Chapter 16
Neuromuscular Disease

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16.1 Introduction

The presence of neuromuscular disease is common in critical care, especially in the Neuroscience intensive care unit. Patients may present with acute, subacute, or chronic neuromuscular failure. Early identification, treatment, and management are the keys to preventing further complications. The field of neuromuscular disease encompasses a wide array of conditions that affect the upper and lower motor neurons. Etiologies include genetic, infectious, autoimmune and degenerative. The most severe cases may result in respiratory failure.

APCs play a crucial role in the management of patients with neuromuscular disease, from early diagnosis to recognition of decline and monitoring of treatment. This chapter begins with a discussion on the basics of neuromuscular respiratory failure

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and then details the most common neuromuscular diseases seen in the Neurocritical care unit.

16.2 Case Example

A 46-year-old female presents to the emergency department for evaluation of what she describes as "pins and needle" sensation starting in her toes and ascending to her mid-thigh. She states that the "pins and needles" sensation started 36 h ago. As the sensation progressed also noticed that she was tripping and having a hard time lifting her feet up. She explains that she feels like she is tripping over a rug when there is nothing beneath her. She is concerned that her symptoms are getting worse. Her past medical history if significant for hypothrydoism, for which she takes levothyroxine. She describes herself as "healthy." The patient does describe recent cold/flu like symptoms she experienced 10 days ago. She states that her symptoms went away on their own with rest and fluids.

Over a 2-h course in the emergency department, the patient lost 75% of her lower extremity strength and experienced drooling, dysarthria and double vision. She was intubated for airway protection given concern about her ability to appropriately clear secretions. Intubation was successful but large variations in her blood pressure were observed. This was likely secondary to autonomic dysfunction.

After stabilization, an EMG showed slow conduction velocities in motor nerves, representing demyelination and supporting a diagnosis of Guillain-Barre syndrome. The patient was started on IVIG immunotherapy at 0.4 g/kg daily for 5 days. Over the course of her ICU stay she developed complete paralysis. She received a second course of IVIG and gabapentin for dysautonomia and neuropathic pain secondary to nerve demyelination. Tracheostomy and percutaneous gastric tube were placed on ICU day 14 for long term mechanical ventilation and nutrition. After hemodynamic and airway stability were achieved, the

patient was transferred to an acute rehab facility where she was eventually weaned off the ventilator. She recovered the ability to walk and swallow over her 6-month rehabilitation. The patient re-gained much of her functional status and was able to return home with the help of her husband.

16.3 Initial Evaluation

16.3.1 Neuromuscular Respiratory Failure

Neuromuscular respiratory failure is a type of ventilatory failure caused by weakness of the respiratory muscles, followed by ineffective ventilation and subsequent hypercapnia. While some patients may become hypoxemic, it is important to emphasize that this phenomenon appears late in the course of the clinical event. Oropharyngeal muscle weakness can also lead to airway obstruction with secretions, increasing the risk of aspiration and pneumonia [1]. Neuromuscular respiratory failure in the neurocritical care unit can be caused by primary neuromuscular diseases, like Myasthenia gravis, Guillain-Barre syndrome or amyotrophic lateral sclerosis; or can be the result of critical illness neuromyopathy and deconditioning [5].

Signs and symptoms of neuromuscular respiratory failure include shortness of breath, staccato speech, restlessness, tachycardia, tachypnea, diaphoresis, accessory muscle use and paradoxical breathing (inward rather than outward movement of the abdomen during inspiration) [2]. Decreased level of arousal due to hypercarbia can be seen in advanced stages.

When diagnosing neuromuscular respiratory failure, a complete history of present illness should be taken into account. Details regarding the events leading up to presentation may be helpful to diagnose the underlying disease process causing the respiratory failure. A complete physical examination should be

Table 16.1 Pulmonary function test critical values

Parameter	Normal value	Critical value
Forced vital capacity (FVC)	40–70 mL/kg	20 mL/kg
Maximal inspiratory pressure (MIP)	Men: >−100 cmH_2O Women: >−70 cmH_2O	−30 cmH_2O
Maximal expiratory pressure (MEP)	Men: >200 cmH_2O Women: >140 cmH_2O	40 cmH_2O

Table adapted from Wijdicks et al. [8]. By permission of Mayo Foundation for Medical Education and Research

performed. Chest x-ray, arterial blood gas (ABG) and pulmonary function tests (PFT) are all helpful in classifying the type of respiratory failure [2]. Table 16.1 outlines general parameters and values for patients exhibiting signs of neuromuscular respiratory failure. Critical values can be remembered in the "20-30-40" sequence. It is important for the APC to use the information in the table below in conjunction with the patient assessment and ABG.

It is important to identify if the patient requires ventilatory assistance, which can be provided in the form of non-invasive ventilation using the Bilevel Positive Airway Pressure (BiPAP), or via orotracheal intubation and conventional invasive mechanical ventilation. BiPAP may be particularly helpful in patients in myasthenic crisis and may prevent an intubation. Patients with Guillain-Barre syndrome experiencing respiratory distress secondary to neuromuscular failure should undergo prompt endotracheal intubation and mechanical ventilation as BiPAP is contraindicated. Patients may require long-term respiratory management and tracheostomy [6].

The role of the APC is essential for the prevention and timely recognition of secondary complications such as infection, gastric ulcer and deep vein thrombosis. Aggressive pulmonary toileting, early and frequent mobilization and volume management should also be priorities in the management of these patients.

16.4 Interventions and Management

16.4.1 Guillain-Barre Syndrome

Guillain-Barre Syndrome (GBS) is an autoimmune, inflammatory disease causing peripheral nerve damage to the myelin sheath portion of the nerve cell (Fig. 16.1). The inflammatory damage interferes with nerve conduction. GBS often presents after a bacterial or viral illness, thought to be the precipitating event for the development of auto-antibodies. The incidence is slightly higher in men than women, and increases with age. There are a few variants to this disease, although in this chapter we will discuss the most common, generalized and demyelinating form (acute inflammatory demyelinating polyradiculoneuropathy) [4].

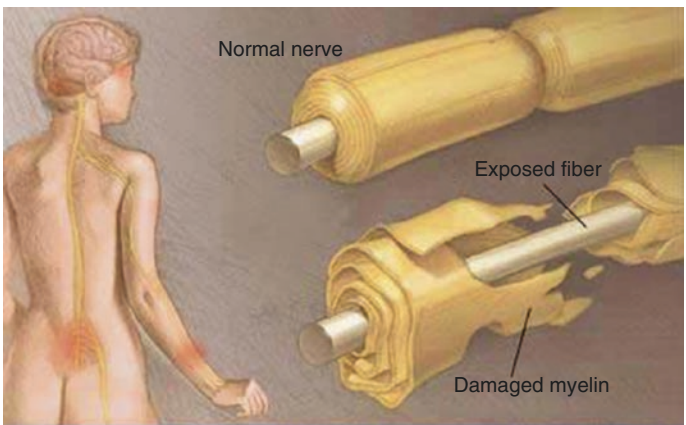

Fig. 16.1 Demyelination in nerve roots and peripheral nerves in Guillain-Barre Syndrome

16.4.1.1 Clinical Presentation

The most common clinical presentation consists of acute, symmetric, ascending weakness, sensory changes and decreased to complete absence of deep tendon reflexes. Initial symptoms often include paresthesias (or "pins and needles" sensation), especially in the feet and legs. Low back pain is also a frequent early complaint. Motor symptoms follow shortly after and subsequently predominate. As the disease progresses, the neuropathy can be mild, moderate, or severe.

Motor weakness is progressive, starting in the lower extremities and ascending to the hips and trunk followed by shoulders, arms and neck. Cranial nerves are frequently involved. Patients may develop ophthalmoparesis causing diplopia and bulbar muscle weakness (bilateral facial weakness, oropharyngeal muscle weakness) causing dysarthria and dysphagia. The degree of motor weakness may range from mild to complete (paralysis). The speed and severity of weakness are strong indicators of the risk of respiratory failure. Bulbar muscle weakness also predicts need for intubation and mechanical ventilation [4].

Respiratory failure requiring mechanical intubation occurs in one third of cases of GBS. Careful assessment and monitoring is needed to intervene when respiratory failure is imminent. Presence of paradoxical breathing pattern signifies diaphragmatic failure and should be considered a sign of impending neuromuscular respiratory failure. Bulbar muscle weakness may impair coughing and result in inability to manage secretions [7].

Autonomic dysfunction is another major manifestation of GBS. Patients may present with arrhythmias, dramatic swings in blood pressure (both hypotension and hypertension), ileus, bladder dysfunction and body temperature dysregulation.

16.4.1.2 Diagnosis

Initial evaluation consists of taking detailed history of present illness and conducting a thorough neurological examination. Patients may present anywhere on the symptom spectrum and may rapidly progress.

Nerve conduction studies (NCS) and electromyography (EMG) are helpful diagnostic tools that assess nerve conduction and degree of denervation. In the patient with the most typical form of GBS, acute inflammatory demyelinating polyradiculoneuropathy, NCS studies will show slowing of the motor nerve conduction velocity. The degree of slowing velocities in the motor nerves represents a good indicator of the severity of the demyelination. Some patients have more severe axonal form of GBS and those cases show decreased amplitude of the motor nerve action potentials. NCS/EMG is helpful in initial diagnosis and may be helpful to repeat later in the disease course to gauge the peak severity of the disease and monitor recovery [2].

Cerebrospinal fluid (CSF) should be obtained via lumbar puncture. Most often, CSF will have an elevated concentration of protein but normal cell count.

Baseline and serial pulmonary function tests (PFTs) should be obtained to monitor the degree of weakness of respiratory muscles. PFTs are a reliable measure of weakness progression in GBS, but only when patients are appropriately coached before the testing. APCs should become familiar with the technique of PFTs to assist respiratory therapists during their performance.

16.4.1.3 Treatment

Management of GBS includes supportive care and administration of immunomodulatory therapies. Prevention and early

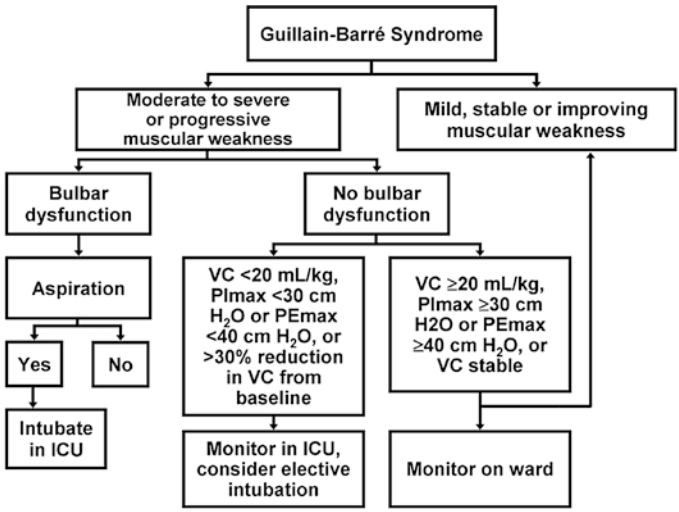

Fig. 16.2 Algorithm for respiratory management of Guillain-Barre Syndrome (Wiley-Blackwell, "The Practical Management of Guillain Barre Syndrome and myasthenic crisis" in *Emergency Management in Neurocritical Care.* Image used with permission from the Mayo Foundation for Medical Education and Research)

identification of secondary complications should always be a priority in the mind of the APC, in particular the recognition of early signs of respiratory failure. It is important for the APC to use critical thinking skills when monitoring for respiratory failure. Not all patients need mechanical ventilation. A general rule is that the GBS patient should be intubated if their forced vital capacity (FVC) falls below 15–20 ml/kg (Fig. 16.2). However, this rule does not apply to every patient and each case should be individually assessed considering all relevant factors (presence of bulbar weakness, dysautonomia, comorbid conditions, etc.) [4].

Patients should be closely monitored for breathing pattern and airway safety. It is worth emphasizing that pulse oximetry

may show acceptable saturation values even in the setting of severe muscle weakness, especially when the patient is receiving supplemental oxygen. Once the patient develops signs of respiratory failure or airway compromise, orotracheal intubation is indicated without delay. Non-invasive ventilation is not safe in patients with severe GBS. Tracheostomy may be necessary for long-term respiratory management.

Dysautonomia is common in GBS. Patients should be monitored on cardiac telemetry for bradycardia and tachyarrhythmias. Blood pressure variations may be sudden and profound. Hypertension should be treated cautiously. Short acting agents such as captopril and hydralazine should be first line medications. Beta-blockers are not preferred as they may cause prolonged hypotension and bradycardia with pauses. Hypotension should be managed conservatively with the use of positioning changes and volume expanders. These interventions are recommended to prevent large blood pressure variations. The APC must be cautions when performing nasotracheal and endotracheal suctioning, as it may induce a vagal response causing hypotension and bradycardia.

Patients with GBS often need enteral nutrition due to dysphagia. Placement of a nasogastric tube may be necessary to reduce the risk of aspiration and to meet caloric requirements. Gastroparesis and ileus are commonly caused by dysautonomia. Patients may require intermittent nasogastric suctioning if high gastric residuals are present or ileus develops. Stool softeners should be administered routinely as constipation is common with decreased gastrointestinal motility.

Neuropathic pain in GBS may be mild to severe, requiring opioid medications and frequent repositioning to keep the patient comfortable. However, it is necessary to keep in mind that opioids can worsen ileus and therefore must be used sparingly in patients with GBS. Gabapentin and other antineuropathic pain medications can be helpful to patients who are experiencing neuropathic pain.

GBS is an autoimmune, inflammatory disease and treatment with immunomodulatory therapies has been proven to be effective in accelerating the recovery from the disease. Available options are intravenous immunoglobulin (IVIG) and plasma exchange (PLEX). Both are equally effective in treating the disease.

IVIG is often the first line treatment because it does not require a central venous line and can be given peripherally. Proposed mechanisms of action include inhibition of activated complement and favorable modification of cytokine patterns. Treatment dose is 0.4 g/kg daily for 5 days initially, although repeated courses may be necessary. Side effects include headache (sometimes with meningeal signs), transfusion reactions, and increased risk of acute kidney injury and thrombotic events [4].

PLEX consists of removing large volumes of plasma from the circulation in exchange for replacement fluid with the objective of eliminating inflammatory mediators. PLEX requires a central venous line. The typical regimen is exchanging 1.5–2 plasma volumes per treatment session and to pursue five treatments alternating every other day. More treatments may be needed and efficacy is best if initiated early in the disease course and symptom onset. Complications from PLEX are mostly related to the placement of the central venous catheter. There is also the possibility of hypotension while pulling fluid from a patient who may have labile blood pressures. If the patient's blood pressure is unstable, PLEX needs to be initiated cautiously [4].

16.5 Myasthenia Gravis

Myasthenia Gravis (MG) is an autoimmune neuromuscular condition caused by autoantibodies that interfere with normal neuromuscular synaptic transmission. The antibody attaches to the

post-synaptic acetylcholine receptor, thus decreasing the amount of acetylcholine able to bind those receptors. This reduces the strength of muscle contraction and is responsible for the characteristic fatigability with repeated effort.

MG can remain restricted to the ocular muscles (Ocular Myasthenia), but most commonly affects all muscle groups (Generalized Myasthenia). Respiratory failure caused by MG is known as Myasthenic Crisis [4].

16.5.1 Clinical Presentation

The most defining symptom of MG is muscle fatigability, which is weakness that becomes progressively worse over periods of activity followed by recovery with rest. Signs and symptoms of MG, or an exacerbation of known MG, may occur after a recent illness or medication change. This fluctuating weakness often worsens in the afternoon and evening causing ptosis, diplopia and a nasal speaking voice.

Unlike GBS, patients with MG do not typically have any sensory symptoms as the disease affects the neuromuscular junction. Also in contrast with GBS, deep tendon reflexes are normal or only slightly decreased in MG [4].

16.5.2 Diagnosis

Presentation of MG can be distinct and specific, allowing for a purely clinical diagnosis. Response to medications that enhance acetylcholine transmission may confirm the diagnosis. Yet, the diagnosis is typically supported by serological and electrophysiological data.

NCS in patients with MG may display a decrease in the compound muscle action potential (CMAP) of at least 10% from the first to the fourth stimulus upon repetitive stimulation at a rate

of 2–5 Hz before and after isometric voluntary contraction. Findings on single-fiber EMG may show neuromuscular dysfunction in the form of jittering.

Acetylcholine receptor antibodies should be tested first because they are the most common (nearly 80% of patients with generalized MG have these antibodies). When acetylcholine receptor antibodies are not detected, it is advisable to check for antibodies against muscle-specific receptor tyrosine kinase (MuSk), which may produce MG with greater involvement of bulbar and respiratory muscles. Patients with a new diagnosis of MG should have a chest CT to evaluate the thymus for abnormalities (hyperplasia is common, but thymoma is also possible).

PFT should be used to assess for respiratory failure. PFT may not be as helpful in patients with MG experiencing bulbar weakness as they may not have the ability to create an appropriate seal on the mouth of the spirometer. Also, the fluctuating nature of the weakness may result in varying results with this testing [4].

16.5.3 Treatment

Treatment of MG in the ICU consists of providing respiratory support when necessary and administering immunomodulatory and anti-inflammatory therapies, immunosuppressant and cholinesterase inhibitors. A proposed algorithm is presented in Fig. 16.3.

Non-invasive ventilation may be invaluable in patients with severe myasthenic exacerbation and early myasthenic crisis. When initiated early – particularly before the development of hypercapnia – non-invasive ventilation with BiPAP may avert orotracheal intubation and substantially reduce the length of stay in the ICU. Most patients with MG tolerate BiPAP well, even if respiratory secretions are increased. In fact, the risk of

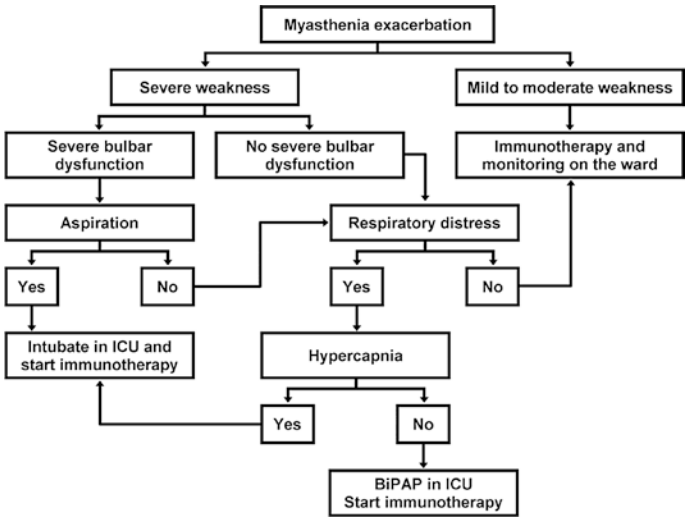

Fig. 16.3 Algorithm for the early management of myasthenia gravis exacerbation (Wiley-Blackwell, "The Practical Management of Guillain Barre Syndrome and myasthenic crisis" in *Emergency Management in Neurocritical Care*. Image used with permission from the Mayo Foundation for Medical Education and Research)

pneumonia is greater in patients treated directly with intubation and invasive mechanical ventilation compared with patients started on non-invasive ventilation [6].

IVIG or PLEX may be used to treat myasthenic exacerbations and myasthenic crisis. There is no evidence that one treatment is superior to the other. IVIG should be dosed 0.4 g/kg and administered for 5 days. The course may be lengthened if necessary. PLEX treatment should be administered every other day for five treatments.

Oral or IV steroids should be used in the patient with MG to reduce the inflammatory response. Steroids should be started with caution as they can produce weakness per se before

improving the myasthenia. Thus, the starting dose varies according to the patient's condition. When patients are already on steroids before hospitalization, the dose should not be reduced unless complications attributed to steroids are identified. For long-term maintenance, steroids may be partially or completely replaced by immunosuppressants (steroid-sparing agents) with better side-effect profile, such as azathioprine or mycophenolate mofetil.

An acetylcholinesterase inhibitor, typically pyridostigmine, should be part of the regimen for any symptomatic patient with MG. The purpose of this medication is to increase the amount of acetylcholine available at the level of the neuromuscular synaptic terminal by reducing its degradation. Thus, it represents a symptomatic treatment that complements the immune therapies aimed at correcting the underlying pathophysiology. Yet, it is crucial to use a sufficient dose of pyridostigmine when trying to avoid intubation in patients being treated with non-invasive ventilation and to liberate patients from invasive mechanical ventilation. Side effects include cramps, fasciculations, diarrhea, increase in respiratory secretions and bradycardia. Increased respiratory secretions be problematic in myasthenics with weak cough. The usual dose can range from 60 to 90 mg three to five times a day, but higher doses may be necessary in the most severe cases.

Thymectomy, surgical removal of the thymus, may be necessary in patients with thymoma or thymus hyperplasia. Thymectomy is indicated in the first year after symptoms and diagnosis [4].

16.6 Critical Illness Neuromyopathy

Critical Illness Neuromyopathy (CINM) is a term used to encompass polyneuropathy and myopathy acquired throughout

the course of a critical illness. It is also referred by the term ICU-acquired weakness. Patients with CINM may experience a wide variety of symptoms such as muscle weakness, atrophy and neuromuscular respiratory failure. The diagnosis of CINM is primarily clinical. Characteristically it is seen after septic shock complicated with multi-organ failure and resultant prolonged mechanical ventilation. However, it may occur after any critical illness and may develop within days of the ICU admission. It is most often recognized when patients are no longer receiving continuous sedation and cannot be weaned from mechanical ventilation. NCS and EMG may be helpful to confirm the diagnosis and exclude other causes of neuromuscular weakness. However, these electrophysiological studies may be confounded by peripheral edema, cold limbs, or inability of the patient to cooperate with the examination (e.g. when the patient is not awake enough to try to contract the muscles when instructed to do so during the needle examination). The term CINM has been favored to name this condition because there is often a coexistent involvement of peripheral nerves (critical illness polyneuropathy) and muscles (critical illness myopathy) in this disorder [3].

Critical Illness polyneuropathy affects the nerves and may cause axonal degeneration. Weakness is usually generalized affecting the body symmetrically. Respiratory muscle and core weakness are often affected which can lead to prolonged mechanical ventilation. NCS typically show reduced amplitude of motor/sensory nerve action potentials. EMG may show denervation.

Critical illness myopathy is characterized by myosin loss on biopsy specimens. Yet, muscle mass may decrease during critical illness due to inadequate nutrition and decreased mobility. On NCS nerve conduction velocity may be normal or minimally reduced, amplitude may be reduced and duration of compound muscle action potentials may be increased. Electromyography can confirm the diagnosis by showing spontaneous electrical

activity when the needle electrode penetrates the affected muscles.

16.6.1 Treatment/Prevention

There is no specific treatment for CINM. Thus, the best strategy is prevention. Early mobilization of patients in the ICU has been shown to reduce deconditioning and ICU-acquired weakness. Sedation holidays with spontaneous breathing trials have been shown to be helpful. Prolonged used of paralytic medications should be avoided when possible. Treating severe hyperglycemia may be helpful in avoiding nerve damage [3].

Summary Points

- Respiratory failure may be a result of primary neuromuscular diseases such as Myasthenia gravis, Guillain-Barre syndrome or amyotrophic lateral sclerosis; or it may occur after the development of weakness in the ICU (critical illness neuromyopathy and deconditioning).
- The APC should identify if the patient requires ventilatory assistance, which can be provided in the form of non-invasive ventilation using the BiPAP mask or via orotracheal intubation and conventional invasive mechanical ventilation.
- BiPAP is most beneficial in patients with myasthenic crisis and may prevent an intubation. Patients with Guillain-Barre syndrome should not be initiated on BiPAP and instead mechanically ventilated if respiratory failure is evident.

- Guillain-Barre Syndrome (GBS) is an autoimmune, inflammatory disease causing peripheral nerve damage to the myelin sheath portion of the nerve cell.
- Management of GBS includes supportive care, such as intubation and administration of immunomodulatory therapies.
- Myasthenia Gravis (MG) is an autoimmune neuromuscular condition caused by autoantibodies that interfere with the normal neuromuscular synaptic transmission.
- Treatment of MG in the ICU consists of providing respiratory support when necessary and administering immunomodulatory and anti-inflammatory therapies, immunosuppressant and cholinesterase inhibitors.

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