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Review article

Anesthetic implications of neuromuscular disease

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Introduction

General anesthesia involves the use of multiple agents with differing pharmacodynamic properties to achieve the aims of amnesia, analgesia, and muscle relaxation. This concept of "balanced anesthesia," first named by J.S. Lundy of Rochester, became possible with the introduction of curare in 1942 by Griffith and Johnson [1]. However, the introduction of this drug brought its own problems. A review by H.K. Beecher of 600000 anesthetics administered at 10 university hospitals revealed a significantly higher mortality associated with the use of muscle relaxants. This was initially ascribed to inherent drug toxicity but was more probably due to inadequately treated residual postanesthetic muscle paralysis. Additionally, the use of muscle relaxants in patients with neuromuscular disease presents its own hazards. These diseases can have a pathophysiologic basis at the level of the central nervous system, peripheral nerves, neuromuscular junction, or muscle fiber. As well as abnormal responses to muscle relaxants, these diseases may be associated with systemic problems that may profoundly affect the conduct of anesthesia.

This review will address the anesthetic implications of some of the more common neuromuscular diseases, including multiple sclerosis, myasthenia gravis, muscular dystrophy, critical illness polyneuropathy, spinal cord injury, and Guillain-Barré syndrome.

Multiple sclerosis

Multiple sclerosis (MS) is a relapsing and remitting demyelinating disease of the central nervous system with sparing of the peripheral nerves. It is the most frequent cause of neurologic disability of early to middle adulthood. There is a striking relationship between geographic latitude and the incidence of MS. The incidence is low near the equator, and in the temperate climates of Europe and North America, it has an incidence of 75 to 150 per 100000 [2]. The highest incidence is in the Orkney and Shetland Islands north of Scotland [3]. The exact cause of MS is still unclear. A higher than expected incidence in first-degree relatives has been shown, and there are also some common histocompatibility antigens. A viral etiology has also been suggested, although no virus has yet been identified.

The signs and symptoms reflect the areas of demyelination and can include optic neuritis, gait disturbances, limb parasthesias, and urinary incontinence. The symptoms typically develop over the course of a few days and can last for weeks, followed by remission. However, the overall course is one of deterioration, as the CNS does not remyelinate.

Although there is no cure for MS, treatment consists of corticosteroids, which may help shorten the duration of attacks. Other agents used in the treatment of MS include diazepam and dantrolene for muscle spasticity, and azathioprine and cyclophosphamide as immunosuppressive agents.

Patients with MS may present for any type of surgery, including obstetric interventions. The preoperative assessment should focus primarily on the degree of neurological impairment and the sequelae of MS [4]. The patients are often young, and therefore primary cardiac disease is unusual. However, autonomic dysfunction is common, and these patients may have abnormal responses to a Valsalva maneuver [5]. Additionally, cyclophosphamide may cause a myocarditis, which should be ruled out for patients taking this drug. In advanced disease, patients may develop kyphoscoliosis, which may cause a restrictive lung disease, and respiratory function tests should be ordered as appropriate. A detailed neurologic assessment should be performed and

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document the preoperative neurologic deficits. The presence of epilepsy should also be noted, since its prevalence is increased in MS [6]. Laboratory tests should help to reveal any abnormalities resulting from the secondary effects of drug treatment, such as hepatic dysfunction in patients taking dantrolene and adrenal suppression in patients taking long-term steroids.

Drugs used for premedication, such as diazepam, are helpful, since they may relieve spasticity. However, any premedication with a drug having anticholinergic properties should be avoided, because it may impair temperature regulation.

The drug of choice for induction of general anesthesia is probably propofol, but thiopentone is also safe [7–9]. The maintenance of general anesthesia appears to be safe with the volatile agents halothane and isoflurane [4]. Methohexital and enflurane should not be used if there is a history of epilepsy.

Caution should be exercised with the use of muscle relaxants. Succinylcholine has been known to cause hyperkalemia in patients with MS [10] and should be avoided. The response to nondepolarizing muscle relaxants can be variable. Resistance to atracurium has been reported [11], which may be due to an increased number of extrajunctional acetylcholine receptors. Patients taking long-term anticonvulsants such as carbamazepine may also exhibit resistance to nondepolarizing relaxants [12,13]. This is probably due to induction of liver enzymes responsible for metabolizing the relaxant drugs, increased postsynaptic acetylcholine receptors, or changes in binding of the muscle relaxants to plasma proteins [14]. However, the disease may also be associated with impaired neuromuscular transmission resembling myasthenia [15].

The use of neuraxial anesthesia in patients with multiple sclerosis is controversial. Although neuraxial anesthetic techniques may be relatively contraindicated in a patient with neuromuscular disease for fear of a postoperative decline due to the anesthetic technique, there may be situations, such as obstetrics, when neuraxial anesthesia is of benefit. Lumbar puncture itself has not been shown to be harmful in MS [16]. However, postoperative exacerbations of MS have been attributed to spinal anesthesia [17]. Epidural anesthesia and regional nerve blocks appear to be safe [18–20]. It is likely that spinal anesthesia exposes the unprotected nerve root to a higher concentration of local anesthetic, causing a local neurotoxicity. When planning an epidural anesthetic in a patient with MS, the anesthesiologist should use a combination of local anesthetic solutions with opioids to help reduce the concentration of local anesthetic that is available to cause direct injury. The duration of epidural infusions should be kept as short as possible to minimize exposure of the nerve roots to local anesthetic.

The level of intraoperative monitoring should be dictated by the nature of the surgery or other comorbidities of the patient. However, in light of the frequency of autonomic dysfunction in patients with MS, the anesthesiologist should have a lower threshold for using more invasive hemodynamic monitoring. Neuromuscular function should be closely monitored, bearing in mind the unpredictability of response to neuromuscular blocking drugs.

Postoperative decline in neurologic function has been reported in patients with MS [8]. This cannot be easily related to any particular anesthetic technique but seems to be related to postoperative fever. Drugs with anticholinergic properties, particularly those used to counteract the cholinergic effects of reversal agents, should be used sparingly. Close attention should also be paid to avoiding postoperative infection. Use of thromboembolic prophylaxis should be encouraged in all patients, since platelet aggregation is increased in MS and may predispose to deep vein thrombosis [21]. Although epidural anesthesia is likely to be safe, a prolonged infusion of local anesthetic for postoperative pain relief may increase the risk of local anesthetic neurotoxicity.

Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disease caused by antibodies to nicotinic acetylcholine receptors at the neuromuscular junction [22]. The antibodies reduce the number of receptors by either competitive blockade or increased degradation of receptors. In chronic MG, the number of receptors is reduced to approximately 30%, and many of the remaining receptors are bound by antibody [23]. This substantially reduces the safety margin for reliable neuromuscular function, which requires 25% to 30% of the receptor pool [24]. The annual incidence is 0.25 to 2 per 100000, with a substantially increased age-related frequency in those over 60 years of age. The characteristic clinical presentation is one of weakness with exertion. The muscle groups affected may be limited to the ocular and bulbar muscles or may become more generalized. Bulbar and respiratory muscle weakness may lead to aspiration and respiratory failure. Osserman and Genkins have classified MG as follows: class I, ocular myasthenia only, with ptosis and diplopia; class IIA, generalized moderate weakness; class IIB, generalized moderate weakness and/or bulbar dysfunction; class III, acute fulminating presentation and/or respiratory dysfunction; class IV, late severe generalized. Up to 10% of patients with MG may also have other autoimmune diseases complicating their presentation or management [25]. These can include hypothyroidism, rheumatoid arthritis, systemic lupus erythematosus (SLE), and anemias.

Patients with MG may present for any type of surgery, including obstetric procedures. One procedure commonly performed for patients with MG is thymectomy, which may induce remission, especially in those patients with a thymoma [26].

In general, treatment of patients with MG has three aims: enhancing neuromuscular transmission with the use of cholinesterase inhibitors; decreasing circulating antibodies by the use of plasmapharesis [27], utilizing four to eight exchanges over 1 to 2 weeks; and immunosuppressive therapy with either corticosteroids or azathioprine [28,29]. Acute administration of corticosteroids should be initiated in an inpatient setting, because it may result in increased weakness before the more prolonged improvement of neuromuscular function is observed.

Preoperative assessment should focus on the respiratory and bulbar function of the patient. The patients usually have intact respiratory drive and CO_2 response, but spirometry can reveal a low vital capacity [30,31]. The presence of a large thymoma may cause some degree of tracheal compression, which can be detected by the use of flow volume loops and chest and neck CT scan. The presence of a very large thymoma will put the patient at risk for acute airway collapse during induction of general anesthesia. Evidence for lack of upper or lower respiratory tract infection should be ascertained to reduce the risk of perioperative infection.

Patients with MG may have cardiac conduction arrthymias, such as atrial fibrillation, sinus bradycardia, and premature ventricular contractions. Electrocardiography may reveal ST and T wave changes [32]. Some patients, particularly those with thymoma, develop a myocarditis, which histologically resembles inflammatory changes in skeletal muscle observed with MG [33].

The association with rheumatoid arthritis necessitates a detailed examination of the neck to ascertain any impairment and predict the difficulty of tracheal intubation. The degree of any bulbar involvement should also be closely assessed.

Preoperative medical management of the myasthenic patient should aim to optimize muscle function. There is controversy over whether anticholinesterase drugs should be continued up until the time of surgery. Anticholinesterase therapy can cause potentiation of vagal responses and decrease the metabolism of ester local anesthetics and hydrolysis of local anesthetics [34]. Anticholinesterase therapy may also prolong the effect of succinylcholine, if it is used at the time of tracheal intubation. If patients are reliant on their anticholinesterase drugs, they should probably be continued perioperatively. Patients with milder disease may be able to withstand a break from these drugs during the perioperative period.

Plasmapharesis is an effective treatment for patients with more severe MG. It has been shown to improve vital capacity, forced expiratory volume in the first record (FEV_1), and mean expiratory force to a greater degree than pyridostigmine [35]. However, the reduced plasma esterases will reduce the metabolism of drugs such as succinylcholine, mivacurium, and remifentanil. Plasmapharesis may be effective even for class IV patients and should be considered for any patient with a vital capacity of less than 21 [36].

Premedication of myasthenic patients with sedative drugs is not advised because of the potential for respiratory embarrassment. Preoperative administration of anticholinesterase drugs may affect the duration of action of succinylcholine, if it becomes necessary for airway management. These drugs may also potentiate vagal responses.

Induction of anesthesia can be safely performed with intravenous agents such as propofol, thiopental, or etomidate. The maintenance of anesthesia can be with either an intravenous agent or a volatile agent. The volatile agents themselves have significant neuromuscular blocking effects in patients with MG. Halothane can produce a significant depression of neuromuscular transmission [37], with isoflurane approximately twice as potent in this regard [38]. The degree of depression of neuromuscular response after halothane or isoflurane does not seem to correlate with the clinical severity of MG disease.

The use of neuromuscular blocking agents in patients with MG requires a thorough understanding of their different effects. Although some anesthesiologists prefer not to use muscle relaxant drugs at all, relying on the effect of the volatile agents to cause relaxation, high-dose inhalational anesthesia may lead to cardiovascular depression. Patients with MG have been shown to be relatively more resistant to succinylcholine than controls, with an ED_{95} of 2.6 times normal [39]. When doses of 1.0 to 1.5 $mg \cdot kg^{-1}$ are used, which are three to five times the ED_{95} of 0.3, the clinician should expect a clinically insignificant effect (i.e., approximately normal efficacy and duration of action). However, when lower doses of 0.5 $mg \cdot kg^{-1}$ are used, clinical resistance to its effects may be observed [40]. This may be due to functional blockade of the acetylcholine receptors by antibodies, requiring higher doses of succinylcholine to overcome the blockade.

The reduced number of acetylcholine receptors at the neuromuscular junction makes patients with MG exquisitely sensitive to nondepolarizing neuromuscular blocking drugs. The spectrum of disease severity means that responses can be unpredictable, with as little as one tenth of the usual dose being required [41]. Patients with MG appear to be most sensitive to the long-acting relaxant drugs, such as pancuronium [42,43]. The

medium-acting drugs, such as atracurium and vecuronium, have been used successfully in patients with myasthenia gravis. The ED_{95} for vecuronium is 56% of normal, and it produces a longer duration of block [44]. The dose requirement for atracurium is also approximately half the normal dose, and again, it has a longer duration [45]. An advantage of atracurium is that it undergoes spontaneous Hoffmann degradation, and therefore reversal agents are less likely to be required. The use of reversal agents in patients with MG is complicated by the variable response to them and the perioperative use of anticholinesterase drugs. Excessive doses of reversal agents may precipitate a cholinergic crisis, characterized by muscle weakness, bradycardia, increased secretions, and gut motility.

The variable response to the neuromuscular blocking drugs does not appear to correlate with the clinical severity of the myasthenia, although there may be some correlation between the preoperative train-of-four and the dose requirement of relaxant [46]. Thus, although numerous reports demonstrate their use in patients with MG, they should be administered with caution and carefully titrated with the use of neuromuscular monitoring to judge dose requirements. It should also be borne in mind that numerous drugs interact with relaxants to potentiate their effect. In patients with MG, this potentiating effect may be more prolonged. Drugs that may accentuate the weakness in patients with MG include magnesium sulfate, aminoglycosides, vancomycin, quinidine, procainamide, narcotics, furosemide, dantrolene, beta-blockers, and calcium channel blockers [47].

Regional anesthesia should be used where possible in patients with MG, although the doses of local anesthetics, particularly ester types, should be reduced in patients receiving anticholinesterase drugs. Even the use of high doses of amide local anesthetics can exacerbate symptoms [48]. Neuraxial anesthesia should be carried out with care to avoid a high level of blockade and subsequent muscular weakness.

The course of MG during pregnancy is variable, although postpartum exacerbations are common. The use of anticholinesterase drugs during pregnancy may increase uterine tone and contractility, although an increase in the spontaneous abortion rate has not been demonstrated [49]. During labor these drugs should be given intravenously, as oral absorption can be unpredictable. Regional anesthesia is ideal for analgesia during labor, but with attention paid to the level of block and avoidance of ester-type local anesthetics such as chloroprocaine. Preterm labor is more common in patients with MG [50], although the length of labor is not affected. Magnesium sulfate given for preeclampsia should be used only with extreme caution, as it may excessively exacerbate weakness in patients with MG. Skeletal muscle weakness may result in difficulties in second-stage labor. Because the antibody to the acetylcholine receptor crosses the placenta, the newborn infant may develop neonatal MG, which usually resolves within a few weeks [51].

The two main postoperative issues are the need for mechanical ventilation and the treatment of pain. Much work has been devoted to predicting the need for postoperative mechanical ventilation. Several factors have been identified and were classified by Leventhal [52] for patients undergoing transsternal thymectomy as follows: duration of myasthenia greater than 6 years (12 points); a history of chronic respiratory disease other than that due to MG (e.g., chronic obstructive pulmonary disease) (10 points); preoperative dose of pyridostigmine $>750\,mg\cdot day^{-1}$ (8 points); and preoperative vital capacity $<2.9\,l$ (4 points). A total score of greater than 10 points indicated the need for postoperative ventilation. However, this only applies to transsternal thymectomy and not to other types of surgery or to transcervical thymectomy.

Postoperative pain may be difficult to manage because of an apparent sensitivity of these patients to respiratory depressive side effects of narcotics and sedatives. The use of regional anesthesia for postoperative pain relief has been described [53]. In this study patients receiving lumbar epidural morphine required less intravenous morphine, had lower levels of pain, and had no increase in respiratory depression, as well as having better postoperative forced vital capacity.

Eaton-Lambert syndrome

Eaton-Lambert syndrome (ELS) (also known as mysthenic syndrome) is a rare neuromuscular disorder resulting from a defective release of acetylcholine at the presynaptic terminal [54]. The disease presents with muscle weakness and hyporeflexia. Unlike MG, ELS rarely affects ocular or bulbar muscles, strength often improves with activity, and autonomic dysfunction is common, especially dry mouth but also dry skin, orthostatic hypotension, and bladder and bowel dysfunction. ELS is frequently associated with cancer, especially small-cell lung carcinoma. The pathophysiologic defect is reduced quantal release of acetylcholine from the nerve terminal. The nerve weakness is not improved by anticholinesterase but can be treated with 3,4-diaminopyridine, which increases transmitter release [42]. Immunosuppressive therapy may also help. A thorough search for any tumor causing the ELS should be undertaken, and the tumor should be treated appropriately. The main factor affecting anesthetic management in these patients is their extreme sensitivity to both depolarizing and nondepolarizing neuromuscular

blockers. After administration of neuromuscular blocking agents, paralysis may be long-lasting and difficult to reverse with anticholinesterase.

Muscular dystrophy

The term muscular dystrophy refers to a group of genetic disorders causing progressive degeneration of skeletal muscle without any abnormality of the motor neuron. Common types include Duchenne's and myotonic dystrophy. Duchenne's muscular dystrophy (DMD) is an X-linked recessive condition affecting 1 in 3500 male births [55]. The onset of symptoms is usually around the age of 4 years, with delayed motor milestones, proximal muscle weakness, and Gower's sign. Pseudohypertrophy of the calves is common. During the teenage years, immobility is followed by development of skeletal deformities such as scoliosis. Respiratory failure often results, since the intercostal muscles are affected. Cardiomyopathy is also common. Patients with DMD may require anesthesia for treatment of scoliosis or relief of contractures. The preoperative assessment should include thorough evaluation of respiratory function and any cardiac rhythm abnormality.

The main concerns during anesthesia are the use of muscle relaxants and post-operative respiratory dysfunction. There are many reports in the literature of cardiac arrest in patients with DMD undergoing anesthesia, often in patients who were not suspected preoperatively of having any muscle disease [56,57]. There have also been reports of perioperative rhabdomyolysis [58,59]. The cardiac arrest is frequently due to hyperkalemia. Masseter spasm is also commonly observed in patients with DMD. There is also a known association of DMD with malignant hyperthermia [60]. Thus, the use of succinylcholine and other malignant hyperthermia-triggering agents, including inhaled agents such as halothane, should be avoided in patients with DMD. Nondepolarizing agents, although their use is safe, should still be employed with caution. Vecuronium has been shown to have a variable effect in patients with DMD. Some patients have close to normal initial requirements, whereas others have increased sensitivity. However, all patients appear to show a prolonged recovery from vecuronium [61,62]. Similarly, a variable response has been seen with mivacurium, although increased sensitivity does not seem to correlate with preoperative clinical status [63]. Patients with DMD frequently have delayed gastric emptying [64], which may predispose them to regurgitation and aspiration.

Myotonic dystrophy is an autosomal dominant disorder with an incidence of approximately 1 in 8000. It has a male predominance, and its onset is in late adulthood. It is characterized by progressive muscle weakness, with difficulty initiating movements and delayed muscle relaxation. There is an association with frontal balding, cataracts, and cardiac conduction deficits [65]. The hazards of administering anesthetics in these patients mostly relate to the use of neuromuscular blocking agents. Succinylcholine can cause a prolonged contracture and has been reported to cause cardiac arrest [66]. Nondepolarizing neuromuscular blocking agents have been used, but reduced doses are required [67]. If muscle relaxation is required, the shorter-acting nondepolarizing drugs should be used, and anticholinesterase drugs should be avoided because they may precipitate an attack of myotonia [68]. Because the disease is intrinsic to muscle and does not involve the neuromuscular junction, muscle relaxation can be difficult to achieve during a myotonic crisis. Quinine and procainamide have been used to treat these myotonic crises [69].

The cardiac conduction abnormalities observed in patients with myotonic dystrophy mandate careful electrocardiographic monitoring. The temperature should also be closely monitored, since hypothermia and shivering may precipitate a myotonic crisis. An association between myotonic dystrophy and malignant hyperpyrexia has been suggested but not confirmed.

Pregnancy carries additional risks for patients with myotonia. The symptoms often worsen during pregnancy, and the parturient is at risk for obstetric complications such as premature labor and postpartum hemorrhage secondary to failure of the uterus to contract adequately [50]. Because of the problems associated with muscle relaxants, regional anesthesia is preferred. Magnesium should be avoided if possible, since it may worsen muscle weakness.

Spinal cord injury

The problems of spinal cord injury are divided between the acute phase and the management of more chronic states. Acute management of these injuries is complex. Injuries to the cervical cord are often associated with head injury. The depressed level of consciousness may require tracheal intubation. Respiratory insufficiency may also ensue, since intercostal muscle paralysis can decrease alveolar ventilation by up to 60% [70]. Facial injury and a stomach full of blood may make tracheal intubation a challenge, especially in the presence of cervical spine immobilization [71]. Fiberoptic laryngoscopic tracheal intubation is probably the preferred technique in this situation [72], with the patient either awake with topical/regional anesthesia or under sedation. Great care should be taken during awake intubation or topical/regional anesthesia to avoid unnecessary neck movement. The respiratory system may also be

compromised by pulmonary edema, which can occur in up to 50% of cases of spinal cord injury [73]. The mechanism of pulmonary edema is probably an explosive autonomic discharge resulting in hypertension and bradycardia. This results in vasoconstriction and greatly increased cardiac afterload, precipitating frank left ventricular failure and pulmonary edema.

After this initial stage, a period of "spinal shock" may ensue as the sympathetic outflow is interrupted, resulting in a vasodilated and bradycardic patient. This is usually only significant for lesions above T4. Aggressive fluid resuscitation may further worsen pulmonary edema. Invasive hemodynamic monitoring is indicated for these patients, especially if multiple associated traumatic injuries are present. Respiratory and cardiovascular stability is essential for these patients, as hypotension and hypoxia may further worsen any spinal cord injury. Administration of high-dose methylprednisolone for cord resuscitation should be considered to minimize the extent of spinal cord injury [74]. However, there is increasing controversy regarding this practice. Attention must also be paid to temperature control, since these patients can become poikilothermic below the level of the spinal cord injury. Their inability to have effective temperature control appears to arise because of interruption of communication between peripheral temperature sensors and the hypothalamus and an inability to transmit a signal for the shivering and peripheral vasoconstriction reflexes.

If a patient survives the acute injury, the anesthesiologist may also be presented with a number of specific problems. Hyperkalemia and cardiac arrest have been described in paraplegic patients following administration of succinylcholine [75,76]. The mechanism is an increase in the number of postsynaptic receptors due to an up-regulation resulting from decreased exposure to acetylcholine [77]. Extrajunctional receptors also proliferate; these are of a more immature type, which has a prolonged channel-opening time, causing a greater degree of potassium efflux [66]. The onset of this hyperkalemic response occurs within a week of injury, and possibly sooner [78]. Although succinycholine is safe to administer within the first 24 h after injury, it is probably best avoided after 48 h postinjury. The period of time during which there is hypersensitivity to succinylcholine is undefined but is likely to be at least several months; hypersensitivity has been reported up to 6 months after injury [79].

An additional challenge in the management of the paraplegic patient is autonomic hyperreflexia. This is a syndrome of massive reflex sympathetic discharge that occurs in patients with spinal cord lesions above the major splanchnic outflow (T4–6). It is seen in 85% of patients with lesions above T6 and is unlikely in patients with spinal cord lesions below T10. The response is classically elicited by distension of a viscus, such as the bladder [80], but surgical stimulation can also elicit the response. Afferent impulses to the cord below the lesion cause a mass sympathetic response, resulting in vasoconstriction and hypertension. Baroreceptor reflexes result in bradycardia and vasodilatation above the lesion. The hypertension can result in cardiac ischemia and in cerebral and retinal hemorrhage. Thus, even if a patient is undergoing surgery below the level of the lesion, anesthesia is advised to prevent the occurrence of this pathologic reflex. Both general and regional anesthesia can be employed. The disadvantage of regional blockade is that the level of block can be difficult to evaluate. Autonomic hyperreflexia has even been described in patients undergoing extracorporeal shockwave lithotripsy for renal calculi, a common problem in patients with spinal cord injuries, despite the use of a spinal anesthetic [81]. An inadequate block may have been the culprit in these patients. Spinal or epidural opiates may also be administered to avoid the degree of sympathetic blockade associated with the use of local anesthetics. Epidural meperidine has been described for control of autonomic hyperreflexia in a paraplegic parturient [82]. Although cord injury above T6 results in painless labor, the uterine contractions may precipitate autonomic hyperreflexia. The paroxysms of hypertension and headache may be mistaken for preeclampsia, and regional blockade is indicated in this situation.

Critical illness polyneuropathy

With the introduction of intensive care units and the prolonged treatment of critically ill patients, a pattern of neuromuscular dysfunction has been recognized in patients whose initial disease was non-neurological. This disease has been termed critical illness polyneuropathy (CIP) and is characterized by muscle weakness, difficulty in weaning from mechanical ventilation, and prolonged rehabilitation [83]. Clinically the patient exhibits muscle atrophy and a flaccid tetraparesis. Reflexes are often reduced, but they may be normal in up to a third of patients [84]. Clinical examination may be unreliable in critically ill patients, and diagnosis is often by electrophysiological methods. This demonstrates features of fibrillation potentials and positive sharp waves consistent with an axonal polyneuropathy [85]. There also appears to be a predominance of motor nerve involvement [86]. The diagnosis also requires the exclusion of neurological causes of muscle weakness. Many potential factors have been implicated in this disorder, including long-term administration of neuromuscular blockers, malnutrition, hyperglycemia, and chronic use of steroids. However, none of these have

been definitely proven. There does seem to be an association between sepsis and CIP, and the mechanisms responsible for multiple organ failure in sepsis may be the same as those causing axonal degeneration [87]. The release of cytokines such as tumor necrosis factor, histamines, and arachidonic acid metabolites results in disturbed microvascular circulation, leading to endoneurial ischemia and nerve damage.

Administration of infusions of neuromuscular blockers to critically ill patients has been known to cause prolonged paralysis [88]. However, there are many coexistent factors, such as electrolyte disorders, use of aminoglycoside antibiotics, and renal failure leading to accumulation of active metabolites of vecuronium, which may also be contributory to the prolonged paralysis. There is a suggestion that the steroid-based neuromuscular blockers may cause more prolonged weakness. Patients in intensive care may have abnormal responses to neuromuscular blockers. Immobility itself can lead to an up-regulation of acetylcholine receptors, and this can lead to hyperkalemia and cardiac arrest after the administration of depolarizing neuromuscular blocking drugs [89]. By the same mechanism, relative resistance to the nondepolarizing neuromuscular blocking drugs can occur [90]. There is no known specific treatment for CIP other than supportive therapy. Care should be taken with positioning, to avoid undue pressure points and to avoid factors that may worsen nerve damage, such as hypoxia and hypotension. Sepsis should clearly be aggressively managed.

Guillain-Barré syndrome

Guillain Barré syndrome (GBS) is an acute inflammatory demyelinating polyradiculopathy that is the number one cause of acute neuromuscular weakness [91]. Often there is a history of preceding mild infection of the upper respiratory or gastrointestinal tract. Organisms commonly associated with GBS include *Campylobacter jejuni*, mycoplasma, Epstein-Barr virus, and cytomegalovirus. It has also been described to occur after epidural anesthesia [92]. The classic clinical presentation is one of ascending symmetrical motor weakness, which plateaus within 28 days. The course is self-limiting, generally with an excellent prognosis. There is often associated autonomic dysfunction and significant muscle pain. Diagnosis is by exclusion of other causes of weakness (such as myasthenia gravis) and nerve conduction studies, which reveal findings consistent with demyelination and superimposed axonal degeneration.

The treatment of GBS is mainly supportive, although plasmapheresis has been shown to be effective [93]. Intravenous immunoglobulin is also frequently administered. This may be superior to plasmapheresis, although the relapse rate is higher. Treatment with methylprednisolone has not been shown to be effective. Pain should also be aggressively treated, and nonsteroidal antiinflammatory drugs are useful in this regard. In addition, consideration should be given to utilizing low concentrations of local anesthetics administered via epidural or peripheral nerve catheters in an attempt to decrease pain without dramatically altering the clinical assessment of muscle strength.

Respiratory failure may ensue if the intercostal muscles are affected, and a number of criteria for tracheal intubation have been proposed, including tachycardia, tachypnea, vital capacity $< 15\,ml \cdot kg^{-1}$, and hypoxemia. Bulbar weakness with inability to protect the airway is also an indication for tracheal intubation. Because the time that respiratory support is required may be prolonged, low-pressure cuff endotracheal tubes should be used, with early consideration for tracheostomy. Additionally, thromboembolic prophylaxis, physical therapy, and nutrition should be aggressively addressed.

Patients with GBS may exhibit abnormal responses to neuromuscular blockers. The up-regulation of acetylcholine receptors leads to proliferation of extrajunctional receptors and a hyperkalemic response to succinylcholine, which has been reported to occur even after clinical resolution of symptoms [94]. Resistance to nondepolarizing drugs has also been demonstrated, although in this case the patient subsequently developed an increased sensitivity to vecuronium [95].

Summary

Neuromuscular disease covers a wide range of conditions, with anesthesia management being required either for problems relevant to the disorder or for comorbid conditions. The diseases often have specific problems that can usually be predicted from their pathophysiology. The anesthesiologist must ensure a thorough preoperative assessment, appropriate choice of anesthetic technique and neuromuscular blocking drugs, and careful monitoring of both hemodynamic parameters and the degree of neuromuscular blockade. With these considerations, the patient with neuromuscular disease, although challenging, can be given anesthetic care in a safe fashion.

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