6
Peripheral Nervous System Disorders

Motor Neuron Disease 31
- Amyotrophic Lateral Sclerosis 31
- Progressive Muscular Atrophy 32
- Bulbar Palsy 34
- Kennedy's Syndrome 35

Peripheral Neuropathies 36
- Guillain-Barré Syndrome 36
- Chronic Inflammatory Demyelinating Polyradiculoneuropathy 38
- Miller Fisher Syndrome 40

Disorders of the Neuromuscular Junction 42
- Botulism 42
- Lambert-Eaton Myasthenic Syndrome 43
- Myasthenia Gravis 45
- Brachial Plexopathy 47
- Femoral Neuropathy 48
- Postpartum Plexopathy 48
- Mononeuritis Multiplex 49

Inflammatory Myopathies 50
- Polymyositis 50
- Dermatomyositis 52
- Inclusion Body Myositis 52

Motor Neuron Disease

Amyotrophic Lateral Sclerosis

Vignette

A 63-year-old TV producer started complaining of difficulty turning the car ignition key and twisting off jar caps with his right hand for six months. His general practitioner thought he had carpal tunnel syndrome, but also noticed wasting in the dorsum of his right hand. Two months later the patient was unable to take his customary one-hour walk because of fatigue and muscular tightness and stiffness. He had no prior medical problems and used to exercise frequently. The neurological examination showed weakness of the small right hand muscles and wrist extensor muscles. Hoffman's sign was present. In his lower extremity, he had great difficulty dorsiflexing his right ankle. There was wasting between the first two metacarpal bones on the right. The right toe was extensor. The left toe was equivocal.

Summary A 63-year-old man with progressive weakness, without sensory complaints. The clinical history and neurological examination help localize the lesion. The initial task is to determine whether the patient's weakness is caused by upper motor neuron dysfunction, characterized by increased deep tendon reflexes, increased tone, slowed rapid movements, and Babinski's sign, or by a lower motor neuron dysfunction, characterized by atrophy, decreased or loss of reflexes, and fasciculations. In the vignette, we have signs of both upper and lower motor neuron involvement. Upper motor neuron signs include the following:

- Slowness, loss of dexterity.
- Weakness of antigravity muscles.
- Hoffman's sign (which consists of flexion and adduction of the thumb accompanied by flexion of the index and sometimes the other fingers after snapping the nail of the patient's middle finger).
- Leg stiffness (spasticity).
- Babinski's sign.

Lower motor neuron signs include wasting of the dorsum of the hand. It is important to notice that there are no sensory, sphincteric, or autonomic disturbances.

Localization

Upper and lower motor neurons.

The first entity to be considered is a disease that involves both upper and lower motor neurons, specifically the anterior horn cells and the corticospinal tract. This disorder, amyotrophic lateral sclerosis (ALS), could explain the clinical findings described in the vignette. ALS is considered the most common form of motor neuron disease of undetermined cause in adults (Belsh and Schiffman).

Spinal cord dysfunction needs great consideration in the differential diagnosis, particularly cervical spondylosis with associated myelopathy and radiculopathy. This disorder may manifest with signs of upper and lower motor neuron involvement, sometimes without apparent sensory symptoms. It is important to always rule out cervical cord dysfunction because it is a treatable disorder and

does not carry the poor prognosis of ALS. Clinical findings that may suggest cervical spondylosis include the presence of pain localized in the neck or in a radicular distribution, the signs of upper motor neuron dysfunction with hyperreflexia below the level of compression, hyporeflexia at the level of the anatomical lesion, sensory findings such as paresthesias distributed along the nerve root, absence of widespread involvement including bulbar and respiratory system, and bladder or bowel dysfunction in some cases of cervical spondylotic myelopathy but never observed in ALS.

In the differential diagnosis, structural abnormalities such as spinal cord tumors, arteriovenous malformations, foramen magnum tumors, and syringomyelia need to be considered because they can manifest with signs of upper and lower motor neuron dysfunction.

Tumors of the spinal cord can simulate a progressive myelopathy or have a combination of signs of spinal cord compression and radicular symptoms. Extradural lesions cause early root symptoms of pain and paresthesias and usually a late involvement of the bladder. Intrinsic tumors, such as astrocytomas, ependymomas, and so on, produce motor dysfunction but also sensory abnormalities such as dissociate anesthesia and early bladder dysfunction. Dural arteriovenous malformation or fistula can also present with signs of upper and lower motor neuron dysfunction and need to be differentiated from ALS, but involvement of the sphincters and sensory abnormalities also occur.

Tumors of the foramen magnum can sometimes simulate ALS because they can present with signs of upper and lower motor neuron dysfunction and cranial nerve abnormalities causing dysphagia and dysartria but other important clinical features are prominent—occipital or posterior cervical pain, headache, paresthesias, dysfunction of the accessory nerve with weakness of the sternomastoid and trapezius muscles, and so on.

Syringomyelia that enters the differential diagnosis of upper and lower motor neuron involvement is associated with prominent sensory symptoms, such as dissociated sensory loss and neck pain, not present in the vignette.

With regard to disorders of peripheral nerves, multifocal motor neuropathy with conduction block needs to be carefully considered because of the possibility of treatment and more favorable prognosis compared with ALS. Multifocal motor neuropathy is a demyelinating disorder characterized by progressive asymmetrical weakness, atrophy, fasciculations, and cramps, without sensory involvement. It can also be excluded, because in this condition there are no signs of upper motor neuron involvement, and weakness and atrophy typically are in the distribution of individual peripheral nerves rather than the spinal segmental root distribution observed in ALS. Conduction block, which is defined as a decrease in amplitude or area of the compound muscle action potential with proximal as compared with distal stimulation, is the hallmark of this disorder.

Disorders of the neuromuscular junction can be easily excluded. Myasthenia gravis characterized by fatigable weakness frequently involving the extraocular muscles does not include upper motor neuron signs or fasciculations. Lambert-Eaton myasthenic syndrome can occasionally simulate the progressive muscular atrophy variant of ALS. Muscle disorders such as polymyositis with the typical findings of progressive, predominantly proxymal, weakness usually associated with myalgia and without any upper motor neuron signs can be also easily excluded from the vignette.

Other entities that need to be mentioned for completion, but can be excluded by the vignette, are:

- Motor disorders associated with paraproteinemia, such as the peripheral neuropathy seen with osteosclerotic myeloma, usually manifest with signs of lower motor neuron involvement and may occasionally simulate progressive muscular atrophy. Upper motor neuron signs are never present.
- Polyglucosan body disease or type IV glycogenosis due to branching enzyme deficiency can manifest in adults with upper and lower motor neuron signs in an asymmetric distribution but other important features are sensory loss, neurogenic bladder, cerebellar ataxia, and dementia.
- The adult variant of hexosaminidase A enzyme deficiency can manifest with weakness and cramps in combination with cerebellar and extrapyramidal signs and cognitive impairment.
- Endocrine disorders, such as hyperparathyroidism and thyrotoxicosis, enter the differential diagnosis as well as tumors, such as lymphoma.

Progressive Muscular Atrophy

Vignette

A 70-year-old retired handyman complained for the last eight months that he has had difficulty buttoning his shirt, picking up small objects or turning the door's knob. He also developed neck stiffness and was treated by a physical therapist for several months without significant improvement. For the last four months he had experienced a tendency to fall, with difficulty getting back on his feet and mild right leg cramps. Thereafter, he began to experience several muscular twitches in his neck and arms and difficulty taking a deep breath. He had a 10-year history of diabetes treated with several oral agents. He stopped smoking seven years ago. The neurological examination showed that he had difficulty lift-

ing his arms above the shoulder and could be easily overcome. He could not spread his fingers apart. He had wasting of the muscles of the distal forearms and of the intrinsic hand muscles. There was moderate weakness of the right leg and wasting. DTRs were (⅕) in the upper extremities and trace in the lower, with an absent ankle jerk bilaterally. Vibration was decreased at both ankles.

Summary A 70-year-old man with progressive weakness of the upper and lower extremities, decreased reflexes, atrophy, fasciculations, and no significant sensory disturbances. (The decreased vibration at both ankles can be age-related.) He has a history of diabetes for 10 years.

Localization

The signs and symptoms of the vignette localize to the lower motor unit. It is important to differentiate which part of the motor unit is involved:

- Anterior horn cell.
- Nerve root.
- Peripheral nerve.
- Neuromuscular junction.
- Muscle fiber.

Disorders of the Anterior Horn Cells

Anterior horn cell disease causes involvement of motor neurons at multiple levels of the spinal cord. Different disorders can be identified in this category:

- Progressive muscular atrophy (PMA): ALS variant.
- Spinal muscular atrophy.
- Post-polio syndrome.
- Motor neuron syndrome associated with the remote effects of cancer.
- Adult-onset hexosaminidase A deficiency.

Progressive muscular atrophy is considered a variant of ALS with no signs of upper motor neuron involvement. It is characterized by progressive weakness and atrophy in an asymmetrical distribution, fatigue, muscle cramps, and fasciculations, affecting preferentially males and rarely with bulbar signs.

Many patients presenting with lower motor neuron dysfunction may later show signs of upper motor neuron involvement. The diagnosis of PMA is highly suggestive of the vignette where only lower motor neuron signs are demonstrated. The occurrence of lower motor neuron dysfunction in the absence of upper motor neuron signs may also indicate the possibility of an inherited motor neuron disorder such as adult-onset spinal muscular atrophy.

The adult-onset SMA is characterized by symmetrical, predominantly proximal muscle weakness and atrophy with onset in the second or third decade of life and showing slow progression of symptoms. The clinical characteristics and absent family history clearly exclude this entity from the vignette.

Post-polio progressive muscular atrophy is responsible for fatigue, muscle pain, progressive asymmetrical weakness and atrophy, particularly in muscles previously affected by poliomyelitis.

Hexosaminidase A deficiency can have a motor-neuron-disease type of presentation with weakness, cramps, fasciculations, and hyporeflexia, but patients are usually younger, in the second or third decade of life. Other characteristics may include signs of cerebellar dysfunction, postural and action tremors, cognitive impairment, and laboratory abnormality showing a severe hexosaminidase A deficiency in serum or leukocytes.

Finally, motor neuron disease can be associated with remote effects of cancer, in particular, a lymphoproliferative disease. According to Dumitru et al., the most frequently associated lymphoproliferative disorders are Hodgkin's disease and non-Hodgkin's lymphoma.

Disorders of the Nerve Root

In a patient presenting with progressive weakness and atrophy, the possibility of cervical and lumbosacral radiculopathy needs to be considered. Radiculopathy, which can involve multiple roots, is usually characterized by sensory disturbances such as pain and paresthesias that may follow a radicular distribution, often with paraspinal muscle spasm and some motor weakness or reflex loss. In the above vignette, the patient presented with progressive muscle weakness and wasting, without sensory symptoms, which make the diagnosis of multiple radiculopathies an unlikely possibility. Plexus dysfunction that is usually caused by trauma, neoplasm, and radiation therapy usually presents with acute or subacute onset of motor paralysis and sensory loss.

Disease of the Peripheral Nerve

Among the pure motor neuropathies, multifocal motor neuropathy (MMN), which is a demyelinating disorder characterized by progressive asymmetrical distal weakness in combination with varying degrees of atrophy, cramps, and fasciculations, and without sensory symptoms, is an important consideration in the differential diagnosis of PMA. Multifocal motor neuropathy is a slowly progressive, potentially treatable disorder in which the asymmetrical weakness typically follows the distribution of individual peripheral nerves rather than the myotomal pattern of ALS. Bulbar involvement is rarely seen and there are no signs of upper motor neuron dysfunction. Important laboratory findings include the detection of antiGM1 antibodies in the serum and the electrophysio-

logical evidence of conduction block in multiple upper and lower extremity nerves.

Diseases of the Neuromuscular Junction

Lambert-Eaton myasthenic syndrome in particular can occasionally simulate the lower motor neuron variant of ALS. LEMS, characterized by proximal muscle weakness that tends to improve after a brief period of contraction, does not include muscle fasciculations or prominent atrophy. Autonomic dysfunction (dry mouth, impotence, constipation, and so on) are important features of LEMS.

Diseases of the Muscle

The clinical characteristics of the muscle disorders polymiositis and dermatomyositis are not features of the vignette. Inclusion body myositis can sometimes enter the differential diagnosis of PMA. This disorder manifests in elderly patients with asymmetrical distal weakness and atrophy, particularly involving the wrist/finger flexor muscles associated with hyporeflexia. There are no fasciculations, and upper motor neuron signs are never seen.

Bulbar Palsy

Vignette

A 70-year-old female housekeeper and amateur singer started to notice some slurring of speech when singing during the past three months. Two months later she also began having difficulty drinking fluids often accompanied by coughing and the feeling that the fluid was stuck in her throat. On examination, she had mild dysartria, mild bilateral facial weakness, a positive snout reflex, and hyperactive jaw jerk. There was full strength in the limbs with symmetrical deep tendon reflexes and no evidence of atrophy. When reexamined one year later, dysartria and dysphagia had worsened. Deep tendon reflexes were hyperactive and fasciculations were noted in the shoulder girdle muscles.

Summary The vignette can be summarized as progressive bulbar dysfunction.

Localization

Multiple localization can be responsible for progressive bulbar palsy. Disorders to be considered are discussed below.

Cerebral Disorders

Patients with hypertension and multiinfarct dementia of vascular origin can present with pseudobulbar palsy causing dysphagia, dysartria, and emotional incontinence due to damage to the corticobulbar tracts. In the vignette there is no indication of any risk factor for stroke, and the evolution with the appearance of fasciculations indicates involvement of the lower motor neuron.

Structural brainstem abnormalities, either vascular or neoplastic, can manifest with signs of bulbar dysfunction but typically have other accompanying findings such as diplopia, gaze paralysis, nystagmus, cerebellar ataxia, dysmetria, dysarthria, and sensory involvement.

Syringobulbia can also present with signs of bulbar dysfunction such as dysphagia, dysarthria, and tongue atrophy, but other features include nystagmus, sensory loss involving the face, and so on.

Disorders of the Anterior Horn Cells

Anterior horn cell disease or ALS with bulbar onset followed by more widespread involvement can explain the symptoms described in the vignette. Abnormality of speech (dysarthria and dysphonia) due to UPM, LMN, or both, are the most common initial symptoms of bulbar muscle weakness in the ALS patient (Belsh and Schiffman). Dysphagia particularly for liquids is another characteristic finding as well as facial weakness. The examination usually discovers tongue atrophy and weakness of the soft palate. Eye movements are never involved. Patients initially presenting with the bulbar form eventually tend to manifest signs of widespread involvement typical of ALS.

Disorders of Peripheral Nerves

Among the neuropathies, in particular diphtheria can cause bulbar symptoms but usually in association with other typical findings such as blurry vision due to accommodation defect, distal paresthesias, and sensory loss.

Disorders of the Neuromuscular Junction

Myasthenia gravis (MG) can present with bulbar dysfunction as an initial symptom in 20 to 30 percent of the cases (Belsh and Schiffman). Typically, fatigable weakness is the hallmark of the disorder. Fasciculations and hyperreflexia are not signs of this disorder, but visual abnormalities, in particular diplopia, ptosis, and ophthalmoplegia, are characteristic findings of MG, as opposed to ALS.

Disorders of Muscle

Polymiositis and dermatomyositis can cause dysphagia, but are usually easily diagnosed and excluded by the vignette. Oculopharyngeal dystrophy can rarely be confused with the progressive bulbar palsy of ALS because the former is a hereditary disorder characterized by slowly progressive ptosis and dysphagia.

Kennedy's Syndrome

Vignette

A 56-year-old teacher had complained of mild difficulty swallowing and speech problems for the last five years. He had a long history of weakness, more marked in his legs, cramps, and twitching. His older brother had marked facial twitching and muscle cramps. On physical examination there was marked gynecomastia and muscle weakness more severe in a limb-girdle distribution. Prominent fasciculations were noted in the perioral facial muscles and the tongue with marked tongue atrophy.

Summary A 56-year-old man with progressive dysphagia and dysarthria, and a prior history of proximal upper extremity weakness and prominent fasciculations, particularly in the perioral area and the tongue associated with tongue atrophy. His older brother had facial fasciculations and muscle cramps.

Localization

There is clinical involvement of the lower motor neuron without upper motor neuron signs. Among the disorders of the motor unit, diseases affecting the motor neuron are considered first. Also, the slow progression of the disorder and the indication of an older brother with perioral twitching and cramps points to an inherited disorder. The disorders to be considered are

- Adult-onset spinal muscular atrophy.
- X-linked bulbospinal neuronopathy (Kennedy's syndrome).

Adult-onset spinal muscular atrophy, characterized by slowly progressive proximal muscle weakness and atrophy with onset in the third or fourth decade of life, can be excluded because bulbar involvement is unusual.

X-linked bulbospinal neuronopathy or Kennedy's syndrome is an X-linked recessive disorder that affects males in the fourth and fifth decade of life and is characterized by progressive spinal muscular atrophy in a limb-girdle distribution, cramps, fasciculations, and typically facial and perioral fasciculations. Mild dysarthria and dysphagia are also present and there is no respiratory dysfunction. Several systemic clinical features include gynecomastia, diabetes, and testicular atrophy.

Laboratory findings that help confirm the diagnosis are

- Increased serum levels of creatine kinase (CK) and estrogen.
- Electrodiagnostic findings indicative of chronic denervation and sensory neuropathy.
- Genetic studies showing an expansion of the CAG repeat sequence(cytosine-adenine-guanine) in the androgen receptor gene.

Kennedy's syndrome has clinical features that help in making a distinction from ALS. In particular, the course of the disorder is slowly progressive with predominant involvement of the proximal muscles and mild bulbar findings in the absence of upper motor neuron involvement. A mild sensory polyneuropathy is usually present.

Diagnostic Tests That Help in Making the Diagnosis of Motor Neuron Disease

Neuroimaging studies are indicated in order to rule out structural pathology, particularly in cases of bulbar onset ALS, but also in order to exclude myelopathy or multiple radiculopathies. Electrodiagnostic tests are very important in confirming the diagnosis of motor neuron disease. Sensory nerve conduction studies are normal and motor nerve conduction studies can demonstrate normal findings, decreased amplitude, or decreased velocity related to the loss of faster conducting axons. It is important to perform an extensive study in order to demonstrate the possibility of conduction block or significant compound muscle action potential (CMAP) temporal dispersion, which are indicative of demyelination. Multifocal motor neuropathy with electrophysiologic evidence of conduction block can sometimes simulate ALS but is potentially treatable and carries a better prognosis.

The needle electromyogram (EMG) examination in ALS may reveal active denervation and reinnervation in widespread distribution that is unexplained by multiple mononeuropathies or radiculopathies (Preston and Shapiro).

Clinical laboratory studies are often obtained and include routine testing such as complete blood count, electrolytes, CK, serum VDRL, thyroid function tests, serum protein electrophoresis and antineural antigen testing (GMI, asialo-GMI). Special studies such as CSF, leukocyte hexosaminindase A assay, or test for cytosine-adenine-guanine repeat in androgen receptor gene (X chromosome) are reserved for selected cases.

Clinical Features and Diagnosis

ALS is the most common form of MND in adults with an incidence of 2 per 100,000 (Bromberg). Patients manifest symptoms related to dysfunction of the anterior horn cells and corticospinal tract. Progressive muscular atrophy, which is considered a variant of ALS and demonstrates only signs of lower motor neuron (LMN) involvement, is more common in men, and has a slower rate of progression.

Primary lateral sclerosis on the other hand only shows upper motor neuron (UMN) findings and like PMA carries a better prognosis with a slower progression. Patients

who present with LMN or UMN signs only at onset and later develop ALS are considered to have LMN- or UMN-onset ALS.

Progressive bulbar palsy manifests with signs of bulbar dysfunction, particularly dysarthria and dysphagia, due to UMN or LMN dysfunction or both. This form may eventually progress to the more widespread ALS.

The El Escorial criteria for the diagnosis of ALS established a combination of upper and lower motor neuron signs and spread or progression of signs and symptoms within a body region and between regions over time. The four body regions established in the diagnosis of ALS are bulbar, cervical, thoracic, and lumbosacral. The diagnosis of definite ALS requires UMN and LMN signs present in the bulbar and at least two other spinal regions, or upper and lower motor neuron signs present in three spinal regions.

Limbs are the initial site of involvement in approximately 78 percent of patients and weakness present in an asymmetric pattern in approximately 60 percent of these patients (Bromberg). There can also be an onset with bulbar signs particularly dysartria and dysphagia.

Signs of upper motor neuron dysfunction include weakness, loss of dexterity, increased deep tendon reflexes, spasticity, Hoffman's sign, extensor plantar responses, clonus, pathologic spread, exaggerated jaw jerk and gag reflex, snout reflex, and emotional lability. Lower motor neuron signs include weakness, atrophy, fasciculations, and muscle cramps. Bulbar signs are represented by dysphagia, dysarthria, tongue atrophy, and weakness of the soft palate. Respiratory dysfunction due to weakness of the respiratory muscles may cause dyspnea related to exertion or at rest.

Etiology

The cause of these motor neuron diseases is unknown. However, possibilities include:

- Exogenous excitotoxins.
- Glutamate toxicity.
- Autoimmune hypothesis.
- Viral etiology.

Hereditary disorders include familial ALS and Kennedy's syndrome.

Peripheral Neuropathies

Guillain-Barré Syndrome (GBS)

Vignette

A 60-year-old businessman was in good health until three days earlier when he started to complain of a dull aching pain in his lower back and intermittent numbness of the soles of his feet. The day after the initial symptoms, he experienced increasing difficulty carrying his bags. One day he felt that his legs were heavy and his gait unsteady. He also noticed right facial numbness and difficulty eating and speaking. He had recently returned from a five-day business trip to Africa where he experienced some intestinal problems and a few bouts of diarrhea. He was a heavy smoker and had hypertension for two years and diabetes for 15 years. On examination he was alert and oriented with intact speech, memory, and calculation. Visual fields, optic disk and extraocular muscles were normal. There was right facial weakness and moderate weakness of neck flexion. He could barely elevate his arm from the horizontal position and his hand grip was very weak. He was unable to lift his legs against resistance and could not stand without support. Deep tendon reflexes could not be elicited, even with reinforcement.

Summary A 60-year-old man presenting with acute motor weakness of all four extremities and right facial muscles, associated with areflexia and some sensory complaints. The weakness involves both the proximal and distal muscles as well as the neck flexor and facial muscles. There is a history of a precedent gastrointestinal illness.

Localization and Differential Diagnosis

The pattern of weakness and diminished deep tendon reflexes obviously localize to the peripheral nervous system. Next it must be determined which segment of the motor unit is affected: the peripheral nerve, the neuromuscular junction, the muscle, or the motor neuron. The differential diagnosis of acute motor weakness needs particular attention, as it is a very important topic for the practicing neurologist, not just the Board candidate. In the differential diagnosis, diseases of the peripheral nerves and root need to be considered first.

Guillain-Barré syndrome (GBS) or acute inflammatory demyelinating polyneuropathy characterized by rapid onset of weakness, accompanied by sensory loss, and areflexia may correspond to the clinical picture presented in the vignette. Among the neuropathies and polyradiculoneuropathies responsible for acute motor weakness, infectious, inflammatory, metabolic, and toxic causes need to be ruled out.

Of the infectious processes, diphtheria may simulate GBS but the evolution of symptoms is longer and systemic manifestations such as fever, pharyngitis, headache, and nausea may dominate the initial picture. Blurry vision due to paralysis of accommodation common in diphtheria is rare in GBS (Ropper).

Cytomegalovirus can be responsible for the development of acute flaccid paralysis, areflexia, and sphincteric

abnormalities in association with pain and paresthesias in the cauda equina distribution typically in severely immunosuppressed HIV patients.

An acute motor weakness simulating GBS may occur early during the HIV infection.

Lyme disease also enters the differential diagnosis of weakness, sensory loss, and areflexia. The peripheral neuropathy is generally not ascending and typically asymmetrical (Ropper).

Acute motor axonal neuropathy characterized by acute ascending weakness, areflexia, cranial nerve deficits, respiratory failure, and lack of sensory symptoms has been described as the most common variant of GBS in Northern China (Dumitru).

Vasculitic neuropathies are usually associated with polyarteritis nodosa, rheumatoid arthritis, systemic lupus erythematosus, and Wegener's granulomatosis. They need to be mentioned as part of the differential diagnosis of acute weakness. Several features distinguish them from GBS, and include the distribution of weakness usually asymmetric, uncommon respiratory or sphincter dysfunction, and involvement of multiple systems and organs.

Among the metabolic disorders causing acute weakness, hepatic porphyria with neuropathy needs to be considered. Acute intermittent porphyria due to porphobilinogen deaminase deficiency can manifest with acute ascending motor weakness simulating GBS. In addition, behavioral abnormalities, seizures, and psychosis can also occur as well as abdominal pain that usually initially predominates.

The periodic paralyses usually have episodic weakness and areflexia with no sensory, cranial nerve, or sphincteric disturbances.

Acute weakness can also be caused by exposure to certain toxins, including arsenic, thallium, dapsone, lead, exacarbon, neurotoxic fish, buckthorn, and tick paralysis.

Diseases of the neuromuscular junction, which can cause acute weakness and are differentiated from GBS, include botulism, myasthenia gravis, and organophosphate intoxication. Botulism results from a neurotoxin elaborated by *Clostridium botulinum* types A, B, and E (Ropper). It is characterized by the manifestation of nausea, vomiting, constipation, dysphagia, dry mouth, blurred vision, ptosis, and dysarthria over the course of 12 to 36 hours after the ingestion of contaminated food. Pupils can be dilated and nonreactive. Respiratory weakness is often marked, even when limb weakness is only mild or moderate, and DTR are frequently preserved even in the presence of significant limb weakness (Ropper).

Myasthenia gravis also enters the differential diagnosis of acute weakness but has certain characteristics such as fluctuation and fatigable weakness. Fatigable ptosis is an important finding of myasthenia gravis. Reflexes and sensory examination are normal.

Muscle disorders include the periodic paralyses as causes of acute weakness. Primary hypokalemic periodic paralysis, which is the most frequent form, is characterized by episodic weakness and areflexia that occur preferably at night, and is precipitated by meals rich in carbohydrates and strenuous exercise. Respiratory and cranial muscles are not involved.

Acute myopathies have been described with the administration of drugs such as clofibrate and lovastatin (Ropper) or after infections such as influenza, *Mycoplasma pneumoniae* and trichinosis. Sensory function and reflexes are normal, CPK levels are elevated: all factors that should help in making the right diagnosis.

Diseases of the anterior horn cells causing acute weakness include poliomyelitis which has an asymmetrical distribution of muscle weakness and is accompanied by systemic symptoms. Among CNS disorders causing acute weakness, transverse myelitis needs to be mentioned but the distinction from GBS should be obvious. Transverse myelitis presents with symptoms and signs of spinal cord dysfunction, such as weakness, increased DTR, Babinski's sign, sensory level, and sphincteric dysfunction.

Etiology

Specific agents are not identified, but GBS has been linked to viral infection cytomegalovirus, Epstein-Barr virus, and HIV, or to bacterial infections such as *Mycoplasma pneumoniae* and Lyme disease. *Campylobacter jejuni* enteritis may be the most common bacterial organism associated with GBS, particularly its axonal forms preceding the disease in approximately 25 to 38 percent of patients (Barohn).

Clinical Features

Acute inflammatory demyelinating polyneuropathy manifests with rapid progressive weakness, sensory loss and areflexia. GBS is the most common cause of acute generalized weakness with an incidence of 1 to 2 per 100,000 people (Barohn and Saperstein). An antecedent infection related to the gastrointestinal or respiratory system is recognized one to four weeks prior to the neurological symptoms, but other factors include prior surgery or immunization.

The characteristic clinical features include progressive relatively symmetrical weakness of more than one limb associated with areflexia or hyporeflexia evolving over the course of four weeks. Other findings are represented by mild sensory symptoms, cranial nerve involvement in particular the seventh nerve that can be affected bilaterally, signs of autonomic dysfunction, elevated CSF proteins, evidence of a demyelinating neuropathy on electrodiagnostic studies and recovery that usually starts 2 to 4 weeks after plateau phase.

The pattern of weakness is an ascending paralysis with onset in the lower extremities but occasionally a descending presentation characterized by neck, face, and pharyngeal involvement and then progression to the arms and legs can also occur. The weakness tends to be symmet-

rical and to involve proximal and distal muscles. Sensory symptoms such as numbness and paresthesias can be prominent as well as pain in the back and limbs and may represent the initial symptoms.

Cranial nerve dysfunction, particularly facial diplegia and oropharyingeal weakness, are seen in 50 percent of patients but ophthalmoparesis is rarely observed (Bosch). Autonomic abnormalities include cardiovascular complications due to tachyarrhythmia, bradycardia, asystole, sustained hypertension, orthostatic hypotension, and so on. Other manifestations of autonomic dysfunction are urinary retention, impotence, constipation, anhydrosis, pupillary abnormalities, and so on. Respiratory complications requiring mechanical ventilation occur in about one third of cases.

The majority of patients reach the nadir by by four weeks, then a variable plateau phase occurs before the onset of recovery, which can last up to 24 months (in 82 percent of patients according to Bosch).

GBS Variants

Several clinical variants of GBS have been described. Acute motor axonal neuropathy (AMAN), characterized by rapidly progressive motor weakness and areflexia without sensory loss, has electrophysiological findings of primarily axonal degeneration and normal sensory nerve action potentials. Antecedent *Campylobacter jejuni* infection was found in 76 percent of AMAN patients from northern China (Bosch). Serum antibodies, mainly of the immunoglobulin G (IgG) class, to several glycolipids, notably GM1 and GD1a, are found in a greater proportion of GBS patients with axonal features (Bosch).

Acute motor-sensory axonal neuropathy is another primarily axonal form that involves motor and sensory axons. Miller Fisher syndrome, characterized by ophthalmoplegia, ataxia, and areflexia, is another variant and is discussed later in this chapter. A pure sensory form with ataxia but no ophthalmoplegia is also described. The pharyngeal cervicobrachial variant is characterized by marked cervical, facial, and pharyngeal weakness in the early stages with later involvement of the limbs. Autonomic variants have also been described.

Diagnosis

The examination of the cerebrospinal fluid after the first week demonstrates increased protein level and normal cell count in most cases. A mild to moderate increase in cell count in the CSF is typically found in GBS associated with HIV infection.

Electrodiagnostic tests in AIDP show evidence of multifocal demyelination. Early findings are prolonged or absent F waves and H responses, an indication of proximal demyelination at the root level. Slow conduction velocities, prolonged distal latencies, conduction block, and temporal dispersion are the important electrophysiological features supportive of demyelination. A secondary axonal loss is suggested by the presence of fibrillation potentials on needle EMG that appear in two to five weeks during the course of the process. The axonal variant demonstrates low amplitude or unobtainable compound motor action potential.

The EMG can represent an important prognostic factor. In particular, the mean amplitude of the CMAP can indicate poor outcome if its value is less than 20 percent of the lower limit of normal recorded 3 to 5 weeks after the onset of symptoms (Katirji).

Several antibodies to various gangliosides (GM_1, GM_1-b, GD_1-b) have been documented in patients diagnosed with GBS. The majority of patients presenting with the Miller Fisher variant have serum GQ1b antibodies.

Treatment

Supportive care with particular attention to respiratory support and correction of autonomic dysfunction is an important part of the treatment. Elective intubation is required when forced vital capacity (FVC) decreases to less than 15 to 20 ml/kg.

Immunotherapies, in particular plasma exchange (PE) and intravenous human immunoglobulin (IVIG), have shown efficacy in the treatmant of AIDP and should be initiated within the first week of symptoms. The dose of PE is 200 to 250 ml/kg of body weight over 14 days. Complications include hypotension, anemia or low platelet count, pneumothorax, pulmonary embolism, and so on. Intravenous immunoglobulin should be given with an infusion of 0.4 g/kg per day for five days (total dose 2.0 g/kg). IVIG side effects include flu-like symptoms, nausea, vomiting, headache, renal failure, hepatitis C, and so on.

Barohn has described factors implicated in the prognosis. In particular, a poor outcome is related to advanced age of the patient, rapid evolution of symptoms, necessity of ventilatory support, low CMAP amplitude, and prior gastrointestinal infection with *C. jejuni.*

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Vignette

A 32-year-old lawyer had been in excellent health until six months ago when he noticed some difficulty climbing a flight of stairs. He also experienced hypersensitivity on the soles of his feet, low back pain, and numbness and stiffness of both hands that slowly worsened. His balance was poor, especially with the eyes closed. There was no dysphagia, dysartria, urinary or bladder dysfunction. No history of weight loss or rash. He was particu-

larly concerned because his father had ALS. On neurological examination, cranial nerves were intact. Neck flexors, deltoid, biceps, triceps, and distal muscles were 4/5 in the upper extremities. In the lower extremities, proximal muscle strength was 3/5 and distal was 4/5. DTR were 1+ in the upper extremities, trace at the knees, and absent at both ankles. Sensory examination revealed decreased vibratory sensation, joint position, and pinprick below the knees. A bilateral postural tremor was noted in the arms.

Summary A 32-year-old man with progressive proximal and distal weakness, sensory loss, hyporeflexia, and postural tremor.

Localization

The clinical findings described in the vignette localize to the peripheral nerves. The pattern of progressive weakness, sensory loss, and hyporeflexia evolving within six months are typically suggestive of a chronic neuropathic process.

The vignette therefore describes a chronic progressive symmetric sensory and motor deficit that includes distal and proximal weakness, sensory loss, paresthesias and hyporeflexia. Symmetrical weakness that involves proximal and distal muscles associated with sensory loss and hyporeflexia or areflexia is highly suggestive of a demyelinating neuropathy, particularly acute/and chronic acquired inflammatory demyelinating polyneuropathy (CIDP). The sensory findings described also point to involvement of the large myelinated sensory fibers. The demyelinating neuropathies can be distinguished into acquired and inherited processes.

Clinically, the vignette fits the diagnostic criteria for CIDP, which are characterized by progressive stepwise or relapsing symmetrical proximal and distal weakness of the upper and lower extremities of at least two months' duration associated with sensory findings and hyporeflexia or areflexia. The involvement of neck flexor and facial muscles can occur, but the extraocular muscles are rarely affected. Sensory complaints can be prominent and usually include distal numbness and paresthesias. Autonomic dysfunction is not frequent particularly compared to GBS and respiratory compromise is rare.

The differential diagnosis includes disorders of the peripheral nerves that can be acquired or inherited. Chronic progressive polyneuropathy with clinical, laboratory, and electrophysiological criteria similar to CIDP can be sometimes associated with an underlying systemic disorder. These cases have been defined by Barohn as "CIDP with" concurrent illnesses such as AIDS, connective tissue disease, monoclonal gammopathy, lymphoma, chronic active hepatitis, and so on.

The polyneuropathies associated with paraproteinemias should be well considered because monoclonal gammopathy occurs in approximately 10 percent of all patients with idiopathic polyneuropathy (Mendell). The paraproteinemias associated with polyneuropathy include multiple myeloma, osteoslerotic myeloma, macroglobulinemia, primary amyloidosis, cryoglobulinemia, and benign monoclonal gammopathy.

Osteosclerotic myeloma occurs in only 3 percent of patients with myeloma (Mendell) and may be associated with the presence of a neuropathy in over half of the cases. The neuropathy that manifests with osteosclerotic myeloma can be clinically indistinguishable from CIDP, presenting with symmetrical weakness of the proximal and distal muscles, sensory loss preferably of the large fiber type, and hyporeflexia or areflexia, and can occur as an early manifestation or even initially during the disease. Other systemic abnormalities can be associated with osteosclerotic myeloma and involve multiple organs representing the POEMS syndrome (polyneuropathy, organomegaly [hepatomegaly, splenomegaly, cardiomegaly], endocrinopathy [diabetes, gynecomastia, amenorrhea], monoclonal gammopathy, and skin lesions (thickening, increased pigmentation, hypertrichosis) (Mendell).

Multifocal motor neuropathy with conduction block also enters into the differential diagnosis of acquired chronic demyelinating neuropathy and in the differential diagnosis of CIDP. Typical clinical manifestations of MMN include progressive, asymmetrical predominantly distal weakness, associated with cramps and fasciculations and without sensory symptoms. Atrophy can occur but less than expected with the degree of weakness that characteristically follows a peripheral nerve distribution. Therefore, MMN can clinically be distinguished from CIDP, which typically presents with progressive predominantly symmetrical and proximal but also distal weakness associated with sensory deficit and characteristic laboratory findings. The patient in the vignette does not have symptoms suggestive of MMN. (Obviously, we don't have laboratory and electrodiagnostic studies to help us with the diagnosis.)

Inherited demyelinating neuropathies, particularly hereditary sensory-motor neuropathies type I or Charcot-Marie-Tooth disease, are the most common form of hereditary chronic polyneuropathies. The absence of family history of this disorder, which has an autosomic dominant pattern of inheritance, and the lack of characteristic features (marked distal weakness and atrophy in the legs; foot deformities such as pes cavus or equinovarus and hammer toes in some cases) make the diagnosis unlikely in this vignette.

Refsum's disease, which is an autosomic recessive disorder due to abnormalities of phytanic acid metabolism, is also associated with a chronic progressive demyelinating neuropathy. But other characteristic clinical features are retinitis pigmentosa manifesting with night blindness, cerebellar ataxia, neurogenic deafness, and so on.

Disorders of other parts of the motor unit, which are differentiated from CIDP (but clinically excluded in the vignette) are presented below.

Anterior horn cell disorders
- ALS: Upper and lower motor neuron signs in the absence of sensory symptoms.
- Spinal muscular atrophy type 3: Hereditary disorder characterized by proximal muscle weakness and atrophy with intact sensation to all modalities, affecting individuals in the third or fourth decade of life.

Disorders of muscle
- Polymiositis: Proximal muscle weakness, normohyporeflexia, normal sensation, myalgia.
- Inclusion body myositis: Slowly progressive asymmetrical proxymal and distal weakness and atrophy, preferentially affecting knee extensor muscles and wrist and finger flexors.

Disorders of the neuromuscular junction
- Myasthenia gravis: Fatigable weakness often affecting the extraocular muscles without sensory findings.
- Lambert-Eaton myasthenic syndrome: Progressive proximal weakness and hyporeflexia that improves with brief muscle contraction associated with autonomic findings.

Clinical Features

CIDP is characterized by progressive, stepwise or relapsing muscle weakness of varying severity and of at least two months' duration, predominantly symmetrical and proximal but also distal, associated with hyporeflexia or areflexia. Facial and neck muscles can also be involved but autonomic and respiratory compromise are rare, particularly compared with GBS. Sensory symptoms can include paresthesias and numbness and can cause severe sensory ataxia or pseudoathetosis due to proprioceptive loss (Small and Lovelace).

Diagnosis

Examination of the CSF shows characteristic albuminocytologic dissociation with markedly elevated protein content (CSF protein >45 mg/dl; cell count $<10/mm^3$). Electrodiagnostic studies demonstrate evidence of demyelination with its characteristic findings of decreased nerve conduction velocity in distal nerve segments to at least 60 percent of normal, absent or prolonged F wave latencies and H reflex latencies, prolonged distal motor latencies, conduction block or temporal dispersion in one or more motor nerves. Nerve biopsy demonstrates predominant features of demyelination

Blood tests that are usually obtained in patients diagnosed with chronic demyelinating neuropathy include
- Serum paraprotein: Serum and urine immunofixation, electrophoresis, quantitative immunoglobulins, cryoglobulins
- Fasting glucose.
- Thyroid function test.
- HIV and hepatitis serology.
- Antinuclear antibody, rheumatic factor, ESR.
- Antibodies to GM_1 and asialo-GM_1.
- MAG (myelin-associated glycoproteins) and sulfated acidic glycoproteins).
- Other studies, such as phytanic acid long-chain fatty acids, and so on, are indicated in selected cases.

Treatment

Corticosteroids remain the first line of therapy. Prednisone can be initiated at an oral dose of 80 to 100 mg a day for four to six weeks and then slowly tapered and changed to alternate-day dosing. The duration of treatment is six months or longer. The side effects are well known. Plasmapheresis is indicated if patients have marked weakness or if they are not fully controlled on a prednisone regimen because of side effects or contraindications. IVIG has also been considered, but is more costly and requires maintenance therapy every 6 or 12 weeks.

Miller Fisher Syndrome

Vignette

A 26-year-old art student, while vacationing in Spain, woke up experiencing double vision, particularly when looking to the right, that worsened toward the end of the day. He began to stagger when walking. The following day while in a local emergency room, a neurologist noted that the student had bilateral incomplete abducens paralysis, ptosis, and mild hyporeflexia. His gait was wide-based and he could only walk with assistance. His past medical history was unremarkable except for some gastrointestinal complaints and bouts of diarrhea after eating fish in the beginning of his vacation. His father had hypertension and his mother had a mild form of multiple sclerosis.

Summary A 26-year-old man with sudden onset of diplopia and unsteady gait. The neurological examination shows bilateral partial sixth and third nerve involvement, hyporeflexia, and ataxia.

Localization

First, it is important to localize the lesion and determine if the pathology involves the central or the peripheral ner-

vous system. Considering the central nervous system the localization more appropriate is in the brainstem and the cause may be attributed to a vascular event, infectious process, nutritional deficiency, space-occupying lesion, or demyelinating process.

Brainstem ischemia due to vertebrobasilar artery occlusion will be unlikely in a 26-year-old without significant risk factors for stroke. The student was in good health prior to the event and did not have any history of heart disease, vasculopathy or coagulopathy, or any predisposing factor for a cerebrovascular accident to occur. Therefore, this possibility does not represent a primary concern. Wernicke encephalopathy due to nutritional deficiency can manifest with ataxia and ophthalmoplegia, but typically includes a severe memory dysfunction as well as mental status changes with a global confusional state. Brainstem encephalitis can also be excluded by the lack of other signs and symptoms as well as fever, headache, and altered sensorium. Posterior fossa tumors other than metastasis are rare in adults and manifest with signs of progressive brainstem dysfunction. Ectasia of the basilar artery, which is a rare condition, can also cause signs of progressive brainstem involvement. Demyelinating disorders, such as multiple sclerosis, may involve the brainstem causing ophthalmoplegia and ataxia but hyporeflexia is not found.

Localizing to the peripheral nervous system, the part of the motor unit that is involved must be determined. The discussion can certainly be limited to disorders of the peripheral nerves and disorders of the neuromuscular junction. Miller Fisher syndrome, characterized by ophthalmoplegia, ataxia, and areflexia, is a very important diagnostic consideration in the vignette and also represents a clinical variant of GBS. Other neuropathies also featuring external ophthalmoplegia include infectious processes such as diphtheria, nutritional disorders such as hypophosphatemia, Whipple disease, diabetes, toxic causes such as thallium intoxication, and so on. Diphtheria has particular clinical features, such as longer evolution of symptoms, that also include systemic manifestations such as fever, sore throat, and myalgia, in addition to palatal paralysis and paralysis of accommodation.

Hypophosphatemia can cause a subacute sensorimotor peripheral neuropathy. Weakness, ataxia, and hyporeflexia can also be noted. Whipple disease, which can be complicated by peripheral neuropathy and supranuclear ophthalmoparesis rather than external ophtalmoplegia, has prominent abdominal symptoms and weight loss. Diabetes can manifest with sudden ophthalmoplegia, particularly involving the third nerve, due to a vascular mechanism in association with signs of peripheral neuropathy usually in older patients with long-standing diabetes. Thallium neuropathy manifests with gastrointestinal symptoms such as nausea and abdominal pain, painful paresthesias, relative preservation of DTR, psychotic behavior, alopecia, and so on.

Disorders of neuromuscular transmission, such as botulism, myasthenia gravis, and tick paralysis, are an important consideration in the differential diagnosis and can manifest with external ophthalmoplegia and, except for myasthenia, hyporeflexia and ataxia. Botulism in particular is characterized by acute onset of diplopia, dysphagia, and dysarthria often preceded by gastrointestinal symptoms. Respiratory distress and weakness of the upper and lower extremities create a dramatic picture. Deep tendon reflexes may be normal or diminished. Autonomic abnormalities include constipation, dry mouth, and abnormal pupils. Myasthenia gravis can present acutely but fatigable weakness that improves with rest is an important characteristic. Ataxia and hyporeflexia are not found. Tick paralysis can manifest with acute weakness, ophthalmoplegia, hyporeflexia, and respiratory compromise.

Clinical Features

Miller Fisher syndrome typically manifests with ophthalmoplegia, gait ataxia, and hyporeflexia or areflexia. Ophthalmoplegia can be asymmetrical and accompanied by ptosis but pupillary involvement is rare. Other symptoms include paresthesias and mild loss of sensation in the distal limbs, and mild oropharyngeal and facial weakness. The ataxia has the features of cerebellar disease (Mendell et al.).

Ropper has established some diagnostic criteria for Miller Fisher syndrome that include the following clinical features

- Bilateral and relatively symmetrical ophthalmoparesis associated with ptosis, limb and gait ataxia with cerebellar tremor, and areflexia. The progression of the symptoms is over three weeks.
- Facial or oropharyngeal weakness or paresthesias are minimal or absent, and the mental status is normal. Signs of upper motor neuron dysfunction or cerebellar dysartria are never observed.

Diagnosis

Laboratory findings include

- CSF shows increased protein content without significant pleocytosis.
- Electrodiagnostic studies demonstrate decreased amplitudes of the sensory nerve action potentials with a return of these responses during recovery, suggestive of a demyelinating sensory neuropathy (Mendell et al.).
- Serum anti-GQ1b antibodies are seen in the majority of patients with Miller Fisher syndrome (95% according to Mendell).

Treatment

The treatment is similar to that for typical GBS with IVIG or PE.

Disorders of the Neuromuscular Junction

Botulism

Vignette

A 45-year-old Chinese waiter woke up with blurry vision and bilateral ptosis. He felt nauseated and vomited several times. The next day he had complete ophthalmoplegia, dysarthria, difficulty swallowing, and shortness of breath. Neurological examination showed marked limitation of horizontal gaze and upgaze, ptosis, facial diplegia, and a weak tongue, with no fasciculations. Pupils were dilated and not reactive. Neck flexors and extensor and proximal limb muscles were weak. Deep tendon reflexes were diminished and sensation was normal.

Summary A 45-year-old man presenting with the acute onset of rapidly progressive bulbofacial, extraocular, respiratory and neck muscle weakness, accompanied by poor pupillary responses and hyporeflexia.

Localization

It is important to determine which component of the motor unit is involved: anterior horn cell, peripheral nerve, neuromuscular junction, or muscle.

Among the disorders of the peripheral nerve causing acute weakness, the entities to consider are Guillain-Barré syndrome, diphtheric polyneuropathy, and porphyric polyneuropathy. Guillain-Barré syndrome is characterized by rapidly progressive, relatively symmetrical weakness involving the proximal and distal muscles, usually with an ascending pattern that tends to involve the lower extremities first and is associated with hyporeflexia or areflexia. Sensory symptoms such as numbness, paresthesias, and even moderate or severe pain involving the limbs and lower back can also occur. A rare descending presentation that can simulate botulism or diphtheria is the pharyngeal-cervical-brachial variant described by Ropper with involvement of the facial, oropharyngeal, neck, and upper extremity muscles, which can create some diagnostic difficulties. Diphtheria, which also enters the differential diagnosis of the case presented in the vignette is characterized initially by fever, nausea, headache, pharyngitis, and other systemic symptoms as well as a longer evolution of symptoms. Weakness of the extraocular muscles and the face are not as prominent as with botulism. Pupillary responses to light and convergence are often normal on examination (Ropper).

The acute porphyrias are hereditary disorders presenting with acute neurological symptoms. Acute intermittent porphyria due to porphobilinogen deaminase deficiency is characterized by neurological manifestations usually preceded by gastrointestinal signs such as nausea, vomiting, and abdominal pain. Behavioral abnormalities, psychosis, and seizures are also seen. The distribution weakness involve the facial, oropharyngeal, and proximal limb muscles often resembling GBS. Deep tendon reflexes can be decreased or not elicitable. Sensory loss may be prominent in a proximal distribution with a shield-like or bathing trunk pattern. Other characteristic features of the acute intermittent porphyrias include autonomic abnormalities, particularly tachycardia, hypertension, postural hypotension, urinary retention, and so on.

After discussing diseases of the peripheral nerves that may explain the symptoms described in the vignette, neuromuscular junction disorders need to be considered, in particular botulism, myasthenia gravis, and organophosphate poisoning. Botulism (food-borne botulism) is the most likely diagnosis. The clinical manifestations start 12 to 36 hours after consumption of the contamined food. Gastrointestinal symptoms include nausea, diarrhea, vomiting, and abdominal pain. Blurred vision and diplopia can be experienced acutely in combination with dysphagia, dysarthria, dysphonia, and dry mouth. Large, poorly reactive pupils are a typical finding but this varies in different cases. Weakness of the upper and lower extremities also occurs together with disturbances of autonomic function with hypotension, tachycardia, and urinary retention. Weakness of respiratory muscles may require ventilatory support and deep tendon reflexes are usually retained but may be diminished in case of severe weakness.

Myasthenia gravis can be excluded because it typically presents with fatigable weakness often affecting the extraocular muscles in an asymmetric pattern and always sparing the pupils.

Organophosphate poisoning manifests with limb weakness and respiratory distress in combination with other signs, such as altered consciousness, seizures, fasciculations, nausea, vomiting, bradycardia, salivation, and so on.

Disorders of the anterior horn cells causing acute weakness include acute polio, which is mentioned for completion. Polymyelitis is responsible for an asymmetrical flaccid paralysis that usually involves the lower extremities. The IX and X nuclei can be involved withh resultant dysphagia and dysarthria. Other symptoms that

may precede the neurological signs are fever, vomiting, fatigue, abdominal pain, and headache.

Clinical Features

Clostridium botulinum is responsible for the production of neurotoxin that has been divided into eight immunologically distinct subtypes of which A, B, and E are the most common. Several clinical forms are identified, particularly

- The classic food-borne botulism, which is the most severe.
- Infantile botulism, which is the most common form of botulism in the United States and affects infants younger than one year of age.
- Wound botulism, which is very rare.
- Hidden botulism, which may be the adult equivalent of infant botulism (Dumitru et al.).

The onset of the manifestations may occur 12 to 36 hours after the consumption of food contaminated with the toxin and are characterized by nausea, vomiting, diarrhea, or constipation. The neurological symptoms can be dramatic with rapidly progressive ophthalmoplegia, often with pupillary dilatation, bulbar weakness causing dysphagia, dysarthria, and dysphonia, and weakness of the extremities. Autonomic dysfunction may cause orthostatic hypotension, urinary retention, impairment of lacrimation, and so on. Deep tendon reflexes are normal but hyporeflexia or areflexia may be observed in severe cases. Respiratory muscle weakness is responsible for reduced forced vital capacity and ventilatory support may be necessary.

Diagnosis

The diagnosis of botulism requires a high index of suspicion, particularly when there is a history of ingestion of contaminated food, a wound's infection, or severe constipation in infants. The botulinus toxin acts primarily at the level of the neuromuscular junction, more specifically on the presynaptic endings.

Electrophysiologic studies are important and may demonstrate a decreased amplitude of the CMAP in the affected muscles and a modest increment between 30 and 100 percent of the CMAP with rapid repetitive stimulation. Other confirmatory studies include the identification of the toxin in serum, stool, and wound cultures.

Treatment

The treatment is supportive, particularly for pulmonary care, and also based on the prompt use of the trivalent antitoxin.

Lambert-Eaton Myasthenic Syndrome

Vignette

A 60-year-old x-ray technician had difficulty climbing stairs and getting up from the toilet seat for the last five months, particularly in the morning on waking up, which seemed to slightly improve a short time thereafter. He also complained of dry mouth and fatigue. There was no dysphagia or dysarthria. He had borderline diet-controlled diabetes and angina. He had smoked two packs of cigarettes per day for 30 years, but had discontinued six years ago. He consumed several alcoholic drinks a day. The neurological examination showed that the cranial nerves were intact except for questionable sluggish pupils. Neck flexion was weak. Deltoids were 4/5. Hip flexion was 3/5. He could hardly walk on his heels and toes. DTR were trace with an absent ankle jerk bilaterally. His gait was cautious and slightly wide-based.

Summary 60-year-old man with progressive weakness predominantly proximal. Other important information given in the vignette includes dry mouth, sluggish pupils, hypoflexia and areflexia, and a long history of heavy smoking.

Localization

There is no doubt that the localization is the peripheral nervous system, indicated by the progressive weakness, hyporeflexia, and absent long tract signs. It is important to determine which part of the motor unit is involved:

- Anterior horn cell
- Peripheral nerve
- Neuromuscular junction
- Muscle

Disorders of the anterior horn cells to be considered are ALS and spinal muscular atrophy. ALS usually presents with progressive asymmetrical weakness and atrophy in combination with upper motor signs such as hyperreflexia, pathological reflexes, and spasticity. The PMA variant does not have signs of upper motor neuron involvement. Dry mouth and autonomic disturbances (represented also by the sluggish pupils in the case described) are not part of the clinical features of MND. Instead, drooling of the saliva if dysphagia is present invariably occurs in ALS. Spinal muscular atrophy is a hereditary autosomal recessive disorder characterized by predominantly symmetrical proximal weakness accompanied by atrophy that manifests in a younger age group, usually in the third decade of life.

Disorders of peripheral nerves are considered next and can be easily excluded by the vignette. Subacute or chronic sensory motor polyneuropathy is characterized by prominent sensory symptoms, distal weakness, and decreased deep tendon reflexes. Particular consideration needs to be given to chronic inflammatory demyelinating polyneuropathy (CIDP) as part of the differential diagnosis. This disorder is characterized by chronic progressive, stepwise or relapsing, relatively symmetrical motor and sensory deficits including distal and proximal weakness, sensory loss, paresthesia, and hyporeflexia (which are not among the symptoms of the patient described in the vignette). Pure motor neuropathies, such as multifocal motor neuropathy, can be also clinically excluded, being characterized by progressive, asymmetrical predominantly distal limb atrophy and weakness that follow a peripheral nerve distribution.

Next are disorders of the neuromuscular junction, typically myasthenia gravis and Lambert-Eaton myasthenic syndrome. The clinical case does not suggest myasthenia gravis, characterized by fatigable weakness often affecting the extraocular muscles with an asymmetric pattern of distribution and always sparing the pupils. Proximal limb weakness as well as weakness of the diaphragm and neck extensors muscles can also be seen. The weakness is typically fatigable, therefore tends to increase with repeated exercise and improve with rest or sleep (just the opposite of what the patient in the vignette is experiencing: he had difficulty climbing stairs and getting up from the toilet seat in the morning on waking up that seemed to improve shortly thereafter). Isolated weakness of the extremities is not very common in myasthenic patients, and dry mouth and other autonomic abnormalities are not seen.

The symptoms described in the vignette clearly reflect Lambert-Eaton myasthenic syndrome. This presynaptic neuromuscular junction disorder is characterized by proxymal limb weakness, preferentially involving the lower extremities, and fatigability. Hyporeflexia or areflexia is also observed. Autonomic nervous system abnormalities, in particular dry mouth but also pupillary abnormalities, decreased sweat and lacrimation, impotence, and so on, are other important characteristics. The weakness as well as hyporeflexia tend to improve temporarily with brief repeated muscle contractions. Therefore LEMS is the best tentative diagnosis.

Finally, the last part of the differential diagnosis involves muscle disorders, such as polymiositis, dermatomyositis and inclusion body myositis. Polymiositis is characterized by progressive, relatively symmetrical proximal weakness of the upper and lower extremities and neck flexor muscles. Deep tendon reflexes are normal or decreased in severe cases. Myalgia, tenderness, and systemic symptoms may also occur. Dermatomyositis has the characteristic rash that may manifest before or after the discovery of the weakness. Inclusion body myositis typically presents with slowly progressive, asymmetrical proximal and distal weakness and atrophy that preferentially affects the quadriceps and wrist and finger flexor muscles.

Clinical Features

LEMS is a presynaptic disorder of the neuromuscular junction caused by antibodies directed against the voltage-gated calcium channels. Men are affected more than women and the onset of symptoms is usually after the fourth decade of life. LEMS is considered a paraneoplastic disorder in the majority of the cases with a strong association with small-cell lung carcinoma and less frequently with lymphoma, and breast and ovarian carcinoma. It can also rarely represent an idiophatic autoimmune disorder without further evidence of cancer. The weakness involves the proximal muscles, particularly of the lower extremities, and may transiently improve with brief contractions (muscle facilitation). Hyporeflexia/areflexia is another feature, but typically the DTR may normalize immediately after brief exercise of those muscles activated by the reflex.

Autonomic symptoms include

- Dry mouth (the most common).
- Decreased lacrimation and sweating.
- Abnormal pupillary responses.
- Impotence.
- Orthostatic hypotension.

Diagnosis

Laboratory studies demonstrate IgG antibodies directed against the voltage-gated calcium channel on the presynaptic nerve terminal. Electrophysiological tests of particular importance are based on repetitive nerve stimulations that when performed at slow rate (3Hz) show a decremental response similar to MG. After rapid RNS (30 to 50 HZ) or brief (10 sec) intense contractions, a marked increase of the CMAP amplitude by more than 200 percent is demonstrated (postexercise facilitation). Single-fiber EMG may show increased jitter with blocking and improvement at high rate of stimulation. Imaging studies such as X-ray or CT of the chest are important in ruling out an underlying malignancy. LEMS symptoms usually precede tumor diagnosis by about 10 months (Dumitru et al.). Broncoscopy can also be performed in selected cases.

Treatment

The treatment is directed primarily to an aggressive search and treatment of a possible underlying malignancy, particularly in older patients with a long-standing history of smoking, because the symptoms may significantly ameliorate with the appropriate cancer therapy.

Immunotherapy is particularly indicated in patients with LEMS who do not have cancer. Steroid treatment is based on the use of oral prednisone or prednisolone at 1.0 to 1.5 mg/kg every other day that may cause marked improvement of the weakness and is administered over several months until the desired benefits are obtained and than slowly tapered toward the minimal effective dose. Azathioprine is also used sometimes in combination with the steroids, with an effective dose of 2 to 3 mg/kg/day and cautious consideration of the adverse effects, such as leukopenia, liver toxicity, bone marrow suppression, and so on. Another important consideration involves the fact that beneficial effects may take several months to appear. Cyclosporine can be administered in patients who have not responded to azathioprine. Plasmapheresis or high-dose intravenous immunoglobulin has also been beneficial.

Other therapies include guanidine hydrochloride, which causes an increase in the amount of Ach release at the nerve terminal. Adverse effects include bone marrow depression, renal tubular acidosis, hepatotoxicity, chronic interstitial nephritis, and so on. The aminopyridines tend to facilitate Ach release at the nerve terminal by blocking voltage-dependent potassium channels. 3,4-Diaminopyridine in particular may cause improvement in strength and autonomic functions in most patients with LEMS. Adverse effects consist of transitory perioral and acral paresthesias. The dose is usually 20 mg three times a day. Most patients experience beneficial effects with this therapy, which last as long as the drug is administered. 4-Aminopyridine carries risks of inducing seizures due to the central nervous system toxicity.

Myasthenia Gravis

Vignette

A 21-year-old homemaker started complaining of double vision, speech difficulty, and dysphagia. For the last month she had tended to slur her speech, dribble saliva while talking, and occasionally choke on food. She had been aware of double vision while watching television in the evening. Her husband had noticed that her left eyelid at times seemed droopy, especially under sunlight. On examination there was bilateral ptosis, worse on the left, and bilateral horizontal gaze limitation. On the right, adduction was complete, but abduction was decreased 60 percent. There was upward gaze limitation and bilateral facial weakness with diminished gag reflex. Motor strength in the limbs, as well as DTR and sensation were normal.

Summary A 21-year-old woman with history of diplopia, dysarthria, and dysphagia, and neurological findings of ptosis, ophthalmoparesis, facial weakness, and diminished gag reflex.

Localization

The first step is to determine whether the lesion involves the peripheral or the central nervous system, and in the latter case, if it is intrinsic or extrinsic to the brainstem.

Brainstem intrinsic pathology that involves the medulla, pons, and mesencephalus are characterized by signs of involvement of the long sensory and motor tracts often realizing a crossed pattern of weakness and sensory loss. Extrinsic brainstem lesions often cause painful involvement of adjacent cranial nerves with minimal involvement of motor or sensory tracts.

Considering peripheral nervous system, lesions, disorders of the different parts of the motor unit can be discussed in order to reach the best tentative diagnosis (peripheral nerves, neuromuscular junction, muscle, anterior horn cell). Among the disorders of peripheral nerves, Miller Fisher syndrome (GBS variant) can cause external ophthalmoplegia associated with dysphagia and dysarthria, but clinical findings important for the diagnosis are also ataxia and hyporeflexia/areflexia, features that do not occur in the vignette.

Disorders of the neuromuscular junction, in particular myasthenia gravis, can explain the symptoms presented in the vignette, characterized by ocular findings of external ophthalmoplegia that spares the pupils and bulbar signs of dysphagia and dysarthria. The phenomenon of fatigability is also implicated in the vignette when it is mentioned that the patient experiences diplopia in the evening when she watches television. Another sign is the intermittent ptosis aggravated by direct sunlight. Other disorders of the neuromuscular transmission, such as LEMS, are clinically differentiated from myasthenia gravis by the weakness predominantly affecting the proximal lower limb muscles and only mild involvement of the ocular and bulbar muscles. There is hyporeflexia or areflexia, but strength and reflexes can be improved by brief period of contraction (muscle facilitation). Autonomic abnormalities, in particular dry mouth, are other important features of LEMS.

In botulism, symptoms usually occur 12 to 36 hours after the ingestion of the contaminated food, with nausea, vomiting, diarrhea, and rapid progressive neurological dysfunction including ophthalmoplegia with unreactive pupils, bulbar paralysis, weakness of muscles of neck, trunk, and limbs, and respiratory compromise.

Muscle disorders that enter in the differential diagnosis include oculopharyngeal muscular dystrophy and mitochondrial myopathies. Oculopharyngeal muscular dystrophy is a hereditary disorder with onset during the fourth to sixth decades of life and characterized by progressive ptosis dysphagia and dysarthria. Fatigability or fluctua-

tions of the weakness, are not features of this disorder and the pupils are also spared. Mitochondrial myopathies such as Kearns-Sayre syndrome (KSS) and progressive external ophthalmoplegia usually have signs of involvement of multiple organ systems (KSS for example has associated retinitis pigmentosa and heart block) that address the correct diagnosis.

Disorders of the anterior horn cells, such as ALS, poliomyelitis, or spinal muscular atrophy, are clearly not represented in the vignette.

Clinical Features

Myasthenia gravis is an autoimmune postsynaptic disorder of the neuromuscular junction characterized by fluctuating weakness and fatigability. The weakness typically affects ocular, facial, oropharyngeal, and limb muscles. Ptosis and ophthalmoparesis are the most common symptoms and are often asymmetrical. Other symptoms include dysphagia, dysphonia, and dysarthria due to weakness of the facial and bulbar muscles. Proximal limb and neck weaknesss is the presenting sign in 20 to 30 percent of patients (Dumitru et al.). Weakness of the diaphragm and respiratory muscles can also occur. The weakness is fatigable and typically worsens with sustained physical activity or during the course of the day, but improves with rest. Exposure to bright light may also worsen the ocular abnormalities. Deep tendon reflexes are usually normal and sensation is intact. MG is an autoimmune disorder caused by an antibody-mediated autoimmune attack directed against acetylcholine receptors at the postsynaptic portion of the neuromuscular junction. Three types of Ach receptor antibodies are detected: binding, modulating, and blocking (AchR binding antibodies are the most frequent subtype) (Dumitru et al.).

Diagnosis

The history of fatigable and fluctuating weakness is characteristic of MG. Pharmacological tests such as the Tensilon (edrophonium) test is important in demonstrating transitory improvement of symptoms, particularly ptosis, within few minutes of injection. Edrophonium chloride, which is a short-acting inhibitor of acetylcholinesterase, is administered in incremental doses, intravenously, with an initial dose of 2 mg (0.2 ml), followed by two more doses of 3 mg and 5 mg, if no untoward side effects occur and if no improvement is observed with a previous dose. A positive test is obtained when objective improvement is noted in some sign, such as ptosis, ophthalmoparesis, muscle strength, or respiratory function. This result is compared with what was obtained from a previous placebo injection of saline or atropine, the latter to block the muscarinic effects of this short-acting anticholinesterase. Hypotension and bradycardia can occur even if they are uncommon and atropine sulfate (0.6 mg intramuscular or intravenously) should be always available for a prompt intervention.

Laboratory studies are based on the detection of AchR antibodies.

Elecrophysiological studies are performed to confirm a deficit in neuromuscular transmission and include routine nerve conduction studies, repetitive nerve stimulation, exercise testing, and, in selected cases, single-fiber EMG. Repetitive nerve stimulation (RNS) can show normal results, particularly in patients with the restricted ocular form of MG. When abnormal, the typical findings observed in MG with repetitive nerve stimulation at 2 to 5 Hz is a progressive decrement of the second through the fourth or fifth response with some return toward the initial CMAP size during the subsequent responses to a train of 9 to 10 stimuli, the so-called U-shaped pattern. A decrement greater than 10 percent is considered abnormal. If RNS shows negative results at rest, the muscle is activated for one minute and then RNS is performed immediately after exercise and once per minute for the next 5 minutes. Single-fiber EMG is used in selected cases when there is clinical suspicion but routine electrophysiologic studies are not conclusive in order to measure the relative firing of adjacent single muscle fibers from the same motor unit and can demonstrate both prolonged jitter as well as blocking of muscle fibers.

CT scan or MRI of the mediastinum is considered to exclude thymoma.

Treatment

Cholinesterase Inhibitors

Anticholinesterase medications are considered the first line of treatment in myasthenic patients. Pyridostigmine (Mestinon) has been used in a dosage of 60 mg every 4 hours if tolerated. Muscarinic side effects include abdominal cramps and diarrhea, which are dose related.

Thymectomy

Thymectomy is usually recommended in all patients with thymoma or in myasthenics younger than age 60 with generalized weakness (Massey). Thymectomy has been discouraged in patients over age 60 because of increased morbidity as well as evidence of atrophy of the involved gland and has also been discouraged in children. The degree of improvement and the time before improvement is noted are variable and may require several years for demonstrated efficacy.

Immunosuppressive Therapy

Corticosteroids have been particularly effective in generalized or ocular MG when symptoms are disabling and not controlled with cholinesterase inhibitors. Patients can be started at relatively high doses (60 to 80 mg) for rapid

improvement, or with low, gradually increasing doses in order to avoid a possible exacerbation of symptoms that may occur one to two weeks after the high-dose steroid regimen is initiated. When there is maximal improvement, which may sometimes take 6 to 12 months, the dose is gradually reduced at a rate of 10 mg every one or two months. Many patients need long-term maintenance on low-dose steroid therapy to prevent relapses. Complications of steroid therapy include weight gain, cushingoid features, cataract, aseptic meningitis, gastrointestinal symptoms, psychiatric symptoms, and increased susceptibility to hypertension, diabetes, and infections.

Azathioprine (Imuran) has been used particularly in patients in whom steroid use is contraindicated. The dose is usually 2 to 3 mg per kg per day, with careful monitoring of liver enzymes and blood counts. An improvement may not be noted for 12 to 24 months. Adverse effects consist of increased susceptibility to opportunistic infections, anemia, leukopenia, trombocytopenia, hepatic toxicity, and possible increased risk of malignancy. Cyclosporine is used for severe MG in patients refractory to other therapies and shows a more rapid beneficial effect than azathioprine that varies from 2 weeks to 6 months. The starting dose is 2 to 5 mg per kg per day and adverse effects include nephrotoxicity, hypertension, headache, and hirsutism. Cyclophosphamide is also a potent immunosuppressive drug and can also be used in intractable patients. The dose is 3 to 5 mg per kg per day orally in divided doses or 200 mg intravenously weekly. Side effects include leukopenia, hemorrhagic cystitis, anorexia, nausea and vomiting, and alopecia.

Plasma exchange or IVIG may also be used in some patients. These treatments are particularly indicated in the settings of acute exacerbations, such as impending myasthenic crisis or actual crisis, exacerbation due to steroids, or prior to thymectomy.

Brachial Plexopathy

Vignette

A 65-year-old retired teacher has been complaining, for the last three months, of severe left upper extremity pain, particularly at night when lying in bed. She felt some weakness when trying to open a jar and tingling and numbness radiating down the medial arm and forearm into the little and ring fingers. On examination there was weakness and atrophy of the left abductor pollicis brevis and first dorsal interosseus. The flexor pollicis longus was quite weak. Hypoesthesia was present in the left fifth finger and medial aspect of the fourth finger and forearm. Five years ago she underwent left mastectomy, followed by radiation and chemotherapy.

Summary A 65-year-old woman experiencing progressive left upper extremity pain as well as left hand weakness, atrophy, numbness, and paresthesias. Past medical history is significant for breast cancer treated by mastectomy, radiation, and chemotherapy.

Localization

This patient presented with weakness of muscles innervated by the C_8–T_1 roots via the lower trunk and medial cord of the brachial plexus. The sensory findings do not suggest an ulnar nerve lesion because there is also involvement of the medial forearm indicating pathology of the plexus or nerve roots. The medial antebrachial cutaneous sensory nerve, which supplies sensation to the medial forearm, originates from the medial cord of the brachial plexus. The patient has a history of breast cancer treated with radiotherapy. This may underlie the possibility of a metastatic process because brachial plexus involvement by breast but also lung carcinoma, melanoma, lymphoma, and sarcoma is well documented. Spread of breast cancer to the lateral group of axillary lymph nodes causes compression or invasion of the lower brachial plexus carrying nerve fibers of the C_8–T_1 roots (Stubgen and Elliot).

Since the patient in the vignette received radiation therapy to treat the neoplasm, it is extremely important to distinguish between metastatic and radiation plexopathy. Brachial plexopathy related to radiation therapy or metastatic cancer may both manifest months to years after the initial treatment. Malignant brachial plexopathy is usually characterized by severe pain and tends to affect the lower trunk in the majority of patients. Therefore, since the lower trunk is formed from the C_8–T_1 roots, all ulnar muscles and the median C_8–T_1 muscles are involved. The area of sensory loss and paresthesias includes the medial arm, medial forearm, medial hand, and fourth and fifth fingers. Horner's syndrome can also develop more commonly in malignant plexopathy due to invasion of the sympathetic trunk. Radiation plexopathy is related to the dose of radiation received and can sometimes be difficult to differentiate from malignant plexopathy. Malignant brachial plexopathy as stated, usually presents with severe pain, preferential involvement of the lower brachial plexus, and Horner's syndrome. In contrast, in radiation plexopathy, which usually occurs months to years after the exposure to doses greater than 6000 rads, pain is mild to moderate and lymphedema can be prominent. Horner's syndrome is not common and myothymic discharges can frequently be found.

Diagnosis

The diagnosis is based on neuroimaging studies that in cases of tumor invasion may demonstrate a hyperintense mass on T_2-weighted images that may enhance with gad-

olinium. In cases of radiation fibrosis, a nonenhancing low intense signal mass on T_2 will be seen. Electrodiagnostic studies may show prominent myothymic discharges and fasciculations in radiation plexopathy.

Electrodiagnostic studies help distinguish plexopathy from radiculopathy. A brachial plexus lesion characteristically demonstrates abnormal sensory nerve action potential (SNAP) amplitudes, as opposed to a lesion at the root level where they remain normal (sensory nerve action potential remains normal in lesions proximal to the dorsal root ganglion). Needle EMG shows normal paraspinal muscles as well as rhomboids and serratus anterior muscles in lesions of the plexus.

Treatment

The treatment of malignant plexopathy is based on management of tumor invasion with chemotherapy or radiation therapy and pain management.

Femoral Neuropathy

Vignette

A 72-year-old diabetic woman started complaining of left leg pain and weakness 10 days after undergoing total hip replacement. Following the operation she developed deep vein thrombosis and was placed on anticoagulant therapy with an INR of 3. On examination, right knee extension and hip flexion were weak (MRC 3/5), with normal thigh adduction and ankle dorsiflexion. There was decreased sensation in the right anterior thigh and medial leg. Right knee jerk could not be elicited. Plantar responses were flexor.

Summary A 72-year-old woman complaining of left leg pain, weakness of left knee extension and hip flexion, hypoesthesia in the area of left anterior thigh and medial leg, and absent left knee jerk. The past medical history is significant for total hip replacement and deep vein thrombosis treated with anticoagulants.

Localization

The distribution of weakness and sensory loss points to left femoral nerve involvement. The weakness typically affects the left quadriceps and ileopsoas muscles with paralysis of left knee extension and left hip flexion. The distribution of sensory loss involves the left anterior thigh and medial leg. Left knee jerk is also absent. The involvement of the ileopsoas muscle causing hip flexion weakness localizes the lesion proximal to the inguinal ligament. Femoral neuropathy needs to be differentiated from lumbar plexopathy and L2–L4 radiculopathy. Typically a plexus lesion causes weakness, sensory loss, and reflex loss that are not limited to the territory of a simple root or nerve. Lumbar plexopathies affect particularly the L_2–L_4 fibers, resulting in weakness of the quadriceps and ileopsoas muscles (innervated by the femoral nerve) and thigh adductors muscles (innervated by the obturator nerves). The knee jerk can be decreased or absent. Sensory loss may extend over the lateral, anterior, and medial thigh and sometimes the medial calf. L2–L4 radiculopathies are characterized by weakness that also involves hip adductors and ankle dorsiflexors muscles, which are spared in cases of femoral neuropathy.

Assuming that this patient has a femoral neuropathy, several important causes need to be discussed:

- Acute retroperitoneal hemorrhage, particularly in patients undergoing anticoagulation or in cases of coagulopathy, should be ruled out promptly by computed tomography (CT) or magnetic resonance imaging (MRI) of the pelvis. This may be the situation that occurred in the patient in the vignette who was treated with anticoagulants after developing deep vein thrombosis (DVT).
- Femoral nerve compression can occur after abdominal aneurysm rupture or femoral artery catheterization complicated by hemorrhage.
- Pelvic masses, such as neoplasm, abscess, cyst, or lymphoadenopathy, as well as abdominal or pelvic surgery may also cause femoral nerve dysfunction.
- Compression of the femoral nerve at the inguinal ligament has been observed after prolonged lithotomy position during laparoscopy, vaginal hysterectomy, and so on.
- Stretch injury or diabetes complicated by nerve infarction can also cause a femoral neuropathy.

Diagnosis

Electrodiagnosis is often useful in differentiating a femoral neuropathy from plexopathy and radiculopathy. Ultrasound and MRI are effective measures for diagnosing iliacus hematoma. Management depends on the etiology.

Postpartum Plexopathy

Vignette

A 28-year-old woman started complaining of difficulty walking and right foot numbness one day after the delivery of her baby. Labor was prolonged and complicated by fetal distress, therefore a decision to perform a cesarean section was made. On examination there was marked weakness of right ankle dorsiflexion, eversion, and inversion and moderate weakness of hip extension and internal

rotation. Hip flexion and knee extension were normal. There was an area of hypoesthesia to pinprick in the right lateral leg and dorsum of the foot. Deep tendon reflexes including ankle jerk were normal and symmetrical.

Summary A 28-year-old woman with acute onset of right lower extremity weakness and numbness one day postpartum. Labor was prolonged and difficult, and complicated by fetal distress.

Localization

In order to localize, we need to consider the weak muscles and the area of sensory loss. Weakness involving the ankle dorsiflexors and evertors of the foot placed the lesion in the territory of the peroneal nerve. Foot inversion due to tibialis posterior muscle has a predominant tibial nerve innervation. Hip extension and internal rotation are gluteal innervated muscles and their involvement indicates a lesion that is not confined only to the peroneal territory. Therefore the pathological process should be placed at the level of the lumbosacral trunk or the L5 root. The lumbosacral trunk consists primarily of the L5 root with an additional component from the L4 root.

When the lumbosacral trunk is affected the weakness includes ankle and toe dorsiflexion eversion, inversion and toe flexion.The gluteus muscles (gluteus medius and minimus and tensor fascia lata which abduct and rotate the thigh internally, and the gluteus maximus which extends, abducts, and rotates the thigh externally) as well as the hamstrings (flexion of the leg at the knee) can also be involved. Plantar flexion and ankle jerk are usually normal. The area of sensory abnormality commonly extends in the L5 dermatomal distribution. It is not always easy to differentiate a lumbosacral trunk lesion from L5 radiculopathy, because the weakness in both conditions involves the L5 myotome. Labor and delivery can be complicated by a lesion compressing the lumbosacral trunk, particularly in prolonged and difficult labor and if other factors such as abnormal presentation, a large fetal head, and a small maternal pelvis are present. The prognosis is usually good with full recovery.

Mononeuritis Multiplex

Vignette

A 65-year-old man had a three-week history of left foot pain and numbness, followed by the abrupt onset of left foot drop. The following week, right wrist drop developed as well as weakness of the left hand grip and numbness involving the ring and the little fingers of the left hand. On examination there was moderate weakness of the right wrist extensors, all finger extensors, and the brachioradialis, and decreased pain and touch on the dorsum of the right hand. On the left upper extremity, first dorsal interossens, abductor digiti minimi and flexor digitorum profundus to digits 4 and 5 were markedly weak, and there was diminished sensation in the left hypothenar region and digits 4 and 5. The left foot had weakness of toe and ankle dorsiflexion and there was diminished sensation below both knees. Past medical history included several months of fatigue, progressive weight loss, and low-grade fever.

Summary A 65-year-old man with history of left foot drop, right wrist drop, and bilateral weakness and sensory involvement associated with systemic signs (fever, weight loss, fatigue).

Localization

There is involvement of multiple peripheral nerves (right radial, left ulnar, and left peroneal) in an asymmetrical pattern typical of mononeuritis multiplex. Mononeuropathy multiplex is characterized by asymmetrical, stepwise progression of individual cranial or peripheral neuropathies (Preston and Shapiro). Specific etiological factors need to be investigated, in particular the possibility of vasculitis and vasculitic neuropathy. Many disorders are described among the vasculitic syndromes but the peripheral nerve is most frequently involved in polyarteritis nodosa, Wegener's granulomatosis, and the allergic angiitis and the granulomatosis syndromes. Mononeuropathy multiplex has long been considered the hallmark of peripheral nerve involvement in systemic necrotizing vasculitis (Aminoff). The symptoms can develop acutely or insidiously and may be accompanied by severe neuritic pain. Cranial neuropathies tend to preferentially involve the trigeminal, facial, and vestibuloacoustic nerves (Aminoff).

Aside from vasculitis, other disorders can present with a multifocal picture. These include chronic inflammatory demyelinating polyradiculoneuropathy; infectious processes such as leprosy; Lyme disease, HIV, HTLV-1, herpes zoster, and hepatitis A. Mononeuritis multiplex can occur in association with cancer and granulomatous disorders due to infiltration of peripheral nerves. Diabetes can also be complicated by multiple focal neuropathies occurring as a result of ischemia or as a result of pressure or entrapment. Other disorders to be mentioned are genetic neuropathies (hereditary neuropathy with liability to pressure palsies).

Vasculitis Neuropathies

Vasculitis characterized by inflammation and necrosis of the vessel wall with subsequent ischemia may involve the

peripheral nerves. The peripheral neuropathy is an early manifestation of vasculitis and can have different presentations, such as features typical of mononeuritis multiplex; overlapping (extensive) multiple mononeuropathies; or distal symmetrical polyneuropathy. Mononeuritis multiplex is characterized by dysesthesia, sensory loss, and weakness along multiple peripheral nerves, cranial nerves, or both. Symptoms may be acute or indolent, and the neuropathy can occur in isolation or as part of systemic involvement with multiorgan failure or connective tissue disorders.

Diagnosis

The diagnosis is based on serological studies, electrodiagnostic studies, and nerve biopsy. Laboratory tests include standard tests, such as complete blood count and chemistry panel, as well immunological tests such as antinuclear antigen, rheumatoid factor, serum complement levels, and so on. Other immunological tests are indicated selectively (e.g., ANCA [antineurophil cytoplasmic antibodies], serum cytokines, antibodies to endothelial cell antigens). Also HIV, HTVL-1, Lyme, hepatitis B and C, and glycosylated hemoglobin can be sought in selective cases.

Electrophysiological studies may demonstrate low amplitude or absent response of the sensory or motor action potential. Conduction block occurs in some patients. Needle EMG shows signs of denervation. Nerve biopsy may demonstrate inflammation and necrosis of the vessel wall in the acute stages and later intimal proliferation and hyperplasia.

Treatment

The treatment of vasculitic neuropathy is based on immunosuppresive therapy, particularly in patients with underlying systemic necrotizing vasculitis. The approach is a combination of agents, including prednisone and a cytotoxic agent (usually cyclophosphamide).

Differential Diagnosis of Mononeuritis Multiplex

- Vasculitis
  - Polyarteritis nodosa
  - Wegener's granulomatosis
  - Churg-Strauss syndrome
  - Lymphomatoid granulomatosis
  - Cryoglobulinemia
  - Sjögren syndrome
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
- Infections
  - Leprosy
  - Lyme disease
  - HIV, HTLV-1
  - Herpes zoster
  - Hepatitis
  - Cytomegalovirus
- Infiltration
  - Granulomatous disease: Sarcoidosis
  - Neoplastic disorders: Leukemia, lymphoma
- Multiple entrapment
  - Hereditary neuropathy with lability to pressure palsies
  - Acquired multiple entrapment neuropathies
- Diabetes
- Multifocal demyelinating neuropathy with persistent conduction block

Inflammatory Myopathies

Polymyositis

Vignette

A 65-year-old housewife began complaining of weakness, fatigue, and shortness of breath after brief physical exercise. She could not exactly tell when her symptoms started, but could recall that less than one year ago she first noticed fatigue on walking long distances and some trouble climbing stairs. Six month ago she developed some difficulty swallowing solid food. Her leg weakness worsened and she needed a cane for support. She also noticed some pain in her shoulders and could not lift her grocery bags from the supermarket. She denied any sensory complaints, as well as diplopia, dysarthria, or visual disturbances. There was no family history of neuromuscular disorders. On examination she had difficulty lifting her arms against resistance and the neck flexors seemed to be weak. She was barely able to flex her hips against gravity. DTR were reduced, plantar responses were flexor, and sensory examination was normal.

Summary A 65-year-old woman with progressive proximal weakness, dysphagia, fatigue, and shortness of breath on exertion. The neurological examination shows proximal and neck flexor weakness, reduced DTR, and normal sensation.

Localization

The localization points to a disorder of the motor unit, which has several components: anterior horn cell, motor axon, neuromuscular junction, and muscle fibers. The case as summarized describes a patient with progressive symmetrical weakness and hyporeflexia in the absence of sensory symptoms, therefore we can narrow the diagnosis to specific pathology. Considering the muscle disorders

first, the pattern of progressive subacute symmetrical proximal weakness points to the possibility of an idiopathic inflammatory myopathy, typically polymyositis, particularly if metabolic, toxic, endocrine, and familiar disorders are excluded (Dalakas). Features supporting the diagnosis and present in the vignette are the distribution of the weakness which is proximal and symmetrical, the lack of dermatological findings such as a rash, as well as lack of ocular or facial dysfunction. Dysphagia can also be part of the clinical manifestation. Muscle pain and tenderness is usually an early finding. Hyporeflexia and areflexia can be observed particularly in cases of severe weakness and atrophy. The absence of sensory symptoms and the presence of myalgia support a myopathic process but lack of sensory abnormalities is also associated with motor neuropathies and anterior horn cell disorders. The dyspnea on exertion can be explained by interstitial lung disease, which occurs in approximately 10 percent of patients affected with polymyositis, at least half of whom have Jo-1 antibodies (Amato and Barohn).

Other inflammatory myopathies, such as dermatomyositis and inclusion body myositis, need to be excluded before confirming the diagnosis. Dermatomyositis is accompanied or preceded by the characteristic rash characterized by a purplish discoloration of the eyelids (Amato and Barohn) often accompanied by periorbital edema. Inclusion body myositis, which affects predominantly older men, is characterized by early weakness and atrophy and preferential involvement of certain groups of muscles, such as the quadriceps, wrist and finger flexors, and foot extensors muscles.

Muscular dystrophies such as facioscapulohumeral dystrophy (FSH) and myotonic dystrophy need to be considered in the differential diagnosis. FSH is an autosomic dominant disorder characterized by marked facial weakness and scapular winging. The tibialis anterior muscle is usually the earliest affected muscle in the lower extremities (Dumitru et al.). Patients with myotonic dystrophy have a characteristic facial appearance due to weakness and atrophy of the facial and masseter/temporalis muscles (Dumitru et al.). Frontal balding is also observed. The distribution of weakness in the lower extremities is predominantly distal. Myotonia characterized by a delayed muscle relaxation after contraction is very important for the diagnosis.

In the differential diagnosis of polymyositis, systemic etiologies need to be excluded, in particular infectious processes, and endocrine and toxic disorders. Viral, parasitic and fungal infections (HIV, HTLV-1, echovirus, coxsackievirus, trichinosis, toxoplasmosis, etc.) can all cause a myopathy usually associated with other systemic symptoms.

Endocrinopathies are frequently associated with myopathies, in particular thyroid disorders (hypothyroidism, hyperthyroidism, hyperparathyroidism), Cushing's syndrome, and pituitary disorders. Myopathies associated with electrolyte disturbances include, in particular, hypokalemia, hyperkalemia, hypophosphatemia, and hypermagnesemia. Toxic myopathies are numerous and the best known is the steroid myopathy. Other drug-induced myopathies are associated with the use of cimetidine, procainamide, levodopa, phenytoin, colchicine, vincristine, and so on. Toxic myopathies are associated with chronic alcohol abuse, toluene inhalation, and so on.

Other systemic disorders that can cause muscle disease are diabetes, amyloidosis, neoplastic and paraneoplastic disorders, and sarcoidosis.

Considering the neuromuscular junction disorders, myasthenia gravis and Lambert-Eaton myasthenic syndrome enter the differential diagnosis. There is nothing in the vignette to suggest a neuromuscular junction defect. Patients with generalized myasthenia gravis can manifest with proximal weakness, but fatigability and fluctuation of the symptoms that frequently involves the extraocular and bulbar muscles are important characteristics. LEMS typically presents with proximal weakness and hyporeflexia that improves with brief muscular contractions. Autonomic symptoms, in particular dry mouth, are also an important part of the diagnosis.

Anterior horn cell disorders include ALS and spinal muscular atrophy. ALS has signs of upper and lower motor neuron dysfunction and is unlikely to be mistaken for a myopathy. Spinal muscular atrophy characterized by proximal weakness and marked atrophy associated with hyporeflexia or areflexia is a hereditary disorder that manifests in the third decade of life and can be easily excluded by the vignette.

Considering disorders of the peripheral nerves, chronic inflammatory demyelinating polyneuropathy (CIDP) characterized by progressive, stepwise or relapsing muscle weakness, predominantly proximal, also enters the differential diagnosis. Sensory symptoms are an important part of this disorder and can be prominent, and manifesting different degrees of severity from mild distal numbness and paresthesias to severe sensory involvement and even sensory ataxia (Mendell et al.).

Clinical Features

Polymyositis is an inflammatory disorder of muscles more prevalent in women characterized by progressive symmetrical weakness of the upper and lower extremities and neck muscles. The distribution of weakness is predominantly proximal but distal muscles can be affected in more advanced stages of the disease. Deep tendon reflexes are usually normal but can be diminished or absent in cases of severe weakness and atrophy. Sensation is always intact. Extraocular muscles are normal and facial muscles are only rarely and mildly affected. Frequent complaints are muscle pain, tenderness, and fatigue. Due to the proximal weakness, affected patients notice difficulty climbing stairs, blow drying and combing their hair, and getting up from a low seat.

Polymyositis is defined by Dalakas as a diagnosis of exclusion. Characteristic features that exclude this disorder are the presence of a rash, extraocular or facial muscle weakness, family history significant for neuromuscular disorders, endocrine disorder, toxic or drug-related myopathy, inclusion body myositis, neurogenic disease, dystrophy or biochemically defined muscle disease. Dysphagia can also occur and can vary in severity due to pharyngeal and esophageal muscle weakness and impaired motility. Systemic complications are due to cardiac involvement manifesting with pericarditis, congestive heart failure, dilated cardiomyopathy, pulmonary hypertension and so on. Interstitial lung disease, which affects at least 10 percent of patients, at least half of whom have Jo-1 antibodies (Amato and Barohn), manifests with nonproductive cough and dyspnea. Connective tissue disorders, such as systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome, can also be associated with polymyositis. According to Dalakas, the risk of malignancy, which is increased in dermatomyositis, is not frequently associated with polymyositis or inclusion body myositis (Dalakas).

Diagnosis

The laboratory studies in polymyositis include primarily the determination of serum CK level, which may be increased up to 50 times the upper limit of normal. However, it does not consistently correlate with disease activity or severity and can be normal in some cases. Other enzymes, including SGOT, SGPT, and LDH, may also be elevated. Myositic specific autoantibodies (MSA) to nuclear and cytoplasmatic antigens involved in protein synthesis may be found in polymyositis, in particular anti-Jo-1, which is detected in 20 percent of patients and is associated with interstitial lung disease (Dumitru).

Electrodiagnostic studies may demonstrate normal motor and sensory nerve conduction and profuse spontaneous activity on needle EMG. The fibrillation potentials are more commonly seen in the paraspinal muscles (thoracic), followed by the proximal shoulder and hip muscles (Shapiro and Preston). In acute and subacute cases MUAPS are short in duration, low in amplitude, and polyphasic with early recruitment (myopathic units). In chronic polymyositis (lasting longer than one year) MUAPS become long in duration with many components, but the early recruitment points to the myopathic process.

Muscle biopsy demonstrates endomysial inflammation with invasion of nonnecrotic muscle fibers, variability in fiber size, and so on.

Treatment

Corticosteroids are the first line of treatment. A single, high daily dose of 80 to 100 mg can be given for four weeks and than changed to an alternate-day regimen for four to six months which is thereafter tapered at a rate of 5 mg every two to three weeks until the lowest effective dose is reached. Adverse effects of corticosteroids include weight gain, hyperglycemia, menstrual irregularities, hypertension, edema, osteoporosis, hypertension, and psychosis.

Nonsteroidal immunosuppressive therapy is indicated if patients do not respond to the use of steroids, relapse during taper, or have intolerable side effects. Azathioprine is given at a dose of 2 to 3mg per kg per day but has the disadvantage of taking several months in order to show its efficacy. Adverse effects include bone marrow suppression, pancytopenia, nausea, anorexia, abdominal pain, liver toxicity, and pancreatitis. Methotrexate can be tried intravenously at weekly dose of up to 0.8 mg/kg, or orally up to a total of 25 mg weekly. Adverse effects include alopecia, pneumonitis, stomatitis, renaltoxicity, hepatotoxicity, and malignancies. Cyclophosphamide is given intravenously or orally at 1 to 2 mg/kg. Side effects include nausea, vomiting, alopecia, hemorrhagic cystitis, and bone marrow toxicity.

Plasmapheresis did not show efficacy in several studies. IVIG can be used if steroids and nonsteroidal immunosuppressive therapies have failed. When the treatment of polymyositis is ineffective, other possible diagnoses should be considered (inclusion body myositis or other diseases).

Dermatomyositis

Dermatomyositis, which affects children in the first decade of life and adults, preferentially women, is characterized by the typical rash that can accompany or precede the onset of muscle weakness. The skin manifestations are characterized by a bluish discoloration of the eyelids often associated with periorbital edema and a flat, erythematous rash involving the face, neck, anterior chest, shoulders, and upper back. Subcutaneous calcifications of different sizes over pressure points can be observed in children with severe disorder and inadequate treatment, but are rare in adults. Muscle weakness is subacute and progressive, and involves the proximal muscles, often accompanied by myalgia, fatigue, low-grade fever, dysphagia, and dysarthria.

Systemic complications are common and tend to involve the heart and lungs. The association with cancer is increased in patients with dermatomyositis. Ovarian cancer is most frequent, followed by intestinal, breast, lung, and liver cancer (Dalakas). Muscle biopsy reveals the characteristic perifascicular atrophy.

Inclusion Body Myositis

Vignette

A 62-year-old banker complained of difficulty walking for the last five years, with occasional tripping

and falling. His left leg was especially bothersome when climbing stairs. He also noticed some difficulties using his right hand, particularly when opening cans. He claims that all his problems started after his left knee replacement surgery. No other medical history could be found. On examination, he had mild weakness of the neck flexor muscles and right wrist and finger flexors. There was also moderate weakness and atrophy of bilateral knee extension and ankle dorsiflexion worse on the left. DTR were symmetrically present and plantar responses were flexor. No sensory abnormalities were noted.

Summary 62-year-old man with a history of slowly progressive (five years) weakness of neck and right upper and both lower extremities with atrophy. Weakness mainly involved neck flexor, right wrist and finger flexors, bilateral knee extensors, and ankle dorsiflexors. No sensory or reflex abnormalities.

Key words: Asymmetrical pure motor weakness.

Localization

There is no doubt that the localization in this difficult vignette is the motor unit. The element involved (anterior horn cell, motor axon, neuromuscular junction, or muscle) must be decided. Progressive asymmetrical muscle weakness can be caused by disorders of the anterior horn cells, polyradiculopathies, multiple mononeuropathies, polyneuropathies, and myopathies. Clinical consideration in the differential diagnosis of this vignette should be given to motor neuron disease/motor neuropathy or myopathy. There are definitely no elements suggesting a neuromuscular junction defect. Considering first a motor neuron disease, ALS can initially present with signs of lower motor neuron involvement characterized by weakness, atrophy, cramps, and fasciculations. In the majority of patients, later on signs of upper motor neuron involvement usually appear with spasticity, hyperreflexia, and pathological reflexes. Only a minority of patients (8 to 10 percent) diagnosed with the clinical variant of ALS, progressive muscular atrophy, have pure lower motor neuron signs.

Disorders of peripheral nerves, such as multifocal motor neuropathy, can present with progressive asymmetrical distal weakness and atrophy in the distribution of individual peripheral nerves. Cramps, fasciculations, and hyporeflexia also occur and sensation is intact. A demyelinating neuropathy with conduction block in multiple upper and lower limb nerves is the hallmark of this disorder. Therefore, even if MMN should be part of the differential diagnosis, it does not explain all the findings of the vignette.

Considering myopathic processes, inclusion body myositis (IBM) may clearly explain the findings in the vignette, especially the typical distribution of weakness, which preferentially involves the quadriceps, wrist and finger flexors, and ankle dorsiflexors; the age of the patient; and the long evolution of the process.

Clinical Features and Diagnosis

Inclusion body myositis, which tend to affect older males after the fifth decade of life, is characterized by insidious, slowly progressive asymmetrical weakness that involves proximal and distal muscles. Some muscle groups are preferentially involved, particularly the quadriceps, wrist and finger flexors, and ankle dorsiflexors. Dysphagia is also common. Extraocular muscles are never affected. Chronic progressive asymmetrical quadriceps and wrist/finger flexor weakness that occur in a patient over age 50 strongly suggests the diagnosis of IBM. IBM is not complicated by cardiac or pulmonary dysfunction, and is not associated with increased risk of malignancy. Laboratory studies show minimal to mild elevation of the serum CK. EMG shows motor units of different amplitude and duration, prominent fibrillations, and positive sharp waves. Muscle biopsy shows rimmed vacuoles in muscle fibers and endomysial inflammatory cells invading nonnecrotic fibers. Amyloid deposition can be demonstrated using Congo red staining.

Treatment

There is no definitive treatment. Steroid therapy and immunosuppressive treatments as well as high doses of intravenous immunoglobulin infusion only show a modest and transitory beneficial effect.

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