KEY POINT:
- Specific aspects of the examination that may be especially pertinent include extraocular muscle involvement or ptosis, presence of fasciculations of the tongue or limbs, ability to lift the head off the pillow, evidence of specific muscle wasting, paradoxical respirations, reflex activity, and distribution of weakness.

EMERGENCY NEUROLOGIC CONSULTATION IN THE INTENSIVE CARE UNIT: NEUROMUSCULAR DISORDERS

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ABSTRACT

Neurologists are often asked to see patients in the intensive care unit because of diffuse limb weakness. It is important to entertain a broad-ranging differential diagnosis in such patients. The possibility of a previously unrecognized high cervical myelopathy cannot be ignored. Among neuromuscular disorders to be considered are Guillain-Barré syndrome, motor neuron disease, myasthenia gravis, and critical illness polyneuropathy and myopathy. Clinical features, electrophysiologic studies, and selective biopsies may help to differentiate these disorders and direct treatment appropriately.

CLINICAL ASSESSMENT

As under other circumstances, the consulting neurologist should compile as much historical information as possible when asked to see a patient in the intensive care unit (ICU) with unexplained weakness, realizing that with critically ill patients, an adequate history may be difficult to obtain. The patient, if awake, must be questioned directly, and consultation with relatives and family should be sought. A thorough evaluation of the current and previous medical records is essential. Examples of especially important features to pursue include a history of preexisting muscle weakness, muscle cramping, fasciculations, muscle wasting, and dysphagia (suggestive of motor neuron disease), ptosis and diplopia (raising the possibility of myasthenia gravis), and recent viral illness or vaccination (which might implicated Guillain-Barré syndrome). Exposure to glucocorticoids and or nondepolarizing muscle-blocking agents, episode of sepsis, and changes in creatine kinase (CK) levels, among other pertinent information, should emerge from a thorough record review.

The neurologic examination of patients in an ICU can be challenging as all neurologists recognize, but should also be as thorough as possible. Specific aspects of the examination that may be especially pertinent (Table 15) include extraocular muscle involvement or ptosis, presence of fasciculations of the tongue or limbs, ability to lift the head off the pillow, evidence of specific muscle wasting, paradoxical respirations, reflex activity, and distribution of weakness.
distribution of weakness (ie, more prominent distally or proximally), discrepancy between craniofacial and limb involvement, response to noxious stimulation, and presence of a sensory level.

**ELECTROPHYSIOLOGIC EVALUATION**

Routine electrophysiologic testing in patients admitted to the ICU can be performed reliably and easily using portable equipment. Stimulation next to central vascular access lines or pacemaker leads should be avoided, and needle electromyography (EMG) should be deferred if the patient has a significant coagulopathy or is anticoagulated. In some instances a single suitable, noncompartimented, and compressible muscle may be examined with pressure applied afterward to prevent a hematoma. Limb testing should evaluate motor conduction in at least median (wrist, elbow), ulnar (wrist, below elbow, above elbow), peroneal (ankle, fibular head, knee), and tibial (ankle, knee) nerves. The latency, amplitude, duration, area, and conduction velocities of the compound muscle action potentials (CMAPs) should be measured, and F-wave...
KEY POINTS:

- Needle EMG should sample both distal and proximal muscles from the limbs. In some patients, needle electrode recordings from intercostal muscles or the diaphragm may be added, although both procedures carry a slight risk of pneumothorax.

- EMG studies should especially seek fibrillations, positive sharp waves, and fasciculations. Dense runs of fibrillations and positive sharp waves are characteristic of acute denervation of muscle, but it must be borne in mind that fibrillations can also occur in myopathies with prominent fiber necrosis.

- Absent CMAPs may arise from severe myopathy or neuropathy. To distinguish the two, subcutaneous recordings of CMAPs from direct muscle stimulation may be of assistance.

Latencies determined. Limb temperature measured during the studies should be recorded. Routine recordings of CMAPs in at least one “resting” territory after 2-Hz or 3-Hz stimulation should be included to evaluate the neuromuscular junction, but admittedly most patients in an ICU are unable to exercise for a full protocol. Antidromic recordings of sensory nerve action potentials (SNAPs) should include at least median, ulnar, radial, and sural nerves. If the patient has pedal edema and surface-recorded sural potentials are reduced in amplitude, near-nerve needle electrode recording can be considered. Phrenic potentials recorded from the diaphragm assess respiratory system motor fibers (Chen et al., 1995).

Needle EMG should sample both distal and proximal muscles from the limbs. In some patients, needle electrode recordings from intercostal muscles or the diaphragm may be added (Bolton et al., 1992), although both procedures carry a slight risk of pneumothorax. EMG studies should especially seek fibrillations, positive sharp waves, and fasciculations. Dense runs of fibrillations and positive sharp waves are characteristic of acute denervation of muscle, but it must be borne in mind that fibrillations can also occur in myopathies with prominent fiber necrosis. Recruitment of voluntary motor unit potentials on EMG is difficult in patients who are unable to cooperate, but when testable such may be valuable in identifying short-duration, low-amplitude, polyphasic motor unit potentials suggestive of a primary myopathy.

Absent CMAPs may arise from severe myopathy or neuropathy. To distinguish the two, subcutaneous recordings of CMAPs from direct muscle stimulation may be of assistance. Directly evoked CMAPs can be recruited in neuropathies with inexcitable motor nerves, whereas they are absent in severe myopathy with inexcitable muscle membrane (Rich et al., 1995).

ADDITIONAL TESTING

Serum CK levels may be modestly elevated (2 to 3 times the upper limit of normal) in denervation from polyneuropathies or motor neuron disease while very high levels associated with myoglobinuria may be observed in muscle fiber necrosis associated with myopathies. Patients with critical illness myopathy may have normal CK levels. Magnetic resonance imaging (MRI) of the central nervous system (CNS) should be considered in any patient suspected of having a pontine or high cervical cord lesion. While imaging of peripheral nerve has not entered routine clinical practice, focal neuropathies or plexus lesions with suspected compression might be assessed.

DIFFERENTIAL DIAGNOSIS

Central Nervous System Disease

Limb weakness may develop in ICU patients from disease involving the CNS. Imaging studies are clearly crucial in identifying these, while keeping in mind that such patients may also have concurrent peripheral nerve, neuromuscular junction, or muscle disease. Bilateral cerebral infarction is usually easily identified by its presentation with altered consciousness. Central pontine myelinolysis may present with initially flaccid areflexic limbs and bulbar dysfunction. High cervical cord myelopathy must be considered diagnostically: “occult” causes of severe
cervical myelopathy include transverse myelitis, C1-2 atlantoaxial subluxation in rheumatoid arthritis, unrecognized disc protrusion and cord compression, cervical subdural abscess, and acute central cord syndrome, among others (Case 10). Leptomeningeal carcinomatosis, lymphomatosis, or rarely, gliomatosis may present with diffuse limb weakness with a combination of cranial nerve palsies (eg, bilateral sixth-nerve palsy) and sensory loss; weakness might be from infiltration of multiple roots (Figure 19) (Case 11).

Motor Neuron Disease
Respiratory failure may precede the diagnosis of motor neuron disease (eg, amyotrophic lateral sclerosis [ALS]) (Chen et al. 1997). There may have been gradually progressive limb weakness, dysarthria, or dysphagia with acute respiratory failure precipitated by aspiration or pneumonia. Findings on examination may include tongue and limb fasciculations in the setting of weakness and muscle wasting with upper motor neuron signs or inappropriately brisk reflexes. Sensory examination is normal beyond some blunting of vibratory sense in the feet.

Definitive electrophysiologic criteria for ALS require denervation in two territories of each of three limbs (or in bulbar muscles). CMAPs may be reduced with preserved SNAPs. Needle EMG discloses fasciculations, fibrillations, positive sharp waves, and enlarged voluntary motor unit potentials (Figure 20). Fibrillations may also be demonstrated in intercostal muscles or the diaphragm. Unfortunately, patients who are diagnosed with ALS in the ICU may never be successfully weaned. Some decline ongoing long-term ventilation and request extubation. A muscle biopsy in such a patient may add a further level of diagnostic certainty to help with this kind of decision. The biopsy should confirm scattered or grouped fiber atrophy indicative of denervation.

Polyneuropathies
Guillain-Barré syndrome usually precipitates admission to an ICU after several days of worsening motor weakness and sensory symptoms after, for example, an infection or vaccination. Chronic inflammatory demyelinating polyneuropathy rarely causes respiratory weakness. Critical illness polyneuropathy (see below) develops in patients with prolonged ICU stays who develop sepsis and multiple organ failure. Prolonged thiamine deficiency may be associated with ophthalmoplegia from Wernicke's encephalopathy.

Case 10
A 65-year-old-man with rheumatoid arthritis develops vague difficulty walking and urosepsis. He is transferred to the ICU in septic shock with multiple organ failure. He has diffuse limb weakness and remains ventilator-dependent despite stabilization of his sepsis and organ failure. Neurologic examination demonstrates an awake, intubated patient with intact cranial nerve function with retained ability to move his eyes, face, and neck to command. The limbs are flaccid, areflexic, and immobile to voluntary command, and he does not grimace to limb nailbed pressure. Electrophysiologic studies are normal. MRI of the cervical spine identifies C1-2 atlantoaxial subluxation with severe high cervical spinal cord compression.

**Comment.** This case is an example of "occult" myelopathy. Spared bulbar function with severe limb weakness suggests this localization.
Case 11

A 20-year-old male is operated on for the third debulking of a glioblastoma multiform. Postoperatively he deteriorates, with progressive weakness of cranial nerves and limb and respiratory muscles. He requires intubation and admission to the ICU. Neurologic examination documents bilateral sixth-nerve palsies, bifacial weakness, diffuse and severe limb weakness, flaccid tone, and areflexia. Reliable sensory testing is not possible. A diagnosis of Guillain-Barre syndrome is suspected. Cerebrospinal fluid (CSF), however, demonstrates not only a very high protein level (196 mg%) but also a reduced glucose (9 mg/dL) and a mild pleocytosis. Nerve conduction studies of motor and sensory fibers in the limbs are normal, but needle EMG shows diffuse fibrillation potentials, positive sharp waves, and absent voluntary motor unit potential recruitment, suggesting diffuse denervation. MRI demonstrates multiple enhancing nodules involving nerve roots all along the spinal cord, establishing the diagnosis of diffuse meningeal gliomatosis (Figure 19).

Comment. This patient developed severe generalized flaccid weakness with sixth-nerve palsies from diffuse tumor infiltration of the spinal fluid spaces.
and a subacute and severe axonal polyneuropathy; in fact, the observation of unexplained ophthalmoplegia in patients in the ICU should always lead to the consideration of thiamine deficiency. Administration of thiamine under such circumstances should utilize a parenteral rather than oral route.

Neuromuscular Junction Disorders

Myasthenia gravis is generally diagnosed before admission to the ICU. As is familiar to all clinical neurologists, bedside features suggestive of the diagnosis include ptosis, ophthalmoparesis, flexor or extensor neck weakness, and limb weakness with fatigability. The diagnosis may be established in the ICU by combining a Tensilon (edrophonium) test with posttreatment assessment of ptosis, limb strength, eye movements, vital capacity, maximum inspiratory pressure, and repetitive conduction studies. Caution should be applied to interpreting Tensilon tests with limited or equivocal endpoints, because false-positive results have been described with brain stem tumors and other lesions.

The Lambert-Eaton myasthenic syndrome has occasionally been complicated by respiratory failure (Nicolle et al, 1996). Most, but not all, patients have associated small cell carcinoma of the lung. Patients may have diffuse limb weakness, ptosis without ophthalmoplegia, and apparent facilitation of limb strength and reflexes. Initially absent reflexes may be brought out by a brief contraction or repeated taps (Ashby and Lee, 1970). The use of 3,4-diaminopyridine in treatment for this condition can be associated with dramatic improvement (McEvoy et al, 1989).

Patients treated with nondepolarizing muscle-blocking agents may have prolonged paralysis because of delayed clearance of the agent or its metabolite. This has been a particular problem after prolonged infusions of vecuronium (Segredo et al, 1992) (Figure 21). While described in the literature, presynaptic neuromuscular junction blockade from aminoglycosides seems rare, likely because of careful monitoring of patients receiving these agents.

Patients with inherited low plasma pseudocholinesterase activity may have prolonged paralysis from neuromuscular junction blockade associated with the use of succinylcholine and mivacurium (Cerf et al, 2002; Cherington and Lasater, 1973). Other rare causes are listed in Table 16.

**Figure 21** Severe neuromuscular transmission deficit following a prolonged vecuronium infusion in a patient admitted to the intensive care unit with asthma and prolonged respiratory failure. Responses are recorded over the abductor digiti minimi after 2-Hz stimulation. This patient also had evidence of severe critical illness myopathy (note gain; compound motor action potentials are severely reduced in amplitude).

KEY POINTS:

- Definitive electrophysiologic criteria for ALS require denervation in two territories of each of three limbs (or in bulbar muscles).
- Unfortunately, patients who are diagnosed with ALS in the ICU may never be successfully weaned. Some decline ongoing long-term ventilation and request extubation.
- The Lambert-Eaton myasthenic syndrome has occasionally been complicated by respiratory failure.
- Presynaptic neuromuscular junction blockade from aminoglycosides appears to be very rare.
- Patients with inherited low plasma pseudocholinesterase activity may have prolonged paralysis from neuromuscular junction blockade associated with the use of succinylcholine and mivacurium.

Myopathies

Preexisting muscle disorders may first come to attention when patients present with respiratory muscle weakness in the ICU. While uncommon, two inherited myopathies should be considered: myotonic muscular dystrophy and acid maltase deficiency. Myotonic muscular dystrophy, an autosomal dominant disorder associated with a CTG trinucleotide repeat on chromosome 19q13.3, should be suspected by the characteristic facies, premature balding, masseter and temporalis atrophy, and mild ptosis. Myotonia can be elicited in a variety of ways. Lambert weakness may be variable depending on the stage of the disorder and the number of trinucleotide repeats. Unlike other muscular dystrophies...

### TABLE 16 Causes of Diffuse Weakness in Patients Admitted to the Intensive Care Unit

- **Central Nervous System Disorders**
  - Bilateral cerebral infarction or disease
  - Central pontine myelinolysis
  - Other basis pontis disorders: infarction, hemorrhage, multiple sclerosis plaque
  - Cervical cord disease: compression or trauma, multiple sclerosis, transverse myelitis, tumor, other

- **Peripheral Nerve Disorders**
  - Guillain-Barré syndrome
  - Critical illness polyneuropathy
  - Multiple radiculopathy
  - Porphyric neuropathy
  - Thiamine deficiency
  - Chronic inflammatory demyelinating polyneuropathy (rare)
  - Other

- **Neuromuscular Junction Disorders**
  - Myasthenia gravis
  - Lambert-Eaton myasthenic syndrome
  - Prolonged action of nondepolarizing muscle-blocking agents
  - Pseudocholinesterase deficiency
  - Botulism
  - Envenomations
  - Organophosphate poisoning
  - Tick paralysis
  - Aminoglycosides (rare)

Continued on next page
myotonic muscular dystrophy is associated with a peculiar sensitivity to sedatives, in particular, opioids, which can produce acute respiratory failure (Case 12). Increased central respiratory sensitivity to these agents has been postulated to account for this effect (Aldridge, 1985). The clinical

Case 12
A 19-year-old male undergoes an orthopedic procedure for bilateral footdrop. Postoperative care includes routine use of meperidine every 4 hours. At 3:00 AM the morning after surgery, the patient is unresponsive and not breathing. He is intubated and transferred to the ICU. He remains unresponsive the next day and cannot be weaned. Further history emerges that the patient has myotonic dystrophy, and neurologic examination confirms characteristic features of this diagnosis, including myotonia. Naloxone injection is associated with brief improvement, but overall he improves very slowly over the next several days. He is not successfully extubated until approximately 2 weeks after the event. After discharge from the hospital, the patient resumes his normal lifestyle.

Comment. This patient with myotonic muscular dystrophy had prolonged respiration failure from opioid analgesics but eventually recovered.

KEY POINTS:
- Preexisting muscle disorders may present with respiratory muscle weakness in the ICU.
- Myotonic muscular dystrophy is associated with a peculiar sensitivity to sedatives (in particular, opioids) that can produce acute respiratory failure.

TABLE 16  Continued

- Muscle Disorders
  - Critical illness myopathy
  - Myotonic muscle dystrophy
  - Other muscle dystrophies
  - Acid maltase deficiency
  - Polymyositis or other inflammatory myopathies
  - Sarcoid myopathy
  - Mitochondrial myopathy
  - Hypophosphatemic myopathy
  - Carnitine palmitoyl transferase deficiency
  - Trichinosis
  - Human immunodeficiency virus–related myopathy
  - Malignant hyperthermia
  - Periodic paralyses
  - Acquired hypokalemic myopathy
  - Alcoholic rhabdomyolysis
  - Pyomyositis
  - Rhabdomyolysis secondary to toxic shock syndrome, Legionnaire’s disease, other
EMERGENCY CONSULTATION IN THE ICU

KEY POINTS:
- Adult acid maltase deficiency is an autosomal recessive deficiency of alpha glucosidase (acid maltase) that renders proximal limb, trunk, and respiratory muscle weakness.
- Critical illness myopathy develops in patients already admitted to the ICU with other diagnoses, and it may sometimes be difficult to distinguish from critical illness neuropathy.
- The presence of normal SNAPs in an anesthetized arm or hand suggests that the lesion is proximal to dorsal root ganglia.
- GBS may be associated with life-threatening respiratory muscle weakness. In patients with imminent respiratory failure, predicting the need for intubation and artificial ventilation is essential when the vital capacity declines below 20 ml/kg.
- The actions of these agents seem to wear off slowly, giving false initial impressions of the severity of the neurologic deficit. Patients with myotonic dystrophy can generally be weaned from the ventilator satisfactorily given enough time and avoidance of sedatives and opioids. There is no evidence that specific treatment of the myotonia is of benefit in this situation.
- Adult acid maltase deficiency: an autosomal recessive deficiency of alpha glucosidase (acid maltase), is responsible for proximal limb, trunk, and respiratory muscle weakness. EMG demonstrates fibrillations, complex repetitive potentials, and myotonic discharges. Biopsy shows muscle fibers with vacuoles containing glycogen and fiber degeneration. It is important to establish the correct diagnosis in these patients, since some may later be successfully weaned from the ventilator.
- Other disorders that have been rarely associated with respiratory failure include polymyositis, sarcoid myopathy, and mitochondrial myopathy. Severe acquired hypokalemia can be associated with generalized limb and respiratory muscle weakness.
- Critical illness myopathy (CIM) develops in patients already admitted to the ICU with other diagnoses, and it sometimes may be difficult to distinguish from critical illness neuropathy. Severe and diffuse involvement of limb, bulbar, and respiratory muscles is characteristic. The use of corticosteroids and nondepolarizing muscle-blocking agents is a risk factor for its development, and it may appear concurrently with prolonged neuromuscular junction blockade (see above).

Focal Weakness in the Intensive Care Unit

Focal weakness may be difficult to identify in patients admitted to the ICU. When present, CNS disorders should be considered first. After a motor vehicle accident or other form of trauma, brachial plexopathy or multiple cervical root avulsion may cause flaccid paralysis of the arm, scapular winging, diaphragm paralysis, and Horner's syndrome. Focal loss of reflexes and sensation also appears. Sensory loss of CMAPs and the appearance of fibrillations after peripheral nerve injury do not appear immediately, it is important to delay electrophysiological studies so that the full extent of the injury can be mapped (1 to 2 weeks). The presence of normal SNAPs in an anesthetized arm or hand suggests that the lesion is proximal to dorsal root ganglia and may actually be root avulsion (Figure 22). MRI of the cervical intraspinal space is then helpful in identifying prominent meningoceles at the sites of the root injuries.

Several other focal neuropathies are important causes of focal weakness in patients admitted to ICU's. Brachial plexopathy may follow cardiac surgery (Ben-David and Stahl, 1997). Unilateral or bilateral phrenic neuropathies as may complicate cardiac surgery. Anterior interosseous median neuropathy may develop from inappropriate directed antecubital venipuncture. Radial neuropathy at the level of the spiral groove may be associated with humeral fracture.

In the lower limb, embolic ischemic lumbosacral plexopathy may occur in patients with severe peripheral vascular disease who undergo femoral angiography, aortic aneurysm repair or intra-aortic balloon pumping. Fractures of the pelvis may be associated with lumbosacral plexopathy. Patients who are anticoagulated or have a capsule may develop a compressive iliopsoas hematomata causing lumbosacral plexopathy. Severe neuropathic pain may occur after trauma or hip surgery (Plewnia et al. 1999). It may be recognized by a unilateral footdrop combined with an absent ipsilateral ankle
reflex. Compressive sciatic neuropathy or lumbosacralplexopathies should be decompressed urgently.

**SOME SPECIFIC NEUROMUSCULAR DISORDERS**

**Guillain Barré Syndrome**

Familiar to all practicing neurologists, Guillain Barré syndrome (GBS) is an acute autoimmune inflammatory polyneuropathy that may involve motor, sensory, or autonomic fibers. Classic GBS is associated with acute and widespread demyelination of peripheral nerves, but variants with selective involvement of the axons have more recently been described (acute motor axonal neuropathy; acute motor and sensory axon neuropathy) (Feasby et al. 1986; McKhann et al. 1995). GBS may be associated with life-threatening respiratory muscle weakness (Case 13).

In patients with imminent respiratory failure, predicting the need for intubation and artificial ventilation is essential when the vital capacity declines below 20 mL/kg (see page 55; Ropper and Kehne, 1985). Thus, use of monitored beds (with continuous measures of cardiac rhythm, heart rate, and oxygen saturation) with frequent measurements (eg., every 4 to 6 hours) of vital capacity and close nursing supervision is recommended. Similar monitoring is warranted when patients are first transferred out of the unit after extubation.

While most patients with GBS have an acute demyelinating polyneuropathy, patients with very severe disease may have a combination of widespread demyelination and axonal degeneration. Patients with acute axonal forms of GBS may similarly require ventilator support. In general, severe axonal

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**KEY POINT:**

- Patients with acute axonal forms of GBS may require ventilator support.
- In general, severe axonal involvement, either alone or combined with demyelination, is associated with much more prolonged disability during recovery.

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**FIGURE 22**

Multiple cervical root avulsions following trauma and resulting in focal limb weakness. **A,** Magnetic resonance images of the cervical spine identify a large meningocele on T2-weighted images. **B,** Electrophysiologic studies identify absent compound motor action potentials in the ulnar territory (top three tracings) with normal sensory nerve action potentials in the same territories (bottom three tracings). The lesion is proximal to the dorsal root ganglion.
KEY POINTS:

- It is possible that involvement, alone or combined with demyelination, is associated with much more prolonged disability during recovery. Well-established electrophysiologic features of demyelination include prolonged distal motor latencies, conduction block, conduction slowing, and temporal dispersion. Treatment, axonal degeneration is associated with loss of CMAPs and SNAPs and dense fibrillations on EMG. Therapeutically, intravenous gamma globulin or plasma exchange may be administered in the ICU, but it is inappropriate to expect obvious clinical improvements after the treatments. Therapy in GBS has been associated with a statistical improvement in clinical trials, but a so-called Lazarus effect (for the biblical Lazarus, who arose from the dead) is uncommonly observed with treatment (The GBS Study Group, 1985; Van der Meche and Schmitz, 1992). There is no evidence to date that further courses of intravenous immunoglobulin (IVlg) or combining IVlg with plasma exchange is beneficial (Plasma Exchange Sandoglobulin GBS Trial Group, 1997). Indeed, it is possible that following IVlg with plasma exchange might simply negate the impact of IVlg by removing the agent. Glucocorticoids do not benefit GBS (Hughes et al., 1978).

In addition to acute respiratory failure, GBS patients are at risk for aspiration pneumonia, deep venous thrombosis and pulmonary embolism. Paralyzed GBS patients in the ICU should be provided with intermittent pneumatic compression stockings to prevent venous thrombosis. Beyond these risks, patients with GBS admitted to the ICU are also at risk for acute autonomic instability (Zochodne, 1994). The most serious autonomic disturbances are sudden changes in heart rate and rhythm or blood pressure. Vagal spells are episodes of sudden bradycardia or asystole that can be provoked by suctioning, insertion of nasogastric tubes, or eyeball pressure. Such spells associated with hemodynamic compromise warrant placement of a temporary pacemaker. Patients with GBS should cautiously be given vasopressor agents for hypertension.

**Critical Illness Polyneuropathy**

Charles Bolton originally described a unique and severe axonal polyneuropathy observed in patients admitted to

**Case 13**

A 65-year old woman is admitted to the ICU with herpes simplex encephalitis (HSE). The patient is comatose and on a ventilator. HSE has evolved over approximately 2 to 3 weeks with characteristic clinical, imaging, CSF, and electroencephalogram abnormalities. She then develops diffuse limb weakness and areflexia suggesting irreversible, bihemispheric CNS damage or superimposed critical illness polyneuropathy. Neurologic examination discloses an intubated but unresponsive patient with normal pupillary reactions, corneal reflexes, and oculovestibular reflexes. The limbs are flaccid, unresponsive to deep nailbed pressure (no grimacing or withdrawal), and areflexic. Serum CK is normal. Electrophysiologic studies identify widespread features of primary demyelination with prolonged distal motor latencies, slowing of conduction velocity, conduction block, temporal dispersion, and only occasional fibrillations. The diagnosis is acute GBS following HSE viral infection.

**Comment.** In this case, the patient’s flaccid limbs were presumed to be secondary to CNS HSE. Electrophysiologic studies established the diagnosis.
Case 14

A 56-year-old previously healthy man is admitted to the hospital for emergency repair of a ruptured abdominal aortic aneurysm. Adult respiratory distress syndrome, encephalopathy, and abdominal sepsis complicate postoperative recovery. He requires intubation, antibiotics, and inotropic support over the next 3 weeks, then gradually improves. By 4 weeks after admission, he is awake and responsive but appears to have diffuse limb weakness and cannot be weaned from the ventilator. On neurologic examination, he is awake and has intact cranial nerves but cannot lift his head from the bed. The limbs have prominent wasting without fasciculations and are immobile and areflexic. He does not withdraw or grimace to deep nailbed pressure. Serum CK is normal. Electrophysiologic studies identify very low amplitude to absent CMAPs and SNAPs, normal conduction velocities, and trains of fibrillations without voluntary motor unit potentials in multiple sampled muscles (including intercostals and the diaphragm). Quadriceps muscle biopsy identifies scattered and grouped muscle fiber atrophy indicative of denervation. The diagnosis is severe critical illness polyneuropathy (CIP).

Comment. This patient has the typical scenario in which CIP arises after prolonged ICU admission for a nonneurologic problem.

KEY POINTS:
- The cause of CIP remains obscure, but it is most closely linked to the syndrome of sepsis and multiple organ failure and defined as SIRS.
- Patients meeting the criteria for SIRS have a mortality rate approaching 60% within an ICU.
- Cranial nerves are generally spared, an important clinical finding distinguishing SIRS from GBS.

 ICU for other, nonneurologic problems (Case 14). (Bolton et al., 1984; Zochodne et al., 1987) Despite widening attention, the cause of CIP, or Bolton’s neuropathy, remains obscure, but it is most closely linked to the syndrome of sepsis and multiple organ failure otherwise defined as the systemic inflammatory response syndrome (SIRS) (Benjamin et al., 1992; Bone, 1991): (1) temperature higher than 38 C or lower than 36 C; (2) heart rate greater than 90 beats per minute; (3) respiratory rate greater than 20 min or PaCO₂ less than 32 mm Hg; (4) white blood cells in blood greater than 12,000 cells ml or less than 4,000 cells ml or greater than 10% immature (band) forms. SIRS can develop after several types of insult, including infection (sepsis), pancreatitis, ischemia, multiple trauma with tissue injury, hemorrhagic shock, heat shock, immune-mediated organ injury, and exogenous administration of inflammatory mediators. SIRS associated with infection is termed sepsis, whereas septic shock refers to sepsis with hypotension and multiple organ dysfunction syndrome. Bacteremia and sepsis are not synonymous; the former simply refers to a positive blood culture, which is not an absolute requirement for sepsis. Patients meeting the criteria for SIRS are very ill and have a mortality rate approaching 60% within an ICU. In a prospective series of 132 patients referred for electrophysiologic studies (mean interval of 40 days after admission), Zifko and colleagues (1998) diagnosed critical illness polyneuropathy in 62, or approximately half, of the referred cohort.

Patients may be referred because of diffuse weakness and difficulty in being weaned from the ventilator. Symptoms of polyneuropathy are usually not detected, since patients are intubated and sedated and may have encephalopathy. In some instances, however, patients have reported painful paresthesias during their recovery, and many patients noted muscle weakness during their rehabilitation. Cranial nerves are generally spared, an important clinical finding distinguishing
EMERGENCY CONSULTATION IN THE ICU

KEY POINTS:
- At present, CIP is thought most likely to represent an end-organ complication of SIRS involving a cascade of widespread tissue ischemia, mitochondrial dysfunction, oxidative stress, nitrative stress, and damage from inflammatory mediator molecules.
- Fulminant myasthenia gravis may occasionally produce severe acute limb, bulbar, and respiratory weakness.

This disorder from GBS and some myopathies or neuromuscular junction disorders. The limbs exhibit flaccid weakness and atrophy, although distal atrophy may be obscured by limb edema, and there may be loss of previously normal deep tendon reflexes. Sensory examination may be unreliable during the patient’s acute illness, but distal pannodal stocking-and-glove loss to all sensory modalities can become evident later. Patients with CIP may be awake yet fail to grimace or withdraw their limbs to nailbed pressure.

Electrophysiologic studies (Bolton et al. 1986) identify declines of CMAP and SNAP amplitudes with normal conduction velocities, distal motor latencies, and F-wave latencies. Similarly, the diaphragm CMAP may have reduced amplitude (Zifko et al. 1998). EMG identifies widespread fibrillation potentials and positive sharp waves, including involvement of intercostal muscles and the diaphragm. Patients may not be able to recruit any voluntary motor unit potentials, and those recruited may have small amplitudes and polyphasia. Such “nonsense units” develop during early reinnervation, although they may resemble those recruited in a myopathy. Unlike GBS, CSF protein levels are normal or mildly elevated. Pathologic studies of peripheral nerves in CIP identified acute axonal degeneration and axon loss in distal and proximal motor and sensory fibers (Zochodne et al. 1998) (Figure 23). Muscle biopsies show acute scattered muscle fiber atrophy or chronic grouped fiber atrophy with scattered necrotic muscle fibers. Such changes may involve proximal and distal muscles as well as the diaphragm and intercostal muscles. Both retrospective and prospective studies of CIP have failed to link its development to specific drugs, such as aminoglycosides, nondepolarizing muscle blocking agents, or glucocorticoids. Similarly, it cannot be linked to specific pathogenes or deficiencies of vitamins chromium, linolenic acid, or linolenic acid. At present, CIP is thought most likely to represent an end-organ complication of SIRS involving a cascade of widespread tissue ischemia, mitochondrial dysfunction, oxidative stress, nitrative stress, and damage from inflammatory mediator molecules.

Myasthenia Gravis
Fulminant myasthenia gravis may occasionally produce severe acute limb, bulbar, and respiratory weakness. A carefully planned Tensilon test is helpful diagnostically (see “Neuromuscular Junction Disorders”). This test also is helpful in differentiating acute myasthenic crisis from cholinergic crisis. Repetitive conduction studies may be performed in a proximal muscle (eg, the accessory nerve with recording over trapezius) or with stimulation of the phrenic nerve and recordings from the diaphragm (Mahe et al. 1998). Vital capacity at or below 20 mL/kg or

![Figure 23](image-url)

Transverse section of a deep peroneal nerve in a patient with critical illness polyneuropathy. Severe loss of myelinated fibers and profiles of myelinated fibers undergoing acute axonal degeneration are present.
Case 15
A 35-year-old female with a history of severe asthma requires admission to the hospital and intubation for severe bronchospasm. Despite the use of inhaled and intravenous bronchodilators, she has very high airway resistance; she is therefore paralyzed with a bolus, then infusion of vecuronium is started to facilitate pulmonary oxygen exchange. High doses of intravenous corticosteroids are given. Adult respiratory distress syndrome complicates the pulmonary management over the next 2 weeks, and paralysis is continued for a total of 10 days. After vecuronium is discontinued and presumably eliminated, the patient remains flaccid and immobile for the next 24 hours. On neurologic examination, the patient is found to be intubated. She makes no spontaneous facial, eye, or limb movements. Pupillary responses are intact, but corneal and oculovestibular reflexes are absent. The limbs are flaccid and areflexic, and no limb movement or grimacing is apparent on nailbed pressure. Serum CK is over 10,000, and there is myoglobinuria. Electrophysiologic tests identify a severe neuromuscular transmission deficit when stimulating in the ulnar motor territory at 2 Hz.

One week after discontinuing vecuronium, the patient appears responsive, having fully regained eye and facial movements but not limb movements. The patient grimaces but does not withdraw to nailbed pressure. CK level has gradually declined to 2,000. The neuromuscular junction transmission deficit has disappeared, but CMAPs are very reduced in amplitude and appear prolonged in duration. Conduction velocities and SNAPs are normal. EMG discloses only occasional fibrillations. A few low-amplitude, polyphasic, voluntary motor unit potentials are recruited. Quadriceps muscle biopsy identifies a large number of muscle fibers undergoing acute necrosis, vacuolated muscle fibers, and intact muscle fibers with loss of myosin-thick filaments. Regenerating muscle fibers are prominent. The patient eventually recovers completely. The diagnosis is CIM.

Comment. This case illustrates the risk factors of nondepolarizing muscle-blocking agents and corticosteroids in developing CIM. Paralysis may be severe.

maximum expiratory pressure below 40 cm H₂O (30% predicted) are signs that intubation and ventilation may be required at short notice. For treatment in the ICU, pyridostigmine can be given by feeding tube, suppository, or parenterally, keeping in mind that the parenteral dose is 1/15th to 1/30th of the oral dose. Patients with recent-onset, severe, generalized myasthenia gravis started on high doses of corticosteroids are at risk for paradoxical deterioration during the first 48 to 96 hours of treatment, and therapy probably should best be combined with a course of plasma exchange or possibly intravenous gamma globulin (Verma and Oger, 1992). Pulsed intravenous methylprednisolone may offer more rapid and intensive therapy for

**FIGURE 24** Low-amplitude polyphasic voluntary motor unit potentials in a patient with critical illness myopathy. (Gain is 100 μV, 10 ms/div.)

patients in myasthenic crisis (Arsura et al, 1985). Thymectomy can be considered in patients with new-onset generalized myasthenia gravis during the acute stage. The timing of concurrent corticosteroid use in such patients is worth considering, because of the concerns that it may slow sternalotomy wound healing. The role of mycophenolate mofetil in the ICU is not yet clear, but it has recently been used in severe refractory myasthenia gravis (Ciafaloni et al, 2001). Azathioprine likely acts too slowly to be of value in acute myasthenia gravis.

**Critical Illness Myopathy**

A newly acquired primary myopathy may account for flaccid weakness of patients in ICUs (Case 15). Such myopathies may clinically and electrophysiologically resemble CIP (Lacoomis et al, 2000; Lacoomis et al, 1996; Ramsay et al, 1993; Zuchodne et al, 1994). For this condition, the designation critical illness myopathy (CIM) seems preferable, although several other terms have been used, such as floppy person syndrome, necrotizing myopathy of the ICU, thick filament myopathy, steroid-induced tetraplegia, and acute quadriplegic myopathy. Patients with CIM have most often (although not always) (Hoke et al, 1999) received nondepolarizing muscle-blocking agents, high doses of corticosteroids, or both. If blocking agents have been given, a concurrent prolonged blockade of the neuromuscular junction may be present and may last for several days after their discontinuation (see "Neuromuscular Junction Disorders"). This problem appears in patients given prolonged infusions of vecuronium or pancuronium, especially in the setting of renal failure (Figure 21). CIM may appear earlier than CIP in patients admitted to ICUs. CIM patients also have greater cranial nerve involvement than those with CIP; ophthalmoplegia may be encountered in some instances (Sitwell et al, 1991). CIM patients also have spared sensation (eg, trigeminal, but not withdrawal to nailbed pressure). Some patients may exhibit features of both CIM and CIP. In transplant units, CIM may be particularly linked to the use of high doses of corticosteroids administered to prevent rejection (Campellone et al, 1998). This variant of CIM has been called *acute steroid myopathy*. Muscle biopsy is important in this setting to exclude other forms of myopathy that can occur in such patients, eg, type II plasma gondii myositis or graft-versus-host myositis.

In CIM, electrophysiologic findings are low-amplitude and prolonged CMAPs, relatively preserved SNAP (if edema is absent), some (but less intense than CIP) fibrillations, and positive sharp waves, and small amplitude polyphasic voluntary motor unit potentials when they can be elicited (Figure 24). On muscle biopsy, a selective loss of thick myosin filaments is characteristic of CIM. Why such selectivity occurs is not clear, and it may be that thick filament loss is not entirely specific for this disorder. Other important pathologic feature include type II fiber atrophy, muscle fiber necrosis, vacuolated muscle fibers, and regenerating muscle fibers. The changes observed in a given patient may depend on the timing of the biopsy. In patients with seven weakness, high CK levels, and rhabdomyolysis, fiber necrosis may predominate and obscure thick filament loss. These changes may also be more prominent in patients receiving prolonged infusions of vecuronium. In patients beginning to recover, biopsy may identify prominent fiber regeneration.
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