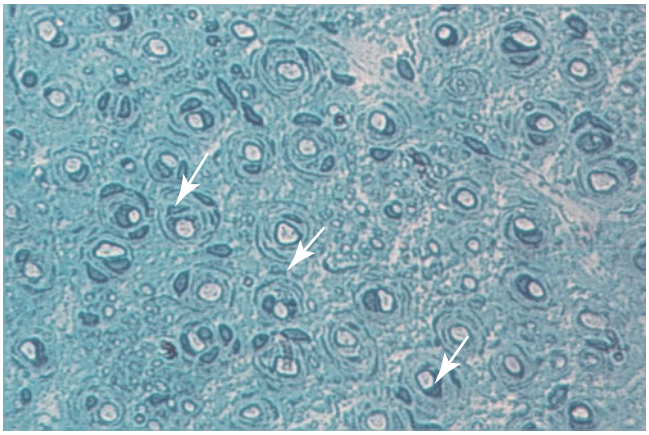

Fig. 9.17 Sural nerve biopsy from a patient with HMSN III (Dejerine–Sottas disease). The biopsy shows severe demyelination with thinly myelinated fibers and formation of multiple onion bulbs (*arrows*)

forms of CMT are more frequent than axonal forms (Fig. 9.17).

Anatomy and Pathophysiology

Depending on the subtype, the disease primarily affects either the axon or the myelin sheet. However, impairments of Schwann cell – axonal interactions, axonal transport, and protein trafficking – are also implicated in CMT. The pathophysiology depends on the genetic defect and to date there are more than 45 CMT-causing genes. In the most frequent form, CMT 1A, a *PMP22* duplication, results in an increased peripheral myelin protein 22 (PMP22) expression with abnormal Schwann cell differentiation, onion bulb formation, and secondary axonal dysfunction.

Symptoms

In CMT1A, the "classic" presentation is a patient with weak ankles, a mildly clumsy gait preventing participation in sports, and recurrent calluses secondary to foot deformities. Over time, many patients experience weakness and clumsiness of their hands. The complaint of numbness is not typical for CMT1A, and commonly symptoms of pain are musculoskeletal in nature resulting from foot deformities and altered biomechanics. Rarer forms of CMT are associated with additional specific features which result in specific symptoms (Table 9.6).

Signs

Characteristic foot deformities with a high arch and hammertoes secondary to atrophy of the intrinsic foot muscles, weakness of ankle dorsiflexion leading to a steppage gait, absent ankle reflexes, and pan-modal sensory impairment in the feet constitute the "classic" signs of CMT1A (Figs. 9.18, 9.19, and 9.20). Over time, a patient experiences atrophy and weakness of the hand muscles with sensory impairment. CMT1A and primarily axonal forms of CMT, designated CMT2 (see Table 9.6), are difficult to distinguish by clinical signs and symptoms alone, although reflexes may be retained in CMT2. Additional features such as optic atrophy, proximal weakness, scoliosis, tremor, vocal cord palsy, hearing loss, Adie's pupil, or neuromyotonia can occur and may be specific in some forms of CMT (see Table 9.6).

Causes

CMT is caused by mutations in more than 45 genes. The most relevant genes are *PMP22*, *MPZ*, *GJB1*, and *MFN2*.

Diagnosis

The diagnosis of CMT is based on the classic clinical picture, family history, and exclusion of other etiologies, especially in de novo or atypical cases. Further classification is based on nerve conduction studies and mode of inheritance: demyelinating forms are classified as CMT 1 when inheritance is autosomal dominant and as CMT 4 when inheritance is autosomal recessive. CMT 2 and AR-CMT 2 denote dominant and recessive axonal CMT; CMTX is X-chromosomal inherited. The diagnosis can be made by appropriate genetic testing. Recent studies indicate that four genes account for more than 90 % of all molecular CMT diagnoses. The PMP22 duplication is the most frequent cause of CMT 1, and mutations in the GTPase mitofusin-2 (*MFN2*) are the most frequent cause of CMT 2.

The following algorithm for the genetic diagnosis of CMT has been proposed (Fig. 9.21). In cases with specific associated features, testing is guided by these features (see Table 9.6).

Electrophysiology Nerve conduction studies are essential in classifying CMT and in guiding genetic testing. In demyelinating CMT (CMT1 and 4), median motor nerve conduction velocities (NCV) are <38 m/s, in axonal CMT (CMT2) velocities are >38 m/s, and an intermediate form is defined by median motor NCV between 25 and 45 m/s. Sensory nerve action potentials are absent in most cases of CMT1 and 2. In CMT1A, in spite of slowed conduction velocities, there is no temporal dispersion or block of compound muscle action potentials, i.e., the slowing is uniform. In CMTX nerve conduction studies can show nonuniform slowing, temporal dispersion, and conduction block; mimicking acquired autoimmune neuropathy.

Imaging MR, CT scan, and ultrasound: Nerve enlargements can be seen, but this is not specific to CMT.

Laboratory Appropriate genetic testing (discussed above). CSF protein can be elevated in CMT.

Differential Diagnosis

Differential diagnosis includes other inherited neurologic disorders that are present in early life. The spinocerebellar ataxias and leukodystrophies can be distinguished by the

Table 9.6 Known CMT syndromes, the disease-causing genes, and distinct features as of early 2013

	Gene	Specific feature
Autosomal dominant demyelinating – CMT 1		
CMT 1A	*PMP22*	Classical
CMT 1B	*MPZ*	Frequently hypoacusis
CMT 1C	*LITAF*	Classical
CMT 1D	*EGR2*	Very early onset; previous Dejerine–Sottas syndrome
CMT 1 F	*NEFL*	Classical
Autosomal recessive demyelinating – CMT 4		
CMT 4A	*GDAP1*	Hoarseness, vocal cord, and diaphragm palsy
CMT 4B	*MTMR2 SBF2*	Facial weakness, glaucoma
CMT 4C	*SH3TC2*	Scoliosis
CMT 4D	*NDRG1*	Hypoacusis, deafness, tongue atrophy, gypsy
CMT 4E	*EGR2*	Onset at birth
CMT 4 F	*PRX*	Very early onset; Dejerine–Sottas syndrome
CMT 4G	*HK1*	Cranial nerve involvement
CMT 4H	*FGD4*	Classical
CMT 4 J	*FIG4*	Severe
CCFDN	*CTDP1*	Gypsy; congenital cataract, facial dysmorphism, neuropathy
Autosomal dominant axonal – CMT 2		
CMT 2A1	*KIF1Bβ*	Classical
CMT 2A2	*MFN2*	Can have optic atrophy; frequently severe
CMT 2B	*RAB7*	Sensory predominant CMT 2. Can be similar to hereditary sensory neuropathy (HSN1)
CMT 2C	*TRPV4*	Hoarseness, stridor, vocal cord and diaphragm palsy; allelic to distal SMA and scapulo-peroneal syndrome
CMT 2D	*GARS*	Rare; allelic to hereditary distal motor neuropathy
CMT 2E	*NEFL*	Classical; can have intermediate NCV
CMT 2 F	*HSPB1*	Classical; allelic to hereditary distal motor neuropathy
CMT 2G	–	Rare
CMT 2I	*MPZ*	Late-onset classical
CMT 2 J	*MPZ*	Classical + hearing loss
CMT 2 K	*GDAP1*	Late-onset classical
CMT 2 L	*HSPB8*	Classical; allelic to hereditary distal motor neuropathy
CMT 2 M	*DYNM*	Early cataracts, ophthalmoparesis
CMT 2 N	*AARS*	Classical
CMT 2O	*DYNC1H1*	Rare; allelic to spinal muscular atrophy with lower limb predominance
CMT 2P	*LRSAM1*	Rare; classical
CMT 2Q	*DHTKD1*	Rare; classical
Autosomal recessive axonal – AR – CMT 2		
AR-CMT 2A	*Lamin A/C*	Proximal weakness; mutations also cause cardiomyopathy and muscle dystrophy
AR-CMT 2B	*MED25*	Classical
AR-CMT 2 K	*GDAP1*	Hoarseness, vocal cord palsy
AR-CMT2 + pyramidal signs		Rare
AR-CMT2 + severe early onset	*NEFL*	Rare
AR-CMT2/distal HMN	*HSPB1*	Mild sensory loss
AR-CMT2 + acrodystrophy	*ATSV*	Rare
AR-CMT2	*LRSAM1*	Rare
AR-CMT2 + early onset optic	*MFN2*	Early onset, severe
AR-CMT2 + neuromyotonia	*HINT1*	Clinical mild action myotonia; neuromyotonia in EMG
X-chromosomal – CMT X		
CMT X Type 1	*GJB1*	CMT 1 or intermediate. Frequently asymmetric NCV, temporal dispersion and conduction block in NCV. CMT 2 in females, who may also be affected
CMT X Type 2	–	Early onset; mental retardation
CMT X Type 3	–	CMT 2
CMT X Type 4	*AIFM1*	Early onset; CMT intermediate, mental retardation, and deafness
CMT X Type 5	*PRPS1*	Early onset CMT2, deafness, and optic neuropathy
CMT X Type 6	*PDK3*	Rare

Modified from http://neuromuscular.wustl.edu/time/hmsn.html#IX. April 2013

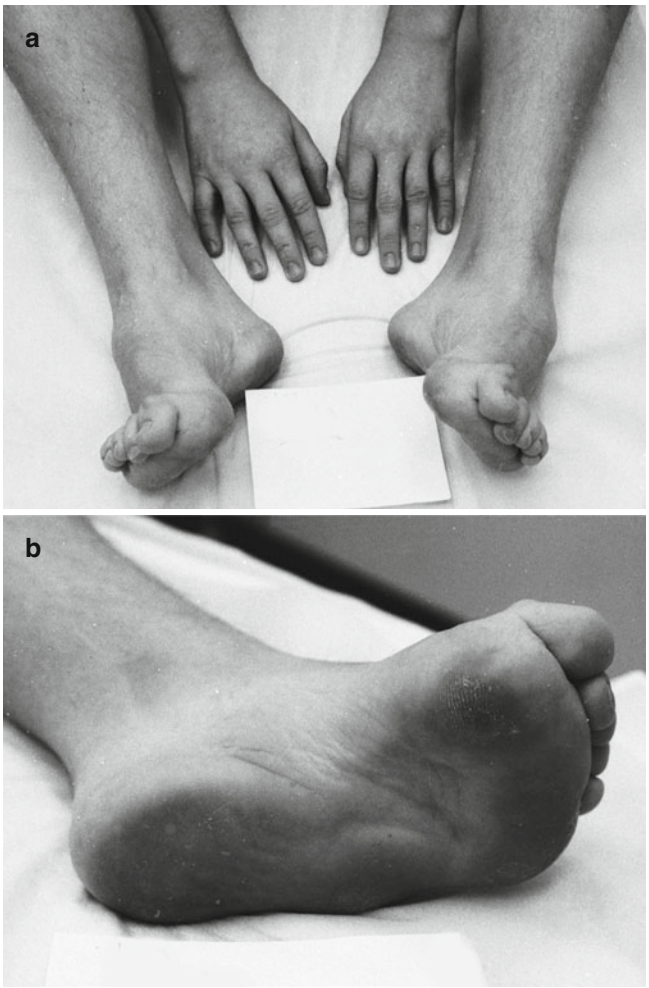

Fig. 9.18 Physical findings in a patient with CMT. (**a**) Foot deformity. (**b**) Pes cavus

presence of cranial nerve, cerebellar, and long tract signs that are not found in CMT. Hereditary neuropathy with pressure palsies (HNPP), secondary to a loss of a copy of *PMP22*, may resemble CMT, but the history of pressure palsies and extremely prolonged distal latencies, in the presence of mild slowing of motor NCVs, identify the disorder as HNPP. Electrodiagnostic studies are usually asymmetric in inflammatory neuropathies with temporal dispersion, conduction block, and significantly elevated CSF protein. Finally, inherited myopathies and spinomuscular atrophy show no impairment of sensory function unlike CMT.

Therapy

To date, no drug treatment is available. Physical therapy, orthotics, and occasional surgery are the available treatment options. The major goal of treatment is to retain optimal function throughout the course of the patient's life.

9.9.2 Other Hereditary Motor and Sensory Neuropathies

- Hereditary neuropathy with liability to pressure palsies (HNPP)
- Hereditary sensory and autonomic neuropathy (HSAN)
- Hereditary neuralgic amyotrophy (HNA)
- Distal hereditary motor neuropathies (dHMN)

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy
+++	NCV	To exclude other disorders	CT/MRI: may show nerve enlargement	Occasionally

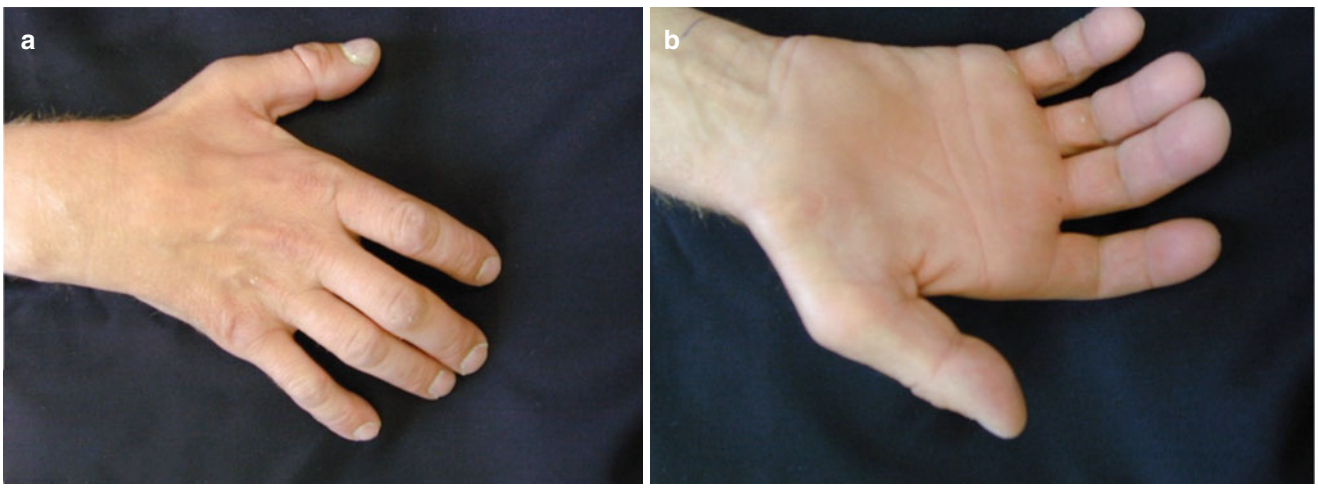

Fig. 9.19 Physical findings in a patient with CMT. (**a**, **b**) Claw hands. (**c**) Atrophy in the lower legs. (**d**) Foot deformity

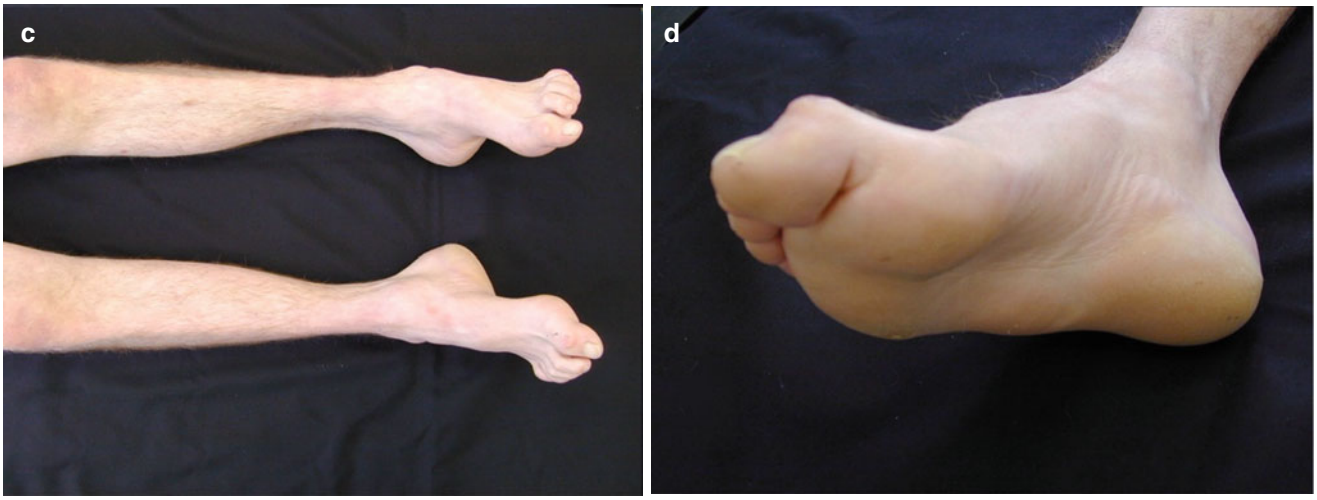

Fig. 9.19 (continued)

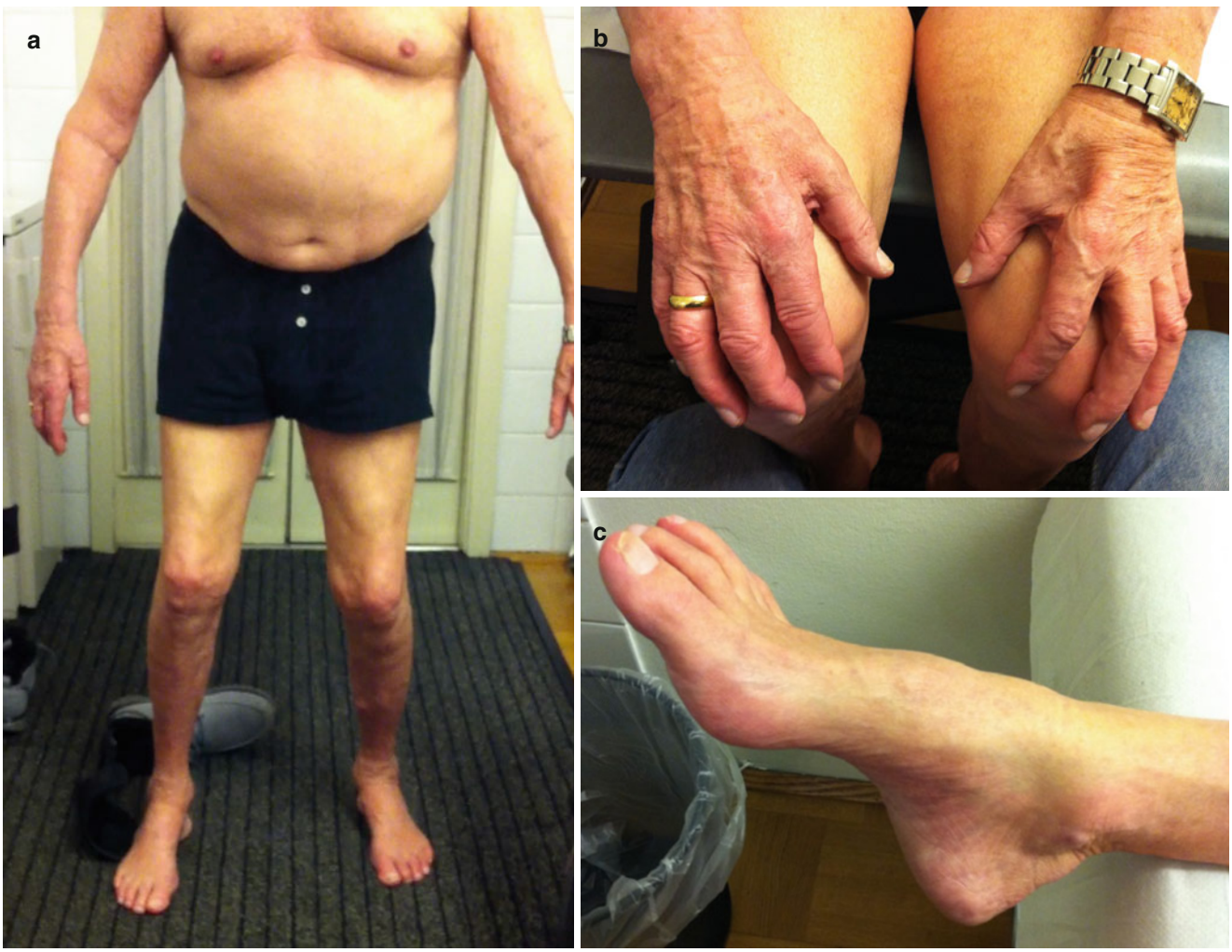

Fig. 9.20 Late-onset CMT (genetically not classified). This patient was previously healthy and had the onset of peroneal weakness. Over a 10-year period, the patient developed a severe, predominately motor neuropathy. (**a**) Broad-based stance with disproportionate muscle mass between the thigh and lower leg. (**b**) Hand atrophy, slightly asymmetric, predominately ulnar nerve distribution. (**c**) Foot atrophy

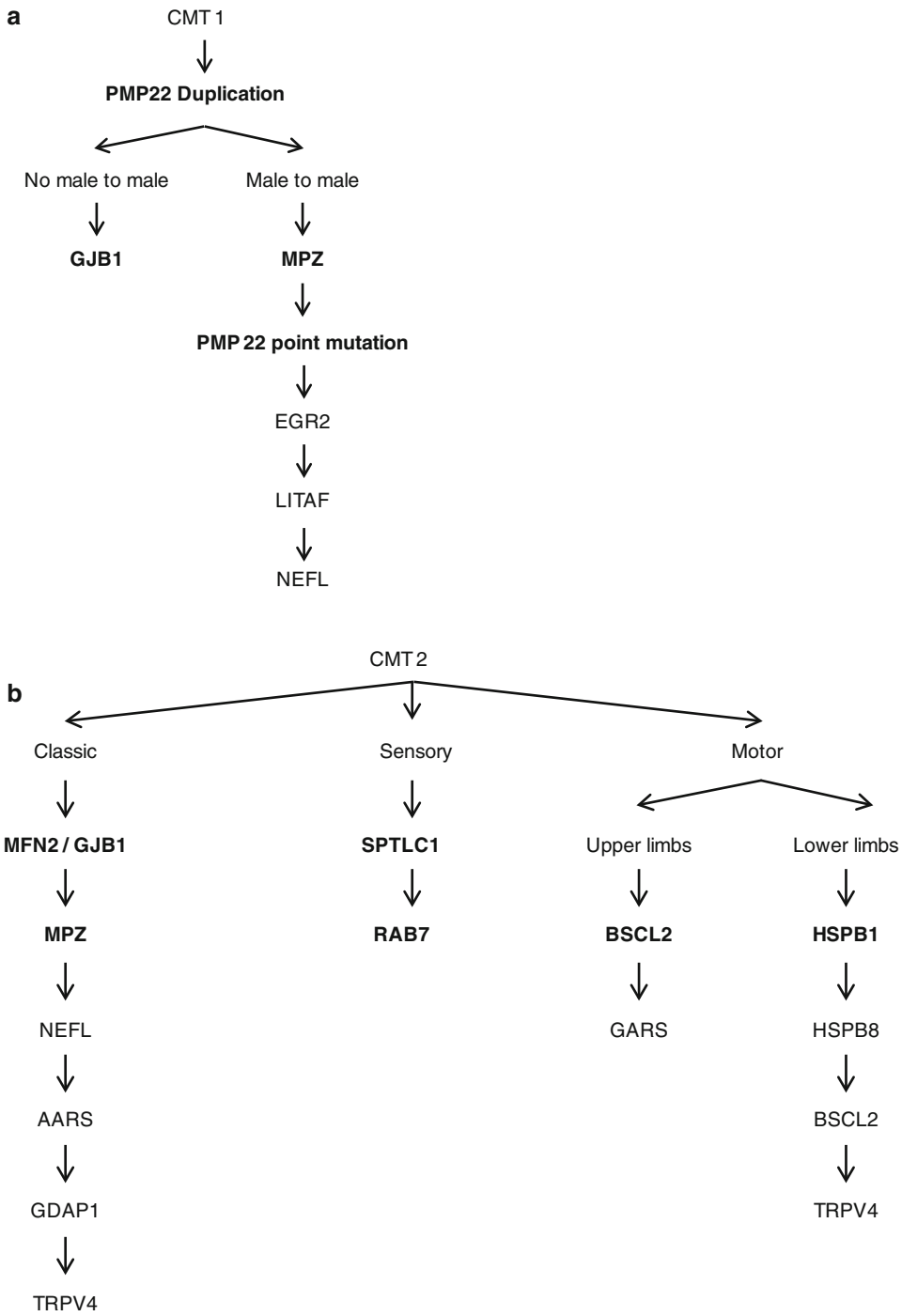

Fig. 9.21 Algorithm for diagnosing hereditary neuropathies. This figure provides an algorithm for the genetic diagnosis of (**a**) demyelinating and (**b**) axonal CMT. Genes in bold should be offered, other genes can be tested in certain circumstances

Epidemiology

These disorders are much rarer than the other CMT syndromes. Reliable data do not exist, but HNPP seems to be the most frequent.

Anatomy and Pathophysiology

Depending on the disorder either myelin sheet, dorsal root ganglia, axon, or motor neurons are affected. The pathophysiology is a source of investigation, as the genes are now known for these disorders.

Symptoms

In HNPP repeated episodes of transient weakness and numbness in isolated peripheral nerve territories are reported. Age of onset is ~25 years. In HSAN patients hurt themselves without experiencing pain, frequently with burns and wounds

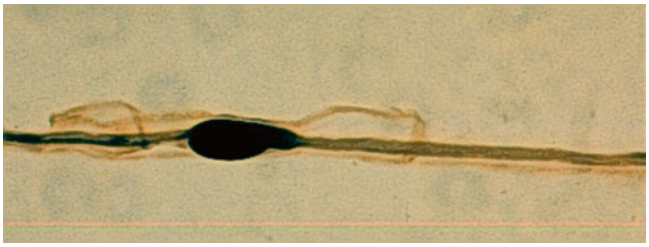

Fig. 9.22 Hereditary neuropathy with liability to pressure palsies (HNPP). Teased fiber preparation from a patient with HNPP. The myelin shows a large sausage-shaped myelin enlargement (tomaculum – little sausage)

that do not heal properly. Age of onset is ~25 years. In HNA repeated episodes of shoulder pain are followed by weakness. Surgery, infection, and pregnancy can trigger these episodes. Weakness can be transient but usually persists to some degree with the onset of symptoms between 10 and 30 years of age. In dHMN patients initially complain of distal upper or lower extremity weakness.

Signs

In HNPP sensory loss and weakness corresponding to typical nerve compression syndromes and signs may initially be transient but tend to persist after repeated injury. Signs of generalized neuropathy are present but mild (Fig. 9.22). In HSAN predominantly small-fiber sensory loss is present first in the lower than in the upper extremities. Large fiber impairment and weakness occur later in the course. Wound healing is impaired, with chronic ulcers and mutilation of digits. In HNA signs of brachial (and rarer lumbosacral) plexus palsies are present with frequent scapular winging. Weakness and atrophy can persist after repeated attacks while sensory signs are mild. Hypertelorism, small facies, and short stature are typical signs in HNA. Depending on the subtype of dHMN distal lower and upper extremity weakness develops without sensory signs. Upper motor neuron signs can be present.

Causes

Table 9.7 lists the disease-causing genes.

Diagnosis

The diagnosis is based on the typical clinical picture, family history, and sometimes exclusion of other causes, especially in de novo or atypical cases, which are frequent in HNPP. Genetic testing is feasible in HNPP, HSAN, HNA, and some cases with dHMN (see Table 9.7).

Electrophysiology In HNNP nerve conduction slowing is seen at typical nerve entrapment sites, e.g., median and ulnar nerve at the wrist, ulnar nerve at the elbow, and peroneal nerve at the fibular head. Signs of generalized neuropathy are mild and include prolonged distal latencies and mild nerve conduction slowing. In HSAN sensory nerve action potentials are reduced or absent, NCV are normal or intermediate. In HNA signs of axonal damage are confined to affected nerves. In dHMN CMAPs are reduced or absent, sensory nerves are normal. EMG shows chronic denervation.

Table 9.7 Causing genes of hereditary motor and sensory neuropathies

	Gene	Specific feature
Genetics of hereditary neuropathy with liability to pressure palsies (HNPP)		
HNPP	*PMP22*	Deletion in most cases; point mutations are rare. High rate of de novo deletions
HNPP	*KARS*	Very rare
Genetics of most frequent hereditary sensory and autonomic neuropathies (HSAN)		
HSAN 1A	*SPTLC1*	Most frequent form of HSAN
HSAN 1B	*SPTLC2*	
CMT 2B	*RAB7*	Axonal CMT syndrome; can be sensory predominant with ulcerations. Some weakness usually exists. Differential to HSAN 1
Genetics of most frequent hereditary neuralgic amyotrophy (HAN)		
HNA 1	*SEPT9*	Recurrent attacks; most frequent form. Other forms (chronic HNA2 and HNA3 exist; genes not known)
Genetics of most frequent distal hereditary motor neuropathies (dHMN)		
HMN 2B	*HSPB1*	Adult-onset leg weakness; arms later in the disease course
HMN 5A	*GARS*	Onset in hands (thenar and first dorsal interosseous); legs affected a few years later; pyramidal signs rare
HMN 5C	*BSCL2*	Most frequent form. Early hand weakness (thenar more and earlier affected than first dorsal interosseous); distal leg weakness; brisk reflexes in legs; muscle tone in legs can be increased. Plantar response flexor. Allelic to SPG 17 and congenital lipodystrophy, type 2

Imaging MR, CT scan, and ultrasound: Nerve enlargements at entrapment sites can be seen in HNPP.

Laboratory Genetic testing for diagnosis (see below). CSF protein can be elevated in HNPP.

Differential Diagnosis

Other inherited neurologic disorders that are present in the early decades of life should be considered. HNPP can be distinguished from idiopathic entrapment syndromes by their repeated occurrence without relevant history and the electrodiagnostic studies. Fabry's disease is distinguished by widespread organ involvement from HSAN and laboratory testing. HNA is distinguished from idiopathic neuralgic amyotrophy by family history and repeated episodes of

weakness. dHMN can be distinguished from distal myopathies by EMG and muscle biopsy. In cases with upper motor neuron signs, the slowly progressive course distinguishes dHMN from ALS. There is a reported overlap with familial spastic paraplegias.

Therapy

To date, no drug treatment is available. Physical therapy and orthotics are the treatment options available. Prevention of nerve compression, e.g., during surgery is helpful in HNPP. In HSAN prevention of skin lesions and wound care is necessary.

9.9.3 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 hepatotoxic drugs, 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 ALA dehydratase deficiency, acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria.

Diagnosis

Electrodiagnosis shows predominately motor impairment. The primary diagnostic 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 intravenous 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 antiepileptic drugs 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 remain because of the axonal degeneration.

9.10 Cancer and Neuropathy

9.10.1 Paraneoplastic Neuropathies

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy	Other
	+	+ CSF studies Onconeuronal antibodies			

Paraneoplastic neuropathies are a heterogeneous group of neuropathies that can affect the peripheral nerves (sensory, sensory/motor); the DRG (dorsal root ganglion neuron) and can be associated with posterior column degeneration. Some neuropathies are associated with antineuronal antibodies in particular anti-Hu. Paraneoplastic neuropathies in cancer patients can also be part of a multifocal paraneoplastic encephalomyelitis complex (PEM). The most frequent type of paraneoplastic neuropathy is subacute sensory neuronopathy. Nerve vasculitis is rarely associated with paraneoplastic syndromes. Demyelinating neuropathies occur in association with lymphoma and Hodgkin's disease.

Anatomy/Distribution

Although the sensory ganglionopathy is an anatomically defined entity characterized by inflammation of the DRG

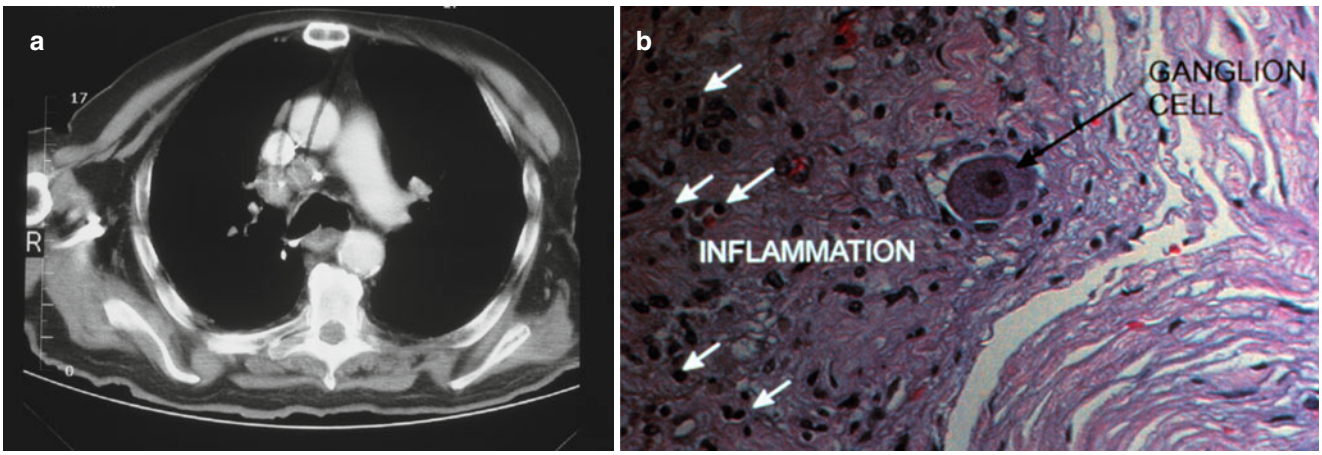

Fig. 9.23 Paraneoplastic ganglionopathy in a patient with small cell lung cancer. (**a**) Chest X-ray showing enlargement of the mediastinal lymph nodes. (**b**) Single dorsal root ganglion (*large arrow*) and inflammatory cell infiltrates (*small arrows*)

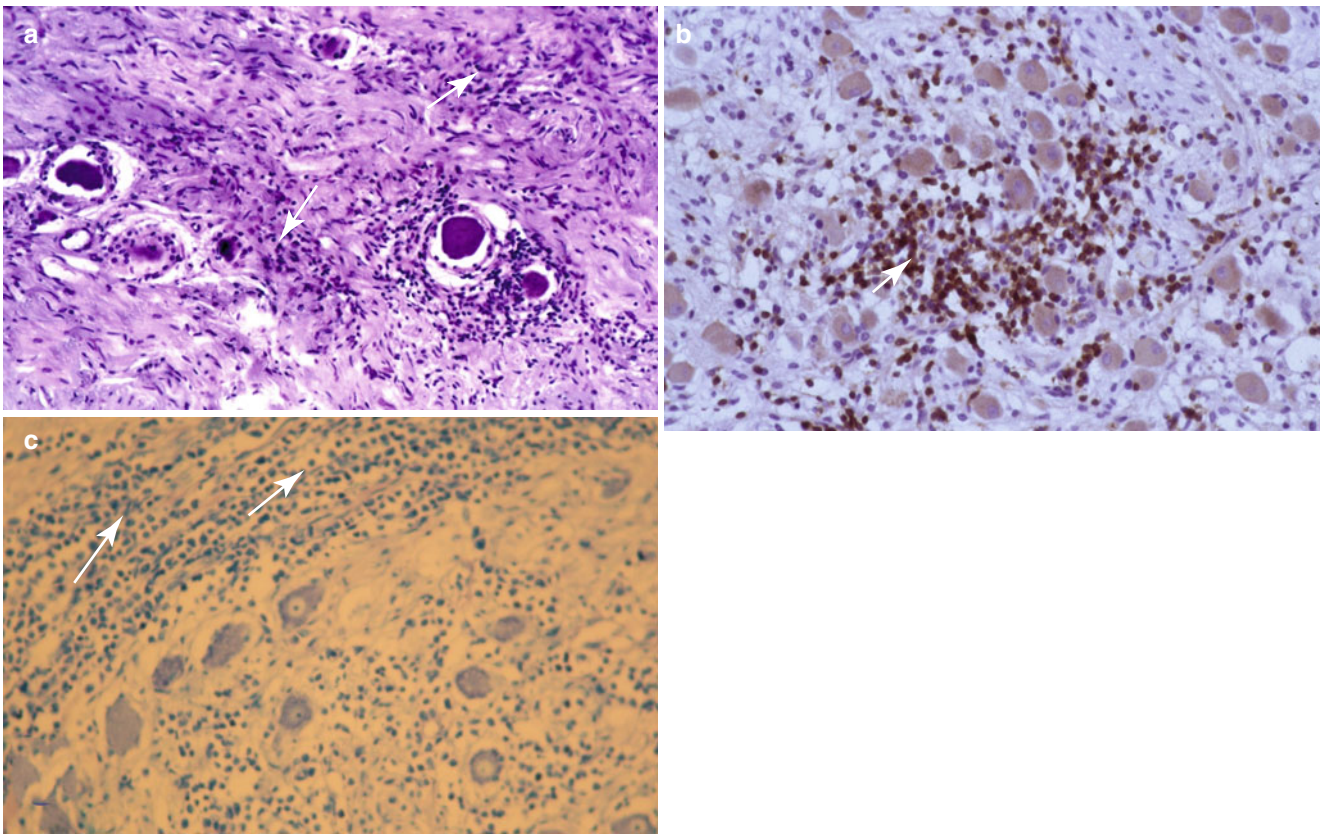

Fig. 9.24 Dorsal root ganglion (DRG) pathology. (**a**, **b**) Examples of an inflammatory paraneoplastic ganglionitis (*arrows*). (**b**) An infiltrate which is immunostained for T-cells (*arrow*). (**c**) Rare example of neoplastic infiltration of a DRG by lymphoma cells (*arrows*) of a Burkitt-like lymphoma. This patient had additional meningeal infiltration

and additional posterior column degeneration, the anatomy is less well defined for other less characterized paraneoplastic neuropathies (Figs. 9.23 and 9.24).

Symptoms

Sensory neuronopathy (SSN) ("Denny-Brown's syndrome") is characterized by subacute development of sensory neuropathy, with ataxia, and pseudoathetoid movements of the upper extremities and ataxia of the lower extremities. It is unclear if there is additional involvement of the motor system in SSN ("sensorimotor neuronopathy").

Autonomic neuropathies can cause gastrointestinal symptoms (e.g., pseudo-obstruction), sexual dysfunction, and orthostatic hypotension. Demyelinating neuropathy like AIDP or CIDP has been described on rare occasions and has no special characteristics. Vasculitic neuropathy is

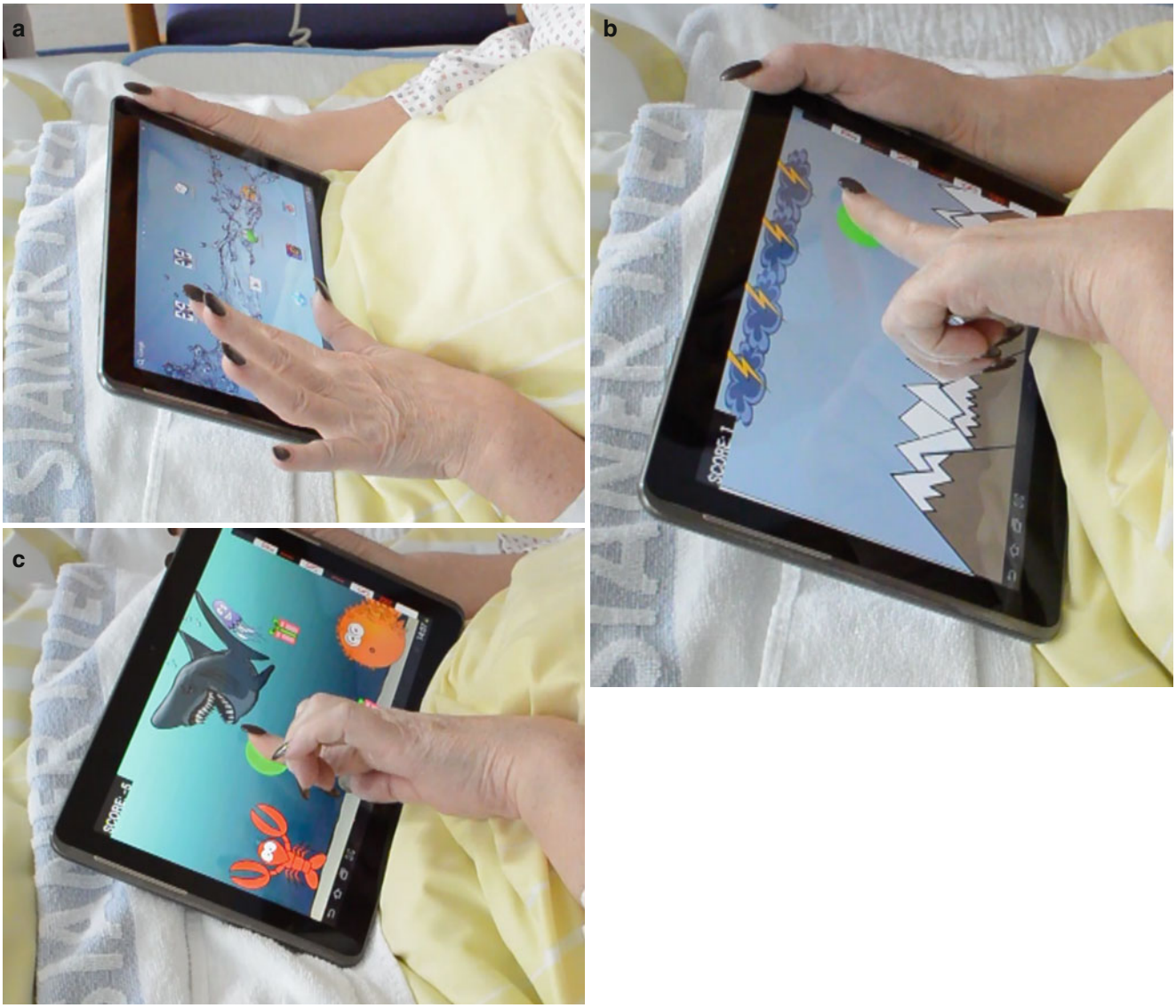

Fig. 9.25 Sensory neuronopathy (SSN). The patient suffers from sensory ataxia due to SSN. Both hands have bizarre ataxic pseudoathetoid movements when trying to move objects on the screen (**a**–**c**) (Images are adapted from a video sequence)

characterized by painful mononeuritis multiplex. Distal symmetric polyneuropathy can occur but is usually a subclinical finding. Sensory neuropathies can be painful.

Clinical Syndrome

SSN often presents acutely with the onset of painful asymmetric severe sensory loss with sensory ataxia. Loss of manual dexterity and the ability to stand in place with severe gait ataxia usually follows. Sensorimotor neuropathies are not characteristic of SSN (Fig. 9.25).

Signs

Sensory neuronopathy is characterized by an often asymmetric onset, areflexia, ataxia, pseudoathetoid movements, and pain. Motor involvement is atypical. Demyelinating neuropathy cannot be distinguished from AIDP or CIDP. SSN occurs typically before the diagnosis of the cancer. Distal symmetric polyneuropathy, with a glove and stocking-like distribution, is usually very mild and subclinical.

Pathogenesis

The pathogenesis of paraneoplastic neuropathies is unclear but is believed to be the result of numerous onconeuronal autoantibodies associated with cancer, the most prominent being anti-Hu. The sensorimotor type has been associated with anti-CV2 antibodies. Demyelinating forms are more likely associated with lymphoma and Hodgkin's disease.

Diagnosis

The diagnosis of paraneoplastic neuropathies is primarily based on the case history and clinical presentation. Nerve conduction velocities reveal unspecific sensory axonal loss

with absent sensory conduction velocities in SSN. Anti-Hu antibodies, especially in cases of lung cancer, may be detectable; other onconeuronal antibodies as CV2 or CRMP 5 have been described. Biopsies are rarely indicated, except for the exclusion of suspected vasculitic neuropathy.

Differential Diagnosis

The syndrome of sensory neuronopathy SSN is not exclusively paraneoplastic, but may also be idiopathic or associated with Sjögren's syndrome. In the course of cancer, chemotherapy-induced neuropathy is a common possibility, and concomitant metabolic diseases, malnourishment, and weight loss should be excluded.

Therapy

No recommended treatments other than treating the cancer are available for the sensorimotor polyneuropathy and autonomic syndromes. For sensory neuropathies and neuronopathies, immunomodulatory therapies have been suggested and range from steroids to IVIG, plasmapheresis, and immunosuppression, without evidence. Symptomatic treatment can be useful. Demyelinating neuropathies of the GBS and CIDP type need treatment according to the current standard of practice. Vasculitic neuropathy can be treated with steroids and immunosuppression (which may be part of the cancer therapy).

9.10.2 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 there is weakness with retained sensation.

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, and 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 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.

9.10.3 Neuropathies and Neuromyopathies

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy	Other
	+				

In advanced stages of cancer, there is often a mild neuropathy, with loss of reflexes and distal minor sensory or motor symptoms. The mechanism and pathology underlying this neuropathy is not known. A similar type of neuropathy occurs in infectious and chronic diseases suggesting that collectively these neuropathies are secondary to a global illness. Neuromyopathies involve proximal muscles (usually the thighs) with atrophy but relatively preserved strength. In addition to a mild axonal neuropathy, this presentation can mark the onset of cancer.

9.10.4 Neuropathies in Lymphoma and Leukemia

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy	Other
	+	+	(+)	(+)	
		CSF studies			

Neuropathies in lymphomas and leukemias most commonly occur due to chemotherapy. Paraneoplastic neuropathies and neoplastic neuropathies can also be due to invasion by lymphoma cells (neurolymphomatosis) or leukemia (neuroleukemiosis), although these neuropathies are rare. Meningeal infiltration can also mimic neuropathy.

Anatomy/Distribution

Toxic neuropathies are dependent on the individual drug but most commonly distal sensory neuropathies occur with ataxia.

Paraneoplastic neuropathies as sensory or chronic inflammatory neuropathies (CIDP) can occur in lymphoma and are rare in leukemia.

The type of infiltration depends on the type of lymphoma or leukemia. In general diffuse and symmetric infiltrations occur, as well as focal tumor invasion of the nerve.

Symptoms

Sensory neuropathies are characterized by distal symmetric distribution and usually have no motor involvement. Motor involvement is rare, except in lymphoma associated CIDP. Neuroplastic lymphoma (neurolymphomatosis) can mimic sensory or sensorimotor neuropathy; also meningeal infiltration can mimic sensorimotor neuropathy.

Diagnosis

Diagnostic procedures are routine except when there is suspected neoplastic involvement. This can be confirmed by nerve biopsy, CSF analysis for meningeal involvement, and increasingly imaging studies of peripheral nerves.

Therapy

Therapy is dependent on the etiology and includes symptomatic treatment for sensory neuropathies, immunomodulatory treatment in CIDP, and antineoplastic treatment in neurolymphomatosis. No recommended treatments other than treating the cancer are available for sensorimotor polyneuropathies and autonomic syndromes. For sensory neuropathies and neuronopathies, immunomodulatory therapies have been suggested and range from steroids to IVIG, plasmapheresis, and immunosuppression, all without evidence. Symptomatic treatment can be useful. Demyelinating neuropathies of the GBS and CIDP type need treatment according to the current standard of practice. Vasculitic neuropathy can be treated with steroids and immunosuppression (which may be part of the cancer therapy).

9.10.5 Neoplastic Neuropathies

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

Neoplastic neuropathies are rare and occur almost exclusively in patients with lymphoma, leukemia, and even rarer in solid tumors. Infiltration of individual peripheral nerves by lymphoma is known as neurolymphomatosis. Leukemia can affect nerves and 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. Local carcinomatous invasion of the plexus and cranial nerves is discussed separately in the respective chapters.

Anatomy

Neoplastic neuropathies are secondary to both focal and diffuse infiltration of cancer cells. Diffuse infiltration occurs within the nerve via the perineurium, via the vasculature, or via fascicular spread. DRG can be infiltrated with cancer cells and multiple radiculopathies in meningeal carcinomatosis can mimic neuropathies. Rarely nerve metastases occur, which typically present as painful mononeuropathies.

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 in a separate chapter. 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 SNAPs and CMAPs and denervation in innervated myotomes. If there is primary nerve root infiltration,

needle examination reveals anterior and posterior (paraspinal muscles) myotome denervation. In CIDP like cases, there is symmetric demyelination.

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. Increasingly, ultrasound of peripheral nerves is used to examine the nerve plexus and peripheral nerves and can show nerve thickening and nerve enlargement.

Nerve Biopsy There is direct infiltration of nerve, resulting in axonal loss and the presence of tumor deposits in the nerve (Fig. 9.26). Disorders that can affect multiple named nerves or nerve roots, such as vasculitis or infectious neuropathies, need to be excluded, and histological studies are required to distinguish between inflammatory and neoplastic cells.

Therapy

Cancer treatment either by chemo- or immunotherapy can be helpful. 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 the final stages of the disease.

9.10.6 Polyneuropathy and Chemotherapy

Genetic testing	NCV/EMG	Laboratory	Imaging	Biopsy	Other
	+				Drug assessment, cumulative dose

Chemotherapy-induced neuropathies (CIPN) are usually dose dependent and may resolve after termination of the chemotherapy. Increasingly, CIPN is being recognized as a late effect in long-term cancer survivors. Acute effects of chemotherapy occur predominately in oxaliplatin treatment. Little is known about the influence of preexisting polyneuropathies for the development of a CIPN (except hereditary sensorimotor neuropathies) and the toxicity of chemotherapy drug combinations. Additionally, also biological agents such as antibodies, interferons, cytokines, and vaccines are used in cancer therapy and may have a risk of inducing polyneuropathies.

Pathogenesis

The pathogenesis of drug-induced neuropathy is dependent on the substance used and varies with different classes of drugs. For example, platinum drugs target the DRG, whereas vinca alkaloids act on tubulin, also the taxanes and epothilones induce excessive tubulin polymerization. The mechanism of proteasome inhibitors on the peripheral nervous system has not been fully elucidated.

Clinical Distribution

Most neuropathies caused by chemotherapeutic agents are symmetric and length dependent, with a stocking–glove distribution of sensory loss. Distal weakness (lower extremities) rarely occurs. Cranial nerves are usually not involved, except in acute oxaliplatin toxicity where patients experience cold-induced face and throat pain. Clinically, the development of distal sensory symptoms (numbness or paresthesias) can be used as a clinical sign of neurotoxicity.

Symptoms

Most chemotherapy-induced neuropathies are sensory. Tingling or numbness in the feet or fingers is often an early sign. Also "positive" sensory symptoms occur, including paresthesias, dysesthesias, tingling, itching and burning, tight, stabbing, sharp (lightening like), or aching pain.

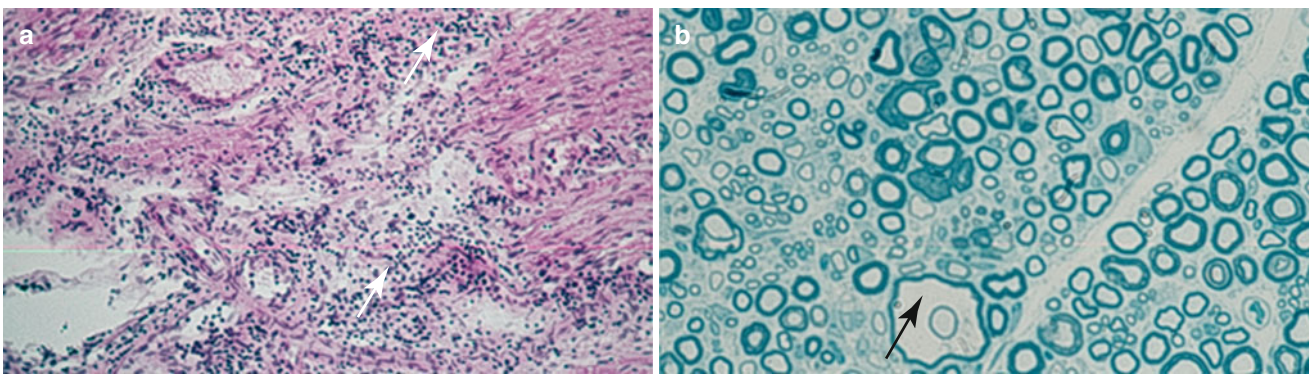

Fig. 9.26 Sural nerve biopsy from a patient with lymphoma. (**a**) Infiltration of the peripheral nerve by collections of B cells, with disruption of normal sural nerve architecture (*arrows*). (**b**) Disruption of myelin, with myelin spaying and partial loss of myelin (*arrow*)

Sensory loss in the feet and legs can cause sensory ataxia and gait disorders. Loss of sensation in the hands is often perceived as "clumsiness." Myalgias have been described with gemcitabine and taxane therapies.

Signs

Diminished sensory perception for touch, pinprick, and vibration. Ankle reflexes are often absent. Finger-to-nose, knee-to-shin, and Romberg are abnormal. Weakness is rarely a feature (except with some cases of vinca alkaloids and bortezomib treatment). Raynaud's syndrome has been observed in long-term survivors. Even with drug withdrawal, signs may continue to progress, a phenomenon known as coasting.

There are a large number of different drugs used for chemotherapy; some of the biological agents currently in use are also reported to have neurotoxic effects in individual cases (Table 9.8). The main substances causing chemotherapy-induced neuropathies are platinum compounds, vinca alkaloids, taxanes, bortezomib, and thalidomide. Toxicity is dose dependent and cumulative; acute effects occur in oxaliplatin and possibly in taxanes. Although most CIPN is considered to be reversible, long-term effects emerge in cancer survivors and can significantly impact the patient's quality of life.

Drugs Used for Chemotherapy

Platinum Compounds

- *Cisplatin*: The neuropathy is predominantly sensory with complaints of distal numbness or paresthesias with sensory ataxia and a positive Lhermitte's sign. Coasting is a unique feature. Many patients experience residual neuropathic pain after improvement in their neuropathy. Ototoxicity can result in hearing loss and dizziness.
- *Carboplatin*: In higher cumulative doses than cisplatin, carboplatin also produces a sensory neuropathy similar to cisplatin.
- *Oxaliplatin*: Acute effect: 80 % of patients develop cold-induced paresthesias and dysesthesias in the throat, mouth, face, and hands. The symptoms settle a few days after the infusion is completed. Oxcarbazepine is modestly effective as a prophylactic agent. The dose-related sensory neurotoxicity resembles cisplatin-induced neuropathy.
- *Vinca Alkaloids*: Vinca alkaloids produce a dose-related sensorimotor neuropathy. Vincristine and vindesine have more severe neurotoxicity compared with vinblastine and vinorelbine.

Clinical Features Early symptoms are painful paresthesias of the hands (particularly the fingers) and feet. Weakness can occur in wrist extensors and toe dorsiflexors. Rarely, patients experience autonomic dysfunction or cranial nerve mononeuropathies.

Laboratory Studies Nerve conduction studies show axonal neuropathy with reduced or absent SNAPs with mildly reduced conduction velocities.

Taxanes

Both paclitaxel (Taxol) and docetaxel (Taxotere) are widely used alone and in combination with other agents for the treatment of breast, ovarian, lung, and other cancers. Paclitaxel produces a more severe neuropathy than docetaxel.

Clinical Features Sensory symptoms are dose related. Both drugs induce either loss of sensation, paresthesias, or allodynia in the feet and hands. Proprioceptive sensory loss can result in gait ataxia. Weakness is mild or absent with rare reports of proximal muscle weakness. Myalgias and arthralgias can occur with paclitaxel therapy.

Laboratory Studies Electrophysiological testing reveals reduced or absent SNAPs.

Proteasome Inhibitors

Bortezomib is a polycyclic derivative of boronic acid that inhibits the mammalian 26S proteasome. Carfilzomib is a new proteasome inhibitor in current clinical trials with reportedly less neurotoxic side effects.

Clinical Features The neuropathy is dose related and cumulative. It is predominantly sensory, distal, and length dependent. It often causes neuropathic pain and autonomic

Table 9.8 Drugs used for chemotherapy

Drug	Cumulative dose	Immediate (acute) effects	Other effects
Cisplatin	300–400 mg/m^2		Coasting
Carboplatin	600 mg/m^2		Coasting
Oxaliplatin	800 mg/m^2	Acute toxicity. Cold dependent	
Vincristine	5–15 mg/m^2		Cranial and peripheral nerve mononeuropathies, autonomic neuropathy, myopathy
Paclitaxel	200 mg/m^2	Acute toxicity likely (distal pain)	Myalgias, myopathy
Docetaxel	400–600 mg/m^2		
Bortezomib	1–1.3 mg/m^2		Painful
			Rarely demyelinating
Thalidomide	20 g (total)		Poor reversibility

neuropathy with postural hypotension probably due to small-fiber involvement. Neuropathy occurs in 37–44 % of patients receiving this drug.

Laboratory Studies Electrophysiological changes demonstrate axonal loss with low or absent SNAPs.

Thalidomide and Lenalidomide

Thalidomide has been used in the treatment of multiple myeloma, Waldenström's macroglobulinemia, myelodysplastic syndromes, and acute myeloid leukemia.

Clinical Features The neuropathy is predominantly sensory and develops in 20–40 % of patients. The frequency of neuropathy increases with age and the cumulative dose. Lenalidomide (alpha-3-aminophthalimidoglutarimide) is an analogue of thalidomide that seems less neurotoxic, also pomalidomide, a newer analogue, is designed to be less neurotoxic. Electrophysiology demonstrates axonal neuropathy with reduced or absent SNAPs.

CIPN

Long-Term Effects As the number of cancer survivors increases, persistent CIPN is impeding their quality of life and resulting in significant morbidity. Common persistent problems are sensory neuropathy, neuropathic pain syndromes, muscle cramps and fasciculations, altered smell and taste, and vestibular dysfunction.

Prevention To date, preventative treatment with vitamins, antioxidants, and growth factors prior to or at the time of chemotherapy has not prevented the onset and progression of CIPN.

Symptomatic Treatment Neuropathic pain treatment is required with anticonvulsants, antidepressants, in severe cases opioids and also topical local anesthetics. Physical and occupational therapy are helpful to compensate for loss of proprioception and increase function.

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Neuromuscular Transmission: Endplate Disorders

10

Wolfgang N. Löscher

See Fig. 10.1.

10.1 Myasthenia Gravis

Genetic testing	NCS/EMG	Laboratory	Imaging	Biopsy
–	++	++	++	–

10.1.1 Epidemiology

The prevalence and incidence of MG have increased over the years, especially in elderly men. Current estimates are 0.17–1.04/100,000 for incidence and 0.3–20/100,000 for prevalence. MuSK-Ab-positive MG commonly affects women.

Coexisting autoimmune diseases are frequent in MG with autoimmune thyroid disease being the most common. Autoimmune diseases occur more often in female and seronegative patients.

10.1.2 Anatomy and Pathophysiology

In AchR-Ab-positive MG, the number of AchR is reduced, their function partially blocked and AchR turnover is increased. If untreated, the endplate becomes structurally damaged.

MuSK is necessary for AchR clustering, but the pathophysiology of MuSK-Ab MG is incompletely understood.

10.1.3 Symptoms

Use-dependent weakness and increased fatigability. Initial complaints are about double vision or hanging eyelids, difficulties chewing and swallowing, softening of voice when speaking over prolonged periods of time, shortness of breath or increased fatigability of arms or legs on prolonged use. Typically these symptoms fluctuate and worsen during the day. The disease fluctuates over weeks or months and severe exacerbations ("myasthenic crisis") can occur (Fig. 10.2).

10.1.4 Signs

Extraocular muscle weakness and ptosis are often asymmetrical and fluctuating. Speech may become nasal during prolonged talking and swallowing may be impaired. Neck extensor weakness is rare. When breathing is impaired, it gets worse in supine position. In the extremities, weakness and fatigability usually affect proximal muscles.

Myasthenia was previously classified according to Osserman, but recently the MGFA classification has been established (Tables 10.1 and 10.2). The Besinger score is useful to assess severity of MG.

MuSK-Ab-positive MG tends to present with bulbar and respiratory symptoms and signs, and myasthenic crises are frequent. MuSK-positive patients can develop facial myopathy and tongue atrophy, which can be seen on MRI (Figs. 10.3 and 10.4).

10.1.5 Myasthenic Crisis

Severe impairment of respiration, bulbar functions and severe generalised weakness; mechanical ventilation is frequently necessary.

Myasthenic crises can be triggered by various drugs (see drug-induced MG) and infections; it affects 10–15 % of patients during the course of their disease. MG crises are more frequent in MuSK-Ab-positive MG.

10.1.6 Causes

MG is an autoimmune disease. Approximately 80 % of patients with generalised and 50 % with ocular MG have

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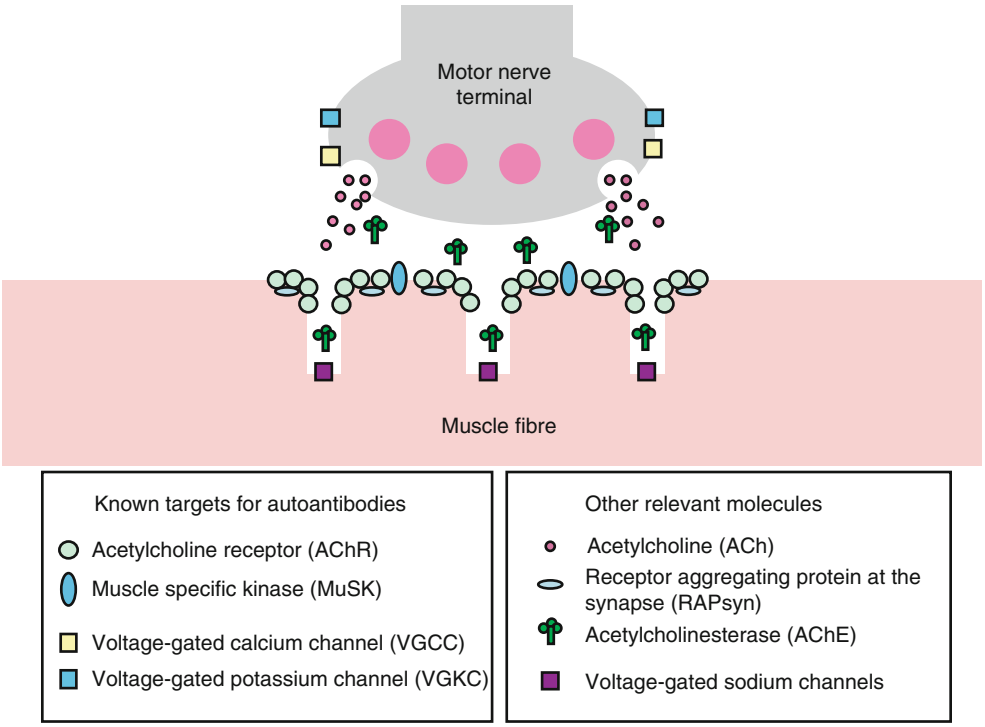

Fig. 10.1 Schematic representation of neuromuscular junction membrane proteins and structures relevant to the pathophysiology of NMT disorders (With permission from Vincent 2006)

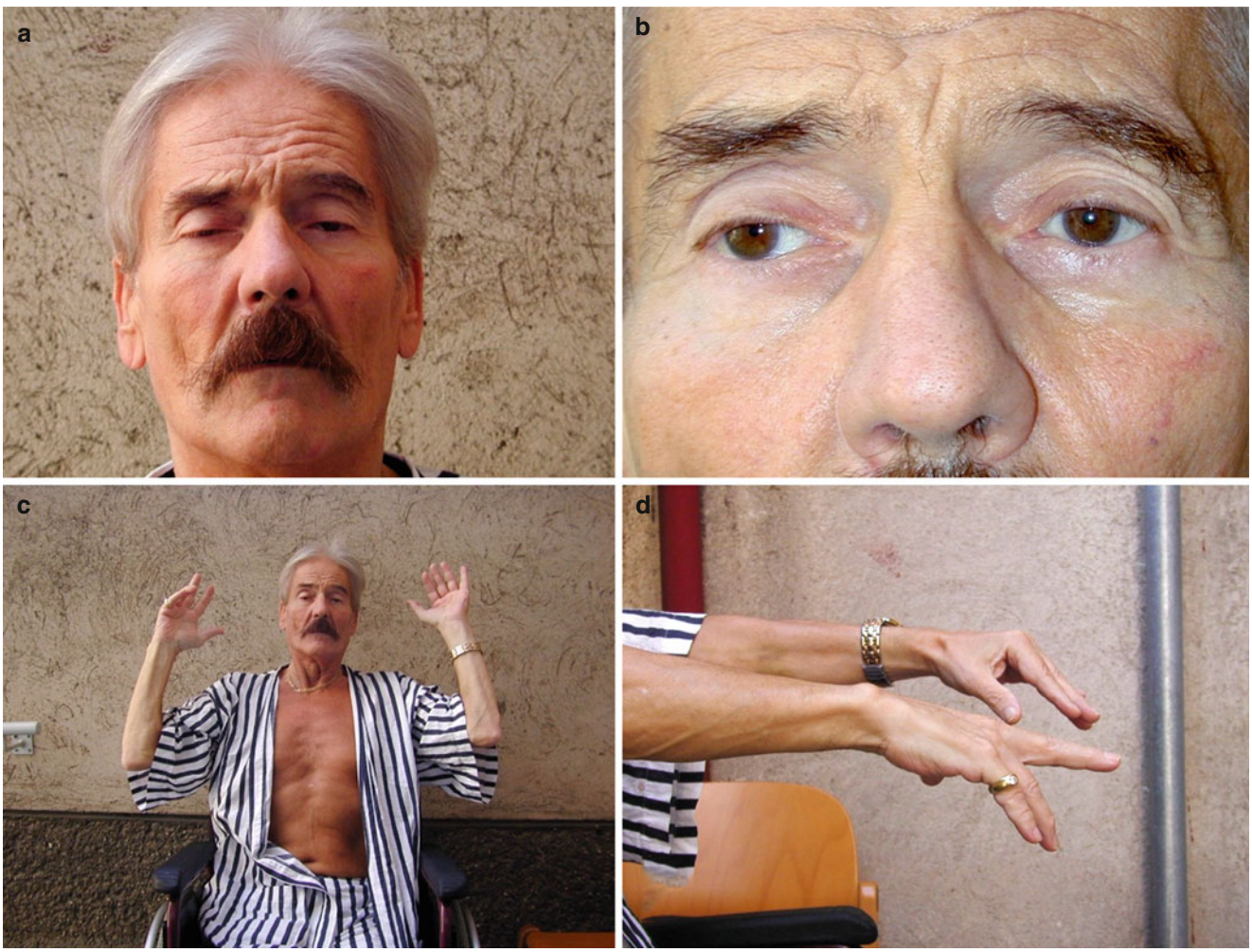

Fig. 10.2 Generalised myasthenia gravis. (**a**) Bilateral ptosis. (**b**) Attempted gaze to the right. Only right eye abducts partially. (**c**) Proximal weakness upon raising the arms. (**d**) Holding the arms and fingers extended, the extensor muscles weaken and finger drop occurs

Table 10.1 Classification of MG according to the Myasthenia Gravis Foundation of America (MGFA)

Class I	Any ocular muscle weakness; may have weakness of eye closure, all other muscle strength is normal
Class II	Mild weakness affecting other than ocular muscles; may also have ocular muscle weakness of any severity
IIa	Predominantly affecting the limb, axial muscles or both; may also have lesser involvement of oropharyngeal muscles
IIb	Predominantly affecting oropharyngeal and respiratory muscles or both; may also have lesser or equal involvement of the limb, axial muscles or both
Class III	Moderate weakness affecting other than ocular muscles; may also have ocular muscle weakness of any severity
IIIa	Predominantly affecting the limb, axial muscles or both; may also have lesser involvement of oropharyngeal muscles
IIIb	Predominantly affecting oropharyngeal and respiratory muscles or both; may also have lesser or equal involvement of the limb, axial muscles, or both
Class IV	Severe weakness affecting other than ocular muscles; may also have ocular muscle weakness of any severity
IVa	Predominantly affecting the limb, axial muscles or both; may also have lesser involvement of oropharyngeal muscles
IVb	Predominantly affecting oropharyngeal and respiratory muscles or both; may also have lesser or equal involvement of the limb, axial muscles or both
Class V	Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb

Table 10.2 Subtypes of myasthenia

	Percentage of MG	Age	AchR-Ab	MuSK-Ab	Thymus	Gender M:F	Clinical features
Early onset	20–25	<40	~85 %	Negative	Hyperplastic in ~80 %	1:3	Ocular and generalised
Late onset	30–40	>40	~60 %	Negative	Atrophy	3:2	Ocular and generalised
MuSK	5–8	<40 (70)	Negative	100 %	Normal or atrophy	1:3	Ocular, facial, bulbar and respiratory; facial myopathy and tongue atrophy can develop
Seronegative	5–10	Variable	Negative; low-affinity Ab to clustered AchR in ~60 %	Negative	Occasionally hyperplastic	1:2	Ocular and generalised
Ocular	15–25	Variable	~50 %	Rarely	Rarely hyperplastic	3:2	Ocular
Distal	3–7	Variable	~70 %	Negative	Not known	3:2	Similar to peripheral palsy
Thymoma-MG	10–15	40–60, but variable	~95 %	Negative	Thymoma, thymus carcinoma	1:1	Ocular and generalised
Neonatal	10–20 of infants of MG mothers	Neonate	~90 %	Rarely	Normal	1:1	Due to transfer of maternal Ab; transient respiratory and feeding difficulties; hypotonia

antibodies against AchR. MuSK-Abs are found in 5–8 % of patients with generalised MG. In the remaining "seronegative" patients, low-affinity antibodies against clustered AchR have been found in 66 %. Recently, antibodies to lipoprotein-related protein 4 (LRP4) have been detected in some AchR- and MuSK-Ab negative patients.

Antibodies against AchR can block the receptor but mainly cause a complement-mediated lysis and increased internalisation and degradation of AchR. The antigen is expressed on thymic myoid cells, and especially in younger patients, thymic hyperplasia is found. Thymomas are found in approximately 10 % of patients with MG.

In MuSK-Ab MG, compliment activation and AchR loss are absent, but these antibodies appear to cause muscle atrophy. The thymus is usually normal in MuSK-Ab-positive MG.

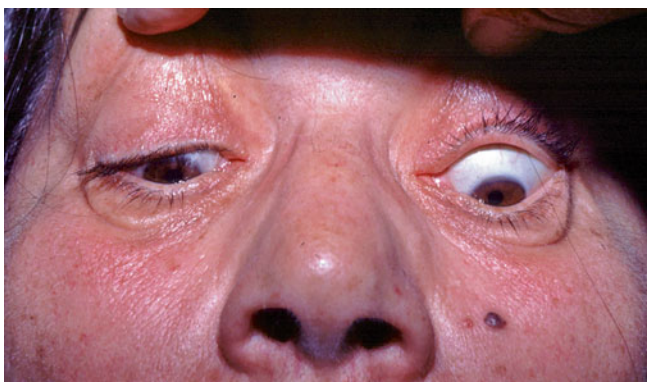

Fig. 10.3 Ptosis and oculomotor function in myasthenia. Uni- and often bilateral ptosis occur. The eye movements are often severely affected. In this case, the downward gaze is reduced on the right

10.1.7 Electrophysiology

Routine motor and sensory NCS and EMG are normal in MG.

A decremental response in response to low-frequency repetitive nerve stimulation (RNS) can be found. Facial (orbicularis oculi, nasalis or mentalis) or proximal (trapezius, deltoid) muscles give the best diagnostic yield. A decremental response is found in 50–70 % in generalised and in 18–50 % in ocular MG. However, RNS is often normal in MuSK-Ab-positive MG (Fig. 10.5).

Single-fibre EMG shows abnormal jitter in the frontalis muscle in 85–90 % of patients with ocular MG. Treatment with acetylcholinesterase inhibitors can result in false-negative test results.

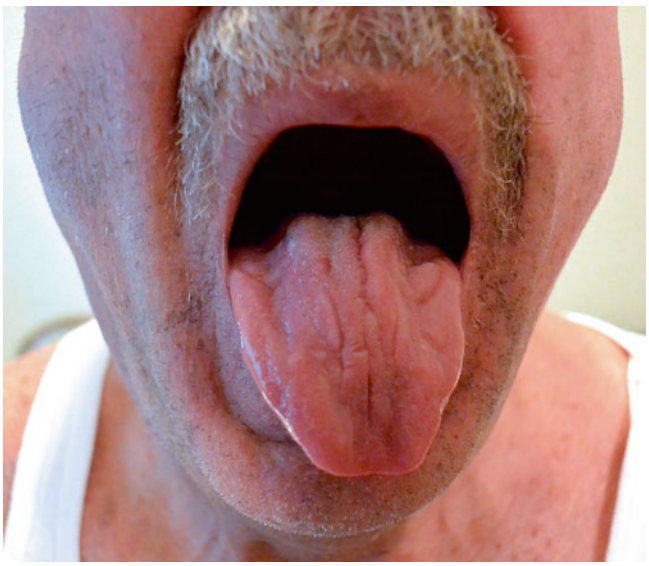

Fig. 10.4 Triple furrowed tongue: this patient suffered about 20 years from MG. Despite modern and intensive treatment, the bulbar symptoms were never completely controlled. The tongue shows the "tripled furrowed tongue" atrophy

10.1.8 Imaging (MR, CT Scan)

Chest imaging studies (MRI or CT) are obligatory to detect a hyperplastic thymus, thymoma or thymus carcinoma.

10.1.9 Laboratory

AchR-Ab should be tested first; when negative, MuSK-Ab and then LRP4-Ab should be sought. Antibodies against titin suggest a thymoma only in young but not in older patients. Antibodies against the ryanodine receptor can be found in MG with thymoma. Antibodies against the striated muscle are frequently found in adult MG, more often with thymoma.

Other autoantibodies occur in increased frequency in MG: antinuclear antibodies (20–40 %), antithyroid antibodies (10–20 %), anti-parietal cell antibodies (10–20 %), smooth muscle antibodies (5–10 %), Coombs antibodies (10 %),

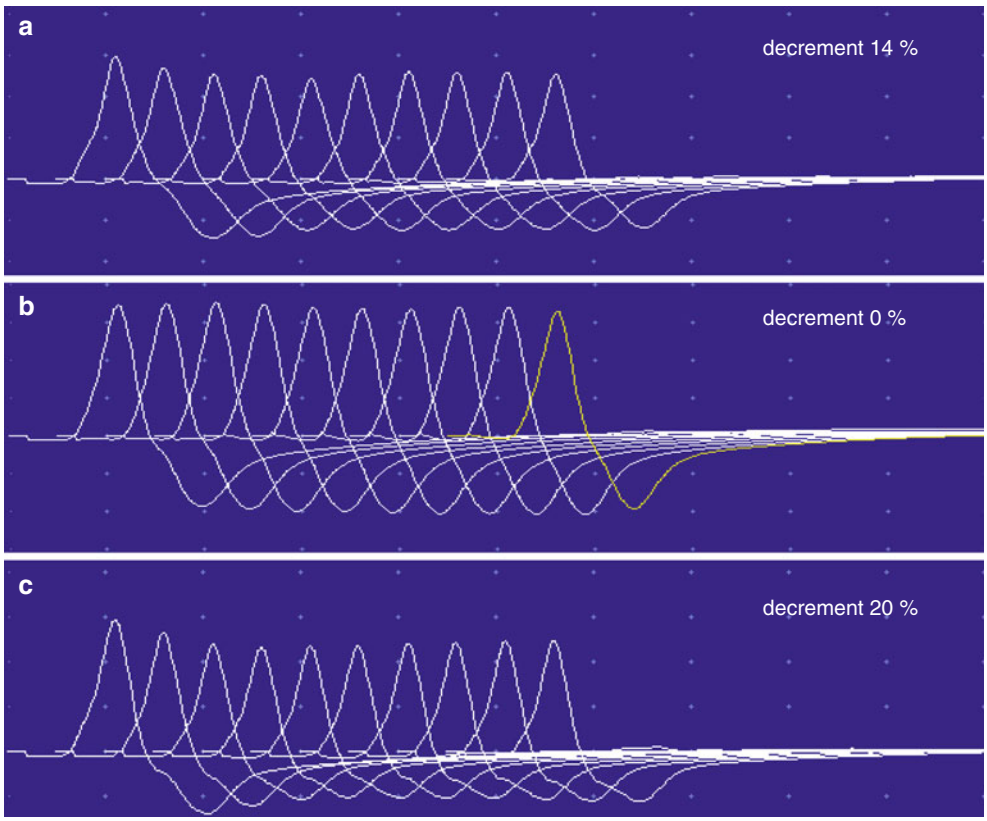

Fig. 10.5 *Top:* repetitive 3 Hz stimulation (stimulation accessory nerve, electrodes placed on the trapezoid muscle) shows decrement. (**a**) Stimulation at rest and (**b**) stimulation after 1 min voluntary contraction and (**c**) after 2 min

Fig. 10.6 Ice (pack) test. The ice pack test is a useful bedside test. (**a**) Patient with ptosis on the right. (**b**) A pack with ice is applied to one eye, usually 2 min is suggested. (**c**) Positive test with remission of ptosis. The effect is based on the fact that acetylcholinesterase activity is inhibited below 29 C

rheumatoid factor (10–40 %) and antilymphocyte (40–80 %) and antiplatelet (5–50 %) antibodies.

10.1.10 Diagnosis

Typical symptoms and signs, electrophysiological tests and antibody tests. Additional diagnostic tests are as follows:

Edrophonium (Tensilon) Test The short-acting acetylcholinesterase inhibitor is given intravenously, and changes of obvious clinical signs such as ptosis, extraocular muscle weakness or nasal speech are noted. In AchR-Ab and seronegative MG, the test is positive in 90–95 %, but it is frequently negative in MuSK MG. The test must not be performed in patients with asthma, AV block or arrhythmias.

Sleep and Rest Test In patients with ptosis, a period of 30 min sleep or 2 min rest with closed eyes can temporarily improve ptosis.

Ice Test In patients with ptosis, a 1–2 min application of an ice bag can improve ptosis (Fig. 10.6). Sleep and ice test are very sensitive and specific for MG.

10.1.11 Differential Diagnosis

Oculopharyngeal muscular dystrophy, progressive external ophthalmoplegia and other mitochondrial myopathies, Lambert-Eaton myasthenic syndrome, motor neuron disease, thyroid eye disease, ocular myositis, psychogenic, congenital myasthenic syndromes, botulism.

10.1.12 Medication and Myasthenia

Several drugs can worsen symptoms of pre-existing MG. Symptoms develop over hours or days and quickly improve after drug withdrawal. Frequently used drugs that can worsen MG are antibiotics and intravenous magnesium. A list of potentially dangerous drugs can be found at https://www.mga-charity.org/web/guest/drugs-which-may-aggravate-mg. High doses of steroids can temporarily worsen MG after 2–7 days.

D-Penicillamine can induce immune-mediated MG, usually of slow onset.

10.1.13 Therapy

Pyridostigmine as symptomatic treatment. Daily doses are 60 mg 3–6 times a day. More than 400 mg/day may lead to cholinergic crisis. Side effects include diarrhoea and muscle cramps.

A delayed release formulation (180 mg) is also available; the daily maximal dose is 4 × 180 mg.

Immunosuppression is necessary in generalised MG. In ocular MG, monotherapy with pyridostigmine can be initiated, but frequently immunosuppression is necessary to achieve symptom control. Some evidence exists that early steroid treatment reduces the risk for generalisation in ocular MG.

Steroids are first-line immunosuppressants. Prednisone, prednisolone and methylprednisolone are used and result in clinical remission in 70–80 % within 4–8 weeks.

Maximum dose is 1–1.5 mg/kg (60–80 mg) prednisone equivalent. Steroid treatment can result in temporary worsening after 2–7 days, especially in patients with bulbar signs.

Alternatively, treatment can be started with 10–20 mg/day and increased 5 mg/week until remission is achieved. This treatment regimen is usually safe in outpatients and also sufficient in ocular or mild generalised cases.

After remission, steroids are slowly tapered; a switch to an alternate day schedule is recommended.

Severity and number of side effects increase with treatment duration and cumulative dose and include weight gain, hyperglycaemia, osteopenia, cataracts and gastric and duodenal ulcers. When long-term treatment with

>7.5 mg prednisone equivalent is expected, prophylaxis with calcium (1,000–1,500 mg/day) and vitamin D (400–800 IE/day) should be started. In postmenopausal woman, bisphosphonates are approved to treat steroid-induced osteoporosis.

When long-term steroid treatment is necessary or remission is incomplete, additional immunosuppression is used.

Azathioprine is a steroid-sparing drug, but an effect is not seen before 6–12 months.

The daily dose is 2.5 mg/kg; when effective, the dose can be reduced to 1 mg/kg. After prolonged periods of steroid-free complete remission, azathioprine can be stopped. Relapses are possible.

Monitor WBC, RBC and liver function. In most responders, MCV increases with treatment.

Side effects include flu-like reactions, arthralgia, rarely severe bone marrow suppression, opportunistic infections and lymphoma. The risk for malignancies is increased.

If allopurinol is taken concomitantly, reduce azathioprine dose to 25 % to avoid severe adverse events.

Methotrexate can also be used. The dose is 7.5–25 mg once weekly. Before treatment, a chest X-ray is necessary and regular monitoring of WBC, RBC and renal and liver function during treatment.

Side effects include nausea, vomiting, oral ulcerations, itching, exanthema, rarely severe bone marrow suppression, opportunistic infections and lymphoma.

Methotrexate must not be used without birth control in men and women. Strict birth control has to be maintained for 6 additional months after termination of treatment.

Ciclosporin A and *tacrolimus* have been effective in smaller studies. Ciclosporin is given at a daily dose of 2.5 mg/kg (maximum 3–4 mg/kg/day) and tacrolimus at 3–5 mg/day. Side effects include tremor, hirsutism, headache, anaemia, hypertension, renal insufficiency and increased risk of malignancies.

Cyclophosphamide has been used to treat single cases. Haemorrhagic cystitis may complicate treatment.

Mycophenolate mofetil was not superior to placebo in two RCT. However, MMF seems to be beneficial in MuSK-positive MG when standard treatment does not work. The daily dose is 1 g b.i.d.

Rituximab can be used in patients who do not respond to standard treatment, especially in MuSK-positive MG. Typically, 1,000 mg rituximab i.v. is given twice with 2 weeks between treatments. Further treatments are based on B-cell count and clinical symptoms. Serious side effects are rare, but some cases with progressive multifocal leukoencephalopathy have been reported.

Thymectomy is recommended in patients with AchR-Ab-positive or seronegative bulbar or generalised MG between the age of 15 and 50 years. When performed within 2 years of disease onset, it doubles the likelihood of complete remission. Transsternal thymectomy has been recommended as treatment of choice, but robot-assisted thymectomy seems as effective and better tolerated.

At present, thymectomy is not recommended in MuSK-positive MG.

Treatment of Myasthenic Crisis Standard ICU treatment and care is mandatory. Disease-specific treatments of equal efficacy are plasma exchange, immunoadsorption and intravenous immunoglobulin. The number of plasma exchanges or immunoadsorptions depends on the individual response; 3–8 treatments are usually necessary. Treatments every other day seem to be as effective as daily treatments. A singe course of IVIG at 1 g/kg/day is sufficient.

10.1.14 Myasthenia and Pregnancy

Pregnancy has no predictable effect on MG; symptoms can worsen, improve or remain unchanged. If worsening occurs, this is more likely during the first trimester or the first month postpartum.

Men and women of childbearing age should avoid immunosuppressant treatment when possible. Of the common drugs used, only methotrexate is associated with a high risk for fetal malformations and therefore must not be used in both men and women of childbearing age.

During pregnancy, methotrexate should be avoided. Other immunosuppressive drugs have a potential risk for fetal development, but when necessary, potential benefits outweigh the risk (classes C and D; FDA classification). If patients who are treated with immunosuppressants get pregnant, treatment with azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil and cyclophosphamide can be continued when necessary. Steroids, pyridostigmine, IVIG and plasma exchange are safe in pregnancy.

Vaginal delivery is usually safe, and Caesarean section should be reserved for obstetric indications. The frequency of obstetric complications, e.g. premature amniorrhexis, is only marginally increased.

Breastfeeding is safe in patients treated with pyridostigmine or steroids, although it is recommended to postpone breastfeeding for 4 h after steroid intake. High doses of acetylcholinesterase inhibitors may produce gastrointestinal disorders in the neonate.

Women with immunosuppression other than steroids should not breastfeed as immunosuppressants may also produce immunosuppression in the neonate.

Neonatal Myasthenia Approximately 10–20 % of infants born to myasthenic mothers develop transient weakness due to passive transfer of IgG antibodies across the placenta. Typical signs are weak cry, hypotonia and respiratory and feeding difficulties. Symptoms last a few weeks. Neonatal MG has been reported in a few neonates born to MuSK-Ab-positive mothers.

Congenital arthrogryposis has rarely been described when the transferred antibodies have a high affinity to the fetal acetylcholine receptor.

10.1.15 Prognosis

About two thirds of patients with ocular MG develop generalised MG within 2 years. Of the remainder, only 10–20 % progress to generalised MG. Mortality of MG has significantly dropped to 5 %. Clinical remission can be obtained in the majority of patients, but many patients depend on lifelong treatment. The probability for drug-free remission is higher in early-onset MG, especially after thymectomy.

10.2 Congenital Myasthenic Syndromes

Genetic testing	NCS/EMG	Laboratory	Imaging	Biopsy
++	+	–	–	+

Congenital myasthenic syndromes are genetic disorders of the neuromuscular junction. Inheritance is recessive in most cases, but dominant forms do occur. Congenital myasthenic syndromes are classified by the site of the neuromuscular junction at which the defect occurs. Mutations in various genes have been described in about a third of the patients (Table 10.3).

Congenital myasthenic syndromes present in infancy or early childhood, but later manifestations are possible. It should be suspected in infants and children with hypotonia, underdeveloped muscles and unexplained weakness, weakness affecting cranial nerves and repeated episodes of respiratory insufficiency and episodic apnoeas. Some congenital myasthenic syndromes also cause myopathy and facial deformities. Autoantibodies are not present, but a decremental response is frequently seen with low-frequency repetitive stimulation. After-discharges are seen in slow-channel syndromes.

10.3 Lambert-Eaton Myasthenic Syndrome (LEMS)

Genetic testing	NCS/EMG	Laboratory	Imaging	Biopsy
–	++	++	++	–

10.3.1 Epidemiology

LEMS is rare. It usually occurs in midlife and is associated with small cell lung cancer in 50–60 % of patients; other malignancies are rare. One to three percent of patients with SCLC have LEMS.

10.3.2 Anatomy and Pathophysiology

Antibodies to the presynaptic P/Q-type voltage-gated calcium channel (VGCC) impair calcium influx, which reduces the number of acetylcholine vesicles released per action potential. Antibodies to the N-type VGCC can also be found, but their contribution to the clinical symptoms probably is small.

Table 10.3 Congenital myasthenic syndromes

Presynaptic defects	Defect in choline acetyltransferase
	Paucity of synaptic vesicles and reduced quantal release
	Congenital Lambert-Eaton-like syndrome
	Reduced quantal Ach release
Synaptic basal lamina defects	Endplate acetylcholinesterase deficiency
	β2 (LAMB2) deficiency
Postsynaptic defects	Primary AchR deficiency with or without kinetic abnormalities
	Reduced expression due to mutations in AchR α, β, δ and e subunits
	Reduced expression due to rapsyn mutations
	Reduced expression due to plectin deficiency
	Primary AchR kinetic abnormality with or without deficiency
	Slow-channel syndrome
	Fast-channel syndrome
	Sodium channel congenital myasthenic syndrome
	Agrin mutations
	MuSK mutations
Presynaptic and postsynaptic defects	Centronuclear myopathies
	Familial limb-girdle myasthenia – Dok-7 mutations
	Familial limb-girdle myasthenia with tubular aggregates – GFPT1mutations

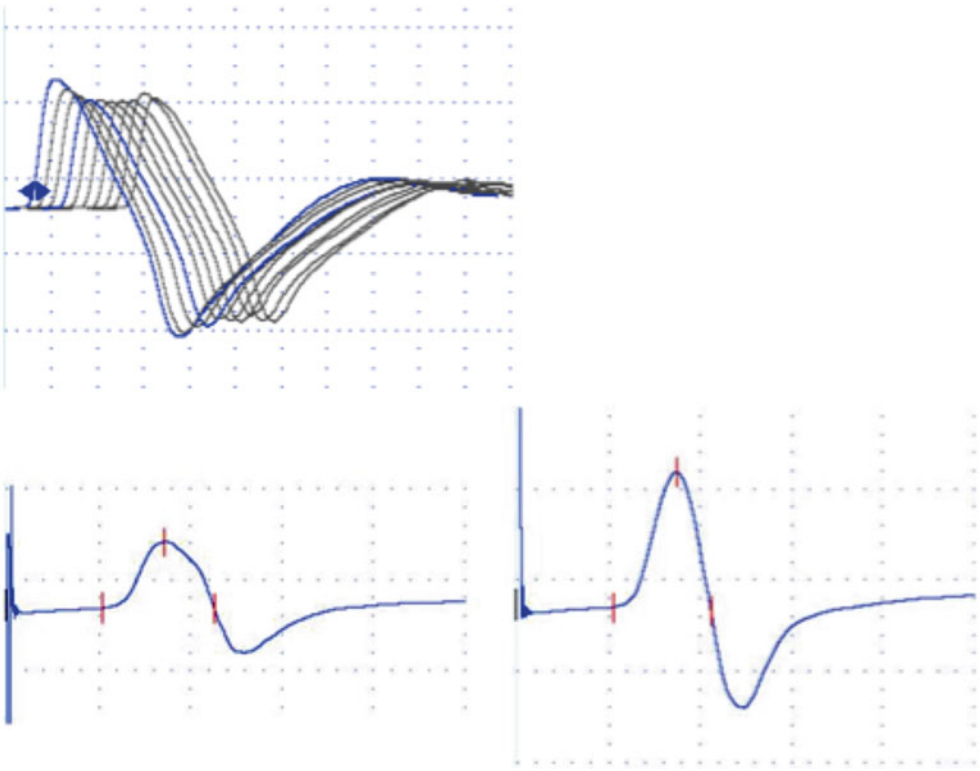

Fig. 10.7 (**a**) *Top:* decremental response in the abductor digiti minimi muscle after 3 Hz repetitive stimulation of the ulnar nerve. (**b**) *Bottom:* responses to single stimulation of the ulnar nerve at the wrist recorded from the abductor digiti minimi muscle. *Left:* CMAP at rest. *Right:* CMAP immediately after a 10 s maximum voluntary contraction

10.3.3 Symptoms

Proximal leg and arm weakness; distal muscles can also be affected but bulbar and ocular signs are rare and mild. Symptoms of autonomic dysfunction, e.g. dry mouth and eyes, impotence, constipation, impaired sweating and orthostatic hypotension, are frequent. LEMS may precede cancer detection by several years.

10.3.4 Signs

Proximal weakness and diminished or absent tendon reflexes. Following a brief sustained exercise of 10 s, strength may improve and tendon reflexes may reappear. Orthostatic hypotension can be detected bedside with the Schellong test. Some patients show signs of cerebellar dysfunction, and anti-Hu-Ab can also be found in these patients.

10.3.5 Causes

LEMS is caused by antibodies against the P/Q-type VGCC in approximately 85 % of patients. It is a paraneoplastic disorder in about 50 %, mostly associated with SCLC. In non-tumour LEMS, there is a strong association with HLA-B8, a female preponderance, and approximately 25 % of these patients have autoimmune disorders such as thyroid disease, pernicious anaemia, celiac disease and vitiligo.

10.3.6 Electrophysiology

Routine NCS show low-amplitude CMAP. Sensory NCS and EMG are usually normal.

Repetitive low-frequency nerve stimulation results in a decremental response similar to MG. The diagnostic yield of stimulation of distal nerve-muscle pairs is higher. High-frequency stimulation of >20 Hz results in an increase of CMAP amplitude. Alternatively, a single stimulation should be performed before and after a 10 s maximum voluntary contraction. A postexercise amplitude increase of >60 % is diagnostic. Acetylcholinesterase inhibitors should be withheld 12 h prior to testing (Fig. 10.7).

10.3.7 Imaging

CT of the thorax is mandatory in patients with LEMS; when the CT scan is normal, bronchoscopy and PET are optional in selected cases. If no tumour is found, follow-up with CT scans should be performed every 6 months for at least 4 years.

10.3.8 Laboratory

Antibodies to the P/Q-type VGCC are found in approximately 85 %. The antibody titre does not correlate with disease severity or tumour presence.

SOX1-antibodies have been found in paraneoplastic but not in non-tumour LEMS.

Anti-Hu antibodies have been found in LEMS in combination with a paraneoplastic cerebellar syndrome.

10.3.9 Diagnosis

Typical symptoms and signs, the characteristic electrophysiological findings and antibody tests.

10.3.10 Differential Diagnosis

Myasthenia gravis, other neuromuscular transmission disorders, myopathy, polyneuropathy.

10.3.11 Therapy

Treatment of the tumour also improves LEMS in SCLC. Symptomatic treatment includes 3–4 diaminopyridine up to 20 mg t.i.d. Side effects are paraesthesias and rarely seizures. Pyridostigmine can improve weakness in some patients.

Immunosuppressive treatments should be considered (steroids, azathioprine, rituximab, plasma exchange and immunoglobulin) if other treatment fails.

10.3.12 Prognosis

In paraneoplastic LEMS, the prognosis depends on the disease-causing neoplasm, but remission may occur after successful cancer treatment.

In non-tumour LEMS, sustained treatment usually is necessary, but life expectancy is not shortened.

10.4 Botulism

Genetic testing	NCS/EMG	Laboratory	Imaging	Biopsy
–	++	+	–	–

10.4.1 Epidemiology

Botulism is rare, with an average of 145 cases per year in the USA. Sixty five percent of these cases are infantile botulism, 15 % food-borne and 20 % wound botulism.

10.4.2 Anatomy and Pathophysiology

Botulinum toxin is produced by the gram-positive anaerobic spore-forming bacillus *Clostridium botulinum*. Several strains exist (A–G) and produce immunologically distinct toxins with the same mode of action. The toxins cleave SNARE proteins, which are necessary for the release of presynaptic acetylcholine vesicles. As a consequence, the number of Ach vesicles released per action potential is reduced and a presynaptic neurotransmission disorder and autonomic symptoms develop. The incubation period is 12–36 h.

10.4.3 Symptoms

Diffused weakness of proximal, extraocular and bulbar muscles, including altered speech, difficulties swallowing and double vision. The weakness typically is of a descending pattern. Photophobia, nausea, constipation or diarrhoea and symptoms of postural hypotension occur.

10.4.4 Signs

Bilateral symmetric ptosis, extraocular muscle weakness with fixed dilated pupils, facial weakness and progressive bulbar weakness. Dysarthria and dysphagia, proximal weakness and respiratory insufficiency develop. Tendon reflexes are absent.

Signs of autonomic failure include fixed dilated pupils, hypohidrosis and hypotension, alterations in resting heart rate and urinary retention. Ileus may develop.

10.4.5 Causes

Botulinum toxin is produced by gram-positive anaerobic spore-forming bacilli. Four forms of botulism exist, classified according to the mode of exposure (Table 10.4)

10.4.6 Electrophysiology

Routine motor NCS show low-amplitude CMAP in affected muscles. Sensory NCS and EMG are normal.

Repetitive low-frequency nerve stimulation results in a decremental response similar to MG in some patients. High-frequency stimulation of >20 Hz results in an increase of CMAP amplitude. Single stimulations performed before and after a 10 s maximum voluntary contraction show postexercise facilitation. These abnormal responses are only found in some muscles.

Table 10.4 Types of botulism

Food-borne	Caused by ingestion of food contaminated with toxin, mostly home-preserved food
Neonatal	Ingestion of organism by infants <6 months of age. The spores proliferate and produce the toxin which causes weak crying, feeding difficulties and limb weakness. Autonomic symptoms and signs occur
Wound	Wound infection with *C. botulinum*. Also seen in drug users who use "skin-popping" to administer heroin
Iatrogenic	After treatment with botulinum toxin

10.4.7 Imaging

None.

10.4.8 Laboratory

Detection of the toxin in serum, stool, food or anaerobic samples from wounds by ELISA has largely replaced the mouse inoculation test. Samples should be taken as early as possible.

10.4.9 Diagnosis

Typical symptoms and signs and electrophysiological findings; other affected family members in food-borne botulism. Toxin detection tests are frequently negative when samples are taken >2 days after toxin ingestion.

10.4.10 Differential Diagnosis

GBS (ascending paralysis), Miller Fisher syndrome, myasthenia gravis, tick paralysis.

10.4.11 Therapy

Supportive ICU care is the mainstay of treatment. A heptavalent botulinum antitoxin is available and should be administered as early as possible. Surgical debridement and antibiotics in wound botulism. For treatment of neonatal botulism, a human botulism immune globulin is available.

10.4.12 Prognosis

Supportive intensive care treatment has decreased mortality to 3–5 %. Recovery from weakness, shortness of breath and fatigability may require 1 year or more.

10.5 Neuromyotonia (Isaacs' Syndrome)

Genetic testing	NCS/EMG	Laboratory	Imaging	Biopsy
–	++	++	++	–

10.5.1 Epidemiology

Neuromyotonia is rare. The cramp-fasciculation syndrome is described as a *forme fruste* of neuromyotonia. Both are within the spectrum of peripheral nerve hyperexcitability syndromes.

10.5.2 Anatomy and Pathophysiology

Antibodies to voltage-gated potassium channels (VGKC) in one third. These antibodies do not directly bind to the VGKC but to proteins associated with the VGKC (LGI1 and CASPR2). The exact mode of action is debated.

10.5.3 Symptoms

Muscle twitching, cramps and muscle stiffness. Distal muscles are usually more affected; trunk, pharynx, tongue and face can also be involved. Excessive sweating is frequent. The combination of these symptoms with severe autonomic dysfunction, disordered sleep and behavioural changes has been termed Morvan's syndrome.

10.5.4 Signs

Muscle twitching, myokymia and muscle hypertrophy; muscle relaxation is delayed, weakness is rare and tendon reflexes are normal or decreased.

10.5.5 Causes

Neuromyotonia is an autoimmune disorder with antibodies to VGKC in about one third of cases. A paraneoplastic form has been described in association with lung and thymus neoplasms and Hodgkin's lymphoma. Neuromyotonia can precede the tumour be several years. Neuromyotonia is also seen in patients taking D-penicillamine.

10.5.6 Electrophysiology

Routine motor and sensory NCS are normal, but repetitive F waves can be observed in cramp-fasciculation

syndrome. Needle EMG shows fasciculations, doublets, triplets or multiplets and high-frequency (up to 300 Hz) neuromyotonic discharges. Motor unit action potentials are normal.

10.5.7 Imaging

Thorax CT is mandatory and PET scan is optional in selected cases. If no tumour is found, follow-up with CT scans should be performed every 6 months for at least 4 years.

10.5.8 Laboratory

VGKC-Abs are found in about one third; AchR-Ab can also be found.

10.5.9 Diagnosis

Typical symptoms and signs and electrophysiological findings. Antibody tests are only positive in some patients.

10.5.10 Differential Diagnosis

Polyneuropathies, focal myokymia or neuromyotonia in multifocal motoneuropathy and radiation injury to nerves/plexus, motor neuron disease.

10.5.11 Therapy

Immunosuppressive treatments (plasma exchange, intravenous immunoglobulin and steroids) can be used, but plasma exchange seems to be more efficient. Rituximab has been used occasionally.

Symptomatic treatment with sodium channel-blocking agents (carbamazepine, phenytoin or mexiletine) usually is successful.

10.5.12 Prognosis

In paraneoplastic neuromyotonia, the prognosis depends on the related neoplasm, but improvement may occur with successful cancer treatment.

In non-tumour neuromyotonia, sustained treatment usually is necessary, but life expectancy is not shortened.

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Muscle and Myotonic Diseases

11

James W. Russell, M.D. Weiss, B.J. Distad, and R.J. Castellani

11.1 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.

11.1.1 Electrophysiology

The basis of the motor system is the motor unit, which consists of the anterior horn cell, axon, muscle membrane, and muscle fiber, and is the final common pathway leading to activation of the muscle. 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. 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. 11.1). 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 dependent on the length and the number of cross bridges between the filaments. Electrodiagnosis is useful in diagnosing the myopathies. Firstly, it helps distinguish between primarily myopathic and 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.

11.1.2 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 specific immunohistochemical studies are needed to make an accurate diagnosis. Biochemical tests may reveal significant enzyme abnormalities that would

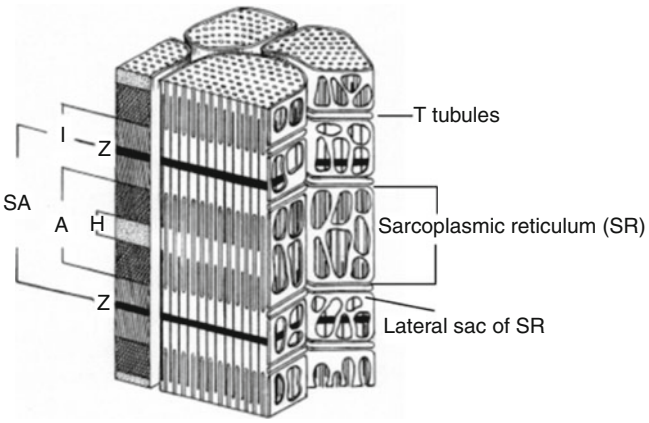

Fig. 11.1 Human skeletal muscle showing the gross and microscopic structure. The sarcoplasmic reticulum (*SR*) is an intracellular membrane system. The *T* tubules are invaginations of the sarcolemma and communicate with the extracellular space. Ultrastructurally, several components of the muscle can 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

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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 is often 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.

11.1.3 Regulation of Gene Defects in Muscle

Characterizing the molecular genetics of muscle has become increasingly important in understanding the pathogenesis of myopathy. Considerable progress has been made since the first edition of this book in identifying new genetic mechanisms, in clarifying previously known genetic disorders, and in developing gene-related approaches to therapy. Most gene defects have been described in the following chapters and are extensively reviewed in the selected references for each section. Even the presence of a specific gene mutation may produce widely varying biochemical changes in the muscle due to the presence of gene-modifying effects. Unfortunately, the cost and often limited commercial availability of genetic studies have made it imperative that the clinician use consummate diagnostic skills to define the type and extent of testing. Thus, clinical judgment still remains very important in differentiating the various myopathies.

11.2 Polymyositis (PM) and Dermatomyositis (DM)

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

11.2.1 Distribution

Weakness generally involves neck flexor and proximal muscles symmetrically.

Time Course Progresses over months.

Age of Onset PM, typically fourth decade; DM, bimodal frequency at 5–15 and 45–65 years of age.

11.2.2 Clinical Syndrome

PM and DM are acquired inflammatory myopathies. Although muscle pain occurs in one-third of patients, it is seldom the chief complaint. Dysphagia and occasionally weakness of respiratory muscles may occur. Cardiac involvement is reflected most commonly in EKG changes and rarely in myocarditis or congestive heart failure. PM is more common in women (9:1). DM is more common than polymyositis in younger individuals and is equally common in men and women. Dermatologic abnormalities include erythema and telangiectasis over the face, with a violet (heliotrope) discoloration around the eyes, papular erythematous changes on the knuckles (Gottron's papules), dilated capillaries at the base of the fingernails (Kernig's sign), nail-fold capillary infarcts, and dry and cracked skin on the palms (mechanic's hands). Approximately 20 % of patients develop arthralgias, joint contractures, and systemic symptoms related to cardiac or pulmonary involvement. The risk of cancer is higher in DM, up to 25 %, vs fewer than 5 % in PM (Figs. 11.2 and 11.3).

11.2.3 Pathogenesis

In PM, a cell-mediated response against muscle fibers is likely. Endomysial inflammatory cells, mainly CD8+ T cells and macrophages, invade non-necrotic muscle fibers. Major histocompatibility complex antigen-1 (MHC-1) is expressed on many muscle fibers, even those distant from the inflammatory cell infiltrate. Perifascicular atrophy and muscle infarcts are seen on histological studies in DM, with perivascular and perimysial inflammatory distribution. Microvasculature is the possible target of this humorally mediated process. Pathologically, DM is, in part, a microangiopathy. Early findings on muscle biopsy demonstrate deposits of membrane attack complex (MAC) on endomysial capillaries and a reduction in capillary density.

11.2.4 Diagnosis

Creatine kinase (CK) is elevated, at least 5–10 times normal, along with increased alanine transaminase (ALT) and aspartate transaminase (AST). Elevated serum levels of gamma-glutamyl transpeptidase (GGT) suggest concurrent liver damage. Muscle-specific autoantibodies may be present, especially anti-aminoacyl-tRNA synthetases. The most common of these, anti-Jo1, is present in 25–30 % of patients, while multiple other antibodies have been described, but in fewer than 5 % of individuals. Mi-2 is found in approximately 20 % of patients with DM. Electromyography demonstrates positive sharp waves and fibrillation potentials, in addition to early recruitment of small-amplitude, short-duration, polyphasic motor unit action potentials. Nerve conduction studies are usually normal. Sites of active inflammation show increased T2 signal and enhancement with gadolinium on MRI. In chronic disease the muscle may be replaced by fat and show atrophy. Muscle biopsy demonstrates variability in fiber size – small to hypertrophied – increased central nuclei, in addition to areas of inflammation.

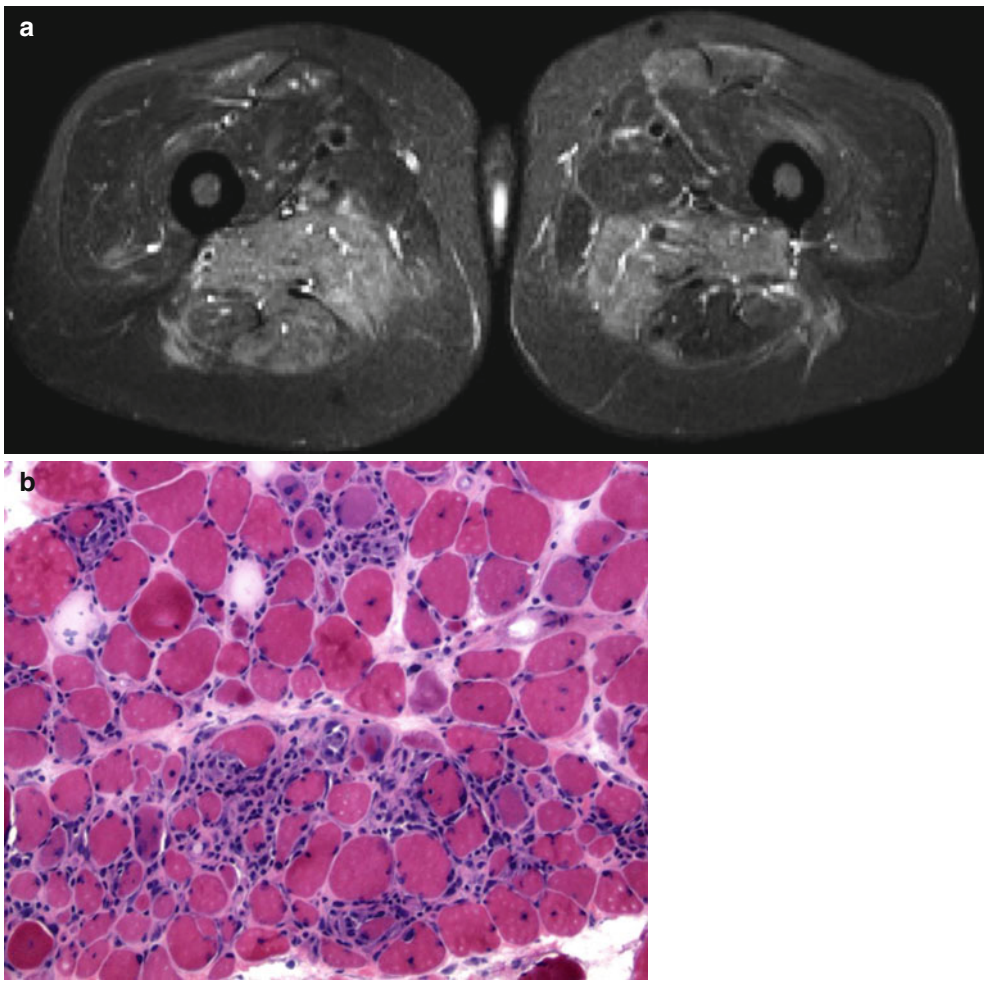

Fig. 11.2 (**a**) MRI – abnormal high T2 signal in the hamstring muscles in the posterior compartment of the thigh bilaterally, which is fairly symmetric. (**b**) Polymyositis showing inflammatory infiltration of muscle fibers

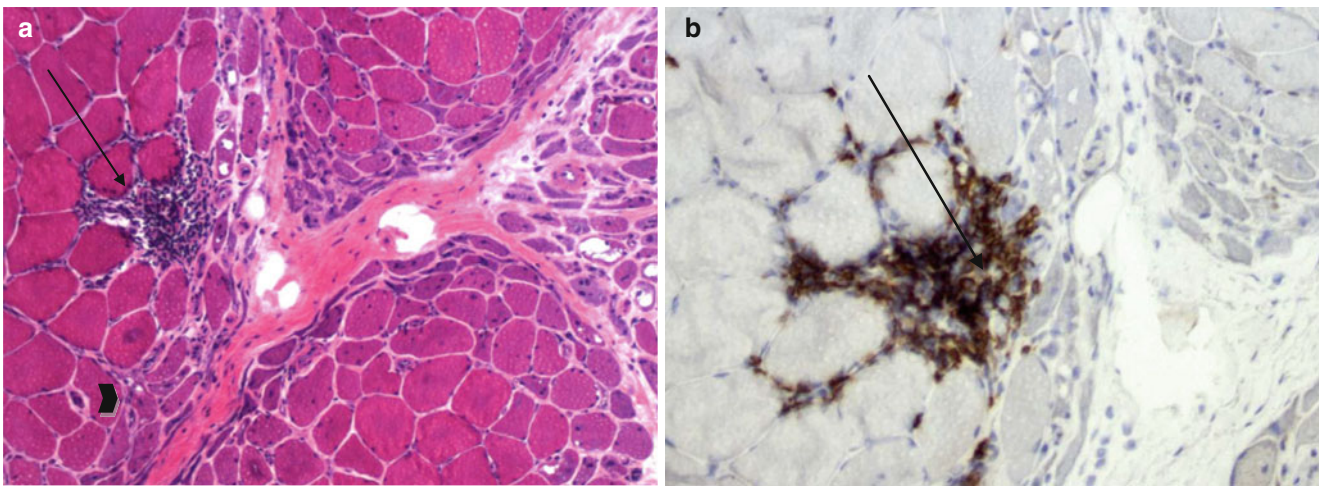

Fig. 11.3 Dermatomyositis. (**a**) Typical perifascicular atrophy (*arrowhead*) and perivascular inflammation (*arrow*), (**b**) CD20 (B-cell) immunostaining in perivascular infiltrate (*arrow*)

11.2.5 Differential Diagnosis

Toxic, endocrine, or metabolic myopathy, muscular dystrophy, inclusion body myositis, neuromuscular junction disorders, polymyalgia rheumatica.

11.2.6 Therapy

Treatment is usually initiated with prednisone, 1 mg/kg daily, up to a maximum of 100 mg/day. If no improvement after 4–6 months of prednisone, a second-line agent is

added (usually methotrexate, azathioprine, or mycophenolate mofetil). Begin methotrexate orally at 7.5 mg per week, and increase the dose by 2.5 mg each week up to 20 mg per week. Azathioprine can be initiated at 2–3 mg/kg per day, divided twice a day. Alternatively, mycophenolate mofetil can be initiated at 500–1500 mg twice daily. For refractory cases, intravenous or oral cyclophosphamide can be helpful. General management for patients on prednisone includes dietary counseling, eye evaluations for cataracts and glaucoma, supplemental vitamin D, elemental calcium 500 mg twice a day, a regular graded exercise program, strength testing, and regular monitoring of serum electrolytes and glucose. CK can be assessed periodically. Once the patient is stable or improved, the prednisone can be tapered by 10 % to an every other day dosage, at monthly intervals. The dose should be maintained or increased slightly, if the patient shows a decrease in strength.

11.2.7 Prognosis

This is generally good with most patients showing response to therapy. Individuals typically have a poorer prognosis in DM, with more treatment resistance and comorbidities.

11.3 Inclusion Body Myositis (IBM)

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

11.3.1 Distribution

Weakness involves quadriceps, forearm flexor, and foot extensor muscles.

Time Course Progresses over years.

Age of Onset Affects males greater than females typically in the sixth decade.

11.3.2 Clinical Description

IBM affects proximal and distal muscles in upper and lower extremities, with distal muscles affected predominantly in 20 %. Muscle weakness is more often asymmetric than in PM and DM. Dysphagia is seen in 30 % of patients. Deep tendon reflexes are normal or decreased with disease progression. A minimal sensory neuropathy is observed in some patients. Systemic involvement is rare.

11.3.3 Pathogenesis

Unknown. No association with malignancy. Inflammation is present but not clearly primary or secondary. Cytotoxic CD8-positive T cells clonally expand in situ and invade MHC-I-expressing muscle fibers. Additionally, there is vacuolization and intrafiber accumulation of degenerative and stressor molecules. Pro-inflammatory mediators, such as gamma interferon and interleukin IL1-β, seem to enhance the accumulation of stressor and amyloid-related misfolded proteins.

11.3.4 Diagnosis

Creatine kinase may be normal or 2–5 times normal, with an occasional elevation in AST and LDH up to 20 times normal. Genetic testing for inherited cases is not currently clinically available. However, genetic susceptibility studies have found a strong association between IBM and HLA-DR3 (up to 75 % of cases in certain populations), HLA-A*01, HLA-B*0801, HLA-DRB1*0301, HLA-DQB1*0201, and HLA-DQA1*05 in Australian, Dutch, and North American white populations and HLA-B*5201 and HLA-DRB*1502 in those of Japanese ancestry.

Nerve conduction studies are usually normal. EMG shows increased insertional activity. Short-duration, polyphasic motor unit action potentials (MUAPs), mixed with longer duration, higher amplitude MUAPs, are frequently observed. These latter MUAPs may be misinterpreted as a neurogenic condition. On muscle biopsy, endomysial inflammation (mainly CD8+ T cells and some macrophages) is seen, with myopathic changes and small groups of atrophic fibers of mixed histochemical type. Initial muscle biopsy may be inconclusive. Frequently, rimmed vacuoles are seen with granular material and filaments. These may comprise several proteins including beta-amyloid, desmin, ubiquitin, emerin, lamin A/C, histone-1, and valosin-containing protein. Immunostaining for TDP-43, a nucleic acid-binding protein, is reported to yield an abnormal distribution in the cytoplasm of IBM muscle, with high sensitivity and specificity for IBM. Cytoplasmic inclusions are another feature, reportedly seen by stains for ubiquitin and visualized via use of an antibody directed against phosphorylated tau (SMI-31) (Fig. 11.4). On electron microscopy, 15- to 21-nm paired helical filaments or tubulofilaments and 6- to 10-nm amyloid-like filaments are seen.

11.3.5 Differential Diagnosis

Motor neuron disease, polymyositis, distal myopathy, and muscular dystrophy.

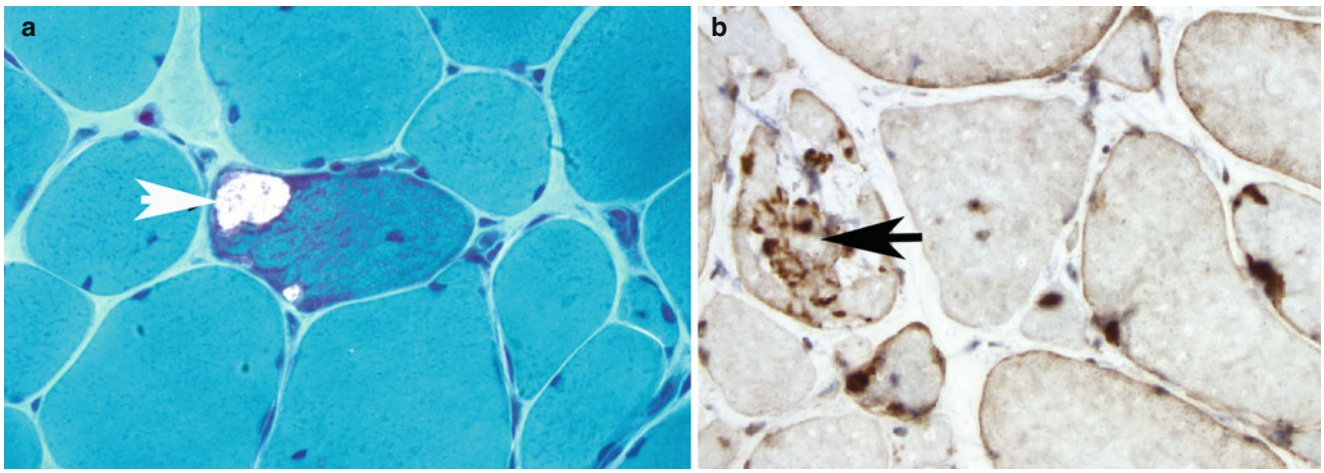

Fig. 11.4 (**a**) Modified Gomori's trichrome stain showing a rimmed vacuole (*white arrow*) in patient with inclusion body myositis. (**b**) SMI31 (40×) stain showing cytoplasmic inclusions (*black arrow*)

11.3.6 Therapy

There is no effective therapy despite trials of prednisone, cyclosporine, azathioprine, methotrexate, and rituxan. Up to 25 % of individuals responded transiently to IVIg.

11.3.7 Prognosis

Survival is usually unaffected, although weakness is progressive and debilitating, with the majority of individuals requiring assistive devices within 5–10 years.

11.4 Immune-Mediated Necrotizing Myopathy (IMNM)

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

11.4.1 Distribution

Severe proximal muscle weakness.

Time Course Acute to subacute.

Age of Onset Most common in those greater than 60 years of age.

11.4.2 Clinical Syndrome

IMNM (also known as necrotizing autoimmune myopathy) has a multifactorial etiology; it can be severe, may have an association with malignancy, statins, or viral infections. In addition to inducing self-limited myalgias or myopathy, statin agents are rarely associated with IMNM, producing:

1. Proximal weakness during (or after) treatment with statins
2. Elevated serum creatine kinase (CK)
3. Persistence of weakness and elevated CK (for at least 1 month) despite discontinuation of the statin
4. Improvement with immunosuppressive agents

11.4.3 Pathogenesis

Autoantibodies to 3-hydroxy-3-methylglutaryl-coenzyme A reductase, (HMGCR), the pharmacological target of statins, have been identified in the serum of these patients. The presence of these antibodies, along with complement deposits which recruit macrophages via an antibody-dependent cell-mediated cytotoxicity, supports an immune-mediated etiology. Regenerating muscle cells express high levels of HMGCR, which may sustain the immune response even after statins are discontinued. The lack of improvement following discontinuation of statins, the need for immunosuppressive therapy, and the frequent relapse when treatment is tapered all suggest an immune-mediated etiology.

11.4.4 Diagnosis

CK is significantly elevated and, if extreme, can be associated with rhabdomyolysis. EMG shows irritative myopathic features, i.e., positive sharp waves, fibrillation potentials, and short-duration, small-amplitude MUAPs with early MUAP recruitment. Muscle biopsies can reveal muscle fiber necrosis, type II fiber atrophy, and/or increased lipid stores in

muscle fibers. The distinguishing features of the muscle biopsy are necrotic and regenerating muscle fibers without significant inflammatory cell infiltrate. Class I major histocompatibility complex (MHC) molecule is expressed on non-necrotic muscle fibers.

11.4.5 Differential Diagnosis

Polymyositis, dermatomyositis, toxic myopathy, and metabolic myopathy.

11.4.6 Treatment

Prednisone is the initial form of treatment. Long term, other steroid-sparing agents may be indicated, such as methotrexate and mycophenolate mofetil. Multiple immunosuppressive agents may be required in some patients. IVIg may be effective.

11.4.7 Prognosis

Good, with the majority responding to immune suppression treatment.

11.5 Connective Tissue Diseases (CTDs) in "Overlap" Myositis

Genetic tests	EMG	Laboratory	Imaging	Biopsy
–	+++	+++	+	+++

11.5.1 Distribution/Anatomy

Proximal muscles are more commonly involved.

Time Course Variable, although involvement of muscle is unusual and tends to be seen more in chronic connective tissue disorders.

Age of Onset Depends upon the specific connective tissue disorder; therefore, it is more common in women in their third to fifth decades.

11.5.2 Clinical Syndrome

Although muscle pain and weakness are frequent symptoms in patients with CTDs, active myositis is uncommon. The following types of connective tissue diseases are associated with and can be considered within the category of myositis "overlap" syndromes:

- Mixed connective tissue disease (MCTD)
- Systemic sclerosis (SSc)
- Rheumatoid arthritis (RA)
- Systemic lupus erythematosus (SLE)
- Sjögren syndrome

In these CTDs, individuals usually present with features of the connective tissue disorder, but muscle disease is often milder. Classification is complicated as many patients present with CTD features – Raynaud's phenomenon, arthritis, and interstitial lung disease – but without a defined connective tissue disease. Further, all of these syndromes may be associated with disuse atrophy. Certain cases have marked proximal muscle weakness and muscle atrophy at initial presentation, for example, patients with SRP-positive myositis.

MCTD Mixed connective tissue disease is an entity characterized by overlapping symptoms of systemic lupus erythematosus, systemic sclerosis, polymyositis/dermatomyositis, and rheumatoid arthritis. Weakness may be associated with an inflammatory myopathy resembling polymyositis, in roughly 10 % of cases (Fig. 11.5).

SSc Myalgia is common in this disorder; inflammatory myositis is rare, present in up to 10 % of patients. There is a slightly higher association with antiU1 RNP, antiPm/Scl, and rarely Scl-70.

RA Causes of muscle weakness include inflammatory myopathy (approximately 13 % of cases) and medications including penicillamine.

SLE Myositis occurs in fewer than 10 % of cases. Other causes of weakness include a vasculitic neuropathy associated with mononeuritis multiplex or an axonal polyneuropathy. Myopathy may also be related to medications such as corticosteroids or chloroquine.

Sjögren Syndrome Noted in fewer than 2 %. Inclusion body myositis (IBM) has been reported in association with Sjögren syndrome.

11.5.3 Pathogenesis

The immunopathogenesis of myositis with connective tissue disease is poorly understood. Like dermatomyositis (DM), MCTD probably is a humorally mediated disease with a major involvement of blood vessels, although there are sufficient components of DM and PM to suggest that there may be characteristic muscle pathology in MCTD. The presence of autoantibodies, e.g., to SRP, RNP, and Jo-1, circulating in immune complexes and reduced complement levels, suggests activation of the humoral system. Myositis-specific autoantibodies are mainly expressed by regenerating myofibers, which

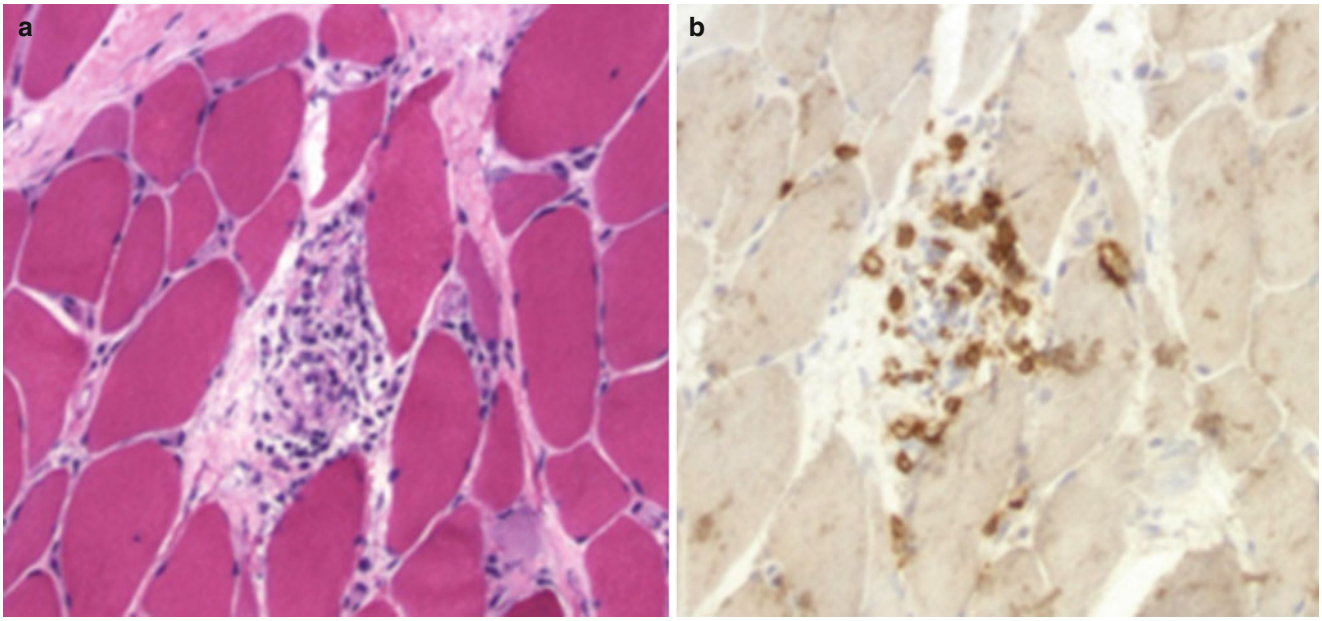

Fig. 11.5 Myositis in mixed connective tissue disease. (**a**) In the H&E stained section, there is an inflammatory response. (**b**) CD3 (T-cell) staining of the inflammatory response

may also express MHC-1 and endogenous ligand-binding toll-like receptors, thus drawing a picture in which the regenerating myofiber plays a central pathophysiologic role.

11.5.4 Diagnosis

CK is often very high, up to 15 times normal. Overlap myositis (OM) may be associated with other connective tissue diseases and a variety of autoantibodies, although these are present in fewer than 10 % of cases. Anti-synthetase, signal recognition particle (SRP), or nucleoporin antibodies are more common markers for chronic myositis, whereas antibodies to U1ribonucleoprotein (U1RNP), Pm-Scl, or Ku are markers for monophasic myositis. Nerve conduction studies may demonstrate an additional neuropathy in many of these disorders. EMG reveals an increase in insertional activity, coupled with short-duration, polyphasic ("myopathic") motor unit action potentials in patients with inflammatory myopathy. The presence of abnormal spontaneous activity in the form of positive sharp waves and fibrillation potentials is suggestive of an inflammatory myopathy, whereas the absence of abnormal spontaneous activity is more suggestive of a disuse or steroid myopathy. In MRI studies, increased signal on T2-weighted images or enhancement with gadolinium indicates areas of active inflammation and muscle necrosis. In chronic disease, muscle atrophy and fatty infiltration predominates. Frequently the muscle biopsy shows changes that resemble those in DM. However, there may be necrotic fibers invaded by inflammatory cells, often in a heterogeneous distribution, with perivascular and endomysial infiltration with lymphocytes. Although vascular density of MCTD biopsies was reduced to levels that were comparable to DM – in contrast to subjects who had PM and in whom vascular density was normal – little detectable membrane attack complex was seen in vessel walls and only low levels of adhesion molecules were seen in the vessels. Atrophy of type II muscle fibers may be observed particularly where there is significant arthritis, joint pain, and disuse atrophy of the muscle.

11.5.5 Differential Diagnosis

DM, IBM, PM, and other causes of weakness, for example, polyneuropathy or mononeuritis multiplex.

11.5.6 Therapy

Treatment takes into consideration the specific cause of the connective tissue disease. In general, immunosuppressive medication similar to that used for the idiopathic inflammatory myopathies (IIMs), PM and DM, is appropriate for the treatment of myositis associated with connective tissue disease. OM is usually responsive to corticosteroids (89–100 % rates). Treatment generally follows the guidelines of that for IIMs. Although clinical trials have not assessed this, typical second-line agents include a variety of immunosuppressant agents, including azathioprine, methotrexate, alkylators, cyclosporine, tacrolimus, mycophenolate mofetil, and tumor necrosis factor inhibitors.

11.5.7 Prognosis

Outcome depends mainly on the severity of the systemic illness. With appropriate control of the disease, the myopathy may become quiescent.

11.6 Viral Myopathies

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

11.6.1 Distribution/Anatomy

The distribution is variable depending on the type of infection.

Time Course Is variable depending on the type of infection.

Age of Onset Any age.

11.6.2 Clinical Syndrome

Influenza-induced myositis is characterized by severe pain, tenderness, and swelling which usually affects the calf muscles but may also affect thigh muscles. Myalgia is common and starts 1 week after the onset of the influenza infection and 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 widespread 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 lymphotropic virus (HTLV), may be associated with a variety of myopathic manifestations. HIV-infected patients may develop one of the following manifestations:

1. An HIV-associated myopathy that resembles polymyositis
2. A retroviral myopathy, which resembles mitochondrial myopathy
3. AIDS-associated cachexia with muscle wasting
4. Opportunistic infections and tumor formation within muscle
5. A myopathy resembling nemaline myopathy
6. 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 the pyomyositis including cryptococcus, CMV, *Mycobacterium avium intracellulare* (MAI), and toxoplasma. HIV, a wasting disease, is associated with fatigue and evidence of type II atrophy (Fig. 11.6).

11.6.3 Pathogenesis

The specific mode of muscle injury depends on the particular pathogen. Several of the viral infections, including HIV, may cause myositis by increasing the release of cytokines and interferons. Viral infections may also cause perivascular, perimysial, or endomysial inflammation.

11.6.4 Diagnosis

CK may be normal or mildly elevated. EMG shows evidence of focal or more diffuse muscle damage, characterized by increased insertional activity or with "myopathic" polyphasic motor unit potentials. In many cases the changes may be focal. MRI studies may show evidence of a focal myositis depending on the specific pathogen. The muscle biopsy changes depend on the specific pathogen. In general, the features are similar to those observed in polymyositis. In certain disorders such as HIV, nemaline rods may be observed.

11.6.5 Differential Diagnosis

Many of the causes of viral myositis resemble one another, and determining the specific cause may require the culture of the organism, specific antibody testing, and muscle biopsy with special staining. The differential diagnosis includes (1) polymyositis, (2) dermatomyositis, and (3) mitochondrial myopathies.

11.6.6 Therapy

Many causes of viral myositis are self-limiting. HIV-induced myopathy may respond to or be caused by retroviral therapy and is beyond the scope of this book. HIV polymyositis is similar to the disease in non-HIV patients and may improve with corticosteroids or other immunosuppressive medications.

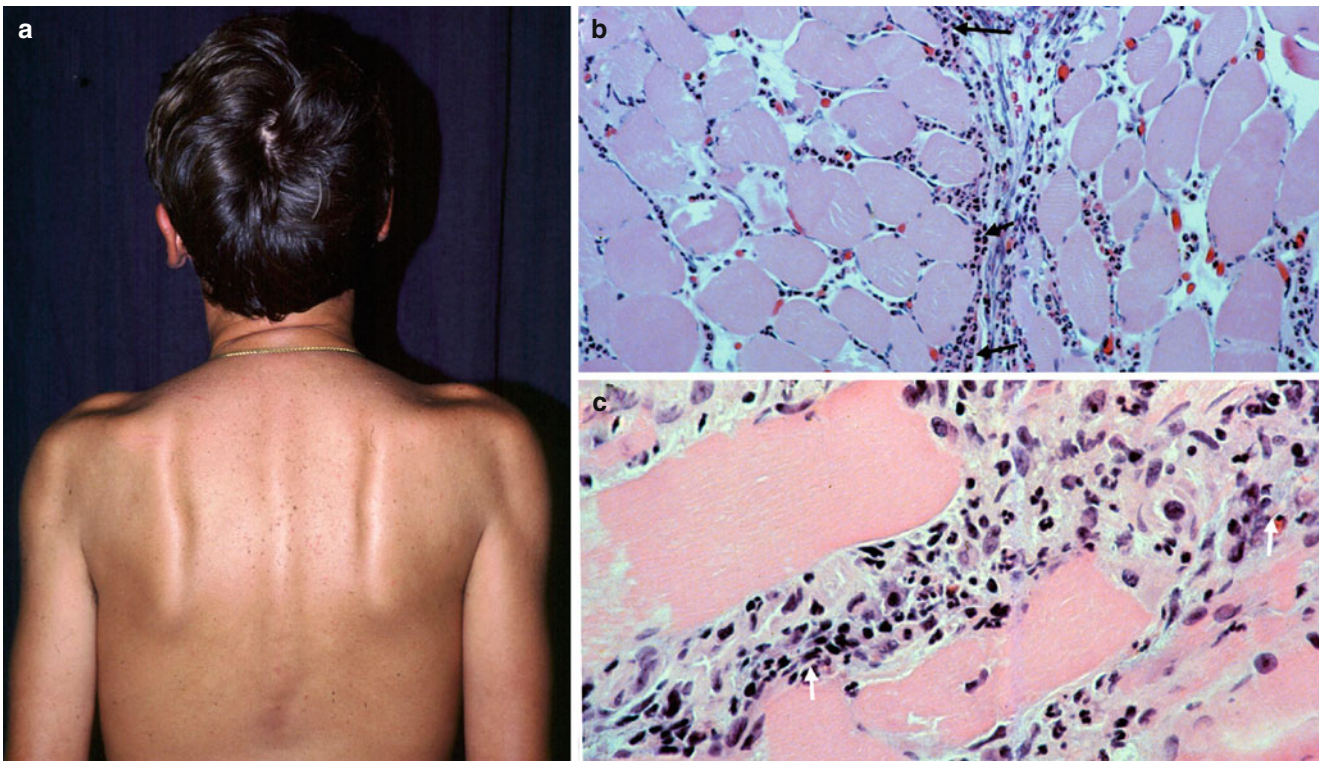

Fig. 11.6 (**a**) HIV myopathy. Proximal arm atrophy and bilateral scapular winging in a patient with HIV myopathy. (**b**) Pyomyositis with marked neutrophil inflammation (*arrows*). The muscle fibers are textureless and have no nuclei, features consistent with acute fiber necrosis. (**c**) H&E. Inflammatory response dispersed between several fibers (*white arrows*)

11.6.7 Prognosis

The prognosis depends on the specific cause of the myositis. For a non-HIV-related viral syndrome, the prognosis is usually good. Where there is HIV infection or opportunistic infection, the prognosis is usually worse.

11.7 Duchenne Muscular Dystrophy

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

11.7.1 Distribution

Usually affects proximal muscles and spares the face.

Time Course Progressive disorder with gradual onset.

Age of Onset Onset is usually around age 3–5 years, though sometimes earlier.

11.7.2 Clinical Syndrome

Duchenne muscular dystrophy (DMD) is the most common form of muscular dystrophy affecting 1:3,500 male infants. DMD starts with symmetric proximal greater than distal weakness in the arms and legs. Infants may have generalized hypotonia and be described as "floppy." By 6–9 years they characteristically exhibit a positive Gower's sign, and by 10–12 years, patients often fail to walk. They frequently have calf 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.

11.7.3 Pathogenesis

Most DMD patients have a frameshift mutation (>95 %), although 30 % may have a new mutation. The molecular abnormality is unknown, although potentially dystrophin, along with dystroglycan, α1-syntrophin, utrophin, and α-dystrobrevin, may play a role in clustering of acetylcholine receptors and development of the neuromuscular junction. In DMD this process is abnormal.

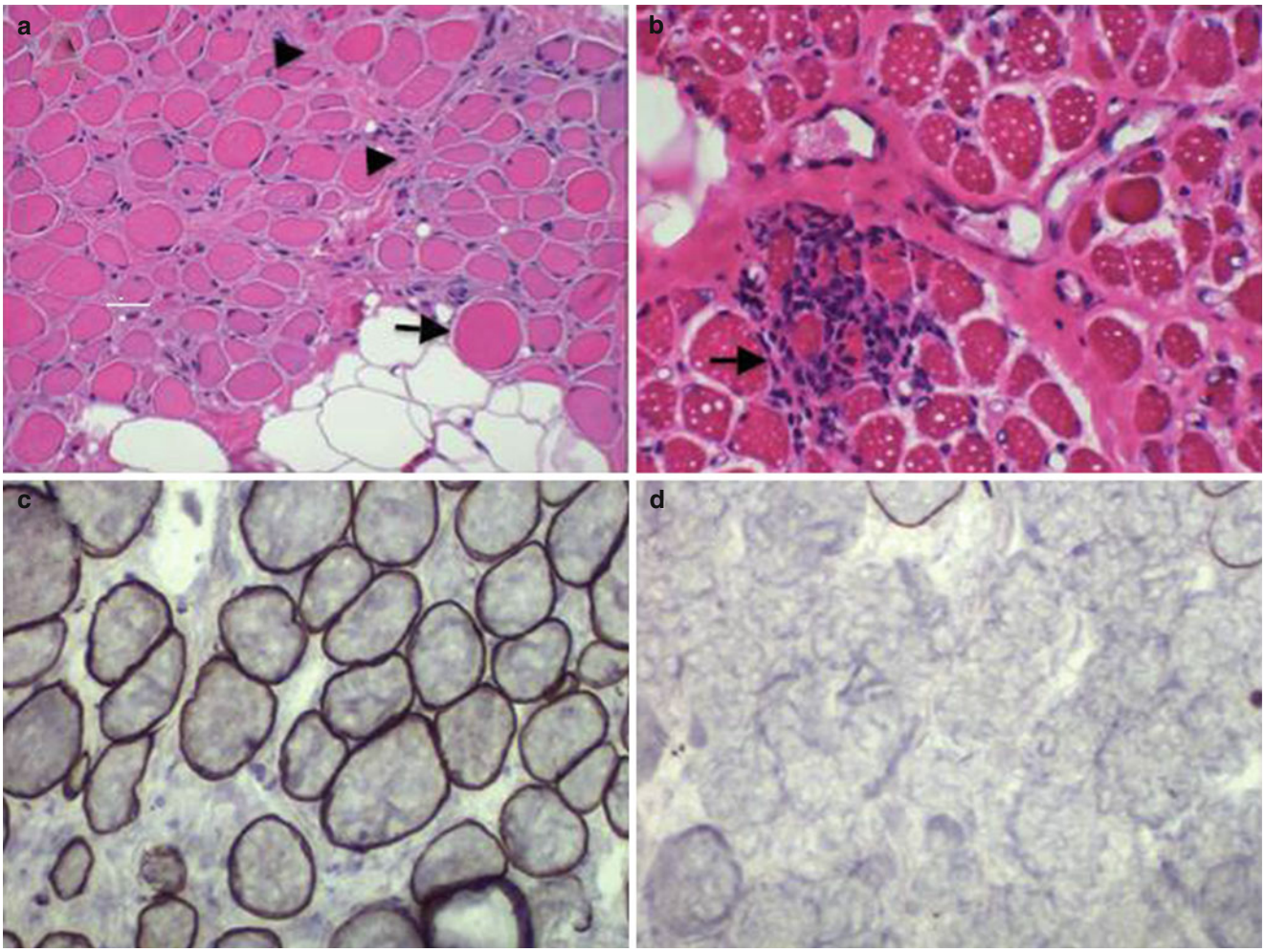

Fig. 11.7 Duchenne muscular dystrophy. (**a**) On hematoxylin and eosin (H&E) staining, considerable fiber-type variation, including an occasional hypertrophic fiber (*arrow*) and fibrosis with fatty infiltration (*arrow heads*), is noted. (**b**) Also on H&E staining, lymphocytic infiltrates are demonstrated (*arrow*). (**c**) Normal dystrophin staining. (**d**) Loss of dystrophin staining in DMD

11.7.4 Diagnosis

In the majority of patients, the CK is typically very high, usually over 5,000. Nerve conduction studies are usually normal. Membrane instability in the form of positive sharp waves and fibrillation potentials is commonly seen. Short-duration polyphasic motor unit action potentials, mixed with normal and long duration units, are noted in the affected muscles. Recent MRI studies suggest that the anterior compartment of the lower leg may be preferentially involved in this disease relative to the posterior compartment muscles, with good correlation to muscle histology. Biopsy usually shows variation in muscle fiber size, an increase in endomysial connective tissue, increased myopathic grouping, necrotic fibers, hypercontracted fibers, and evidence of degeneration and regeneration of muscle fibers (Fig. 11.7). Inflammatory cells can also be seen. Dystrophin is also found to be absent by immunohistochemical staining or Western blotting of muscle from DMD patients. Genetic testing of the dystrophin gene is commercially available and typically shows exonic or multiexonic deletions in about 65–70 %, duplication in 5–10 %, or missense mutations that generate stop codons may be observed in a small percentage of DMD patients.

11.7.5 Differential Diagnosis

Becker muscular dystrophy, inflammatory myopathies, spinal muscular atrophy, congenital myopathy, limb-girdle muscular dystrophy.

11.7.6 Therapy

Few specific therapies exist for DMD patients. Prednisone therapy may prolong the ability to walk by a few years and reduce falling. The doses used are usually 0.75 mg/kg/day as a starting dose and then changing to a weekly dose of 5–10 mg/kg.

Oxandrolone, an anabolic steroid, has also been used at doses of 0.1 mg/kg/day to preserve muscle function. Nonsurgical treatment of contractures consists of night splints and daytime passive stretch. Surgical treatment of contractures consists of early contracture release, Achilles tenotomy, and posterior tibial tendon transfer followed by early ambulation. Scoliosis may require 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. High-dose gentamicin may produce translation with read through of the nonsense codon and localized expression of dystrophin at the cell membrane.

11.7.7 Prognosis

DMD patients typically become unable to walk by age 12 years. Virtually all patients have a dilated cardiomyopathy by age 18 years. Death normally occurs by the late teens to early twenties from respiratory or cardiac failure. However, some patients live longer as a consequence of being on daily corticosteroids or noninvasive ventilation or following cardiac transplant.

11.8 Becker Muscular Dystrophy

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

11.8.1 Distribution/Anatomy

Usually affects proximal muscles and spares the face.

Time Course Progressive disorder with gradual onset.

Age of Onset Onset is usually around age 12, though a later presentation is not uncommon.

11.8.2 Clinical Syndrome

Becker muscular dystrophy (BMD) is another dystrophinopathy that is much milder than DMD with later clinical onset. Patients may have difficulty walking by their late teens. BMD often causes calf pain, cramps, and myalgias. Weakness is present in approximately 20 % of affected patients, typically in proximal > distal muscles and often effecting the quadriceps and hamstring muscles preferentially. 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. Carriers for BMD must also be monitored as they can also develop 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.

11.8.3 Pathogenesis

Most BMD patients have a frameshift mutation (>95 %), although 30 % may have a new mutation. Although dystrophin 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.

11.8.4 Diagnosis

In the majority of patients, the CK is typically very high, usually over 5,000. Nerve conduction studies are usually normal. Membrane instability in the form of positive sharp waves and fibrillation potentials is commonly seen. Short-duration polyphasic motor unit action potentials, mixed with normal and long duration units, are noted in the affected muscles. MRI study often demonstrates focal muscle enlargement and edema, especially observed on T2- and T1-weighted images with gadolinium, in more severely affected patients.

Biopsy usually shows variation in muscle fiber size, an increase in endomysial connective tissue, increased myopathic grouping, necrotic muscle fibers, and evidence of degeneration and regeneration of muscle fibers. There is also evidence of reduced dystrophin staining (Fig. 11.8). Genetic testing remains the definitive test for diagnosing BMD. Genetic testing of the dystrophin gene is commercially available and typically shows exonic or multiexonic deletions in about 80 %, duplication in 5–10 %, or missense mutations that generate stop codons may be observed in a small percentage of BMD patients.

11.8.5 Differential Diagnosis

Spinal muscular atrophy, congenital myopathy, myofibrillar myopathy, limb-girdle muscular dystrophy.

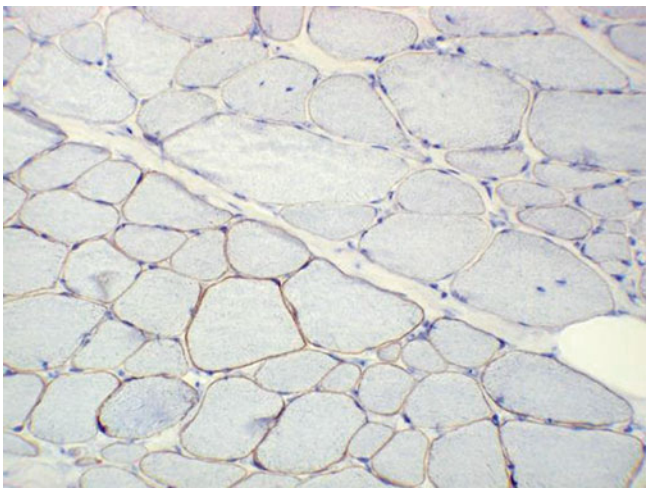

Fig. 11.8 Becker's muscular dystrophy. Immunohistochemistry demonstrates variable reduction of dystrophin using antibodies targeting the rod domain

11.8.6 Therapy

No specific therapies exist for BMD patients. Similar to DMD, there may be a role for prednisone therapy in more severely affected subjects, but compared to DMD, clinical treatment trials using corticosteroids in BMD are lacking. Treatment of contractures, cardiac, and pulmonary disease follows the outlines for DMD. Many subjects have mild symptoms and do not require therapy.

11.8.7 Prognosis

Unlike DMD, the prognosis for BMD patients is highly variable. Some patients become unable to walk as a teenager while others continue to ambulate throughout life. Restrictive lung disease may ultimately require noninvasive ventilation but is a challenge to predict. Some patients may become candidates for cardiac transplant as well. Despite the variability, patients usually die in the fourth or fifth decade of life.

11.9 Myotonic Dystrophy (DM)

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

11.9.1 Distribution/Anatomy

Affects both distal and proximal muscles, as well as many other organ systems.

Time Course Slowly progressive disorder.

Age of Onset Variable age of onset.

11.9.2 Clinical Syndrome

There is considerable phenotypic variation within families. Usually, symptomatic weakness begins in the hands and at the ankles and usually follows years of myotonia. Facial muscle weakness with prominent mouth puckering, weak eye closure, and external ocular muscle weakness is common. Myotonia may be demonstrated in the thenar eminence or tongue. Frequently affected organs include skeletal muscles, the cardiac conduction system, the brain, smooth muscles, and lens. Sinus bradycardia is common, although heart block and cardiac arrhythmias can be present. Dilated cardiomyopathy is unusual. In later years, cognitive impairment, hypersomnolence, hyperglycemia with insulin insensitivity, and cataracts may be prominent. Where the expansion is small (<100 CTG repeats), the phenotype is often very mild with cataracts 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.

11.9.3 Pathogenesis

DM1 is an autosomal dominant disease due to an expanded CTG repeat of the dystrophia myotonica-protein kinase gene (DMPK) on chromosome 19. The expanded repeat is transcribed into mutant DMPK mRNA that forms aggregates in affected nuclei. DMPK localizes to the motor endplate where it may regulate calcium homeostasis. The role of DMWD gene in DM1 is unknown. DM2 is related to an expansion of the CCTG repeat of the ZNF9 gene on chromosome 3 that leads to RNA aggregates similar to DM1. Further genetic defects and mechanism of action are described in Foff and Mahadevan (2011).

11.9.4 Diagnosis

Serum CK is often normal. If the EMG is abnormal, it shows a minimal increase in insertional activity in affected muscles. Myotonic discharges may be seen in distal muscles in particular and may be increased by cooling the muscle. The muscle biopsy in both DM1 and DM2 is similar but nonspecific and shows type I fiber atrophy, central nuclei, atrophied fibers mixed with hypertrophied fibers, and a slight increase in endomysial connective tissue (Fig. 11.9). 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

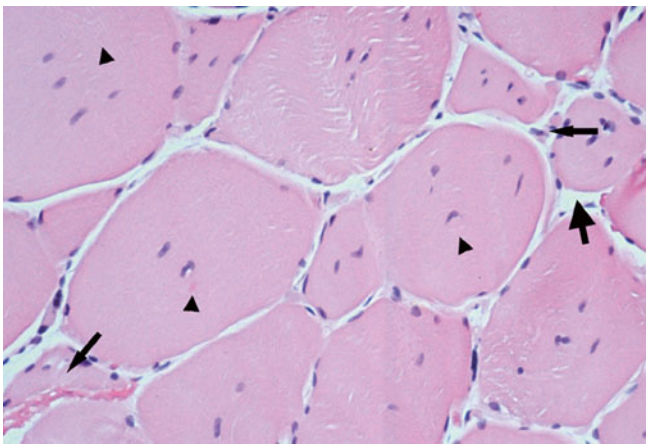

Fig. 11.9 Myotonic dystrophy. H&E section shows atrophied fibers (*small arrows*), mixed with hypertrophied fibers (*arrow head*), numerous centrally migrated nuclei, and a slight increase in endomysial connective tissue (*large arrow*)

reticulum. 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. MRI and PET may be useful in detecting brain lesions. The PET may show decreased glucose utilization.

11.9.5 Differential Diagnosis

The clinical manifestations of DM are very variable, and thus the disorder may remain undiagnosed without a family history. Other conditions to be considered are myotonia congenita and cold-induced myotonia (paramyotonia).

11.9.6 Therapy

There is no specific therapy for DM. Understanding the pathogenesis of RNA toxicity has lead to new approaches emphasizing RNA-based therapeutics and use of small molecules. The following are useful in management:

- Myotonia usually responds to mexiletine 200–600 mg/day but requires EKG monitoring and should not be used if there is a conduction defect.
- Monitoring the EKG for gradual widening of the PR interval (>0.22 ms). This provides a warning for impending heart block and the need for further electrophysiologic testing. An elective pacemaker may be necessary if the patient has a lethal arrhythmia. If the patient has ventricular fibrillation, an intracardiac defibrillator may be necessary.
- Diabetes should be controlled with diet, oral hypoglycemics, or insulin.
- Modafinil may be used for hypersomnolence but is often ineffective.
- Cataracts and blepharoptosis may require surgical treatment.
- Assessment for pharyngoesophageal dysfunction may prevent aspiration.
- Cognitive impairment and personality disorders require a combined approach with medication and psychological support.

11.9.7 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. The most frequent causes of death are pneumonia and cardiac arrhythmias.

11.10 Limb-Girdle Muscular Dystrophy (LGMD)

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

11.10.1 Distribution

Can affect the pelvic girdle or pectoral girdle muscles but spares the face.

Time Course Forms that begin in childhood tend to progress more rapidly than those that appear in late adolescence or adulthood, which may have a more gradual and milder course.

Age of Onset Can occur in childhood, especially autosomal recessive forms, or in adulthood, especially autosomal dominant subtypes.

11.10.2 Clinical Syndrome

Limb-girdle muscular dystrophy (LGMD) is a very heterogeneous disorder, where the clinical presentation depends on the gene defect. Age of onset is variable and depends on the specific cause of the LGMD. LGMD is divided into categories based on the pattern of inheritance, type I, which is autosomal dominant, and type II, which is autosomal recessive. An evolving number of different forms of LGMD type I and type II have been documented. 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. Generally though, it is slow in its progression. It occurs approximately equally in both sexes. In approximately 50 %, weakness begins in the pelvic girdle musculature (the Leyden and Möbius type) and then spreads to the pectoral musculature, and in the other 50 % (the Erb type), the weakness begins with the pectoral girdle musculature. Facial muscles are uninvolved in LGMD until the patient is severely disabled from limb weakness. Pseudohypertrophy 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. Specific phenotypes may be dependent on the gene mutation.

11.10.3 Pathogenesis

LGMD is a heterogeneous disorder with a wide range of molecular defects. LGMD1A is associated with a missense mutation of the myotilin gene on chromosome 5q. It is not clear why patients develop LGMD, since it is difficult to demonstrate a reduction or accumulation of myotilin. However, it is evident that myotilin plays a role in anchoring the myofiber to the Z-disc as other mutations in this gene cause a form of myofibrillar myopathy. LGMD1B is due primarily to missense mutations of the gene for lamin A/C, which plays 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 possibly controlling T-tubule organization. Although collagen VI is ubiquitously expressed in the body, for unknown reasons only skeletal muscle and tendon are affected in patients with Bethlem myopathy. LGMD1D is due to mutations in the gene for DNAJBS, a member of the heat shock protein-2 co-chaperone family. LGMD2A is due to mutations in the gene for calpain-3, which among its other properties can bind and cleave titin, a protein implicated in LGMD2J. In LGMD2B, substitutions or deletions of the dysferlin gene (DYSF) result in nonspecific myopathic changes in skeletal muscle. LGMD2B is also allelic with Miyoshi myopathy, a distal myopathy. The phenotypical variation suggests that additional factors to mutations in the DYSF gene account for the defect. LGMD2C-2F constitutes the sarcoglycanopathies. Loss of sarcoglycan results in structural weakness of the muscle cytoskeleton resulting in a clinical picture similar to Becker 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. LGMD2H is a consequence of a mutation in the gene for tripartite motif-containing protein 32 (TRIM32), which is found in skeletal muscle where it interacts with myosin and ubiquinates actin, possibly affecting their binding. LGMD2I (fukutin-related protein deficiency), LGMD2K (POMT1 deficiency), LGMD2M (fukutin deficiency), LGMD2N (POMT2 deficiency), and LGMD2O (POMGnT1 deficiency) all cause impaired glycosylation of dystroglycan and demonstrate absent or reduced staining of α-dystroglycan on muscle biopsies. LGMD2J is due to a mutation in the gene for titin, which is one of the largest proteins ever known, and anchors thick filament to the Z-disc. LGMD2L is due to a mutation in the anoctamin-5 gene and can present with a Miyoshi myopathy phenotype.

11.10.4 Diagnosis

The serum CK in LGMD is usually elevated especially in the autosomal recessive forms, but a normal CK does not exclude the diagnosis. Electrodiagnostic testing typically demonstrates findings that support a myopathy but are otherwise nonspecific. MRI may play a role in distinguishing among the LGMDs. A recent study suggested that LGMD2I has characteristic MRI changes most prominent in the posterior and adductor thigh muscles, with relative sparing of the gluteal and calf muscles. LGMD2A shows similar involvement of the posterior and adductor thigh muscles but also the medial gastrocnemius and soleus muscles. LGMD2B has variable involvement of posterior and anterior thigh muscles. LGMD2D demonstrates prominent involvement of the anterior > posterior thigh muscles. The muscle biopsy is also nonspecific and depends on the particular type of LGMD. In general there are a wide range of degenerative changes seen, including fiber splitting, ring fibers, and lobulated fibers. Individual muscle fibers can also show hyalinization, vacuolation, and necrosis. Other changes include an increase in connective tissue with nesting of muscle fibers, and muscle atrophy (Fig. 11.10). Regenerating fibers with prominent nucleoli and basophilic sarcoplasm are often seen. Rarely, mononuclear cellular infiltrates are seen near necrotic muscle fibers, especially in calpainopathies, sarcoglycanopathies, and dysferlinopathies. At present, genetic testing is commercially available for LGMD1A-1C, 2A-2G, and 2I-20 (www.genetests.org).

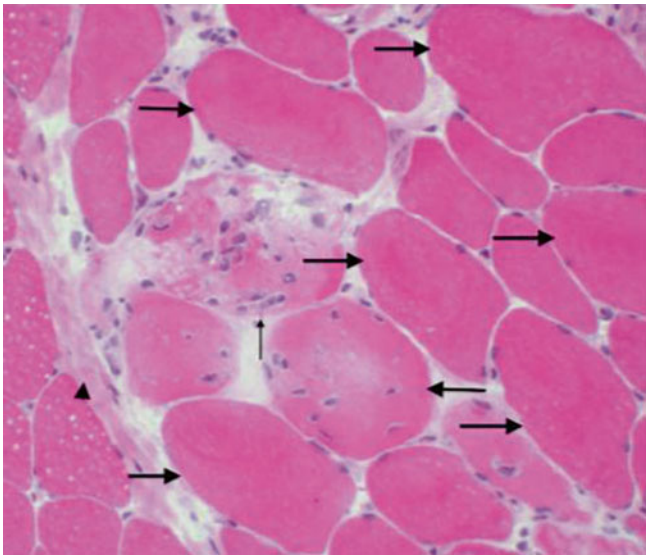

Fig. 11.10 Limb-girdle muscular dystrophy 2C. Hematoxylin and eosin staining shows fiber size variation, hypertrophic fibers (*large arrows*), limited inflammatory infiltrate (*small arrow*), and increased fibrosis (*arrowhead*)

11.10.5 Differential Diagnosis

Facioscapulohumeral dystrophy, myotonic dystrophy, myofibrillar myopathy, Duchenne and Becker muscular dystrophies.

11.10.6 Therapy

No specific therapy is known for any form of LGMD at this time, other than perhaps the use of corticosteroids for the treatment of LGMD2M as denoted above. 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.

11.10.7 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 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.

11.11 Oculopharyngeal Muscular Dystrophy (OPMD)

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

11.11.1 Distribution

OPMD causes ptosis and affects pharyngeal muscles, extraocular muscles, and proximal limb muscles.

Time Course The condition is very slowly progressive in most cases.

Age of Onset Presents in the fourth to sixth decade most frequently with ptosis.

11.11.2 Clinical Syndrome

Autosomal dominant OPMD is more common than the autosomal recessive form. 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. Mild neck weakness also occurs. Strict clinical diagnostic criteria for dominant OPMD have been shown to have 100 % specificity for many patients:

- A positive family history of OPMD
- At least one palpebral fissure at rest smaller than 8 mm (or previous blepharoplasty)
- A swallowing time greater than 7 s when asked to drink 80 ml of ice-cold water.

11.11.3 Pathogenesis

Mutation of the PABPN1 gene (GCN)(n)/polyalanine mutations. PABPN1 acts as a nuclear to cytosolic shuttle for mRNA. Mutated PABPN1 is an inefficient transporter and results in cell death.

11.11.4 Diagnosis

Serum CK is usually normal or mildly elevated. Needle EMG is nonspecific and shows myopathic and polyphasic

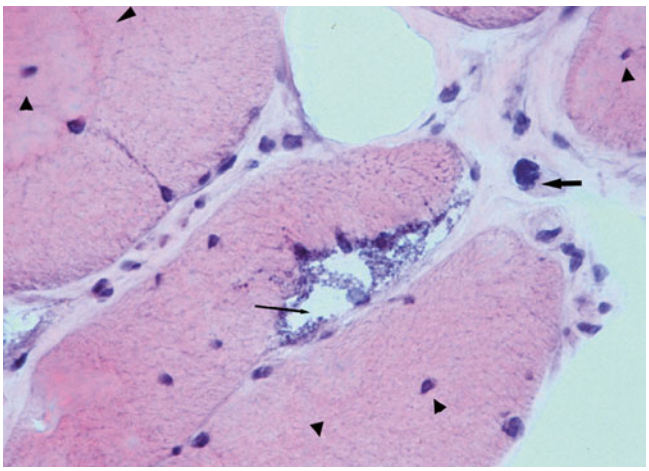

Fig. 11.11 H&E section with a prominent rimmed vacuole (*small arrow*) and a mixture of atrophied (*large arrow*) and hypertrophied fibers with central nuclei (*arrowheads*)

motor unit potentials similar to most myopathies. On muscle biopsy, there is evidence of variation in fiber diameter, and the presence of atrophic, angulated, hypertrophic, or segmented muscle fibers (Fig. 11.11). 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. Genetic testing is highly useful in diagnosis. 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. PCR is required to establish the carrier status of an individual. The test has a sensitivity and specificity greater than 99 %. Genetic testing for targeted mutation analysis, sequencing, carrier status, and prenatal testing is available (see www.genetests.org).

11.11.5 Differential Diagnosis

Centronuclear or myotubular myopathy, mitochondrial myopathies, oculopharyngodistal myopathy.

11.11.6 Therapy

Nutritional support is important because the dysphagia worsens prognosis. Pharyngoesophageal sphincter abnormalities may benefit from cricopharyngeal myotomy if the lower esophageal sphincter is intact. Surgical correction of the ptosis (resection of the levator palpebral aponeurosis or frontal suspension of the eyelids) is appropriate if orbicularis oculi strength is sufficient to allow closure of the eyelids after surgery.

11.11.7 Prognosis

Depends on the degree of pharyngeal and esophageal involvement and thus the risk of aspiration.

11.12 Facioscapulohumeral Muscular Dystrophy (FSHD)

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

11.12.1 Distribution

FSHD affects the face, scapula and proximal shoulder girdle, and the lower extremities in a peroneal distribution.

Time Course Slow progression with a normal life span.

Age of Onset Late childhood or adolescence.

11.12.2 Clinical Syndrome

Winging of the scapulae is a prominent feature and is not related to position. The pectoral muscles are often poorly developed and there is frank pectus excavatum. The scapula weakness means that the arms cannot be raised to shoulder level even though strength in the supraspinati, infraspinati, or deltoids may be normal. However, the hands maintain function. In the legs there is distal muscle weakness resulting in a scapuloperoneal syndrome (Fig. 11.12). 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, FSHD may be associated with hearing loss and retinopathy but the heart is usually spared. Approximately 10–30 % of all familial cases are asymptomatic. Sporadic cases are more likely to have the onset in childhood or infancy and have a more severe course, and hearing impairment and retinopathy are more common in childhood-onset FSHD. With DNA diagnosis, it is apparent that the presentation of FSHD may be atypical with a facial-sparing scapuloperoneal myopathy, distal myopathy, asymmetric arm weakness, or limb-girdle muscular dystrophy.

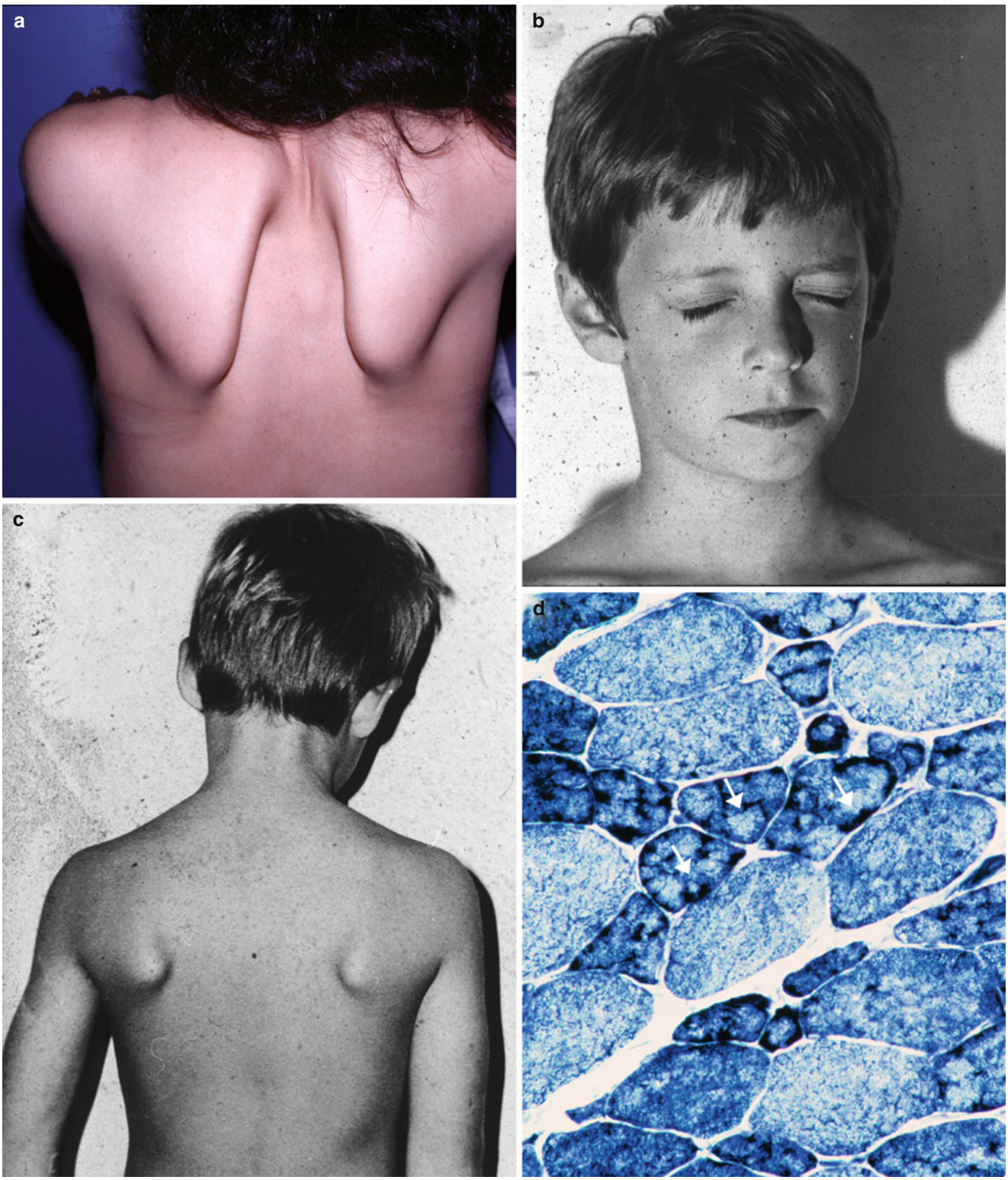

Fig. 11.12 (**a**–**c**) Patients with FSHD. There is prominent scapular winging, bilateral ptosis, and facial weakness. (**d**) Lobulated type I fibers (*white arrows*) that are smaller than the type II fibers (succinic dehydrogenase)

11.12.3 Pathogenesis

FSHD is an autosomal dominant disorder. Most patients (FSHD1) carry a large deletion in the D4Z4 macrosatellite repeat array at 4q35 and present with 1–10 repeats whereas non-affected individuals possess 11–150 repeats. A similar repeat array is present at 10q26. Each D4Z4 unit contains a DUX4gene. Synthesis of the DUX4 transcription factor may target several genes which inhibits myogenesis, sensitizes cells to oxidative stress, and induces muscle atrophy. Widespread D4Z4 hypomethylation, coupled with the absence of large 4q D4Z4 deletions, results in the far less common FSHD2.

11.12.4 Diagnosis

Serum CK is normal or mildly elevated. On EMG there are usually a mixture of small, short duration, and larger polyphasic motor unit potentials. Muscle biopsy shows lobulated type I fibers, with isolated angular and necrotic fibers. Moderate endomysial connective tissue proliferation may be observed. The biopsy may show variation in severity and may include clusters of inflammatory cells (40 %). Muscle biopsy is not needed if genetic testing that measures the length of the D4Z4 allele is abnormal (see www.genetests.org). About 5 % of individuals with FSHD do not have a D4Z4 contraction (FSHD2).

11.12.5 Differential Diagnosis

Spinal muscular atrophy, inflammatory myopathy, limb-girdle muscular dystrophy, mitochondrial myopathy, Emery–Dreifuss muscular dystrophy, Dawidenkow's syndrome of scapuloperoneal neuropathy.

11.12.6 Therapy

No medication significantly alters the disease. Consider the following: physical and occupational therapy, low-intensity aerobic exercise, pain therapy, ventilator support for hypoventilation, lubricants to prevent scleral drying, ankle/foot orthoses, and surgical fixation of the scapula to the chest wall for arm range of motion.

11.12.7 Prognosis

FSHD is usually slowly progressive and survival is normal. Over 50 % of patients continue working. Less than 10 % need a wheelchair. There are no cardiac risk factors and medical complications are few.

11.13 Distal Myopathies

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

11.13.1 Distribution

Characteristically affects distal leg or arm/hand muscles depending on the specific disease.

Time Course Slowly progressive and usually limited to distal muscles.

Age of Onset May present in childhood but typically is seen in early adulthood to middle age.

11.13.2 Clinical Syndrome

The distal myopathies represent a genetically heterogeneous group of disorders with shared clinical features. Welander (type I) distal myopathy (WDM) affects finger and hand extensors and later flexors may be affected. Cold sensation may be decreased distally. Markesbery (type II) distal myopathy (MDM) affects tibial muscles early, with foot drop developing later. MDM is usually milder than WMD and many patients remain asymptomatic. Nonaka distal myopathy (NDM) 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) causes progressive weakness of the posterior gastrocnemius muscles. Other distal muscles may be affected. Laing distal myopathy (LDM) begins in the neck flexors and anterior leg muscles, followed by finger extensor weakness, and ending with shoulder girdle weakness. Distal desmin body myofibrillar myopathy (DBM) is similar to other distal myopathies, but cardiomyopathy and conduction defects are common.

11.13.3 Pathogenesis

The genetic and molecular pathogenesis is described in Udd (2011).

11.13.4 Diagnosis

CK is usually minimally elevated except in MIDM where it may be >100 times normal. On EMG, there may be "myopathic units" in distal muscles. WDM shows variation in fiber size, fiber splitting, and rimmed vacuoles along

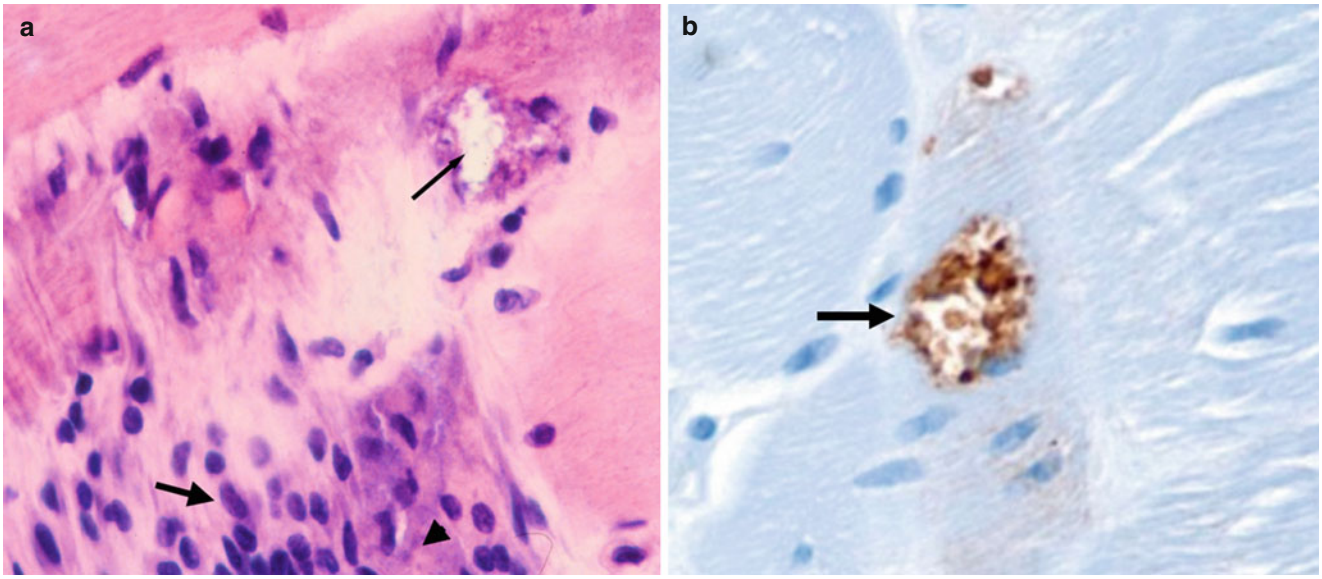

Fig. 11.13 (**a**) H&E section of an uncharacterized distal myopathy showing a rimmed vacuole (*small arrow*), degenerating fiber (*arrowhead*), and minimal inflammation (*large arrow*). (**b**) Ubiquitin immunostaining of a rimmed vacuole (*arrow*)

with filamentous inclusions (15–18 nm; Fig. 11.13). Characteristically there is loss of Aδ fibers on the sural nerve biopsy. Rimmed vacuoles are seen in MDM and NDM, but usually not MIDM. There may be immunostaining for desmin in DBM. Genetic testing is available for several distal myopathies (see www.genetests.org).

11.13.5 Differential Diagnosis

HMSN (Charcot–Marie Tooth disease), SMA, FSHD, IBM, nemaline myopathy.

11.13.6 Therapy

There is no medical treatment, although more severely affected patient may benefit from orthotics. Cardiac complications in DBM and NDM may require use of a pacemaker.

11.13.7 Prognosis

Variable – worse in DBM and MIDM than WDM and MDM.

11.14 Congenital Myopathies

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

11.14.1 Distribution/Anatomy

Central core disease (CCD) – generalized or limited to upper or lower limbs. In multi or minicore disease (MCD), nemaline 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.

Time Course Variable. In CCD, progression is slow. 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 and infants may die from respiratory failure.

Age of Onset In CCD 20 % of patients present between 0 and 5 years, 30 % between 6 and 20 years, 30 % between 21 and 40 years, and 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.

11.14.2 Clinical Syndrome

Consists of the following groups:

- Myopathies with protein accumulations. Examples include NM where there are accumulations of Z-line proteins called nemaline rods and variants such as zebra body myopathy. Myosin storage (hyaline body) is associated with accumulations of myosin thick filaments.

- Myopathies with cores. The cores are regions devoid of oxidative activity. They are a feature of CCD and MCD.
- Myopathies with central nuclei: examples include autosomal and X-linked (myotubular) forms of CNM.
- Myopathies with fiber size variation: examples include CFD characterized by selective atrophy of type I fibers.

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 and decreased reflexes occur in 50 % of subjects. Other associations are kyphoscoliosis or lordosis, foot deformities, congenital hip dislocations, contractures, hypertrophic cardiomyopathy, and arrhythmias. 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. Cleft palate or arthrogryposis may be seen. Minimal proximal and distal weakness may be present. 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. Approximately 20 % of patients have ophthalmoplegia.

NM There are several types including congenital forms that vary in severity: severe infantile, intermediate congenital, typical congenital, and juvenile (Fig. 11.14a–c). The infantile form is rapidly fatal. Infants have severe hypotonia, facial diplegia, failure to thrive secondary to inability to suck, respiratory complications, hypotonia, depressed deep tendon reflexes, proximal weakness, bulbar weakness, respiratory impairment, and ophthalmoplegia. Patients are thin due to reduced muscle bulk and facial weakness. In contrast, the adult form may only present with weakness in the seventh decade. 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 prominent facial weakness with ptosis, variable external ophthalmoplegia, and pharyngeal muscle weakness. Patients often have a generalized loss of muscle mass including the tongue. Tendon reflexes are often reduced. Congenital contractures, scoliosis, and foot deformities are present in a minority. Cardiomyopathy is rare.

11.14.3 Pathogenesis

This is evolving and complex. Briefly:

CCD and MCD There is an autosomal dominant abnormality of the ryanodine receptor 1 (RYR1). Mutations in the selenoprotein N (SEPN1) are less common.

NM Several gene loci have been identified that include slow alpha tropomyosin (TPM3), nebulin (NEB), cofilin-2 (CFL2), troponin T1 (TNNT1), and beta-tropomyosin (TPM2).

CFD This is a syndrome with a wide range of genetic causes that include AD, α-tropomyosin$_{slow}$ (TPM3), AD, skeletal-α actin (ACTA1), AD, β-tropomyosin (TPM2), and β-Myosin (MYH7).

CNM The X-linked recessive form of myotubular myopathy (XLMTM) with severe neonatal phenotype is caused by mutations in the MTM1 gene; the classical autosomal dominant form with mild, moderate, or severe phenotypes is caused by mutations in the DNM2 gene; and the autosomal recessive form with severe and moderate phenotypes is caused by mutations in the BIN1 gene.

11.14.4 Diagnosis

The serum CK is usually normal or slightly elevated. Nerve conduction studies are usually normal. 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. MRI can differentiate between different forms of congenital myopathy by identifying patterns of selective muscle involvement associated with specific genetic abnormalities. Most congenital myopathies can be diagnosed using light microscopy. Immunohistochemistry is rarely needed. EM is indicated to clarify the light microscopy. Muscle biopsy shows the following features:

CCD There is variation in muscle fiber size and presence of "cores," 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 (Fig. 11.14f, g).

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.

NM Diagnosis depends on the finding of nemaline rods in the muscle biopsy (Fig. 11.14d, e).

CFD There is a predominance of small myofibers, usually type I, with the remaining hypertrophic fibers being type II, particularly IIb.

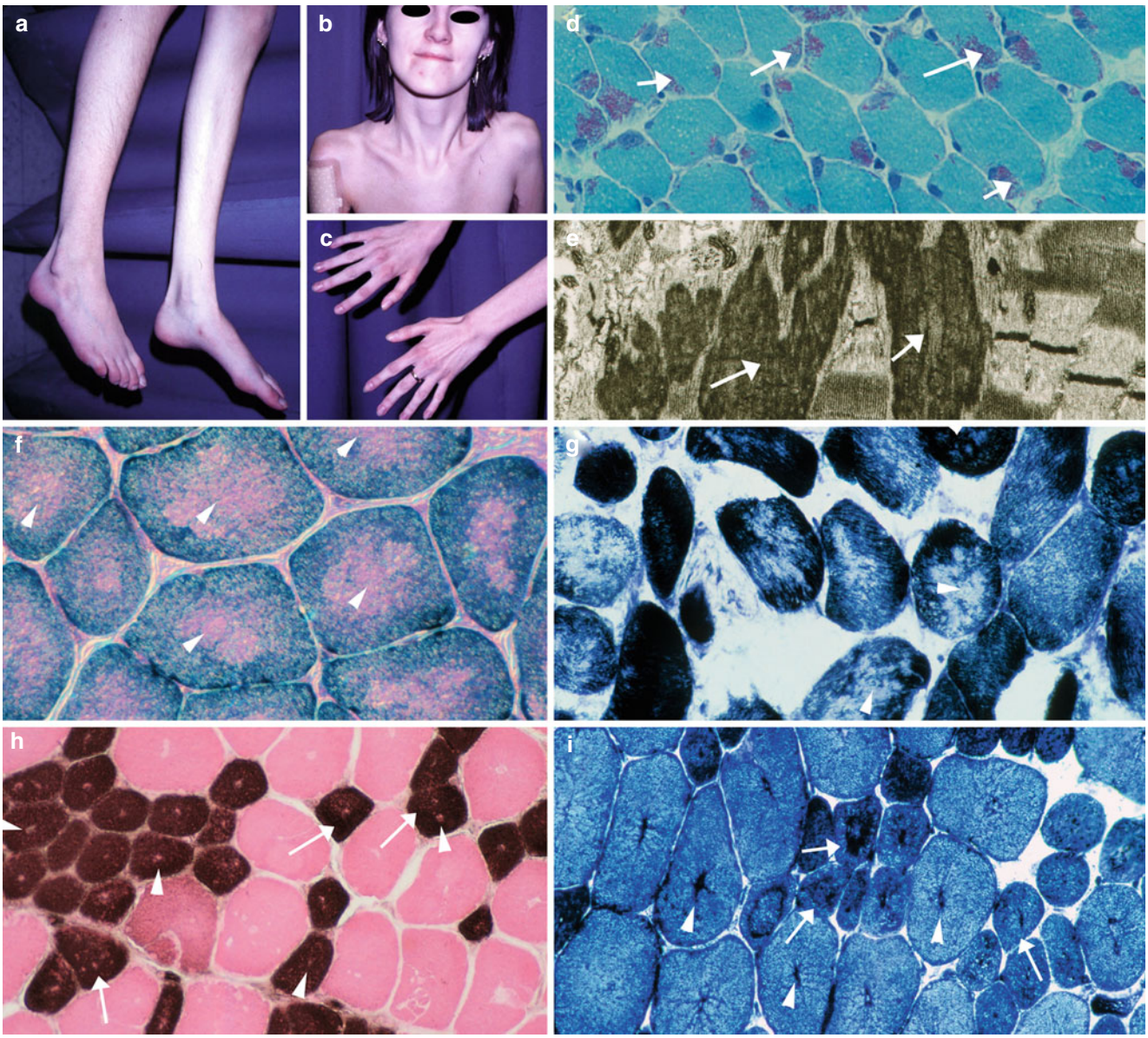

Fig. 11.14 Congenital myopathies. Nemaline myopathy: (**a**) Distal leg atrophy. (**b**) Atrophy of the proximal arm muscles, neck muscles, and weakness of the facial muscles. (**c**) Bilateral hand wasting. (**d**) Collection of red nemaline rods (*arrows*) on Gömöri trichrome stain. (**e**) EM-nemaline rod inclusion (*arrows*). (**f**) Central core disease. Red central cores with trichrome and eosin staining (*arrowheads*). (**g**) Multicore disease – multiple cores (*arrowheads*) using a NADH-tetrazolium reductase stain. (**h**) Centronuclear myopathy. Adult-onset subject with red stained central nuclei (*arrowheads*) seen in small type I fibers (*arrows*). (**i**) Centronuclear myopathy. NADH-tetrazolium reductase showing small type I fibers (arrows), and central nuclei with mitochondria arranged like spokes in a wheel (*arrowheads*)

CNM The muscle biopsy shows the presence of central nuclei, central pallor of the fibers on ATPase (Fig. 11.14h). Type I fibers are predominant and small in many affected patients. Genetic testing is available for several congenital myopathies (see www.genetests.org).

11.14.5 Differential Diagnosis

Muscular dystrophies, myotonic dystrophies, metabolic myopathies, spinal muscular atrophy.

11.14.6 Therapy

Currently, there is no specific therapy for the congenital myopathies; however, recent research into genetic and molecular causes offers promise that therapies in animals may be translated to human disease. Specifically, see genetic therapy and acetylcholinesterase inhibitors for MTM1 (Nance et al. 2012). 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.

11.14.7 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 NM, CNM, and CFD, the prognosis depends on the severity of the initial disorder.

11.15 Mitochondrial Myopathies

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

11.15.1 Distribution/Anatomy

May affect any muscles but usually proximal muscles or facial muscles are affected.

Time Course Slowly progressive in most cases.

Age of Onset May occur at any age. Kearns–Sayre syndrome (KSS) can develop in the second decade.

11.15.2 Clinical Syndrome

In rearrangements of mtDNA or point mutations, symptoms are often mild or absent. mtDNA deletions cause more severe symptoms. The most common and mildest variant is chronic external ophthalmoplegia syndrome (CPEO), 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, and multifocal neurodegeneration.

11.15.3 Pathogenesis

There is toxic damage to the mitochondrial respiratory chain due to mtDNA mutations and/or modification by nuclear genes.

11.15.4 Diagnosis

CK values may be mildly elevated, and there may be elevation in serum lactic acid levels. In most cases, the EMG is normal or shows mildly "myopathic" motor unit action potentials. In general most muscle fibers show evidence of typical ragged-red fibers on trichrome or more specific succinate dehydrogenase (SDH) staining. Genetic testing in serum or muscle is extremely helpful in differentiating the specific mitochondrial disorder (Fig. 11.15).

11.15.5 Differential Diagnosis

Other metabolic myopathies, congenital myopathies, muscular dystrophies.

11.15.6 Therapy

There are no specific pharmacological treatments. Mitochondrial enzyme supplements including coenzyme Q, creatine, and carnitine may be used. Aerobic and, perhaps, strength training improve function and muscle metabolism in some patients.

11.15.7 Prognosis

Usually good but depends on the specific mitochondrial disorder.

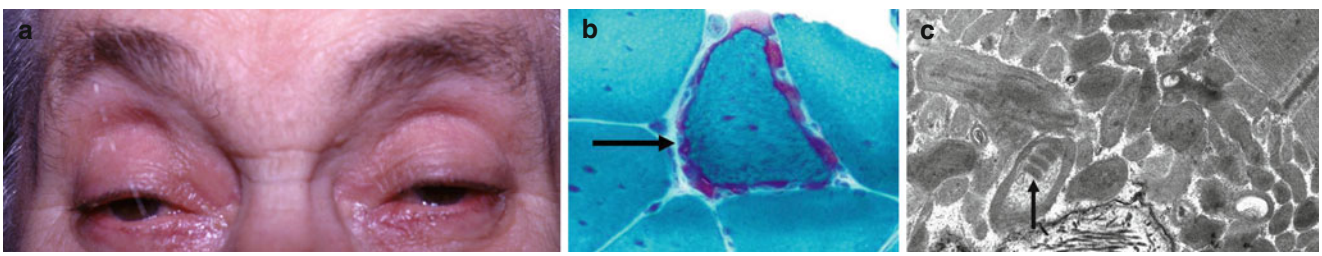

Fig. 11.15 (**a**) Muscle weakness resulting in bilateral ptosis and ocular divergence. (**b**) Ragged-red fiber (*arrow*) is present on a Gömöri's trichrome preparation. (**c**) EM demonstrates a large collection of morphologically abnormal mitochondria, some of which contain "parking lot" paracrystalline inclusions (*arrow*)

11.16 Glycogen Storage Diseases

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

11.16.1 Distribution

Usually affects the limbs but may also affect respiratory and cardiac muscles and the central nervous system.

Time Course Variable depending upon the subtype. Glycogen storage diseases can be mildly progressive and episodic or more dramatic in progression.

Age of Onset Variable depending upon the subtype. Glycogen storage diseases can begin in infancy, early childhood, adolescence, or, less commonly, adulthood.

11.16.2 Clinical Syndrome

Glycogen storage disease (GSD) is a group of disorders in which patients present generally with either exercise intolerance or progressive weakness. Forms in which exercise intolerance occurs include GSDV, VII, and VIII–XIII. GSDV (McArdle disease) usually starts in the early teens; however, it is more common in males. It is characterized by exercise intolerance, 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. GSDVII (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 fatty acids and ketones – the "out-of-wind" phenomenon. GSDVIII–XIII are characterized by intolerance to intense exercise, cramps, and/or myoglobinuria. GSDX occurs almost exclusively in blacks, and heterozygotes may also have exercise intolerance.

Forms of GSD associated with progressive weakness include GSDI–IV. GSDI (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 GSDIa and GSDIb. GSDIb 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. GSDII (acid maltase deficiency) consists of three subtypes:

- Infantile onset with cardiomegaly and heart failure, liver disease, weakness, and hypotonia
- Childhood onset with proximal symmetrical weakness with enlarged muscles due to glycogen accumulation, with respiratory failure (RF)
- Adult onset with fatigue early in the disease, followed by proximal weakness, and eventually RF.

RF may be the presenting feature in 30 % of patients. GSDIII (debrancher deficiency) is more common in men than women (~3:1) and has three subtypes:

- An infantile form associated with deposition in muscle and liver, with hypoglycemia, recurrent seizures, severe cardiomegaly, and hepatomegaly
- A childhood form associated with hypoglycemia, seizures, growth retardation, weakness, liver dysfunction, and hepatomegaly
- An adult form that develops in the third to sixth decade and is slowly progressive.

It is associated with muscle weakness and wasting, fatigue and myalgia, exercise intolerance, respiratory failure, milder cardiomyopathy, hepatic dysfunction, and sometimes an axonal neuropathy. GSDIV (brancher deficiency), prevalent especially in Ashkenazi Jews, is associated with myopathy, cardiomyopathy, and liver disease. In addition, the brain and spinal cord can be affected, resulting in progressive involvement of the upper and lower motor neurons, sensory loss, sphincter problems, and dementia, often mimicking motor neuron disease.

11.16.3 Pathogenesis

GSD are a group of predominantly autosomal recessive disorders. GSDI is caused by deficiencies in the activity of the glucose-6-phosphatase (G6Pase) system consisting of two membrane proteins that work in concert to maintain glucose homeostasis, G6PT (11q23) and G6Pase (17q21). Deficiencies in G6Pase and G6PT cause GSDIa and GSDIb, respectively. GSDII is an autosomal recessive disorder due to deficiency of l acid a-1,4-glucosidase. GSDIII results from nonsense, small deletions or insertions, or splice site changes on chromosome 1p21. In GSDV, there is a deficiency of muscle phosphorylase A, resulting in impaired ATP generation from aerobic and anaerobic glycolysis. GSDVII is due to a deficiency of 6-phosphofructokinase. Other listed enzyme deficiencies and gene mutations resulting in defects of glycogen storage include the following: GSDXII, aldolase A, 16q22; GSDXIII, b enolase, 17pter; GSDXI, lactate dehydrogenase, 11p15; GSDIX, phosphoglycerate kinase, Xq13; GSDX, phosphoglycerate mutase, 7p12; and GSDVIII, phosphorylase b kinase, Xq12.

11.16.4 Diagnosis

CK is often normal between episodes of exercise intolerance or elevated for those forms of GSD causing progressive weakness. In GSDII and III, EKG abnormalities can often be seen. The ischemic forearm test shows an insufficient rise in venous lactate, but is nonspecific for the GSD,

relies on patient compliance, and may have complications such as myoglobinuria. GSDVII is associated with a compensated hemolytic anemia. Electrophysiologic testing is sometimes helpful. Nerve conduction studies are usually normal; however, in GSDIII there is often evidence of an axonal neuropathy. On needle EMG, during contractures, the muscle is electrically silent in GSD. There is 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 adults with GSD II, recent studies suggest that muscle MRI may demonstrate early involvement of the adductor magnus and semimembranosus muscles with later involvement of the long head of the biceps femoris, semitendinosus, and anterior thigh muscles and selective sparing of the sartorius, rectus, parts of the vastus lateralis, and gracilis muscles even in advanced stages. On muscle biopsy, GSDI and II are characterized by prominent PAS-positive lysosomal vacuoles with enlargement of muscle fibers (Fig. 11.16). There is little muscle fiber degeneration. Electron microscopy shows glycogen in cytoplasm with membrane-bound, autophagic vacuoles. In GSDIII, GSDV, and GSDVII, there can be subsarcolemmal and intermyofibrillar vacuoles, though often muscle architecture is normal in GSD V and VII. In GSDV and VII, routine immunohistochemistry reveals decreased or absent staining of muscle fibers for myophosphorylase A and PFK, respectively, though partial reductions of PFK to 20 % of normal may be artifactual due to the lability of the enzyme in incorrectly handled fresh frozen muscle. Enzyme analysis from muscle (and dried blood spot analysis for acid maltase levels for GSDII) is often the key to making a diagnosis of any GSD, showing substantial deficiencies of specific enzymes. Genetic testing is commercially available for GSDI–VII, X, and XI and can help confirm the diagnosis of GSD.

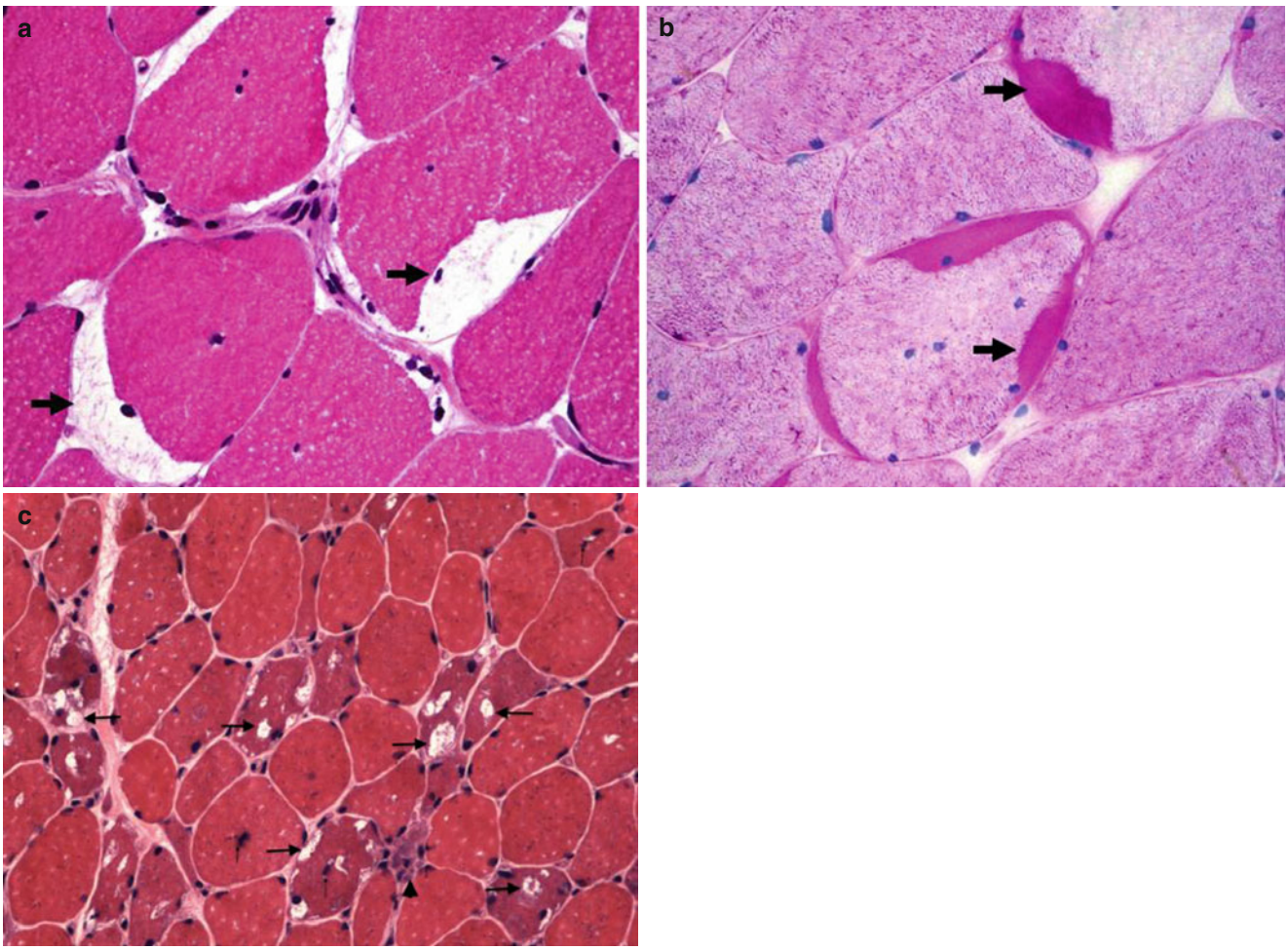

Fig. 11.16 Acid maltase deficiency. (**a**) Subsarcolemmal vacuoles (*arrows*) that are PAS-positive. (**b**) *Arrows* indicating glycogen, in a patient with myophosphorylase deficiency, or McArdle's disease. (**c**) High-magnification H&E. There are numerous subsarcolemmal vacuoles (*large arrows*) in addition to fiber size variation, a few central nuclei (*small arrow*), and regenerating fibers (*arrowhead*)

11.16.5 Differential Diagnosis

Carnitine palmitoyltransferase II deficiency, limb-girdle muscular dystrophy, congenital myopathy, polymyositis, mitochondrial myopathy.

11.16.6 Therapy

GSD patients in general must not perform strenuous exercise to prevent rhabdomyolysis. In GSDVII, patients should avoid high-carbohydrate meals that exacerbate the "out-of-wind" phenomenon as well as eat frequent small meals. Sucrose loading in GSDV patients prior to exercise may improve aerobic exercise based on recent study. These patients also benefit from carbohydrate-rich diets. There may also be a role for pyridoxine supplementation. Enzyme replacement therapy is now available for the infantile and late-onset forms of GDSII, having been shown to significantly modify the course of the disease, though it remains expensive.

11.16.7 Prognosis

In GSDII (infantile form), death occurs before 1 year of age, and in the childhood form, before 25 years. In infantile GSDIII, death occurs before 4 years, though patients with the childhood and adult forms survive longer.

GSDV has a normal life expectancy. In other forms of GSD, life expectancy may be normal unless severe myoglobinuria and muscle necrosis occur.

11.17 Defects of Fatty Acid Metabolism

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

Carnitine palmitoyl transferase 2 deficiency (CPT2), primary carnitine deficiency (PCD), very-long-chain acyl-CoA dehydrogenase deficiency (VACD), and multiple acyl-CoA dehydrogenation deficiency (MADD) are discussed in this section. Neutral lipid storage disease with ichthyosis (NLSDI or Chanarin–Dorfman syndrome) and myopathy (NLSDM) are discussed in the references for this section.

11.17.1 Distribution

In most cases of CPT2, there is no weakness. Proximal weakness is seen in PCD, VACD, and MADD.

Time Course CPT2 may have an acute onset, whereas other forms of PCD and VACD produce more chronic myopathic symptoms.

Age of Onset Onset depends on the specific disease. Most cases of CPT2 start between 6 and 20 years, PCD before 7 years of age, and VACD can occur in infants or adults.

11.17.2 Clinical Syndrome

The phenotype is heterogeneous. Constant or progressive muscle weakness with or without metabolic crisis is often seen in lipid storage myopathy (LSM) patients. In contrast, recurrent provoked rhabdomyolysis usually occurs in patients with disorders affecting intramitochondrial fatty acid transport and β-oxidation, such as deficiencies of CPT2 and VACD. In infantile onset patients, the clinical manifestations are similar between lipid disorders and include hypotonia, encephalopathy, hepatomegaly, and cardiomyopathy.

In CPT2, there are at least three different phenotypes: a myopathic form with juvenile–adult onset; an infantile form with hepatic, muscular, and cardiac involvement; and a lethal neonatal form with developmental abnormalities. Adult 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 that develops after prolonged fasting, low-carbohydrate high-fat diets, exercise, infection, cold exposure, and general anesthesia. In most patients, strength is normal. CPT2 deficiency is more common in males (6:1) with females having milder disease. In CPT2, here is a good correlation between genotype, metabolic dysfunction, and phenotype. VACD is clinically similar to CPT2 deficiency. PCD may be asymptomatic or may be more severe. In children, PCD is associated with cardiomyopathy and myopathy and, in infants, with recurrent acute episodes of hypoglycemic encephalopathy with hypoketonemia.

MADD has a heterogeneous presentation with (1) neonatal onset forms having hypotonia, hepatomegaly, nonketotic hypoglycemia, metabolic acidosis, and early death, and (2) milder and/or later onset forms with proximal myopathy, hepatomegaly, and episodic metabolic crisis that can be lethal. Both forms may have cardiomyopathy.

11.17.3 Pathogenesis

Fatty acid oxidation in the mitochondrial matrix is a major source of energy in muscle, and defects in this system usually lead to acute rhabdomyolysis in provoking conditions such as infection, fasting, and prolonged exercise. CPT2 is

associated with a mutation of p.S113L in more than 50 % of mild late-onset patients. There are at least 20 CPT2 gene mutations. PCD is usually associated with nonsense mutations of the genes encoding OCTN2, a high-affinity sodium-dependent carnitine transporter and SLC22A5, an organic cation transporter. Secondary carnitine deficiency may be due to mitochondrial disorders, renal failure, muscular dystrophy, chronic myopathy, and liver failure. VACD catalyzes the long-chain fatty acyl-CoA that has been incorporated into the mitochondrial CPT2. Therefore, the clinical features of VACD deficiency are very similar to CPT2 deficiency. VACD is due to a defect of the *ACADVL* gene and is associated with at least 60 mutations. MADD is caused by the defects in electron transfer flavoprotein (ETF) and many are associated with mutations in the electron transfer flavoprotein-dehydrogenase (ETFDH) gene.

11.17.4 Diagnosis

In CPT2, VADC, and MADD, the CK is normal between episodes of myoglobinuria. In CPT2 and VADC, carnitine is usually normal but decreased in MADD. During episodes of rhabdomyolysis, CK is high in all the disorders of free fatty acid metabolism. Diagnosis of CPT2 and VACD relies on showing an elevation of long-chain acylcarnitines. In PCD, free carnitine and all acylcarnitine species are usually severely reduced. However, as the plasma carnitine level can occasionally be normal in PCD, carnitine transport studies in fibroblasts may also be used to confirm the diagnosis. Secondary carnitine deficiency shows decreased free carnitine levels but elevated specific species of acylcarnitine should be excluded. MADD shows increased urinary organic acid profiles, plasma carnitine, and acylcarnitines and reduced respiratory chain enzymes. Mutation analysis of ETF enzymes may be diagnostic for MADD. In all disorders of fatty acid metabolism, EMG is often normal or shows minimal evidence of myopathy between episodes of myoglobinuria. Genetic testing is available (see www.genetests.org).

Muscle pathology is often not diagnostically helpful. In CPT2 the muscle biopsy is normal with the exception of a decrease in CPT activity. In VACD, the muscle biopsy is normal with no increase in lipid droplets but immunohistochemistry may show decreased VACD. There are increased lipid droplets in muscle fibers often close to enlarged mitochondrial in PCD, MADD, NLSDI, and NLSDM.

11.17.5 Differential Diagnosis

Other disorders of fatty acid metabolism, glycogen storage diseases, other metabolic myopathies, mitochondrial myopathies.

11.17.6 Therapy

The treatment for CPT2 deficiency consists of a high-carbohydrate low-fat diet with frequent and regularly scheduled meals. A long-chain fat-restricted diet with medium-chain triglyceride (MCT) supplementation is recommended. Bezafibrate restores normal fatty acid oxidation in muscle in mild CPT2 deficiency and may improve physical activity. PCD responds to carnitine supplementation (100–400 mg/kg per day) and may improve cardiomyopathy and other organ damage. Activation of peroxisome proliferator-activated receptor α (PPARα) can increase of intracellular carnitine and may be a potential treatment. Patients with VACD are treated with a high-carbohydrate, low-fat diet, with or without supplementation with MCT oil (less effective than with CPT2), riboflavin, or L-carnitine. In MADD, riboflavin supplementation (100–400 mg/day) markedly improves clinical symptoms, particularly with ETFDH mutations and in the later-onset form. Carnitine and CoQ10 supplementation may be useful where there is secondary carnitine or CoQ10 deficiency, respectively.

11.17.7 Prognosis

In later-onset CPT2 and treated PCD, prognosis is usually good. In VACD and MADD, prognosis depends on the disorder type.

11.18 Toxic Myopathies

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

11.18.1 Distribution/Anatomy

Usually proximal muscles are involved but may be more diffuse.

Time Course The time course is variable, depending on the type of toxic agent.

Age of Onset Can occur at any age.

11.18.2 Clinical Syndrome

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, there may be inflammation, myalgia, and myoglobinuria. In mitochondrial or vacuolar damage, the myalgia is usually painless. The most common

iatrogenic causes are statin and fibrate cholesterol-lowering medications, but there is a wide range of etiologies for toxic myopathies. The toxic myopathies can be divided into several etiological groups. Necrotic myopathies may be due to acute alcohol exposure, amiodarone, chloroquine, cocaine, emetine, clofibrate, heroin, combined neuromuscular-blocking agents and steroids, perhexiline, and statins (HMG CoA reductase inhibitors). Meta-analysis indicates that the highest risk of rhabdomyolysis occurs with atorvastatin and the lowest risk with fluvastatin, whereas there is an intermediated risk with simvastatin, lovastatin, and pravastatin. There is an increased risk of rhabdomyolysis with the coadministration of a statin and a fibrate drug, which is especially true of gemfibrozil. Several disorders may predispose to statin-induced injury, including undiagnosed congenital myopathies, myasthenia gravis, and inflammatory myopathies. Genetic factors may contribute to the susceptibility to statin myopathy susceptibility. The most important genetic variant is the SLCO1B1 gene that encodes the organic anion-transporting polypeptide (OATP1B1) hepatic transporter for statins. Another cause of muscle injury in necrotic myopathies is crush injuries which occur in comatose or motionless patients who are taking drugs for addiction. Steroids may also cause a myopathy with type II fiber atrophy due to a variety of mechanisms that include protein suppression and abnormalities of glycolysis. In the vacuolar myopathies, there is accumulation of autophagic (lysosomal) vacuoles. This is observed with amiodarone, chloroquine, colchicine, and vincristine and amphotericin. 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. Similar changes are seen with clevudine and statins. Clevudine may cause a slow progressive proximal myopathy with mitochondrial DNA depletion. An inflammatory toxic myopathy with similar clinical features to dermatomyositis may be seen with D-penicillamine, phenytoin, procainamide, hydralazine, L-dopa, and streptokinase. Myofibrillar myopathy is seen with emetine and acute quadriplegic myopathy.

11.18.3 Pathogenesis

A range of mechanisms have been described in toxic myopathies and are described as part of the clinical grouping above.

11.18.4 Diagnosis

CK levels are variable ranging from normal, with steroid myopathies, to very high with rhabdomyolysis. On EMG, there may be increased insertional activity in inflammatory and vacuolar myopathies but is usually normal in type II fiber atrophy. The motor units range from small short-duration action potentials typical of myopathy to polyphasic motor unit action potentials similar to those seen in dermatomyositis. Various changes may be observed in the muscle biopsy including necrosis, vacuolar changes, mitochondrial defects, and inflammatory changes (Fig. 11.17).

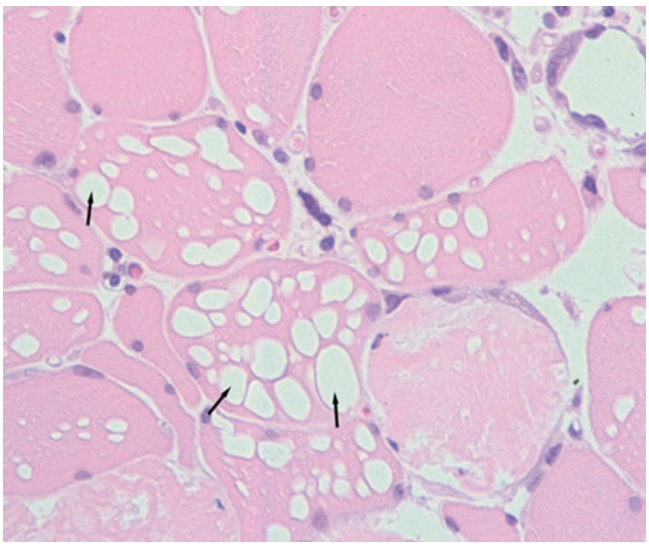

Fig. 11.17 Colchicine myopathy showing a vacuolar myopathy with numerous autophagic subsarcolemmal vacuoles of varying sizes (*arrows*)

11.18.5 Differential Diagnosis

PM, DM, IBM, muscular dystrophy, mitochondrial myopathies.

11.18.6 Therapy

There is no specific treatment for most toxic myopathies. Early recognition of a potential toxin and removal of the toxin are essential in limiting the muscle injury. In most cases, where statins are implicated and are discontinued, symptoms improve, and there is recovery over a period of 2–3 months. If there is no improvement, a muscle biopsy should be considered to determine the presence of a necrotizing autoimmune myopathy or an inflammatory myopathy, which should be treated with corticosteroids or immunosuppressive medication. Coenzyme Q10 supplementation may help. If other cholesterol-lowering medications cannot be used or are ineffective, then a gradual rechallenge with a lower-risk statin, e.g., rosuvastatin may be attempted.

11.18.7 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.

11.19 Critical Illness Myopathy

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

11.19.1 Distribution/Anatomy

Critical illness myopathy is usually more severe in proximal muscles.

Time Course Time course is variable but usually develops over days to months.

Age of Onset May develop at any age. More common in older patients.

11.19.2 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 rapidly after treatment or be associated with admission to the intensive care unit after surgery or in septic or malnourished patients. Recovery if it occurs usually happens within days to months after removal of the offending drug.

11.19.3 Pathogenesis

There is loss of thick filaments, muscle myosin loss, and muscle necrosis.

11.19.4 Diagnosis

CK levels may be mildly elevated or normal. On EMG, insertional activity is normal or minimally affected and motor units may show evidence of "myopathic" motor units. Muscle biopsies may show evidence of massive loss of myofilaments (Fig. 11.18).

11.19.5 Differential Diagnosis

Neuromuscular junction defects, inflammatory myopathies, muscular dystrophy, previously undiagnosed motor neuron disease.

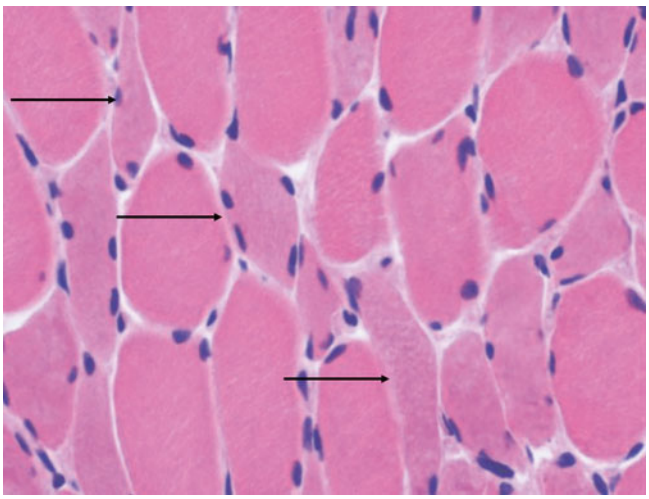

Fig. 11.18 H&E stain shows marked fiber atrophy with disruption of contractile elements (*arrows*) in a subpopulation of fibers

11.19.6 Therapy

There is no specific therapy. Any potentially causative medications should be discontinued.

11.19.7 Prognosis

Variable, depending on the severity of the illness.

11.20 Myopathies Associated with Endocrine/Metabolic Disorders and Carcinoma

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

11.20.1 Distribution/Anatomy

Variable; however, proximal muscles are most usually affected.

Time Course Most of these myopathies progress slowly, although thyrotoxicosis-induced myopathy is rapid.

Age of Onset Any age, although most are observed in adults.

11.20.2 Clinical Syndrome

Hypothyroidism may be associated with a painful myopathy that can simulate polymyalgia or polymyositis. Severely hypothyroid children develop weakness, slow movements, and striking muscle hypertrophy.

Thyrotoxicosis may be associated with muscle atrophy and weakness, a progressive extraocular muscle weakness, ptosis, periodic paralysis, myasthenia gravis, spastic paraparesis and bulbar palsy (similar to amyotrophic lateral sclerosis), hypoparathyroidism related tetany, muscle spasm, and occasionally weakness. Hyperparathyroidism results in proximal weakness, muscle atrophy, hyperreflexia, and fasciculations. Cushing syndrome may cause muscle atrophy and weakness. Acromegaly may be associated with mild proximal weakness. Diabetic amyotrophy may be associated with muscle necrosis or inflammation, although usually diabetes is not associated with myopathy. Hypoglycemia may be associated with muscle atrophy. Chronic renal failure may cause proximal weakness or rhabdomyolysis. Muscle may be affected as part of a paraneoplastic syndrome or by direct invasion with leukemias and lymphomas.

11.20.3 Pathogenesis

The pathogenesis depends on the specific muscle disorders indicated above.

11.20.4 Diagnosis

Biochemistry helps determine the specific metabolic defect. The CK is usually normal. The EMG results are dependent on the specific disorder but may show "myopathic changes." In hypo- and hyperthyroidism, the muscle biopsy is often normal. In hyperparathyroidism and acromegaly, there may be type II fiber atrophy. Inflammation and muscle infarction may be observed in diabetic amyotrophy (Fig. 11.19). Inflammation may occur in carcinomatous or paraneoplastic myopathy.

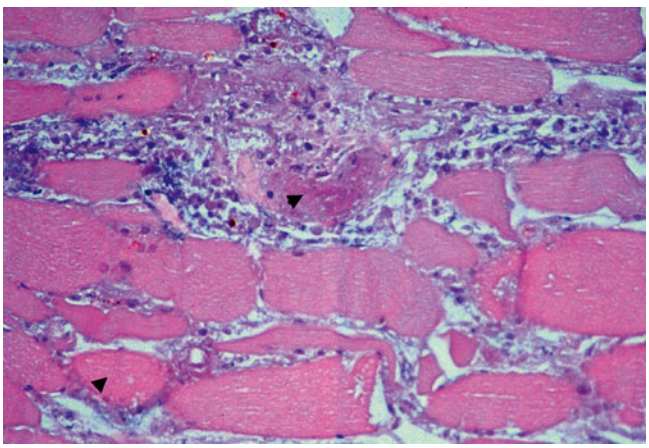

Fig. 11.19 High-magnification H&E shows acute segmental fiber necrosis or myolysis in a diabetic patient (*arrows*)

11.20.5 Differential Diagnosis

Other metabolic myopathies, polymyositis, dermatomyositis, inclusion body myositis.

11.20.6 Therapy

The therapy of the underlying endocrinopathy often leads to improvement of the myopathy.

11.20.7 Prognosis

This is dependent on the specific disorder but is usually good for the endocrine disorders.

11.21 Myotonia Congenita

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

11.21.1 Distribution/Anatomy

Can affect the limbs as well as the face.

Time Course Mild progression with gradual onset. Some patient may develop fixed weakness later in life.

Age of Onset Usually begins in infancy or early childhood.

11.21.2 Clinical Syndrome

Myotonia congenita is a hereditary neuromuscular disorder typified by difficulty with muscle relaxation, often affecting both limb as well as facial muscles. The condition can be inherited either in autosomal dominant or recessive fashion. The autosomal dominant form of myotonia congenita, also known as Thomsen's disease, presents with myotonia beginning in infancy that is usually mild, though approximately 50 % of patients may have percussion myotonia. The myotonia (Fig. 11.20a, b) is associated with fluctuations and may worsen with cold, hunger, fatigue, and emotional upset. Muscle hypertrophy is seen in many patients (Fig. 11.20c, d). Patients may report a "warm-up" phenomenon, in which the myotonia decreases after repeated activity. Muscle strength is usually normal. In the autosomal recessive form, also known as Becker's disease, the condition presents later in life, usually in early childhood, and 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.

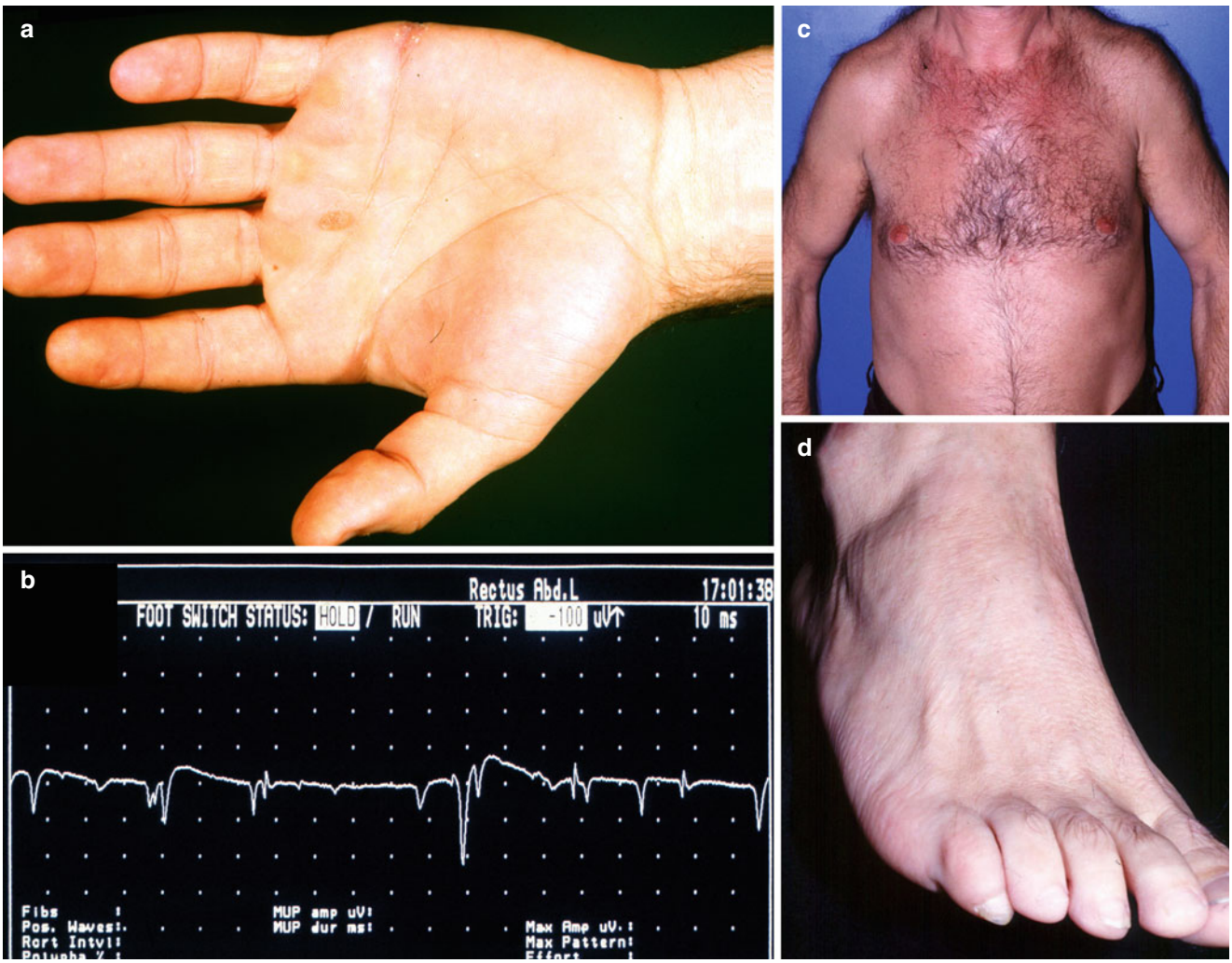

Fig. 11.20 Myotonia congenita with muscle myotonia in the hypothenar muscle (**a**). Myotonic discharges on EMG (**b**). Increased muscle bulk in the arms and chest in a patient with Thompson's disease (**c**). Hypertrophy of the extensor digitorum brevis muscle (**d**)

11.21.3 Pathogenesis

Both Thomsen's and Becker's disease is due to a defect of the skeletal muscle chloride channel (CLCN1) gene localized on chromosome 7q35, usually missense mutations. Impaired chloride conductance causes cation conductance after depolarization and spontaneous triggering of action potentials, leading to myotonia.

11.21.4 Diagnosis

The CK is typically normal, though occasionally it can be mildly elevated. Electrophysiologic testing is of great value in assisting in the diagnosis. Short exercise testing (repeated single supramaximal stimulation of a motor nerve, typically ulnar, over a minute after 10 s of exercise) can demonstrate a decrement that repairs with repeated tests. Cooling does not affect the nerve response. On needle EMG, myotonic discharges are abundant, especially in distal muscles. In Becker's disease there may be a "warm-up" effect with fewer myotonic discharges after maximal contraction. Muscle biopsy is often unremarkable or demonstrates nonspecific changes. In more severe cases there may be increased fiber diameter variation, internalization of nuclei, and vacuolation. Genetic testing for mutations of the CLCN1 gene is commercially available.

11.21.5 Differential Diagnosis

Paramyotonia congenita, myotonic dystrophy, hyperkalemic periodic paralysis.

11.21.6 Therapy

Medications that primarily block skeletal muscle sodium channels may potentially help stabilize the muscle membrane

and control myotonia. Some of these medications include the following: mexiletine (150–1,000 mg/day), quinine (200–1,200 mg/day), dilantin (300–400 mg/day), procainamide (125–1,000 mg/day), tocainide, carbamazepine, and acetazolamide (125–1,000 mg/day). Procainamide and tocainamide are rarely used because of concerns with bone marrow suppression.

11.21.7 Prognosis

Overall, most patients with myotonia congenita have a good prognosis. However, in some patients, the myotonia can be severely disabling when untreated. The prognosis for Thompson's disease is especially benign, with mild progression over many years. Patients with Becker's myotonic dystrophy may develop significant persistent weakness later in life.

11.22 Paramyotonia Congenita

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

11.22.1 Distribution

Can affect the proximal and distal limbs as well as the face and neck.

Time Course Mild progression with gradual onset. Some patients may develop fixed weakness later in life.

Age of Onset Usually begins in late adolescence can begin earlier, even in infancy.

11.22.2 Clinical Syndrome

Paramyotonia congenita is a hereditary neuromuscular disorder typified by difficulty with muscle relaxation and transient weakness. Many patients with myotonia exhibit minimal to no symptoms at all. In more severely affected subjects, myotonia may affect both proximal and distal muscles. The disorder may present at any age, most commonly in late adolescence. Weakness can occur, usually beginning in late adolescence, although myotonia may present earlier, often in infancy. Myotonia is often worse in the cold and with exercise and may affect the face, neck, and upper extremities (Fig. 11.21). Episodic weakness may occur after exercise or cold exposure or may occur spontaneously. The weakness usually lasts for a few minutes but may extend to several days. Myotonia is usually paradoxical in that it worsens with exercise, in comparison to myotonia congenita.

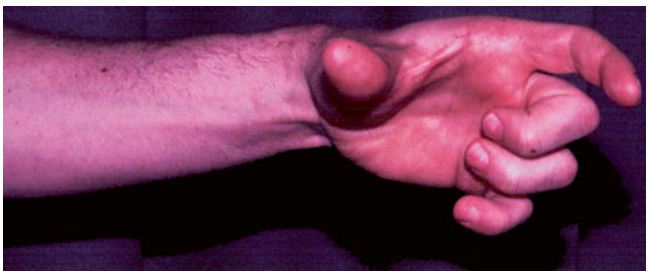

Fig. 11.21 Myotonia of the hand in a patient with cold-induced myotonia (Von Eulenburg's disease). The patient is trying to open his hand

11.22.3 Pathogenesis

Paramyotonia congenita is an autosomal dominant disorder associated with a gain of function mutation of the skeletal muscle sodium channel (SCN4A) gene on chromosome 17q23. At least 11 missense mutations have been described. Disruption of fast inactivation of sodium channels in this disorder is thought to lead to leakage of sodium ions into the muscle fibers, causing more persistent depolarization and producing myotonia.

11.22.4 Diagnosis

The CK is typically normal, though occasionally it can be mildly elevated. Electrophysiologic testing is of great value in assisting in the diagnosis. Short exercise testing (repeated single supramaximal stimulation of a motor nerve, typically ulnar, over a minute after 10 s of exercise) can demonstrate a decrement that becomes greater with repeated tests and even more so with cooling. Long exercise testing (repeated single supramaximal stimulation over 45 min after 5 min of exercise) also shows an early decrement in the response that can persist throughout the testing. On needle EMG, myotonic discharges are abundant, especially in distal muscles. With cooling, the myotonic discharges may initially worsen, but with prolonged cooling there is usually muscle paralysis, and the discharges disappear. Muscle biopsy is often unremarkable or demonstrates nonspecific changes. In some areas there may be subsarcolemmal vacuoles. Genetic testing for mutations of the SCN4A gene is commercially available and can help confirm the diagnosis.

11.22.5 Differential Diagnosis

Myotonia congenital, myotonic dystrophy, hyperkalemic periodic paralysis.

11.22.6 Therapy

Medications that primarily block skeletal muscle sodium channels may potentially help stabilize the muscle membrane

and control myotonia. Some of these medications include the following: mexiletine (150–1,000 mg/day), quinine (200–1,200 mg/day), dilantin (300–400 mg/day), procainamide (125–1,000 mg/day), tocainide, carbamazepine, and acetazolamide (125–1,000 mg/day). Procainamide and tocainamide are rarely used because of concerns with bone marrow suppression.

11.22.7 Prognosis

Overall, most patients with paramyotonia congenita have a good prognosis with few limitations. However, in some patients, the myotonia can be severely disabling when untreated. Some patients may also develop significant persistent weakness later in life.

11.23 Hyperkalemic Periodic Paralysis (HyPP)

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

11.23.1 Distribution

Proximal muscles symmetrically.

Time Course Flaccid, episodic weakness.

Age of Onset Usually in the first decade and progresses slowly over several decades.

11.23.2 Clinical Syndrome

The weakness frequently occurs in the early morning before eating and may also be associated with rest after exercise, fasting, and K + loading and usually spares facial and respiratory muscles. Reflexes are reduced. Episodes last up to 60 min on average. 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.

11.23.3 Pathogenesis

The periodic paralyses involve dysfunction of ion channels which regulate muscle membrane excitability, and weakness occurs when muscle fibers become electrically inexcitable.

HyPP is an autosomal dominant disorder. In HyPP, one or more of several missense mutations lead to a gain of function of the muscle sodium channel. Due to incomplete fast inactivation of sodium channels, a persistent inward sodium flow tends to depolarize muscle fibers causing uncontrolled repetitive firing of action potentials.

11.23.4 Diagnosis

Serum K+ is greater than 4.5 mEq/L. Serum CK is usually elevated during an attack. An oral potassium load provokes weakness in a fasting patient. The study should only be done if serum potassium and renal and cardiac functions are initially normal and monitored. The patient is given approximately 60 mEq KCl in a glucose-free liquid. Weakness typically occurs in 1½–2 h. Thirty minutes of exercise can also induce an attack and is associated with a second hyperkalemic period 15–20 min after exercise. On nerve conduction studies (NCS), the CMAP amplitude increases greater than normal immediately after 5 min of sustained exercise and reduces by 40 % or greater after resting 20–40 min. On electromyography, myotonic discharges may be seen in 50 % of individuals. With progression of the disease, muscle biopsy may show dilation, degeneration, or proliferation of the T-tubular system leading to vacuolar myopathy. Genetic testing for mutations in the alpha subunit of the human skeletal muscle voltage-gated sodium channel (SCN4A) on chromosome 17q23-25 is present in the majority of cases.

11.23.5 Differential Diagnosis

Paramyotonia congenital, hypokalemic periodic paralysis, acetazolamide-responsive myotonia congenital, thyrotoxic periodic paralysis, Andersen–Tawil syndrome.

11.23.6 Treatment

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. Unpublished reports suggest a good response to dichlorphenamide in single cases.

11.23.7 Prognosis

Most patients have a fairly good prognosis. However, one mutation (T704M) is associated with severe myopathy and permanent weakness.

11.24 Hypokalemic Periodic Paralysis (HoPP)

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

11.24.1 Distribution

Symmetric, legs greater than arms.

Time Course Acute episodes of flaccid weakness, approximately 25 % experience degenerative myopathy of limbs over years.

Age of Onset Teenage years.

11.24.2 Clinical Syndrome

In contrast to hyperkalemic periodic paralysis, the hypokalemic variant is associated with less frequent attacks, although the attacks are often longer and more severe. Males have more frequent attacks. HoPP 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.

11.24.3 Pathogenesis

Hypokalemic periodic paralysis is inherited as an autosomal dominant disorder.

11.24.4 Diagnosis

Potassium levels during an attack are usually low (<2–3 mEq/L) and rarely normal. CK levels are usually normal but may be increased during attacks. Glucose and insulin infusion can induce paralysis, but this should only be assessed with cardiac monitoring. On NCS, CMAP amplitudes are decreased during attacks and increased immediately after sustained (5 min) maximal contraction. In most affected subjects, there is then a progressive reduction in the CMAP amplitude during rest 20–40 min after the initial increment. HyPP is associated with a defect in several genes. These include loss of function mutations of the calcium channel α-1 subunit on chromosome 1q31-32 (CACNA1S) most commonly. Testing for sodium channel α subunit on chromosome 17q23 (SCN4A) or potassium channel (KCNE3) subunit MinK-related peptide 2 (MiRP2) may be useful in individual cases. Clear central vacuoles are observed on muscle biopsy. Vacuoles are thought to arise from proliferation and degeneration of the sarcoplasmic reticulum and the tubular system. Myopathic changes include variation in fiber size, split fibers, and internalized nuclei, in addition to tubular aggregates.

11.24.5 Differential Diagnosis

Thyrotoxic periodic paralysis, HyPP (Table 11.1), Andersen–Tawil syndrome.

11.24.6 Therapy

Oral potassium supplementation of 40–80 mEq 2–3 times per day will often decrease the severity of the attacks. Acetazolamide sustained release tablets (500–2,000 mg/day) or dichlorphenamide (50–150 mg/day) may reduce the frequency of the attacks. Use of potassium-sparing diuretics (triamterene or spironolactone) in combination with acetazolamide or dichlorphenamide may reduce the frequency of periodic paralysis attacks.

11.24.7 Prognosis

With appropriate treatment, the prognosis is usually good. Rarely, severe variants have respiratory failure.

Table 11.1 Comparison of hyper- and hypokalemic periodic paralysis (APs action potentials)

Features	HyPP	HoPP
Precipitating factors	Potassium, cooling, rest after strenuous exercise, fasting, stress	Rest after exercise, high-carbohydrate meal, glucose
Attack severity	Mild to severe	Severe
Duration of attack	1–4 h	Hours to days
NCS	CMAP amplitude significantly increased after 5 min of exercise and rapidly declines within 20 min of rest	CMAP amplitude decreased during attack, increased immediately after 5 min of intense exercise
EMG	Myotonic discharges	
Consequence of depolarization	Mix of autonomous APs and Na channel inactivation	Na channel inactivation prevents APs
Mutation	SCN4A 50–70 %	CACNA1S 75 %, SCN4A 10–15 %
Therapy	Mild exercise, carbohydrates; thiazides, acetazolamide	Potassium, acetazolamide

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Motor Neuron Diseases

12

Wolfgang N. Löscher and Eva L. Feldman

12.1 Amyotrophic Lateral Sclerosis

Genetic testing	NCS/EMG	Laboratory	Imaging	Biopsy
+ in familial ALS	++	–	(+)	–

12.1.1 Epidemiology

The incidence of amyotrophic lateral sclerosis (ALS) is 1.5–2.5/100,000, prevalence 4–6/100,000. Mean age of onset is between 58 and 63 years; men are slightly more affected. The disease is sporadic in most cases, but approximately 5 % are familial.

12.1.2 Anatomy and Pathophysiology

Loss of upper and lower motor neurons occurs and is seen on autopsy. TDP-43-positive ubiquitinated cytoplasmatic inclusions are found in motor neurons in sporadic ALS; the pathology is slightly different in some forms of hereditary ALS. Inclusions can also be found in frontotemporal lobes.

Glutamate excitotoxicity and free radical formation have been implicated in the pathophysiology of sporadic ALS. Mitochondrial abnormalities, autophagy, disrupted axonal transport, sodium-potassium ion pump dysfunction, insufficient release of neurotrophic factors by astroglia, and TDB-43 aggregates may play a role in triggering ALS.

12.1.3 Symptoms

Progressive focal painless weakness and atrophy without any sensory symptoms. Cramps and fasciculations are frequent. In patients with bulbar onset, speech is affected first and dysphagia develops later. Head drop and dyspnoea are rare initial symptoms. Dyspnoea usually is worse in supine position, and symptoms of nocturnal hypoxia, e.g., morning headache, daytime sleepiness and lack of concentration, can develop. Leg stiffness and loss of handedness are symptoms of predominant upper motor neuron disease.

Extraocular movements, bladder and bowel function, and sensation are spared. Obvious frontotemporal dementia (FTD) develops in 5–15 % of patients; 20–50 % show symptoms and signs of FTD on detailed cognitive and neuropsychological assessment.

12.1.4 Signs

Signs of upper (UMN) and lower motor neuron (LMN) dysfunction are evident in several body regions, e.g., the combination of weakness, atrophy, fasciculations, increased muscle tone, exaggerated reflexes and pathological reflexes. Disease onset is spinal in about two thirds and bulbar in the remainder. Bulbar symptoms include tongue atrophy (Fig. 12.1), dysarthria, and later on dysphagia and drooling. The masseter reflex is exaggerated. Hand weakness typically shows a "split-hand" pattern, with greater weakness in the radial

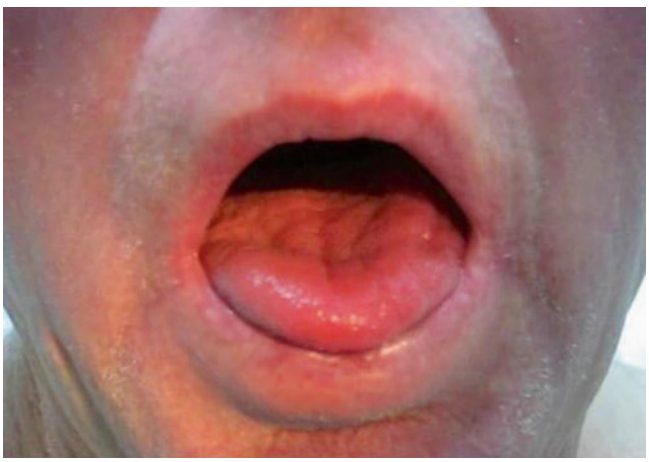

Fig. 12.1 Tongue atrophy is a striking feature in motor neurone disease. The atrophy is usually symmetric

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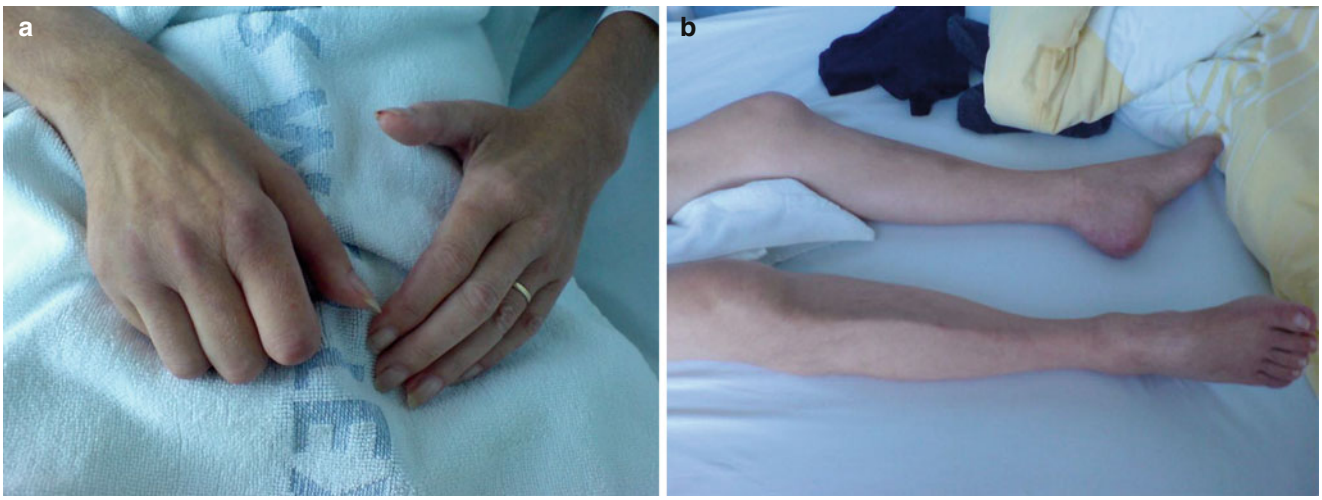

Fig. 12.2 Atrophies of the hands (**a**) and legs (**b**). This patient started with asymmetric proximal weakness of the lower extremities. One year later, the atrophy had progressed. This patient was positive for SOD1 gene

Table 12.1 Subtypes of sporadic amyotrophic lateral sclerosis

	Typical features	Prognosis
Classic ALS	UMN and LMN; FTD in app 5–15 %	Poor
Progressive muscular atrophy	Progressive LMN	Relatively poor
Flail arm/flail leg syndrome	Progressive LMN syndrome in the arms/legs. Confided to arms/legs for at least 12 months after symptom onset	Relatively good
Progressive bulbar palsy	Bulbar onset and no other symptoms for at least 6 months after symptom onset	Very poor
Respiratory	Respiratory signs and symptoms at onset, only minor bulbar or spinal signs in the first 6 months	Extremely poor
Primary lateral sclerosis	Absence of LMN signs for at least 4 years after disease onset	Good
Upper motor neuron predominant ALS	Pure LMN syndrome for 3 years but signs of LMN in the 4th year	Relatively good

aspect of the hand. Signs of frontotemporal dementia include pathological laughing and crying, impaired judgement and other deficits of executive function of language or personality (Fig. 12.2).

The disease is progressive, and approximately 50 % of patients die within 30 months of symptom onset; only about 20 % survive 5–10 years. Table 12.1 lists features and prognosis of ALS subgroups.

12.1.5 Causes

ALS is mostly sporadic. The cause for sporadic ALS remains unknown.

ALS is familial (fALS) in approximately 5 %. fALS is currently diagnosed in cases with a first or second degree relative that is also affected with ALS. Most known fALS-causing genes are inherited in an autosomal dominant trait with variable penetrance. Clinically, fALS is indistinguishable from sporadic ALS in most cases. A hexanucleotide repeat expansion in *C9ORF72* causes approximately 20 % of fALS. Mutations in *SOD1*, *FUS* and *TARDBP* cause approximately 10, 5 and 5 %, respectively, of fALS. There is a clear overlap with FTD in *C9ORF72*, *FUS* and *TARDBP* fALS.

12.1.6 Diagnosis

Diagnostic criteria depend on the number of body regions showing signs of UMN and LMN dysfunction. Four regions (bulbar, cervical, thoracic and lumbar) are defined. The revised El Escorial criteria have been replaced by the Awaji-Shima criteria (Table 12.2).

Electrophysiology NCS exclude other disorders, especially multifocal motor neuropathy with conduction block. In ALS, motor nerve conduction studies can show low-amplitude CMAP. Sensory NCS are normal.

EMG demonstrates evidence of lower motor neuron degeneration. Complex fasciculations, fibrillation and sharp waves and unstable and chronic neurogenic motor unit potentials are accepted (Awaji-Shima criteria). At least two muscles in arms and legs and one bulbar and one thoracic

Table 12.2 Awaji-Shima criteria (LNM affected clinically *or* electrophysiologically)

Clinically possible ALS	Clinically probable ALS	Clinically definite ALS
UMN and LNM in 1 region		
or		
UMN in 2 regions	UMN and LNM in 2 regions	UMN and LNM in 3 regions
or		
LMN signs above UMN signs		

muscle should be studied. Transcranial magnetic stimulation does not reveal ALS-specific findings.

Imaging (MR, CT Scan, Ultrasound) Ultrasound of the tongue can reveal fasciculations. At present, MRI is not recommended to diagnose or monitor ALS. Imaging is necessary to exclude ALS-mimicking disorders.

Laboratory Erythrocyte sedimentation rate; full blood count; glucose, urea, and electrolyte analysis; renal, liver, and thyroid function; B12 and ANA measurement; rheumatoid factor test; and serum protein electrophoresis and immunofixation should be obtained to exclude other causes.

In atypical or young cases, CSF analysis, hexosaminidase A and B, HTLV-1 testing, and urine heavy metal screening are included. Genetic testing is performed in suspected fALS.

12.1.7 Differential Diagnosis

Depending on the phenotype: cervical myelopathy, Hirayama disease, spinal muscular atrophy, spinobulbar muscular atrophy, poliomyelitis and post-polio syndrome, hexosaminidase deficiency, multifocal motor neuropathy, heavy metal poisoning, hereditary spastic paraplegia, hereditary motor neuropathies, HIV myeloradiculoneuropathy, subacute combined degeneration, inclusion body myositis, hyperparathyroidism.

12.1.8 Therapy

Riluzole 100 mg daily is safe and probably prolongs survival by about 2–3 months in patients with ALS. Liver function monitoring is needed during riluzole treatment.

PEG tube, non-invasive ventilation to treat dysphagia, and respiratory insufficiency.

Anticholinergic antidepressants, anticholinergic drugs, and botulinum toxin injections in salivary glands to treat sialorrhoea.

Physiotherapy, muscle relaxants, anticonvulsants, and opioids to treat cramps and musculoskeletal pain.

Braces, ambulatory support, and communication devices.

Benzodiazepines and opioids to alleviate respiratory distress and anxiety.

A multidisciplinary treatment approach is recommended.

12.2 Spinal and Bulbar Muscular Atrophy (SBMA, Kennedy Syndrome)

Genetic testing	NCS/EMG	Laboratory	Imaging	Biopsy
+++	+	(+)	–	–

12.2.1 Epidemiology

SBMA is a rare X chromosome-inherited adult-onset motor neuron disease.

12.2.2 Anatomy and Pathophysiology

CAG repeat expansion of the androgen receptor on the X chromosome. A toxic gain of function is suspected. Age of disease onset is inversely linked to the size of the expansion.

12.2.3 Symptoms

Initial symptoms are hand tremor and proximal leg weakness. Nasal speech and dysphagia at later stages. Median onset of tremor is around 35 years, weakness at 45 years, dysarthria at 50 years and dysphagia at 55 years of age. Fifty percent of patients are wheelchair bound at 61 years. Survival is minimally reduced compared to controls.

12.2.4 Signs

Proximal leg and, to a lesser degree, arm weakness, nasal speech, tongue atrophy and dysphagia. Fasciculations in tongue and face; perioral fasciculations are typical. Tendon reflexes are reduced or absent, and a postural tremor of the hands is frequently observed. Gynecomastia is seen in approximately 50 % and testicular atrophy in some (Fig. 12.3).

12.2.5 Causes

CAG repeat expansion of the androgen receptor on the X chromosome. Repeat length is between 40 and 60 repeats.

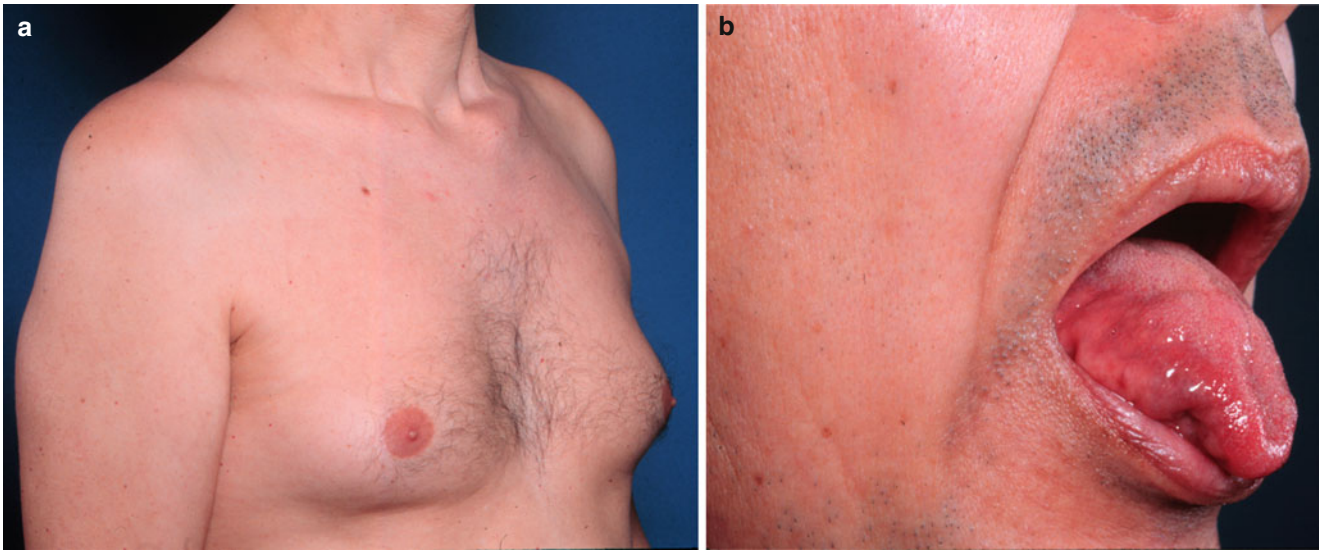

Fig. 12.3 Kennedy syndrome: (**a**) gynecomastia, (**b**) tongue atrophy

12.2.6 Diagnosis

Genetic testing when SBMA is suspected. Muscle and nerve biopsies are not recommended.

Electrophysiology Routine motor nerve conduction studies are normal or show low-amplitude DMAP. SNAPs of the sural nerve are reduced or absent. EMG shows high-amplitude, long-duration motor unit action potentials. Grouped discharges can be seen.

Imaging None.

Laboratory Ck is elevated (<1,000 U/l). Serum hormone levels are generally normal.

12.2.7 Differential Diagnosis

Lower motor neuron variant of ALS, spinal muscular atrophy, post-polio syndrome.

12.2.8 Therapy

Supportive treatment.

12.3 Spinal Muscular Atrophies (SMA)

Genetic testing	NCS/EMG	Laboratory	Imaging	Biopsy
+++	+	–	–	+

12.3.1 Epidemiology

SMA is the most common motor neuron disease in infants, children and young adults with an incidence of approximately 11/100,000 live birth. It is rare in adults.

12.3.2 Anatomy and Pathophysiology

The autosomal recessive inherited disease results in a loss of spinal alpha motor neurons. Anterior roots are atrophied.

12.3.3 Symptoms

Based on disease onset, the SMAs are divided into four forms which are shown in Table 12.3

12.3.4 Signs

Weakness in SMA3 and SMA4 is proximal and more so in the legs. Quadriceps and psoas muscles are weaker than the hamstrings. Tendon reflexes are reduced or absent. A fine tremor and fasciculations can be seen in the hands (Figs. 12.4 and 12.5).

12.3.5 Causes

Most cases of SMA are caused by homozygous deletions in exons 3, 6, 7 or 8 of the survival motor neuron gene 1 (*SMN1*)

Table 12.3 Forms of SMA

	Onset	
SMA1 (Werdnig-Hoffmann)	Between 0 and 3 months	Hypotonia, poor feeding, respiratory insufficiency, and failure; 95 % deceased by 18 months
SMA2 (intermediate form)	<18 months	Never able to stand or walk; scoliosis and respiratory insufficiency develops; lifespan reduced
SMA3 (Kugelberg-Welander)	3a: <3 years 3b: 3–30 years	Able to stand and walk; proximal weakness; lifespan may be reduced in type 3a
SMA4	>30 years	Able to stand and walk; proximal weakness; lifespan normal

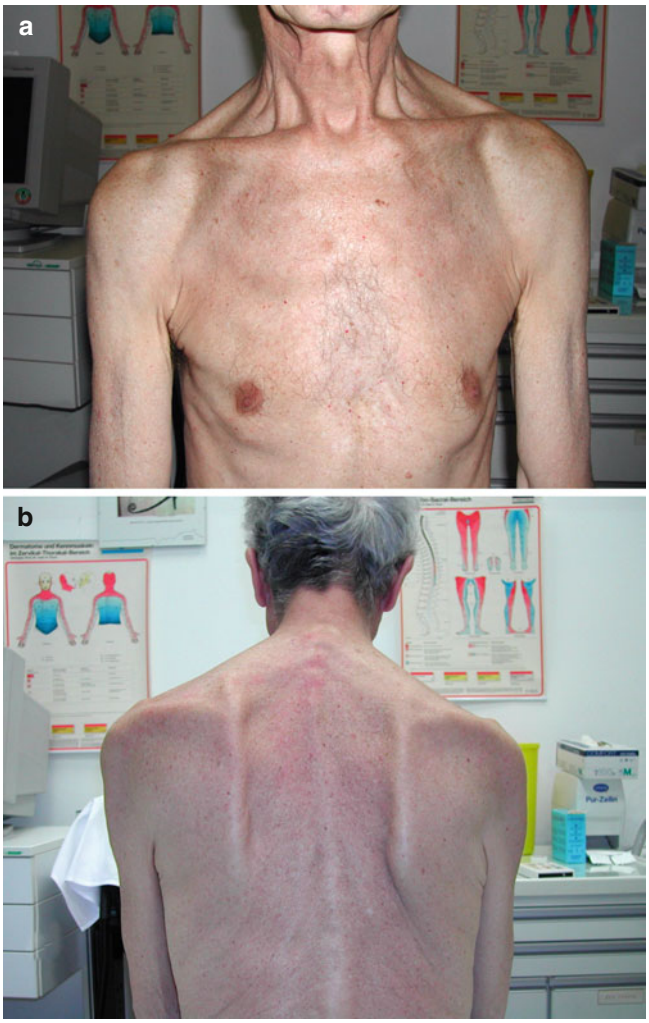

Fig. 12.4 SMA. Marked generalized muscle atrophy due to slowly progressive disease. Symmetric atrophy of the trapezoid muscles (**a**), mild winging (**b**) of the medial borders of the scapula

on chromosome 5q13.2. Mutations in these exons are rare. Disease severity is correlated with the number of copies of the *SMN2* gene; SMA1 usually has 2, SMA2 3 and SMA3 4–8 *SMN2* copies. Deletion of *SMN1* and *SMN2* is lethal.

In the late-onset SMA4 phenotype, *SMN1* deletions/mutations are frequently absent. The carrier frequency of *SMN1* mutations in the general population is 2–3 %.

12.3.6 Diagnosis

Genetic testing in patients with suspected SMA.

Electrophysiology Routine motor nerve conduction study shows low-amplitude CMAP in affected muscles. Sensory NCS are usually normal. EMG shows high-amplitude, long-duration motor unit action potentials; in SMA1 and SMA2, spontaneous activity can be found.

Imaging None.

Laboratory CK can be slightly elevated; Muscle biopsy is not necessary and would show grouped muscle fibre atrophy.

12.3.7 Differential Diagnosis

The differential diagnosis of SMA3b and SMA4 includes limb-girdle muscular dystrophies, hexosaminidase deficiency, polio- and post-polio syndrome, hereditary motor neuropathies, spinal and bulbar muscular atrophy, and the lower motor neuron variant of ALS. In SMA1, consider all causes of floppy infant syndrome; in SMA2 and 3b, differentiate congenital myopathies and juvenile onset limb-girdle muscular dystrophies.

12.3.8 Therapy

Supportive treatment, physical therapy, and braces. Surgery in cases with severe scoliosis.

12.4 Poliomyelitis and Post-Polio Syndrome (PPS)

Genetic testing	NCS/EMG	Laboratory	Imaging	Biopsy
–	+	+++	–	–

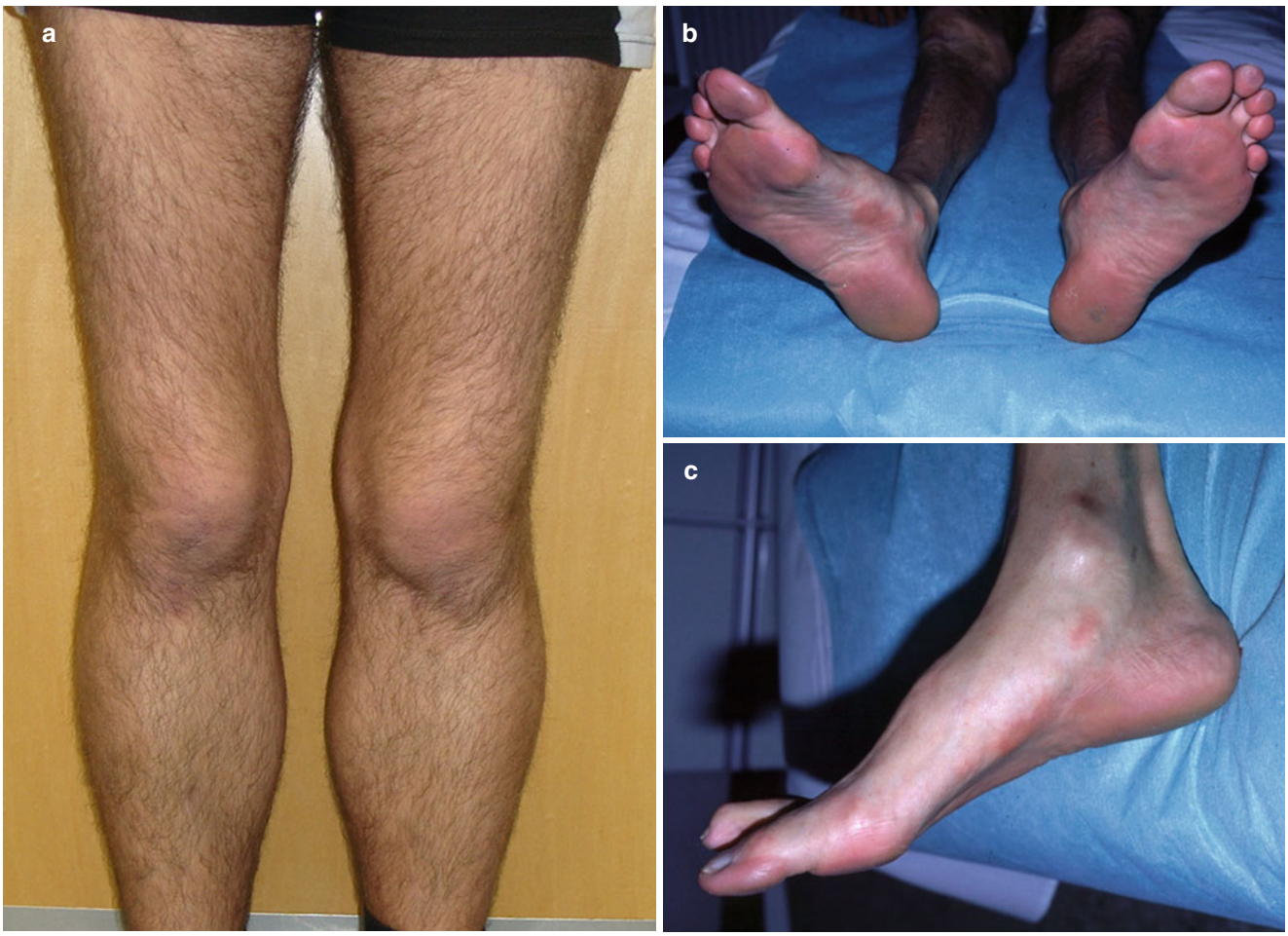

Fig. 12.5 Proximal atrophy in a patient with genetically proven SMA 3. (**a**) Atrophy of thighs. (**b, c**) Foot deformity (courtesy of B. Schoser, Munich Germany)

12.4.1 Epidemiology

Poliomyelitis has become extremely rare in countries with effective immunization programmes, but it is still frequent in resource-poor countries. The risk of developing acute paralytic poliomyelitis (APP) secondary to oral immunization is approximately 1/2.5 million doses administered, and 5–10 such cases are reported in North America each year.

The post-polio syndrome (PPS) is observed in 28–64 % of patients with previous poliomyelitis.

12.4.2 Anatomy and Pathophysiology

In APP, the virus reaches the CNS via the lymphatic system of the pharynx and intestines and haematogenous spread. It affects the anterior horn cells and brain stem nuclei causing an inflammatory reaction. Cell death with denervation and muscle atrophy results, but surviving motor neurons can reinnervate denervated muscles by distal sprouting.

The pathophysiology of PPS remains unclear, but it may be caused by distal degeneration of enlarged motor unit due to immunological mechanisms, the effects of aging, or overuse and disuse.

12.4.3 Symptoms

Ninety five percent of people exposed to the virus are asymptomatic. In the remainder, a minor, major or paralytic form develops within 1–10 days after exposure, and about 50 % of patients with major disease develop APP.

The PPS develops after a mean of 36 years following APP. New muscle pain, fatigue and weakness develop in muscles, which usually have been affected during the acute disease but had regained full strength afterwards.

12.4.4 Signs

The signs are listed in Table 12.4. APP can be fatal in 5–10 % (up to 60 % in patients with bulbar symptoms) due to respiratory and cardiac problems.

Table 12.4 Poliomyelitis and post-polio syndrome

	Symptoms	Signs
Minor disease	Malaise; myalgia; sore throat; diarrhoea	Fever pharyngitis; gastroenteritis
Major disease	Headache; myalgia; nausea; vomiting; restlessness; irritability	Fever; signs of meningitis
Acute paralytic poliomyelitis	Myalgia; hyperesthesia	Weakness in legs > arms > bulbar; can be focal with rapid spreading; fasciculations; areflexia; eventually atrophy develops; urinary retention; blood pressure instability; cardiac arrhythmias; constipation; increased or decreased sweating
Post-polio syndrome	Generalized and muscular fatigue; muscle and joint pain; muscle cramps; cold intolerance	New weakness; new atrophy in some usually later during the disease; dysphagia and respiratory dysfunction

All patients with PPS show new weakness, and 20–30 % develop new atrophy. Dysphagia and respiratory dysfunction occur in some, regardless of whether there was bulbar involvement during the acute disease (Fig. 12.6).

12.4.5 Causes

APP is a viral infection acquired by faecal-oral contamination and caused by one of three forms of enterovirus, a single-stranded RNA virus in the picorna family.

The cause of PPS remains unclear.

12.4.6 Diagnosis

APP is diagnosed by the typical clinical and CSF findings and virus isolation from stool or throat cultures.

The diagnosis of PPS rests upon the typical clinical findings of new weakness, fatigue, and muscle pain; a history of previous APP; a period of neurological recovery followed by an interval of stable neurological function; and the exclusion of other disorders.

Electrophysiology Sensory NCS are normal in APP and PPS. CMAP is low in amplitude when recorded from affected muscles.

EMG in APP initially shows reduced MU recruitment and spontaneous activity in the form of fibrillations and positive sharp waves after 2–3 weeks. Over time, reinnervation results in polyphasic and enlarged MUs.

In PPS, polyphasic and enlarged MUs are found; single-fibre EMG studies show increased fibre density and increased jitter and blockings.

Imaging In APP, inflammation of the anterior horn can be seen on spinal MRI.

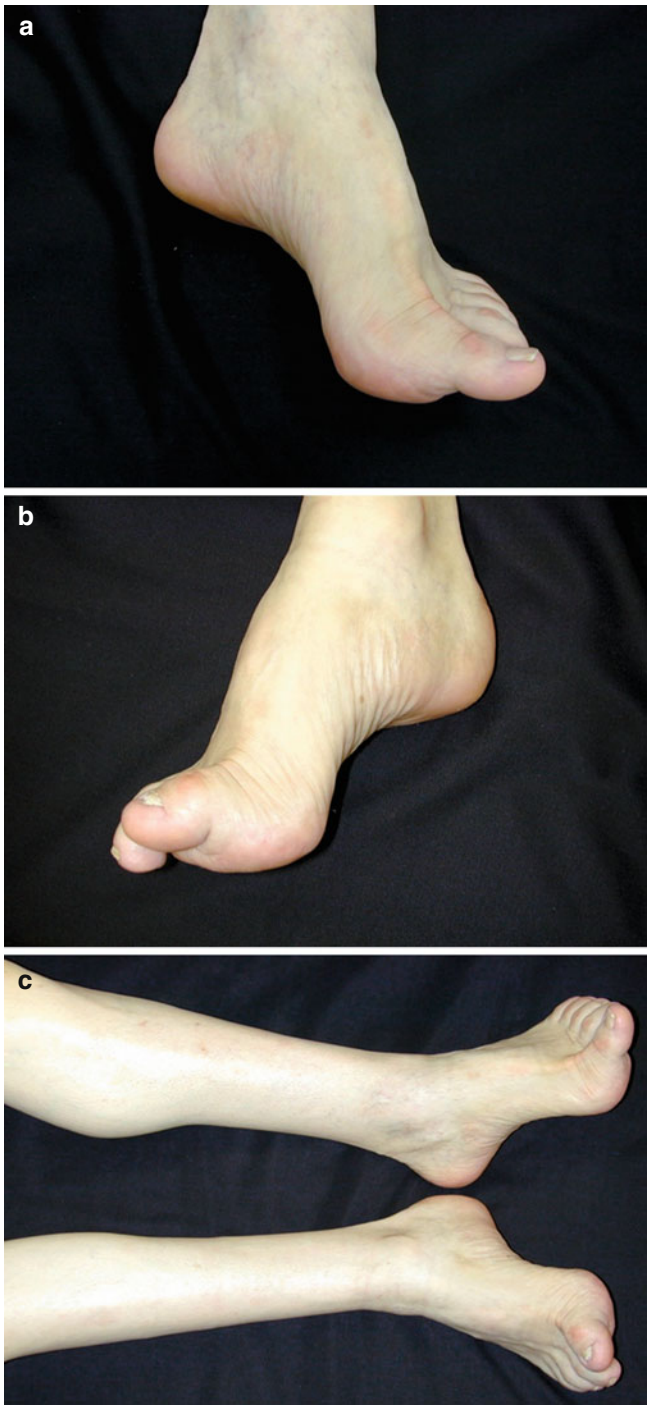

Fig. 12.6 Post-polio syndrome: with polio in early infancy. (**a**, **b**) Foot deformity reveals early onset. (**c**) Often involvement of the lower limbs is asymmetric; in this case, the right calf is more atrophic than the left

Laboratory Virus can be detected in stool and throat cultures during the first 2–3 weeks in APP. A fourfold or greater increase in serum antibody titres in repeated measurements is also considered diagnostic.

CSF in APP shows a polymorphonuclear and later lymphocytic pleocytosis. CSF protein is slightly to moderately elevated. In PPS, CK can be mildly elevated.

12.4.7 Differential Diagnosis

The differential of APP includes Guillain-Barré syndrome, acute transverse myelitis, botulism, tick paralysis, neuromuscular junction disease, and myopathies.

The differential of PPS includes adult spinal muscular atrophies, lower motor neuron variant of ALS, spinal stenosis, multifocal motor neuropathy, inflammatory myopathy and heavy metal toxicity.

12.4.8 Therapy

Treatment of APP is symptomatic. Early physical therapy is recommended to prevent deformities. Assistive devices and orthopaedic surgery can be necessary.

In PPS, a comprehensive management programme which includes management of pain, fatigue, dysphagia, respiratory dysfunction and psychosocial difficulties is recommended. Proper exercise, avoidance of overuse and assistive devices are helpful.

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Autonomic Nervous System

13

Walter Struhal and James W. Russell

13.1 Introduction

The autonomic nervous system (ANS) controls the synergistic action of all visceral organs in the human body (Lahrmann et al. 2011). Autonomic nervous system diseases lead to dysfunction of blood pressure, heart rate, sudomotor function, digestion, urinary function, and sexual function. ANS dysfunction may originate in the CNS or peripheral nervous system (PNS) and may be widespread or focal. Despite the complex distribution of the ANS and the variable consequences of ANS dysfunction, the aim of investigating the ANS is to transform the clinical picture into a coherent explanation of the patient's autonomic problem. More precisely, the aim should be to define the functional and autonomic involvement (sympathetic, parasympathetic, central, or peripheral disease), identify a common autonomic syndrome (orthostatic hypotension, autonomic neuropathy, postural orthostatic tachycardia syndrome, reflex syncope), and treat treatable diseases. To achieve this aim, a comprehensive history, appropriate autonomic tests, and laboratory tests are necessary.

13.2 Anatomy

The anatomy of the ANS is complex. CNS centers serve specific integrative tasks, while spinal and peripheral components are organized into the sympathetic, parasympathetic, and enteric ANS (Low and Benarroch 2008).

13.2.1 Autonomic CNS Structures

Several CNS structures coordinate autonomic afferents and efferents. The *insular cortex* represents the primary viscerosensory cortex and is organized in a viscerotropic pattern. It is the primary area for pain and temperature projection and controls sympathetic and parasympathetic output. The *anterior cingulate* modulates autonomic activation due to motivation and goal-directed behavior, and the *amygdala* is responsible for integrated autonomic and emotional responses. The *hypothalamus* orchestrates organ function: neuroendocrine control by the periventricular zone, homeostasis (including thermo- and osmoregulation, food intake, reproduction) by the medial zone, and arousal and behavior (sleep-wake cycle, feeding, reward responses) by the lateral zone. Several areas are involved in integration of autonomic, somatic, and nociceptive information, especially the *periaqueductal gray* and the *parabrachial nucleus*. An important relay station for taste and visceral afferents as well as all medullary reflexes for circulation, respiration, and gastrointestinal function is the *nucleus of solitary tract*. Vessel constriction, cardiac function, and respiration are controlled by the *ventrolateral medulla*.

13.2.2 Sympathetic Nervous System

CNS Sympathetic preganglionic neurons originate in the T1 to L3 spinal cord levels, primarily in the *intermediolateral nucleus*. Neurons are small myelinated fibers organized in functional units, each responsible for specific organ tasks.

PNS Preganglionic cholinergic neurons project to two types of ganglia: prevertebral and paravertebral ganglia. Neurons originating in prevertebral ganglia (*celiac*, *superior*, and *inferior mesenteric* ganglia) innervate the abdominal and pelvic organs and vessels. Paravertebral ganglia innervate all other tissues. The primary neurotransmitter for all preganglionic neurons is acetylcholine (ACh) and for postganglionic neurons is norepinephrine except for neurons innervating sweat glands that are also cholinergic.

Main Functions

- Blood pressure regulation
- Thermoregulation
- Cardiovascular and metabolic responses to exercise, stress, and emotion.

E.L. Feldman et al., *Atlas of Neuromuscular Diseases*,
DOI 10.1007/978-3-7091-1605-0_13, © Springer-Verlag Wien 2014

Typical Reflex Tests Noradrenergic sympathetic ANS:
- Blood pressure dynamics during the Valsalva maneuver or upon standing
- Plasma catecholamines.

Cholinergic sympathetic ANS (sudomotor function):
- Quantitative sudomotor axon reflex test (QSART)
- Sympathetic skin response test (SSRT)

13.2.3 Parasympathetic Nervous System

CNS Cranial nerves III, VII, and IX main nuclei and functions: *Edinger-Westphal nucleus*, pupil constrictor and ciliary body (III); *superior salivatory nucleus*, lacrimal glands and skull sinuses as well as nasal cavity (VII); and *inferior salivatory nucleus*, parotid gland (IX).

Cranial nerve X: nerve fibers originate from the *dorsal motor nucleus* and the ventrolateral portions of *nucleus ambiguus* and innervation of the heart (mainly fibers from nucleus ambiguus) and respiratory tract and gastrointestinal tract (mainly fibers from the dorsal motor nucleus), terminating at the flexura coli sinistra.

Sacral preganglionic output arises from the *sacral preganglionic nucleus* located in the lateral gray matter of segments S2–S4.

PNS Cranial nerves III, VII, IX, and X as well as the sacral output synapse to postganglionic cholinergic fibers in ganglia close to the target tissues. The primary neurotransmitter for all pre- and postganglionic fibers is ACh.

Main Functions Vagus nerve:
- Beat-to-beat heart rate control
- Esophageal motility, gastric relaxation and evacuation, and gastrointestinal peristalsis.

  Sacral neurons: micturition, defecation, and penile erection

Typical Reflex Tests Heart rate variability during deep breathing and Valsalva

13.2.4 Enteric Nervous System

A huge number of autonomic nerve fibers from two plexuses innervate the intestines: the myenteric plexus (from the pharyngoesophageal junction to the anal sphincter) and the submucosal plexus (small and large intestines).

Main Function Coordinated peristalsis and secretion

Typical Tests Colon transit time

13.3 History Taking and Bedside Tests

A detailed history is of crucial importance. Many patients with cardiovascular autonomic diseases report transient loss of consciousness (TLOC). TLOC is defined as an apparent loss of consciousness with a rapid onset, a short duration, and a spontaneous and complete recovery. The examiner should gather information from as many events as possible from the patient, and if possible an eyewitness, to distinguish TLOC from other causes of falls, including epileptic spells. In addition, the patient should be asked about symptoms occurring in upright position and ceasing in lying position, for example, dizziness, lightheadedness, visual disturbances, headache, nausea, pallor, or evidence of epilepsy. Symptoms might be aggravated in the early morning (due to nycturia) and by a carbohydrate-rich meal, menstruation, or prolonged standing. Most patients with autonomic neuropathies do not have TLOC but may have presyncopal symptoms. Sudomotor involvement is a frequent feature of autonomic peripheral neuropathy and may be focal (e.g., socks still wet after prolonged exercise) or generalized (e.g., severe heat intolerance). Gastrointestinal symptoms may be present, for example, constipation or diarrhea, abdominal cramps, or postprandial symptoms. The presence of incontinence and sexual dysfunction should be documented. Validated autonomic scores provide a standardized system to document and quantify the presence of autonomic symptoms (Zilliox et al. 2011).

A careful history and examination focused on autonomic dysfunction may be supplemented with an office or bedside standing test to assess for symptomatic orthostasis. A common protocol is the Schellong test, but for sake of time, this protocol can be changed. Initial measurements are taken with the patient resting supine for 5–10 min. Steady-state supine measurements are critical as a starting point for further analysis. The patient then stands and blood pressure and pulse are measured at heart level immediately and then at least every second minute for up to 10 min. Critical time point measurements are at 1, 3, and 5 min after standing. To further evaluate patients with dysautonomic neuropathies, standardized testing should be performed in an autonomic laboratory.

13.4 Autonomic Testing

Standardized autonomic tests that can be performed in most autonomic laboratories are discussed below (Assessment Subcommittee of the American Academy of Neurology 1996).

Autonomic testing should be performed in a temperature-controlled room (23 °C). Laboratory assistants should be well trained and a physician experienced in autonomic testing in the room or closely available. Noise or other stress factors (e.g., full bladder) should be avoided. If possible, medications that significantly affect autonomic function should be discontinued prior to testing in order to allow adequate washout of the drug and its effects on the autonomic nervous system.

13.4.1 Cardiovascular Reflex Tests

The patient is usually placed in a supine position for 30 min to obtain a steady state. The heart rate is measured

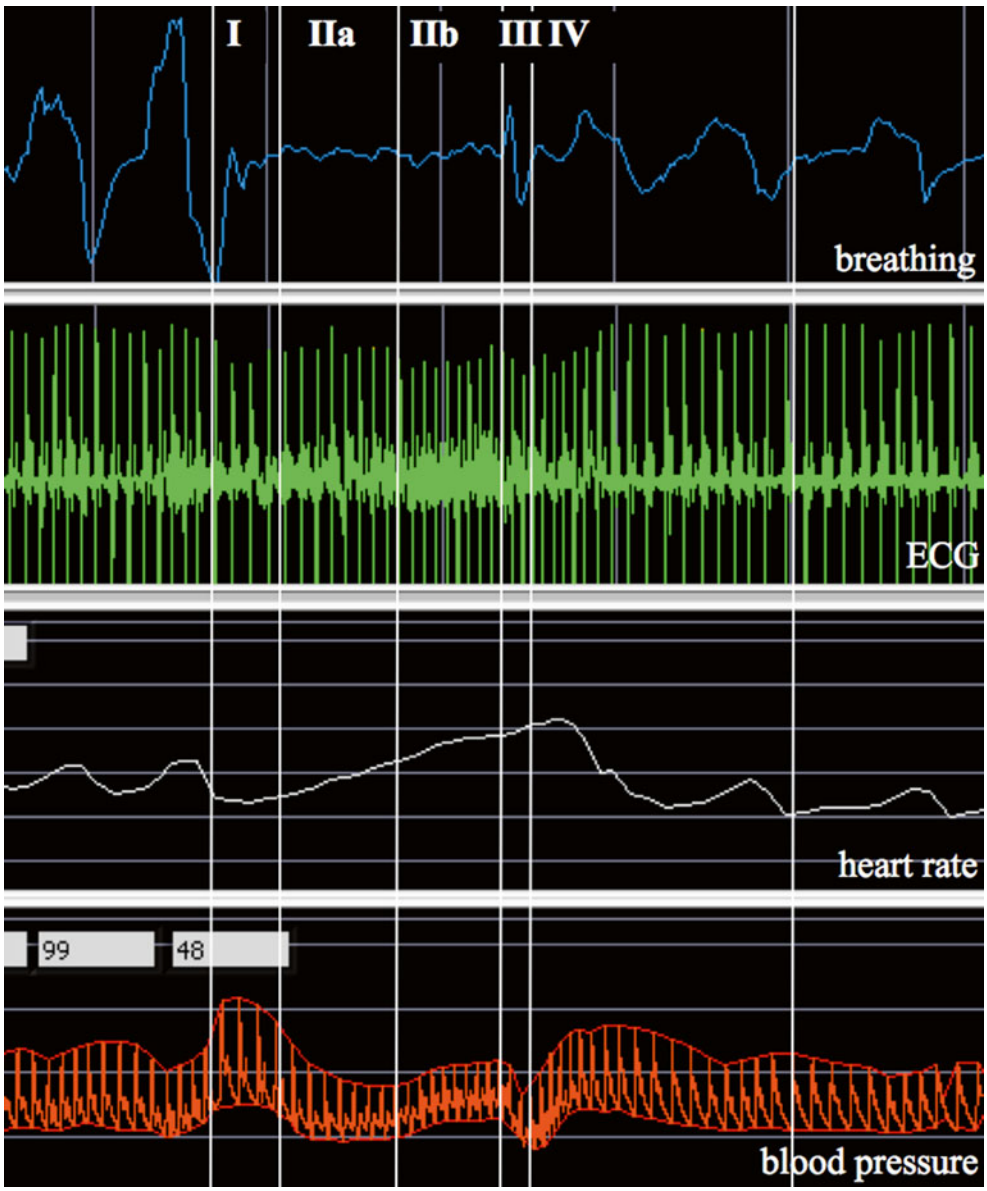

Fig. 13.1 Valsalva maneuver: (*I*) mechanical compression of vena cava with decreased venous return to the heart leads to increased cardiac output, (*II*) reduced blood flow to the heart due to increased intrathoracal pressure with compensatory heart rate increase (parasympathetic reaction) in early phase II (*IIa*) and blood pressure increase in late phase II (*IIb*) (sympathetic reaction), (*III*) dilatation of vena cava due to sudden intrathoracal pressure fall, and (*IV*) compensatory blood pressure increase due to latency in sympathetic response and sympathetic outburst in phase III

employing a 3-channel ECG, respiration by a piezo-belt or a nose-mouth temperature sensor, and blood pressure by noninvasive beat-to-beat measurement (volume-clamp technique). Autonomic testing should obtain beat-to-beat blood pressure measurements, in order to obtain important real-time data on autonomic function.

Deep Breathing

Typically the heart rate is measured at 6 breaths per min (5 s inspiration and 5 s expiration) for 80–90 s. After a waiting period of 2 min, the test may be repeated. Typical evaluations include the expiratory/inspiratory ratio or heart rate range (maximum-minimum) over five consecutive intervals. This test is a valuable tool for measuring parasympathetic vagal activity.

Valsalva Maneuver

The patient is asked to blow into a tube. The air pressure should be measured and maintained with about 40 mmHg for 15 s. A small air leak ensures an open glottis. The Valsalva reaction is divided into four phases (Fig. 13.1). Heart rate changes are evaluated employing the Valsalva ratio (highest heart rate during the Valsalva maneuver divided by the lowest heart rate following the maneuver). The Valsalva ratio reflects parasympathetic vagal function. Blood pressure recovery during late phase II (IIb) primarily is controlled by sympathetic α-adrenergic control and phase IV blood pressure overshoot by sympathetic β-adrenergic control.

Tilt Table

After reaching a steady-state blood pressure and pulse, patients are tilted to a 70° angle for a variable period of

time depending on the autonomic syndrome suspected (e.g., orthostatic hypotension 5–10 min, reflex syncope 45–60 min). After a modest decrease in systolic and diastolic blood pressure during the first minute, the blood pressure should return to baseline and be stable during the test.

13.4.2 Sudomotor Tests

Sudomotor testing evaluates disorders of sweating (hypo- or hyperhydrosis) and their distribution (focal or generalized) (Lahrmann et al. 2011). Evaluation of sudomotor function can provide early diagnosis of small fiber neuropathy and is used to provide a measure of cholinergic sympathetic function. The sympathetic skin response (SSRT) can be used to assess the skin sympathetic response but is relatively insensitive and poorly reproducible. In contrast, the quantitative sudomotor axon reflex test (QSART) is a reproducible test to assess postganglionic cholinergic sympathetic function. The thermoregulatory sweat test provides a subjective global assessment of cholinergic sympathetic function. The QSART and SSRT are discussed below:

QSART This test measures postganglionic axon reflex-mediated sweat production in a small restricted area of the skin over time. The neural pathway consists of the postganglionic sympathetic sudomotor axon. To stimulate the reflex, ACh is applied on the skin and follows an electric potential into the skin (iontophoresis). The axon terminal M3 muscarinic receptors are activated by ACh intradermally and trigger an action potential. The action potential travels antidromically, reaches a branch point, and travels orthodromically to release ACh from the nerve terminal. Quantitative sweat production in microliters is recorded at four defined sites in the forearm, proximal leg, distal leg, and dorsal foot (Figs. 13.2, 13.3, and 13.4).

SSRT This measure of electrodermal activity provides a surrogate marker of sympathetic cholinergic sudomotor activity. An arousal stimulus (electric, acoustic, deep breath) induces a change in skin potential, which is usually recorded from the palms and soles of the feet.

In sympathetic dysfunction, SSRTs are absent in at least one channel or exhibit 50 % amplitude reduction or prolonged latencies compared to normal values. Although this test is very easy to perform and integrated in many commercial EMG devices, there are serious limitations:

1. Habituation
2. High intra- and interindividual variability
3. Normal age-related decline in SSRT response.

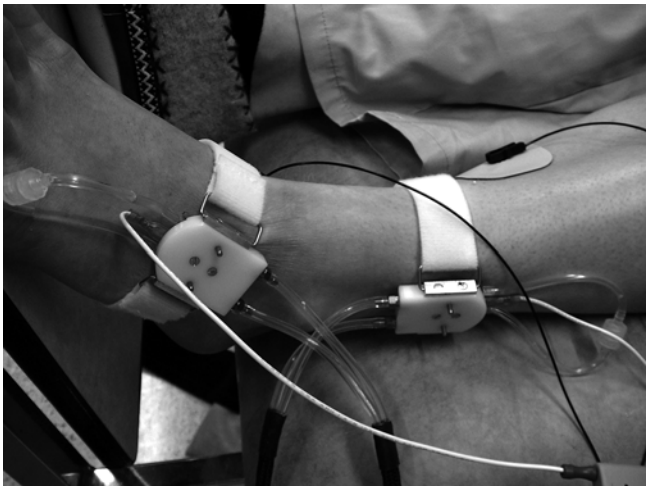

Fig. 13.2 QSART: local quantitative measurement of sudomotor function employing multicompartmental sweat capsules (white capsules) and iontophoresis of acetylcholine into the skin (electrodes)

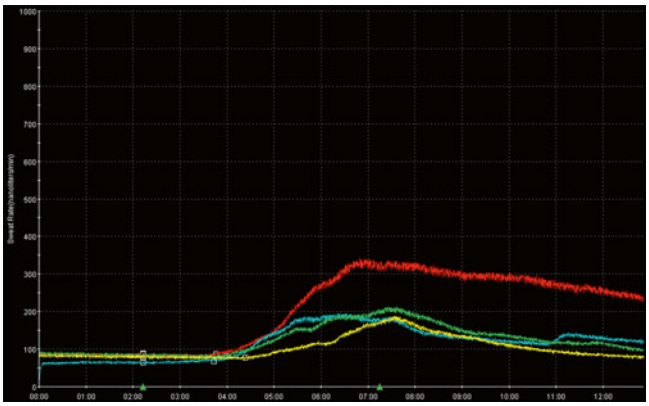

Fig. 13.3 QSART of a healthy control male age 31 years. A steady-state resting sweat production is reached. After starting iontophoresis (*first triangle*), the sweat production increases (*red*, left arm; *green, blue, yellow*, left leg) and then decreases to baseline after stopping iontophoresis (*second triangle*)

13.5 Autonomic Syndromes

13.5.1 Orthostatic Hypotension (OH)

OH is a common, yet underdiagnosed, disorder (Lahrmann et al. 2006). Untreated OH can increase the risk of falls and might contribute to morbidity, disability, or even death because of the potential risk of injury. OH may be the first sign of an autonomic dysfunction. OH may be worsened by age, medication, or dehydration.

Typical prodromi might be reported (lightheadedness, visual disturbances, coat hanger ache, etc.). Blood pressure reduction has to be fast enough to be both noticed by the

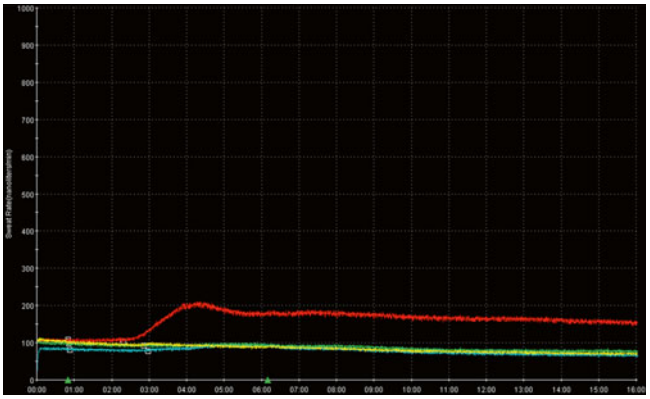

Fig. 13.4 QSART of an 82-year-old male with diabetic polyneuropathy. In this patient there is a small fiber neuropathy showing a pathologic "hung up" response in the upper extremity (probably an equivalent of spontaneous activity in axonal damage in somatic motor nerves). There is no response from the three capsules in the lower extremity

patient and stored to memory in order for the patient to be able to report prodromi. Thus, reports of prodromi might be missing in autonomic syncope, especially in elderly patients.

Red Flags in History

- Symptoms occurring soon after standing up
- In connection with initiation or dose change of autonomic medication
- During prolonged standing in crowded or hot places
- Presence of autonomic neuropathy
- After eating or after exertion.

Criteria Reduction of blood pressure of 20 mmHg systolic or 10 mmHg diastolic from lying to standing position (Fig. 13.5b)

Office Tests for OH Standing test for 5 min.

Autonomic Tests for OH Deep breathing, Valsalva, tilt table for at least 10 min (longer periods may be helpful to test for prolonged OH), active standing (initial OH), and plasma catecholamines.

Therapy Nonpharmacological countermeasures are the first-line therapy.

Things to Do

- Drink 3–4 l of water daily to ensure adequate hydration.
- Stand up slowly.
- Physical counter maneuvers immediately at the onset of presyncopal symptoms: leg crossing with tension of the thigh, buttock, and calf muscles (party position), bending over, and squatting.
- Elastic stockings (at least 30–40 mmHg ankle counterpressure) and abdominal compression bands may be needed eventually.

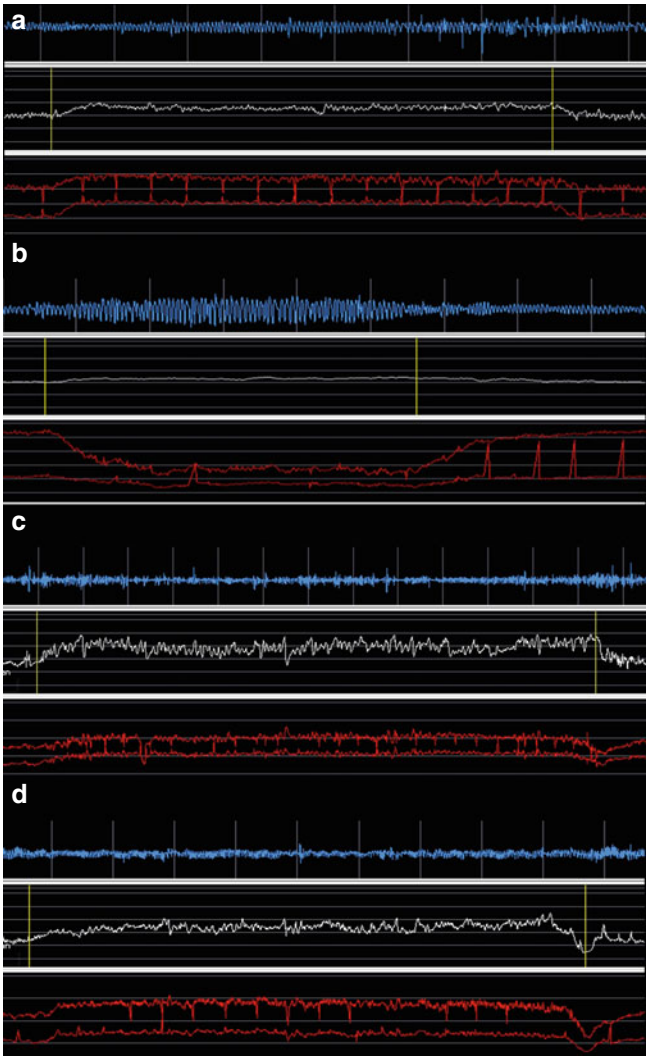

Fig. 13.5 Table tilt testing. (**a**) Normal autonomic response, (**b**) OH, (**c**) marked heart rate increase in PoTS, and (**d**) heart rate and blood pressure decrease due to reflex syncope. *First yellow line*, beginning of tilt; *second yellow line*, end of tilt

- Liberal intake of salt (if there is no cardiac contraindication).
- Individualized exercise training (swimming, aerobics, if possible cycling and walking).

Things to Avoid

- Hot environments including hot baths, showers, and sauna.
- Carbohydrate-rich meals if there are hints of blood pressure drops after eating.
- Lying flat – supine hypertension may be a severe problem, either resulting from medication or being part of the disease. Patients should not be treated with plasma expansion (see below) after 6 pm and should sleep with the bed head elevated (20–30 cm).

Pharmacological Treatment
- Fludrocortisone is a glucocorticoid that acts as a plasma expander.
- Midodrine is a prodrug for the active metabolite, desglymidodrine, which is an α1-receptor agonist that activates alpha-adrenergic receptors in the arteriolar and venous vasculature, thus increasing vascular tone and increasing blood pressure.

13.5.2 Diabetic Autonomic Neuropathy

Please see page 256.

13.5.3 Reflex Syncope

Reflex syncope predominantly is found in younger healthy female patients. The autonomic nervous system is structurally intact, and syncope is caused by overshooting autonomic regulatory responses. Reflex syncope might be of vasodepressor (sympathetic blood pressure reduction), cardioinhibitory (parasympathetic bradycardia/asystole), or mixed etiology. Reflex syncope in elderly patients (>40 years) is typically carotid sinus syncope (CSS), provoked by external pressure to the anterior neck region or head movements.

Typical prodromi are regularly reported.

Red Flags for Reflex Syncope
- A long history of syncope (it is rare that the patient seeks medical advice after the first reflex syncope)
- Syncope following an unpleasant event (optic, acoustic, olfactory, or pain)
- Syncope during standing in crowded, hot places
- During head movements
- Strong sweating during or after syncope
- During swallowing, micturition, and defecation.

Criteria (Pre-)syncope combined with marked blood pressure decrease (eventually including heart rate decrease) (Fig. 13.4d); CSS: asystole >3 s, blood pressure reduction >50 mmHg during carotid sinus massage.

Office Tests for Reflex Syncope A standing test might sometimes provoke a reflex syncope but cannot be regarded as a standard test.

Autonomic Tests for Reflex Syncope
- Deep breathing, Valsalva, and tilt table test for 45–60 min, which might include provocatory tests (e.g., venous puncture).
- Carotid sinus massage in patient where carotid sinus syncope is suspected.

Treatment The primary aim of therapy is prevention of syncope and injury and increase of quality of life.

Nonpharmacological treatments are of major importance:
- Avoidance of situations typically leading to syncope
- Early recognition of prodromal symptoms
- Early initiation of countermeasures
- Prevention of triggers if possible (avoidance of straining in micturitional syncope, light coughing in cough syncope)
- Moderate exercise
- Fluid intake (self-control possible by monitoring urinary color)
- Liberate salt intake.

13.5.4 Postural Orthostatic Tachycardia Syndrome (PoTS)

PoTS is not an entity but caused by different pathophysiologic pathways (Grubb 2008). These include hypovolemic, hyperadrenergic, immune-mediated, and neuropathic mechanisms. PoTS might be primary or secondary. Secondary PoTS is commonly associated with chronic diseases (diabetes mellitus, amyloidosis, sarcoidosis, Lupus, Sjogren's Syndrome, etc.) or various intoxications (alcoholism, heavy metal poisoning, chemotherapy). Primary PoTS might be divided into partial dysautonomic or hyperadrenergic PoTS. Important differential diagnoses include the inappropriate sinus tachycardia syndrome or the chronic fatigue syndrome. Syncope is common in PoTS patients but is not obligatory.

Red Flags for PoTS in History A great variety of symptoms including
- Tachycardia
- Fatigue
- Lightheadedness
- Tremor
- Anxiety
- Visual blurring
- Exercise intolerance
- Cognitive impairment
- Headache.

All symptoms have in common that they cease during rest and occur in orthostatic challenge.

Criteria Heart rate increase of 30/min or above 120/min from lying to standing within 10 min (Fig. 13.4c) without a blood pressure decrease fulfilling the criteria of orthostatic hypotension (see above); and a minimum history of symptoms of 3 months.

Office Tests Standing test for 10 min might prove the diagnosis of PoTS.

Autonomic Testing Deep breathing, Valsalva, tilt table test for 10 min, catecholamines (hyperadrenergic PoTS), and QSART (small fiber involvement in partial dysautonomic PoTS)

Treatment of PoTS (similar to treatment discussed under autonomic syndromes) Treatment of PoTS is often complex and is best left to an expert well experienced with this syndrome.

Non-pharmacological treatment:

- Increased hydration
- Liberal intake of salt
- Individualized exercise training (swimming, aerobics, if possible cycling and walking).

Pharmacological treatment:

- Plasma expansion: fludrocortisone
- Midodrine
- SSNRI: combined serotonin norepinephrine effect (duloxetine or venlafaxine).

This text provides a short introduction into the evaluation of the ANS in neuropathic and related disorders. For further reading we recommend: Low and Benarroch (2008).

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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) Mononeuropathy – radial nerve (compression) Myopathy Acute necrotizing myopathy and myoglobinuria Chronic proximal weakness Hypokalemic paralysis Myoglobinuria Compartment syndromes (prolonged compression)	Alcohol
Familial amyloid polyneuropathies Transthyretin Sensorimotor neuropathy	Amyloid Neuropathy Autonomic

(continued)

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Autonomic involvement	Primary/secondary
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	
Adrenal dysfunction	
Aldosteronism	
AIDS	
Alcoholism	
Amyloid	
Painful neuropathy	
Autonomic involvement	
Carpal tunnel syndrome	
Muscle amyloid – “muscle amyloidosis”	
Amyloidoma (trigeminal root)	
Secondary or reactive amyloidosis (AA)	
Chronic inflammatory diseases, rheumatoid diseases, osteomyelitis	
Deposition of acute phase plasma protein, serum amyloid A	
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	
Cobalamin deficiency, vitamin B12 polyneuropathy	Anemia
Lead poisoning polyneuropathy	
Thalassemia: muscle cramps, myalgia, muscle atrophy	
Pure red cell anemia: autoimmune disease associated with myasthenia gravis	
Malpositioning	Anesthesia
Upper extremity (70 %): mononeuropathies of brachial, radial, ulnar, or median nerves	
Lower extremity (30 %): mononeuropathies of peroneal, sciatic, or femoral nerves	
Regional: epidural or spinal anesthesia may cause cauda equina lesions	
Local : drug toxicity, local hematoma, vasoconstriction, needle injury, infection	
Cardiac bypass operations: nerve stretch, hypothermia, phrenic nerve lesions	
Tourniquet palsy	
Neuromuscular transmission disorders induced by muscle relaxants	
Peripheral: axillary or femoral artery puncture (brachial plexus and femoral nerve)	Angiography
Brachial artery: median nerve	
Cerebral angiography: femoral nerve lesions	
Femoral nerve lesion in inguinal arterial puncture or hematoma	
CIDP	Bone marrow transplant
Inflammatory myopathies	
MG	
Polyneuropathy	
Local damage; sacral plexus	

Facial nerve lower branch Hypoglossal nerve Vagal recurrent nerve Horner syndrome	Carotid surgery
Cranial nerves (meningeal carcinomatosis, base of the skull metastasis, nerve infiltrations, radiation injury) Mononeuropathies (pressure, toxic, following operations), rarely infiltration, or metastasis Radiculopathies (meningeal carcinomatosis, compression or infiltration of roots, multiple spinal metastasis), cauda equina syndrome Polyneuropathies: treatment related (CIPN), rarely autoimmune, paraneoplastic, rarely infiltrative Myopathies: cachexia, dermatomyositis/polymyositis, necrotizing, neuromyotonia, amyloid deposition sarcopenia, type 2 fiber atrophy Neuromuscular transmission: MG and thymoma, LEMS, and (lung) cancer Antineoplastic treatment-associated polyneuropathy: platinum derivates (cisplatinum carboplatin, oxaliplatin) Acute neurotoxicity, oxaliplatin Taxanes (suramin) Vinca alkaloids Thalidomide Bortezomib Epithelons Steroid myopathy Radiation: cranial nerve, optic nerve Plexopathies (brachial, lumbar, sacral)	Cancer
Aortic disease: left recurrent laryngeal nerve palsy; femoral nerve lesion (ruptured aneurysm, aortic surgery); obturator nerve, hematoma in psoas muscle; radiculopathies, compression of L4 and L5 and S1 and S2 by terminal aorta Ischemic monomelic: predominately sensory with causalgia-like pain Cholesterol-lowering drugs: myopathy, cramps (fenofibrate, bezafibrate, 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 and mononeuropathies Monomelic neuropathy Nerve compression by hematoma (femoral nerve, lumbar plexus, sciatic nerve) Carotid surgery Temporary aortic occlusion (surgery) Venous occlusion – phlegmasia cerulea dolens	Circulatory disorders
Cranial nerve lesions Critical illness myopathy Critical illness neuropathy Compartment syndromes Mononeuropathies (malpositioning, pressure palsy) Steroid myopathy Thick filament myopathy	Coma

(continued)

Hip and joint surgery: sciatic and femoral nerve lesions	Complications of medical and surgical treatment
Hypothermia: polyneuropathy	
Injection into nerves: mononeuropathies	
Nerve blockade	
Intramuscular injections	
Knee surgery: peroneal nerve, ramus infrapatellaris	
Shoulder surgery	
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, abscess, 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	
Autonomic neuropathy	Diabetes mellitus
Cranial mononeuropathies	
Mononeuropathies (carpal tunel syndrome)	
Muscle infarction	
Plexopathy (lumbar)	
Polyneuropathy, several distinct types	
Thoracic (truncal) radicular lesions	
Disuse myopathy	Immobilization
Muscle atrophy	
Mononeuropathies: pressure palsies	
Heroin: nerve compression (coma), trauma from injection, brachial and lumbosacral	Drugs and addiction
Plexopathies	
Compartment syndromes	
Phenylcyclidine: rhabdomyolysis	
Cocaine: rhabdomyolysis	
Hypercalcemia: muscle weakness	Electrolyte disorders
Hypocalcemia: tetany	
Hypokalemic paralysis	
Hypokalemic myopathy	
Hyperkalemic paralysis	
Hyperkalemia: potassium-retaining diuretics	
Hypermagnesemia muscle weakness	
Hypomagnesemia muscle weakness	
Hypernatremia: muscle weakness	
Hyponatremia: muscle weakness	
Churg-Strauss syndrome	Eosinophilic syndromes
Eosinophilic fasciitis	
Eosinophilic polymyositis	
Eosinophilia myalgia syndromes (parasitic infections)	
Acute abdomen: porphyria, lead poisoning – polyneuropathy	Gastrointestinal disorders
Chronic diarrhea: malabsorption neuropathies, Whipple's disease, celiac disease	
Celiac disease: myopathy	
Crohn's disease: polymyositis	
Whipple's disease: macrophagic myofasciitis	
Vitamin B 12 deficiency	

Compartment syndromes Polyneuropathy Mononeuropathy	Ischemia/peripheral vascular occlusive
GBS	Hepatic disease
Primary biliary cirrhosis: myopathy, neuropathy Polymyositis Polyneuropathy (hepatitis B, C) Panarteritis nodosa (hepatitis B)	Hepatitis
Demyelinating polyneuropathy Sensory polyneuropathy	Biliary cirrhosis
Hemophilia: Nerve compression (femoral nerve, hemorrhage into iliac muscle) Ulnar nerve compression Median nerve, radial nerve, sciatic nerve, peroneal nerve Complications of anticoagulation Brachial plexus lesions: hematomas in peripheral nerves (median nerve, femoral nerve, obturator nerve, sciatic nerve) Polyneuropathy: POEMS syndrome Castleman's syndrome Waldenstrom's Paraproteinemia IgM (MAG) Macroglobulinemia Lymphoma, HIV	Hematologic diseases
Median nerve mononeuropathy Polyneuropathy Radiculopathy	Hyperuricemia
Polyneuropathies: Amitryptyline Glutethimide Imipramine Li+ carbonate Methaqualone Perazine Phenelzine Thalidomide	Hypnotic drugs
Influenza, swine flu: GBS Mumps: sensorineural deafness Oral polio: GBS Macrophagic myofasciitis (hepatitis A,B, tetanus) Rabies Serum sickness Toxoids: Diphtheria/tetanus: GBS Haemophilus influenzae: GBS Plasma-derived hepatitis B: GBS	Immunization

(continued)

Bacterial meningitis: cranial nerve lesions	Infections
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	
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: Respiratory, cardiac and skeletal muscles	
Viral meningitis:	
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 Isoniazid neuropathy Ethambutol neuropathy Nitrofurantoin neuropathy Streptomycin ototoxicity Sulfonamide vasculitis Metronidazole neuropathy	
Cranial nerves: VI, VII, vagus Mononeuropathies, serum sickness; acute mononeuropathies: long thoracic, radial, suprascapular, musculocutaneous, femoral, sciatic, anterior interosseus, intercostal, and phrenic nerves Polyneuropathy: Migratory recurrent polyneuropathy GBS CIDP Postinfectious and allergic neuropathies Chronic idiopathic 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	Inflammatory and immune diseases
Alpha 1 lipoprotein deficiency: polyneuropathy A-betalipoproteinemia: polyneuropathy Hyperlipidemia: polyneuropathy Statin neuropathy Statin myopathy	Lipid metabolism
Lung cancer: paraneoplastic disease (anti Hu) Sarcoid – polyneuropathy Pneumonia: phrenic neuropathy COPD: neuropathy Churg-Strauss syndrome	Lung disease
Cranial nerves: trigeminal Mononeuropathies (median, ulnar) Polyneuropathy (sensorimotor) (See rheumatoid disease)	Lupus, SLE

(continued)

See also cancer Nerve infiltration Neurolymphomatosis Immune mediated neuropathies Focal nerve lymphoma	Lymphoma
Malnutrition-induced myopathy Polyneuropathy Posterolateral cord degeneration Sarcopenia Strachan's syndrome 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, hyponatremia 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-Kornzweig disease Sicca syndrome: Sjögren's syndrome Xerophthalmia: Sjögren's syndrome, LEMS Optic disk edema: POEMS syndrome, CIDP, GBS	Ophthalmologic complications
Myopathy Muscle pain: generalized, myalgia, ischemia, cramps, drugs Neuropathic pain CRPS Phantom pain Neuralgia Erythromelalgia	Osteomalacia Pain
Cranial nerves: paraneoplastic retinal degeneration, cancer-associated retinopathy "Numb chin syndrome" Polyneuropathy: Distal sensorimotor Sensory, subacute sensory neuronopathy Vasculitic neuropathy "Terminal" neuropathy Immune mediated Paraproteinemic neuropathies: Monoclonal gammopathy of uncertain significance (MGUS) Anti-MAG IgM POEMS syndrome Amyloid neuropathy Neuromuscular transmission: LEMS MG (thymoma) Neuromyotonia, Isaac's syndrome Myopathy: Dermatomyositis, polymyositis Necrotizing myopathy Type 2 fiber atrophy "Cachectic myopathy"	Paraneoplastic neuromuscular syndromes (see also "cancer")

Myopathy, bulbar and respiratory weakness	Parathyroid disease
Thyrotoxic periodic paralysis	
Polyneuropathy	
Ocular myopathy	
In hypoparathyroidism: tetanic muscular reaction	
Acromegaly: entrapment neuropathies: median and ulnar nerve entrapment	Pituitary disease
Proximal myopathy	
Polyneuropathy (proximal also respiration can be involved)	Porphyria
Ascending polyradiculopathy	
Drug side effects	
Optic neuritis	Pregnancy
Cranial nerves: Bell's palsy	
Median neuropathy (CTS)	
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	
Immunotherapy and pregnancy	
Polyneuropathy: malnutrition	
GBS	
Relapse of CIDP	
Psoriatic myopathy	Psoriasis
See "lung"	Pulmonary disease
Polyneuropathy:	Renal disorders
Distal symmetric, sensory, motor	
Cramps, myokymia	
Restless leg syndrome	
Compressive neuropathies: ischemic myopathy related to shunt	
Amyloid deposition: nerve and muscle	
Multiplex mononeuropathies	
Neuromuscular junction: aminoglycoside toxicity	
Myopathy (type 2 fiber atrophy)	
Cachexia, inanition, electrolyte disturbances, rhabdomyolysis	
Ethanol intoxication	Rhabdomyolysis
Drug induced	
Electrolyte disturbances	
General anesthesia	
Heroin	
Multiple organ failure	
Narcotics	
Secondary entrapment – compartment syndromes	
Some myopathies (e.g., metabolic)	

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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, masticatory claudication Polymyalgia rheumatica: muscle pain Wegener's disease: 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	Rheumatoid and connective tissue
Facial nerve (bilateral) Hypercalcemia Rhabdomyolysis Rheumatoid and connective tissue Myositis: proximal muscle atrophy Polyneuropathy (distal sensorimotor, small fiber, and autonomic) Mononeuropathy Radiculopathy GBS	Sarcoidosis
Cachexia Critical care myopathy Critical illness neuropathy Malnutrition and avitaminosis Neuromuscular transmission disorders by anesthetic drugs and aminoglycosides Septic myopathy Thick filament myopathy Therapy induced: steroid myopathy	Sepsis

Angiokeratoma: Fabry's disease Cheilosis/glossitis: vitamin B and folate deficiency Dupuytren'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, adrenoleukodystrophy Hypopigmentation: POEMS syndrome, leprosy (patchy) Hypertrichosis: POEMS syndrome Mechanic's hands: dermatomyositis Skin rash: dermatomyositis Purpura: vasculitis, cryoglobulinemia, amyloidosis Ichthyosis: Refsum's disease Macroglossia: amyloidosis, hypothyroid Mees' lines (nails): arsenic, thallium intoxication Photosensitivity: lupus, porphyria Raynaud's syndrome Collagenosis, autoimmune disease Skin thickening: scleroderma, fasciitis Vitiligo: vitamin B deficiency	Skin changes
Cachexia Myopathy Sarcopenia Strachan's syndrome Wernicke's disease	Starvation
Chronic myopathy, type two fiber atrophy Acute myopathy in status asthmaticus Critical illness myopathy	Steroid therapy
Hyperthyroidism Basedow's disease Entrapment mononeuropathy (CTS) Graves ophthalmopathy Hyperthyroid periodic paralysis (Asian, Chinese) MG and hyperthyrosis Thyroid myopathy Hypothyroidism Median neuropathy Myopathy (pseudomyotonia – Hoffman's sign) Neuropathy	Thyroid disease
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 Trichlorethylene: cranial neuropathies	Toxin exposure/working conditions

(continued)

Amyloid deposition – autonomic Optic neuropathy Mononeuropathies Polyneuropathy Shunt monomelic neuropathies	Uremia
Color vision changes: sulfonamides, streptomycin, methaqualone, barbiturates, digitalis, thiazide diuretics, antihelminthic drugs, nalidixic acid, troxidone Optic neuropathy: chloramphenicol, isoniazid, streptomycin, ethambutol, sulfas, dapsone, chlorpropamide, chlorambucil, penicillamine, indomethacin, ibuprofen, morphine, MAO inhibitors, barbiturates	Visual disorders
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	Vitamin deficiency

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