Part I Evaluation and Treatment of Patients with a Neuromuscular Disorder

Chapter 1

Neuromuscular Diseases: Anterior Horn Cell Disorders, Peripheral Neuropathies, Neuromuscular Junction Disorders, Myopathies

Currently, there is a rapid, ongoing increase in our understanding of genetic neuromuscular disorders at the molecular level: many causative genes have been found, giving hope for targeted genetic treatments, already proven effective in some diseases. In immune-mediated neuromuscular disorders, pathogenetic mechanisms are better understood, and this enables the development of more precise immunotherapies. Increased knowledge has led to a refinement of classifications and has added numerous subtypes to the already hundreds of possible neuromuscular diagnoses. Patients can only benefit from future targeted therapies if an accurate diagnosis is made. Moreover, a diagnosis needs not only to be precise; the diagnostic trajectory needs to be swift, as current and future treatments will be aimed at the prevention or the restriction of irreversible damage.

The best way to diagnose a neuromuscular disease at this point is probably to recognize the phenotypical pattern, to know its differential diagnosis, and to proceed from there. The classic categorization of neuromuscular disorders in diseases of the anterior horn cell, peripheral nerves, neuromuscular junction, and skeletal muscle is not always sufficiently helpful as a starting point in the diagnostic process. For example, inclusion body myositis may mimic an anterior horn cell disease. Kennedy disease, an anterior horn cell disease, affects muscle too, and may present with a myopathy – suggesting CK elevation. In distal weakness, it might be cumbersome to differentiate between neurogenic and myopathic disease, and some drugs can cause both a neuropathy and a myopathy, or a combination of a myopathy and a neuromuscular junction disorder. Yet, from a practical point of view it is useful to keep to this anatomical–functional division: it provides a basic insight in functions, in understanding disease mechanisms, and in applying diagnostic and therapeutic tools. Therefore, we give a brief clinical characterization of the four categories of neuromuscular disorders. Details on physiology and pathophysiology are not discussed here.

Anterior Horn Cell Disorders

Anterior horn cell diseases, except for those caused by the polio virus and some other viruses, are progressive degenerative diseases of the motor neurons in the spinal cord and brainstem. These disorders may be hereditary, such as spinal muscular atrophy (SMA) types 1 to 3 in children and SMA 4 in adults, familial amyotrophic lateral sclerosis (ALS), Kennedy disease, and distal hereditary motor neuropathies (HMN; distal SMA). ALS, progressive muscular atrophy (PMA), primary lateral sclerosis (PLS), and segmental SMA are commonly sporadic. The clinical hallmarks of anterior horn cell disease are the lower motor neuron signs of weakness, wasting (atrophy), fasciculations, and reduced or absent tendon reflexes. In ALS, the upper motor neuron is also involved and in PLS this is the sole manifestation, characterized by hypertonia (spasticity), pseudobulbar symptoms, hyperreflexia, and abnormal plantar response. ALS, PMA, and PLS are collectively classified as *motor neuron diseases.*

Clinical assessment, that is, history taking and neurological examination, and exclusion of mimics usually suffice to establish a diagnosis of ALS or postpolio syndrome (PPS). Electrodiagnostic assessment (nerve conduction studies and needle electromyography) is a crucial step in the diagnostic process of PMA, segmental SMA, and distal HMN. Hereditary diseases (SMA, Kennedy disease) require genetic testing as first-tier ancillary investigation.

Infectious diseases affecting the anterior horn cells such as poliomyelitis anterior acuta are diagnosed by virus isolation from stool or pharyngeal swabs and the polio-like disease caused by West Nile

virus (WNV) by testing of serum or cerebrospinal fluid to detect WNV-specific IgM antibodies.

Therapy is mostly supportive in distal HMN and segmental SMA, including physiotherapy, orthotics, occupational therapy, and pain and fatigue management. In motor neuron diseases, multidisciplinary treatment is required (i.e., a rehabilitation physician for preservation of motor abilities, a gastroenterologist for instalment of a percutaneous endoscopic or radiologic gastrostomy, a pulmonologist for (noninvasive) ventilation, a palliative care specialist, and others).

Significant advances in basic and clinical research paved the way for approved therapies in SMA with a focus on strategies aiming at increased survival motor neuron (SMN) protein expression, either via antisense oligonucleotides, small molecules, or viral gene transfer. These strategies have led to dramatic improvement of survival and motor function.

Peripheral Neuropathies

Disorders of nerve roots, plexus, or peripheral nerves are the most frequent neuromuscular diseases. Conditions caused by compression of one nerve root or nerve are usually handled by the general practitioner or neurologist based in a community hospital. Polyneuropathies are readily distinguishable from disorders of the anterior horn cell, neuromuscular junction, and skeletal muscle by the presence of sensory disturbances, but these may be mild and pure motor neuropathies do exist. Neuropathies can also be purely sensory. Neuronopathies, localized in the dorsal root ganglion, are associated with specific conditions, such as cancer. Typical pain patterns can point to a localization in nerve roots, plexus, or peripheral nerves. Neuropathic pain can be severe and should be treated appropriately.

Polyneuropathies can have many causes. Distinction between subacute and chronic disease course, onset in childhood or adulthood, symmetric and asymmetric symptomatology, length-dependent and non-length-dependent, and axonal and demyelinating pathogenesis is a useful approach for making a differential diagnosis. Nerve conduction studies complemented by ultrasound examination can establish a demyelinating pathogenesis. These are often immune-mediated. Recognition of these disorders has become increasingly important because of the increasing treatment options. Most polyneuropathies are chronic, symmetric, distal, and axonal. The most frequent causes are metabolic. Diabetic polyneuropathy, monoradiculopathy, and plexopathy can occur without a known prior history of type 2 diabetes. Evidence-based guidelines are useful in the diagnostic work-up of polyneuropathies.

Hereditary polyneuropathies can be axonal or demyelinating, as established with nerve conduction studies. In particular, axonal hereditary polyneuropathies can sometimes have their onset in adulthood, and these patients need not have typical deformities such as hollow feet. This is also the case in young children in whom often a pes planus is seen. Weakness can also present more proximal with difficulty rising from the floor and running. Many genes have now been identified, and these disorders can be increasingly diagnosed at the gene level, which is important for genetic counselling. Gene therapies for hereditary polyneuropathies have not been developed yet. Treatment is mainly supportive, including physiotherapy, orthotics, occupational therapy, pain and fatigue management, and – when indicated – orthopaedic surgery.

Neuromuscular Junction Disorders

Myasthenia gravis (MG) is the most common autoimmune disease affecting the neuromuscular junction. If the disease manifests with the typically fluctuating, variable, and fatigable ptosis and diplopia, the diagnosis can be readily made, but ancillary investigations are always indicated. MG can be distinguished into an ocular and generalized phenotype. MG is caused by antibodies directed at the acetylcholine receptor (AChR) situated on the postsynaptic membrane, or, much more rarely, at muscle-specific kinase (MuSK), which is needed for maintenance and clustering of the AChR. In particular, in ocular myasthenia, and rarely in generalized myasthenia, antibodies are absent or not detectable with current methods (e.g., seronegative MG). The diagnosis then rests upon the clinical phenotype, response to symptomatic treatment, and typical electrophysiological findings. The thymus plays a role in the pathogenesis of AChR MG showing hyperplasia or thymoma. Therapeutic strategies range from cholinesterase inhibitors, immunosuppressive or immunomodulatory treatment to immunotherapies that more specifically address distinct targets of the main immunological players in MG pathogenesis. If bulbar or respiratory muscles are affected, an emergency condition may

occur, warranting adequate treatment and close monitoring in an intensive care unit (ICU). A myasthenic crisis is life-threatening, but if recognized early it is generally well manageable, with a good prognosis.

Lambert Eaton myasthenic syndrome (LEMS) is caused by antibodies directed at the voltage-gated calcium^{2+} channel in the presynaptic nerve ending. The influx of calcium is needed for the release of acetylcholine in the synaptic cleft. The clinical features are different from MG (namely, proximal weakness, autonomic dysfunction, and areflexia), and fluctuating weakness is less obvious as compared with MG. Apart from antibody testing, the diagnosis can be made by specific electrophysiological abnormalities. LEMS is strongly associated with small cell lung cancer, which should be screened for.

Congenital myasthenic syndromes (CMS) are extremely rare and heterogeneous genetic diseases with variable phenotypes. Most CMS are treatable. Some agents that benefit one type of CMS can be ineffective or harmful in another type, and therefore an accurate molecular diagnosis prior to symptomatic treatment is paramount.

The neuromuscular junction may be targeted by various drugs and toxins. Botulinum toxin (as drug or foodborne) and snake venoms such as β-bungarotoxin (cobra, mamba) block the ACh release at the presynaptic nerve terminal, which is resistant to anti-venoms. Organophosphates, present in pesticides such as parathion and used as poison (e.g., Novichok), inhibit acetylcholinesterase, which causes an excess of acetylcholine and may result in a possibly fatal cholinergic crisis including paralysis. Curare, snake venoms such as α-bungarotoxin, and muscle-relaxant drugs such as pancuronium competitively block the AChR prohibiting depolarization. Suxamethonium chloride (succinylcholine) is a muscle relaxant that binds to the AChR, causing depolarization, but not allowing for repolarization and subsequent depolarization, because it is broken down slowly. Tetrodotoxin, found in the liver of puffer fish, blocks the voltage-gated Na^+ channel. Diaphragm paralysis can follow very quickly.

Myopathies

Myopathies – diseases of the skeletal muscles – can be acquired or hereditary. The distinction, important because of the differences in diagnostic work-up and treatment options, rests initially upon careful history taking focused on age of onset and rate of progression. Acquired myopathies are commonly immune-mediated, and weakness progresses in weeks or a few months. A more protracted course can, however, occur, and these immune-mediated myopathies may lack inflammatory changes in a muscle biopsy, which may add to the difficulties in differentiating this group of diseases from a muscular dystrophy. An increasing number of autoantibodies is linked to the pathogenesis, and some forms are associated with cancer, which requires screening.

Hereditary myopathies are caused by DNA variants causing dysfunction or absence of proteins involved in, for example, the extracellular matrix, sarcolemmal structure and function, the nuclear envelope, metabolic pathways and mitochondria, the contractile apparatus, and ion channels. In particular, if the sarcolemma is affected, there is leakage of intracellular substances such as CK. A serum CK elevation of more than 10 times the upper limit of normal is commonly consistent with a myopathy. In many myopathies, however, CK activity is only mildly increased and may even be normal.

Many hereditary myopathies have specific complaints or abnormalities on clinical examination, needle electromyography (EMG), or muscle biopsy. Muscle biopsies should best be performed in a neuromuscular centre, in order to allow for appropriate processing. The final diagnosis, however, is made by genetic investigation, and EMG and muscle biopsy are often not indicated in the diagnostic work-up. The possibilities to diagnose a myopathy at the genetic level are expanding very rapidly, albeit a fair proportion is still awaiting a definite molecular diagnosis. Neuromuscular multidisciplinary teams therefore should include, among others, clinical and molecular geneticists, who can help interpret the results of genetic analyses and offer genetic counselling to patients and their families.

Causal treatment of hereditary myopathies is currently mostly restricted to enzyme replacement therapy, which is effective in Pompe disease, in which gene transfer therapy is now also in development. Rehabilitation treatment includes optimizing physical functioning and engagement in social life. In many progressive myopathies, there is an imminent danger of insufficient

swallowing and respiratory function. Cardiac involvement can occur in various myopathies, leading to cardiomyopathy, dysrhythmias, or conduction abnormalities with the risk of sudden death. These complications require close monitoring to ensure timely interventions such as percutaneous endoscopic gastrostomy, noninvasive ventilation at home, or prevention or treatment of cardiac failure or instalment of devices (pacemakers, defibrillators).

Chapter 2

History Taking and Clinical Examination

History Taking

The main aim of a first consultation will concentrate on establishing a diagnosis. However, there are two other major aims: capturing the expectations of the patient and appreciating the impact of the complaints on daily life.

Purpose of the Visit and Expectations

If a patient presents with rapidly progressive weakness, fast-track diagnosing and effective and immediate treatment, if possible, are obviously required. For patients with a chronic disease, however, the purpose of their visit may vary. Some people are concerned about transmitting their disease to their children. Most of the patients are keen on obtaining an accurate diagnosis even if there is no causative treatment. This is particularly important in genetic conditions that will have an impact on family planning. Still others seek relief of symptoms, regardless of the precise nature of their illness. Many patients ask for a consultation in the hope that a severe disease diagnosis can be excluded. These considerations steer the diagnostic and therapeutic trajectory.

Diagnosis

Patients often present their symptoms related to functional tasks, which may provide important diagnostic clues. Examples include having heavy objects slip from the fingers (e.g., in inclusion body myositis), inability to turn a key (e.g., in amyotrophic lateral sclerosis (ALS) or in multifocal motor neuropathy), cannot run or does not shake hands (myotonia), a feeling of a 'folded sock' (sensory abnormality in polyneuropathy), neck pain (weakness of neck extensors). The patient's own words cannot be replaced by structured questions or questionnaires. It is also important to have a child formulate complaints as much as possible before asking the parents.

Notwithstanding the importance of the patient's own words, direct and specific questions should always be raised to pinpoint the onset of the disease, and to assess the rate of progression and the nature and extent of the problems. Relatives may also give valuable additional information.

Time Course and Duration of the Disease

Information about the onset of the disease and rate of progression as precisely as possible is paramount in the diagnostic process. First, if symptoms and signs worsen every day, week, or month, or fluctuate over time, an acquired disorder (usually with autoimmune or acquired metabolic or toxic pathogenesis) is likely. If the disease worsens little over years or decades, a genetic pathogenesis is much more likely. Careful history taking may be needed to determine the onset of the disease and its rate of progression. One should also consider that if patients, for example, lose the ability to walk, they may perceive this as an acute deterioration, whereas, in fact, the muscle weakness in the legs has progressed gradually. Second, assessing the rate of progression also determines therapeutic policies. A patient in whom symptoms and signs of weakness of respiratory muscles occur within a short time frame and increase every hour will need immediate action to safeguard respiration.

The following questions can be helpful in assessing the disease onset and time course: Are motor milestones reached, like rolling over, crawling, and independent walking? Is the patient keeping up with peers at school? At sports? What was the age at first symptoms? Are there fluctuations throughout the day? Do the complaints worsen over time? Over a period: days, weeks, months, years? Over decades? When did the patient start to use a walking aid? When could the patient still do things that are impossible now, such as getting out of a car, rising up from a chair, walking up/down stairs?

Information from the History That Can Point to Specific Clinical Features

- *External ophthalmoplegia and ptosis:*

Double vision? Does double vision disappear at closing one eye? Drooping eyelid(s)? Fixed or fluctuating, on one or both sides? Symmetric?

- *Facial weakness:*

Inability to whistle? Inability to drink through a straw? Inability to blow up a balloon? Difficulty to 'bury one's eyelashes' (squeeze eyes tight shut)? Dry eyes at awakening? Little facial expression when crying?

- *Bulbar weakness:*

Difficulty speaking clearly? Hoarse voice? Nasal speech? Having to swallow repeatedly? A sensation of food getting stuck in the throat? Food or fluids coming through the nose? Coughing or gagging when swallowing? Weight loss? Infants: Weak crying? Poor sucking?

- *Respiratory muscle weakness:*

Exercise-induced shortness of breath? Dyspnoea or feeling uncomfortable lying flat? Sleeping with how many cushions/pillows? Vivid dreams? Morning headache? Morning drowsiness? Daytime sleepiness? These symptoms of hypoventilation during the night are usually not admitted voluntarily and should be specifically asked for.

- *Axial weakness:*

Difficulty holding one's head in an upright position? Difficulty rising from supine to sitting position? Difficulty holding one's head up while swimming or driving a car? Infants: Head lag? Difficulty remaining in an upright position while walking?

- *Weakness and wasting of arm or leg muscles:*

Have arms or legs become thinner? Myalgia? Difficulty lifting objects above the head? Difficulty handling small objects? Difficulty opening a jar? Difficulty rising from a chair? Difficulty walking up or down the stairs? Moving off the stairs to the floor? Tipping over? Falls? Needing walking aid? Wheelchair? Weakness non-fluctuating? Fluctuating? Intermittent? In attacks? Provoking factors (cold, carbohydrates)? Children: Jumping, hopping? Complaints bilateral? Symmetric?

- *Sensory impairments:*

Pins and needles in the feet? In the hands? Pain on slight touch? Numb feeling? Perception of walking on cotton wool or on a folded sock? Burning pain? Symmetric? Insecure walking in the dark?

- *Autonomic dysfunction:*

Dizziness on standing up? Palpitations? Feeling of fullness after a small quantity of food? Changes in micturition? Obstipation or diarrhoea? Problems achieving or maintaining an erection? Abnormal sweating?

- *Fasciculations, myokymia, cramp, myotonia, rippling, contracture, pain:*

A complaint of stiffness may be related to myotonia or muscle contracture, non-neuromuscular neurological signs (rigidity, dystonia, spasticity), or rheumatological conditions. Pain is the main symptom of cramp. Helpful questions include: Are there muscle twitches? Painful, involuntary, and unprovoked, accompanied by abnormal foot or hand posture, lasting up to minutes and shortened by stretching (cramp)? Confined to calves? Symmetric? Only at night-time? Cramp-like stiffness with or without pain provoked by activity? Sustained contraction with delayed relaxation when, for example, making a fist, closing the eyes (myotonia)? Plexopathy: lancinating pain in upper or lower limb? Radiculopathy: irradiating pain? Polyneuropathy: cramp? Pins and needles, pain at light touch (e.g., a bed sheet), burning pain? Myopathy: muscle pain? Stiffness? During exertion? Following exertion? Symmetric and proximal? Focal?

- *Rhabdomyolysis:*

Episodes with dark brown (Coca-Cola-like) urine? Elicited by strenuous exercise, such as running? Accompanied by myalgia?

- *Skin changes:*

Rash? Itching? Photosensitive? Ulceration? Excessive scars? Laxity?

- *Cardiac involvement:*

Palpitations? Unexplained fainting? Swollen feet? Dyspnoea?

Family History

If there is a suspicion of hereditary disease, the family history should be taken systematically (preferably by drawing a family tree). How large is the family? Are there family members with similar complaints? Are the parents related? Does the family belong to an isolated community? Are the parents and siblings alive? At which age did they die? From what cause? Sometimes, specific information concerning family members should be specifically asked for (e.g., cataract in the father at

a relatively young age – myotonic dystrophy type 1). Sudden death (myotonic dystrophy type 1 or 2 and other muscular dystrophies with cardiac involvement)? Features of mitochondrial disease such as epilepsy, migraine, deafness, diabetes mellitus? Cognitive deficit (Duchenne muscular dystrophy (DMD)) or decline, or behavioural changes (e.g., ALS)?

Previous Medical History

The onset of neuromuscular complaints can be preceded by conditions or signs of systematic disease in many neuromuscular disorders (e.g., a syncope preceding a diagnosis of a myopathy with cardiac involvement, epilepsy in a patient later diagnosed with *LAMA2*-related congenital muscular dystrophy). Unrelated conditions in the past may explain present symptoms or signs. A herniated lumbar disc at some time earlier, for example, can explain atrophy or hypertrophy and fasciculations in the ipsilateral calf.

Ask about use of medications, alcohol, and/or drugs. Is there a temporal relation to onset of symptoms?

Impact on Daily Life

For the purpose of offering appropriate treatment options and advice on supportive measures, it is important to obtain information about the home situation and the impact of complaints on daily activities and social life (see also Chapter 8, Management). The possibilities of rehabilitation medicine may be under- or overestimated by patients. Patients may also differ in their perception of the burden of their complaints and impairments. This influences the extent of the diagnostic investigations and the weighing of intended effects of treatments against the possible adverse effects. Obviously, this requires careful shared decision making.

Clinical Examination

Neuromuscular Examination in Infants and Toddlers: Some Points of Attention

Neuromuscular examination in infants and toddlers is best done with improvisation and observation. It is important to gain trust, not to rush, and to allow the child to play while in the meantime checking the various muscles for spontaneous antigravity movement in a random order. Examining a child who is shy can start while the child sits on the parent's lap and work from the feet upward. It may also help not to undress the child immediately, but first study some of the larger muscle groups in this position, for example by having the child reach for objects overhead and making a contest or game out of holding them. This also allows examination of the external eye muscles and facial expression while the child follows the object of interest. Tendon reflexes can also be tested in this sitting position. Axial and proximal leg muscles can be examined when the child lies on the floor and is encouraged to stand and walk towards the parents or an interesting toy. When possible, a next step would be to have the child run towards or alongside one of the caregivers. Proper running requires a moment in which both feet are above the floor and is normally achieved anywhere between two and four years of age. Before this, a child is usually able to jump or make a small hop on one leg. Preschool children are generally also able to walk on their toes and heels if given a clear example. More detailed examination of cranial nerves including mouth and tongue in young children is often best saved for last.

Neuromuscular Examination in Children and Adults

The neuromuscular examination can be best done in a structured manner. See Table 2.1 for an example. The examiner decides which parts of the examination need to be performed extensively, and which do not.

Cognition and Behaviour

Mental retardation, among other features of central nervous system involvement, is a hallmark of some congenital muscular dystrophies, in particular α-dystroglycanopathies. In DMD, and in children and adults with myotonic dystrophy type 1, there is an increased prevalence of various cognitive disabilities on neuropsychological testing, and psychiatric co-diagnoses such as attention-deficit/hyperactivity disorder and autism spectrum disorder. At presentation, patients with myotonic dystrophy, in particular type 1, typically may appear dull and apathetic, which increases the level of the diagnostic suspicion. In about 10% of patients with ALS there is frank frontotemporal dementia, and in about 30–50% there are cognitive

Table 2.1 Example of a structured neuromuscular examination

- General impression, cognition, language and speech, pseudobulbar affect
- Posture and walking pattern (scoliosis, hyperlordosis, waddling gait, bent spine, dropped head, walking on heels and on tiptoes), atrophy, hypertrophy, joint contractures in the legs, rigid spine, Gowers sign, Trendelenburg sign, Romberg sign
- Inspection with patient lying down or sitting: skin abnormalities, fasciculations, atrophy in the hands, myotonia, cramp (during muscle strength testing), joint contractures in the arms, range of motion abnormalities (frozen shoulder), hypermobility, foot or hand deformities, scars
- Cranial nerves, test for fatigability as indicated; forced cough
- Muscle strength testing: neck, arms, hands, trunk (rising from supine to sitting position), legs, feet
- Sensory testing as indicated
- Arms outstretched (tremor? pseudo-athetosis?)
- Coordination (finger-to-nose, heel-to-shin, tandem walking)
- Tendon reflexes

and or behavioural impairments. This information can be obtained from relatives (if asked specifically), or requires observation of language, social cognition, and behaviour (apathy or inhibition), or by using a screening tool such as the Edinburgh Cognitive and Behavioural ALS Screen (ECAS). Behaviour can also be altered in Morvan syndrome. Importantly, a lack of facial expression due to facial weakness should not be mistaken for a sign of cognitive impairment or a psychiatric condition.

Posture, Walking Pattern, Skin

Many physicians prefer starting the neurological examination by observing posture and gait. Observation of the patient in a standing position can reveal focal atrophy and hypertrophy, dropped head, bent spine, winging of the scapula, and abnormal curvature of the spine (scoliosis). Walking with hyperlordosis indicates weakness of the gluteal musculature, walking with locked knees (genu recurvatum) indicates quadriceps weakness, waddling gait indicates weakness of hip abductors. Walking on heels (foot dorsal flexors) and on tiptoe (foot plantar flexors) and testing for Gowers sign (gluteus maximus and quadriceps muscles) and Trendelenburg sign (hip abductors) are more sensitive means for detecting weakness than examination on the bench. Inspection of the whole body allows for detection of fasciculations and skin abnormalities. The latter comprise rashes and scaling (myositis), ulceration (myositis, sensory neuropathies), excessive scars (keloids), and nail dystrophy (amyloidosis), among many others. Amputated toes can be a complication of sensory neuropathies.

Fasciculations, Myokymia, Cramp, Myotonia, Rippling, Contracture, Hypermobility (Laxity), and Deformities

- Fasciculations are non-rhythmic, spontaneous, simultaneous contractions of all muscle fibres belonging to a single motor unit. Fasciculations are visible during the physical examination as twitches, and with ultrasound. They do not result in coordinated movement of a muscle. Electromyography (EMG) shows fasciculation potentials. They occur in neurogenic disorders, and in healthy people.
- Myokymia is a spontaneous, rhythmic or semi-rhythmic, uniform, continuous muscle contraction. Myokymia occurs periodically and is self-limiting in seconds to hours. The lower eyelid is affected commonly in healthy people. In disease, myokymia results from hyperexcitability of peripheral nerve motor axons. The EMG shows myokymic and neuromyotonic discharges.
- Cramp is an involuntary painful contraction of a muscle or muscle group that may result in an abnormal position of the limb. A cramp lasts seconds to minutes and can be shortened by stretching. Cramps may be provoked by exercise, for example during the neurological examination, but occur also in rest. Needle EMG shows continuous motor unit action potential activity. Their origin is in the lower motor neuron (anterior horn cell or nerve), but cramp also occurs in non-neuromuscular neurological diseases (Parkinson disease), non-neurological conditions, and in healthy people.
- In myotonia, as in muscle contracture (see below), there is stiffness following voluntary contraction due to delayed relaxation. This may be painless or painful. Myotonia can occur in any skeletal muscle. It can be elicited by percussion of the thenar, or by asking the patient to squeeze the hands or close the eyes for several seconds, and then suddenly release the grasp or open the eyes. In some diseases, myotonia

decreases after repeated contraction (warming-up effect); in other diseases, it can worsen. EMG shows typical myotonic discharges and complex repetitive discharges.

- Rippling muscle is composed of involuntary rolling skeletal muscle contractions that are mechanically induced by muscle stretching or percussion. Usually, this is accompanied by transitory local muscle mounding and percussion-induced rapid contractions. Needle EMG shows no motor unit action potential activity (EMG is 'silent'), indicating that these contractions originate in the contractile apparatus, and are not induced by depolarization of the muscle fibre membrane.
- Muscle contractures manifest with stiffness due to the inability of the muscle to relax normally in some myopathies. This may be either very painful (McArdle disease) or painless (Brody disease). In severe cases of McArdle disease, patients refrain from any activity out of fear of provoking a painful contracture. Stretching is not helpful. These contractures last for several minutes. As in rippling muscle disease, these muscle contractions are electrically silent on EMG.
- Joint contractures (arthrofibrosis, or rigid contracture of an articular joint) are caused by prolonged immobility of a joint. Joint contractures occur in particular in myopathies that affect the extracellular matrix (e.g., collagen VI-related myopathies) or in other myopathies, such as Emery–Dreifuss muscular dystrophy or *LAMA2*-related congenital muscular dystrophy.
- Joint contractures may result in deformities (scoliosis, hollow feet, hammer toes, claw hands). Hollow foot is best examined when the patient is lying down or in sitting position with the feet dangling. Deformities can also be caused by other conditions, for example Charcot foot in diabetes mellitus.
- Hypermobility (hyperlaxity) is an abnormally increased range of motion in a joint. Hypermobility is a feature of some, mostly congenital, myopathies. Often it is confined to distal joints, but hypermobility can also be generalized. Various criteria sets are in use to assess hypermobility. The simplest is the Beighton score, in which both proximal and distal joints are tested in a predefined way; see Table 2.2.

Table 2.2 Beighton scale for hypermobility

1. Passive dorsiflexion and hyperextension of the fifth MCP joint beyond 90°
2. Passive apposition of the thumb to the flexor aspect of the forearm
3. Passive hyperextension of the elbow beyond 10°
4. Passive hyperextension of the knee beyond 10°
5. Active forward flexion of the trunk with the knees fully extended so that the palms of the hands rest flat on the floor

Scoring: 1–4 are tested bilaterally. Maximum score 9. Abnormal: > 4/9 in adults, >5/9 in children.

External Ophthalmoplegia and Ptosis

External ophthalmoplegia may manifest with diplopia. Monocular diplopia is not due to external ophthalmoplegia. In acquired disorders, ophthalmoplegia is accompanied by diplopia, which is fatigable in myasthenia gravis (see Table 2.5 later in the chapter). Usually, chronic progressive external ophthalmoplegia (CPEO) remains unnoticed by the patient, since there is no diplopia. Ptosis is present when the upper eyelid is lower than its normal anatomical position, typically 1–2 mm below the superior corneoscleral limbus. The levator palpebrae muscle is affected in neuromuscular causes of ptosis. Ptosis due to weakness of the tarsalis superior muscle (Horner syndrome) is never complete. Many healthy people have an asymmetric palpebral fissure. However, asymmetric ptosis with or without diplopia should be examined for fatigability (see below). In disorders of the neuromuscular junction, and in particular myasthenia gravis, ptosis is usually unilateral or asymmetric. Ptosis, unilateral or bilateral, should be differentiated from blepharospasm, in which there is contraction of the orbicularis oculi muscle and no compensatory contraction of the frontalis muscle, as seen in ptosis.

Facial Weakness

Facial weakness is best examined by asking the patient to firmly close the eyes (orbicularis oculi muscle) and whistle or firmly pout the lips. Asymmetric closure of the mouth as in facioscapulohumeral dystrophy can be very subtle. Bilateral facial involvement may also present as reduced facial expression.

Bulbar Weakness

It is notoriously difficult to distinguish the various forms of dysarthria from one another. Bulbar dysarthria is often flaccid and nasal with softening of the

consonants, especially P, T, and K. The speech can be soft and hoarse. Inspiratory stridor and laryngospasm may result from predominance of vocal cord adduction in cases of vocal cord abduction paresis. Dysphagia is diagnosed based on the history. If there is dysphagia, the patient in general will be referred to the ear, nose, throat (ENT) specialist for further characterization by fibre-optic endoscopic evaluation of swallowing (FEES) or videofluoroscopic swallow studies (VFSS). Inspection of the tongue for enlargement (DMD, amyloidosis, Pompe disease, hypothyroidism), atrophy, and fasciculation is best done with the tongue relaxed on the floor of the mouth. Slow and sluggish mobility of the tongue indicates involvement of the central nervous system. Upper motor neuron signs further include a 'pseudobulbar affect' (inappropriate laughing, crying, or yawning), and the less specific pseudobulbar reflexes.

Respiratory Muscle Weakness

Acute (or acute-on-chronic) respiratory failure leads to restlessness, tachycardia, tachypnoea, use of sternocleidomastoid or scalene muscles, or failure to string more than a few words together in a sentence. Counting in one breath can be used for monitoring. In chronic neuromuscular disorders, the clinical signs of respiratory failure may be very subtle. When there is emerging hypercapnia, the patient may easily fall asleep. Weakness of respiratory muscles may be shown by weak coughing (the patient attempts to cough with maximal force after deep inhalation). However, also in the absence of abnormalities on physical examination, if the history reveals complaints that indicate hypoventilation during the night, this should be investigated further during the patient's first visit. Forced vital capacity (usually expressed as percentage of that expected based on age and height) is easily done. A postural drop of more than 20 percentage points in supine as compared with sitting position indicates diaphragm weakness. A capillary blood gas analysis can be used to reveal hypercapnia, respiratory acidosis, or normal pH with compensatory increase of bicarbonate and base excess.

Axial Weakness

Weakness of neck flexors (dropped head) and neck extensors is best examined in supine and prone positions, respectively. If there is a bent spine (camptocormia) that is appearing in standing position, increasing during walking, and abating in supine position (making orthopaedic causes less likely) and no signs of a movement disorder, weakness of paraspinal muscles is likely. If there is no bent spine, the strength of the erector spinae muscles may be difficult to examine, and involvement of these muscles sometimes is shown only on MRI imaging. Weakness of abdominal muscles may be apparent on rising from supine to sitting position. Beevor sign is the upward movement (towards the head) of the umbilicus on lifting the head in supine position, caused by weakness of lower, but not upper, abdominal muscles.

Winging of Scapula

Symmetric winging is normal in young children. In older children and adults, scapula(e) alata(e) points to a dysfunction of nerve or muscle. Medial winging (inferior angle of scapula rotates medially and scapula translates superiorly) is most prominent on push-up and pushing against a wall. It is caused by dysfunction of the long thoracic nerve or the serratus anterior muscle. Lateral winging (shoulder droops with inferior translation of the scapula and the inferior angle rotates laterally) is more prominent by abduction of the arm and external rotation against resistance. This is caused by dysfunction of the spinal accessory nerve or dorsal scapular nerve, or by weakness of the muscles they innervate: the trapezius and rhomboid muscles, respectively. In healthy children, the scapula translates horizontally, without rotation of the inferior angle. Of note, strength of the deltoid muscle cannot be examined in the usual way if there is ipsilateral scapula alata, because most fibres arise from the scapula. To test the strength of the deltoid muscle in these cases, the scapula must be fixated by manual force on the thorax.

Wasting and Weakness of Arms and Legs

Muscle atrophy and hypertrophy can be difficult to assess, in particular in elderly people, if not focal and asymmetric. The tonus of diseased muscle is different from healthy muscle, but appreciation of this requires some experience. Muscle MRI can be helpful. Muscle strength is examined by manual muscle testing (MMT), which allows for testing many muscles in a short amount of time. It is necessary to test many muscles, as wasting and weakness of different muscles occur in different diseases. Using MMT, muscle strength is universally quantified by means of the 6-point Medical Research Council (MRC) scale; see Table 2.3. Some