

Neurologic Complications of Critical Illness: Part II. Polyneuropathies and Myopathies

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ABSTRACT

Objective: To review the metabolic encephalopathies and neuromuscular abnormalities commonly found in the critically ill patient in a two-part presentation.

Data sources: A review of articles reported from 1980 to 2002 and identified through a MEDLINE search on metabolic encephalopathy, polyneuropathy and myopathy in critical illness.

Summary of review: Severe weakness in the critically ill patient may have many causes, although Guillain-Barré syndrome, critical illness polyneuropathy and critical illness myopathy are the motor disorders commonly found in the critically ill patient. Guillain-Barré syndrome is characterised by an acute ascending weakness 1 - 3 weeks after a gastrointestinal or upper respiratory tract infection. Intravenous immune globulin (or plasmapheresis) should be initiated as soon as possible to shorten the duration of ventilation, time to walk unaided and halt the progression of the disease.

Critical illness polyneuropathy and critical illness myopathy often coexist in the critically ill patient and are probably caused by a small number of activated leucocytes that infiltrate skeletal muscle and produce pro and anti-inflammatory cytokines. Axonal degeneration of both motor and sensory fibres with preservation of the myelin sheath causes the neuropathy, and muscle fibre necrosis and atrophy cause the myopathy. Apart from treatment of the underlying cause (e.g sepsis), there is no specific treatment, although a 44% reduction in the incidence of critical illness polyneuropathy has been described in mechanically ventilated critically ill patients who received intensive insulin therapy to maintain the blood glucose level between 4.4 – 6.1 mmol/L. Recovery usually occurs over weeks to months depending on the severity of the disease.

Conclusions: An acute motor weaknesses in the critically ill patient may be caused by Guillain-Barré syndrome, critical illness polyneuropathy or critical illness myopathy. Patients with severe Guillain-Barré syndrome should be managed in an intensive care unit and given intravenous immune globulin. Treatment of critical illness polyneuropathy or myopathy requires largely management of the underlying disorder. (*Critical Care and Resuscitation* 2002; 4: 133-140)

Key words: Polyneuropathy, Guillain-Barré syndrome, critical illness polyneuropathy, critical illness myopathy

GUILLAIN-BARRÉ SYNDROME

This is a disease of unknown aetiology characterised by an acute ascending weakness caused by a predominantly motor polyneuropathy. The polyneuropathy is thought to be due to a humoral or cell-mediated auto-immune mechanism triggered by a wide variety of foreign antigens, which results in a lymphocytic and macrophage infiltration of the myelin sheaths and segmental demyelination along the peripheral nerve axis.¹⁻³ While myelin destruction predominates, in

severe cases axonal disruption and degeneration occurs (i.e. acute motor axonal neuropathy).

Recent neurophysiological and pathological studies have led to a reclassification of the diseases that underlie Guillain-Barré syndrome into acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor and sensory axonal neuropathy (AMSAN) and acute motor axonal neuropathy (AMAN). The acute motor axonal neuropathy (AMAN) involves largely motor nerve fibers with a physiologic pattern suggesting

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axonal damage, whereas the acute inflammatory demyelinating polyneuropathy (AIDP) involves both motor and sensory nerve fibers with a physiologic pattern suggesting demyelination.⁴ AMAN and AMSAN are part of a spectrum of a single type of immune attack on the axon as they share a common immunological profile.⁵ The Miller-Fisher syndrome of ophthalmoplegia, ataxia and areflexia⁶ and a predominantly sensory form⁷ are the most striking variants of the Guillain-Barré syndrome with the few cases studied indicating that they are largely an AIDP.

Significant antecedent disorders include *Campylobacter jejuni* (4-66%), cytomegalovirus (5-15%), Epstein-Barr virus (2-10%), and *Mycoplasma pneumoniae* (1-5%) infections. These infections are not uniquely associated with any clinical subtype but severe axonal degeneration is more common following *Campylobacter jejuni* infection and a severe sensory impairment usually follows a cytomegalovirus infection.⁸ Patients with Guillain-Barré syndrome associated with *Campylobacter jejuni*, usually have a 1 - 3 week preceding history of a gastrointestinal disorder (e.g. diarrhoea) and often have a more severe form of polyneuropathy (e.g. axonal degeneration) with a slower recovery and a poorer outcome.⁹⁻¹¹

Strong evidence supports an important role for antibodies to gangliosides in the pathogenesis. Ganglioside-like epitopes exist in the bacterial wall of *Campylobacter jejuni* which are recognised by B lymphocytes. These produce antibodies that cross-react with a GM1 ganglioside present on peripheral nerve myelin in patients with Guillain-Barré syndrome but not in those patients who have an uncomplicated enteritis. Infection by other organisms (e.g. cytomegalovirus, Epstein-Barr virus, *Mycoplasma pneumoniae*) may also trigger a similar antibody response. The different patterns of Guillain-Barré syndrome are probably due to the diverse interplay between antibodies and T cells of differing specificities.⁸ In the Miller-Fisher syndrome the anti-ganglioside antibodies produce a neuromuscular block.¹²

The Guillain-Barré syndrome may also be precipitated by mumps, herpes simplex virus, hepatitis A virus, or HIV infections.¹³ Other diseases and preceding events include systemic lupus erythematosus (SLE), vaccinations, lymphoma, surgery and pregnancy.

Clinical features

The symptoms include a bilateral ascending motor paralysis ranging from a minimal weakness of legs (i.e. 'rubbery' legs) to a total paralysis. Paraesthesias (e.g. tingling and numbness) of fingers, toes and mouth, occur in 75% and limb pain in 25%; occasionally constipation

and urinary retention occur. A mild respiratory or gastrointestinal infection precedes the weakness by 1 - 3 weeks in 50% of patients. The weakness usually ceases to progress by two weeks in 50%, by 3 weeks in 80% and by 4 weeks in 90% of patients. Recovery usually begins 2 - 4 weeks after the progression stops. The signs include:

Skeletal muscle effects. Signs involving skeletal muscles include, hypo- or areflexia, hypotonia, and reduction in muscle power ranging from minimal leg weakness to a total paralysis of all four limbs, trunk, bulbar muscles, facial muscles and external ophthalmoplegia. Cranial nerve involvement occurs in 50%, causing bulbar weakness and difficulty in swallowing. In 5% of cases the disease begins in the cranial nerves. In unusually severe cases the patient may have complete paralysis of motor functions of the cranial nerves.¹⁴ In up to 30% respiratory failure develops requiring mechanical ventilation.¹⁵ Skeletal muscle wasting is also prevalent with prolonged disease.

Autonomic effects. Autonomic disturbances are observed in 20%, presenting as episodic hypotension, hypertension, tachycardia, bradycardia, arrhythmias (even ventricular fibrillation) and ECG abnormalities of the T wave and QT_c segments.¹⁶

Variants. Clinical variants of the classical syndrome include a temperature at the onset, severe sensory loss with muscle pain, progression beyond 4 weeks, extensor plantar responses and unreactive pupils. The Miller-Fisher syndrome (or Miller-Fisher variant of the Guillain-Barré syndrome) is characterised by the clinical triad of acute ophthalmoplegia, ataxia and areflexia in the absence of clinically important limb weakness.⁶ A predominantly sensory form of the acute inflammatory demyelinating polyradiculoneuropathy has also been described.⁷

The criteria for the diagnosis of Guillain-Barré syndrome¹⁷⁻¹⁹ are listed in Table 1. The differential diagnoses are listed in Table 2.

Investigations

The investigations include:

Lumbar puncture. The cerebrospinal fluid (CSF) protein may be normal for 7 - 10 days following the onset of motor symptoms; thus a lumbar puncture may be necessary at both 7 and 14 days to record the protein rise which may increase up to 15 g/L. The CSF cell count is no greater than 4 polymorphs/mL, with a differential no greater than 50% monocytes, unless an HIV infection is present.

Table 1. Criteria for the diagnosis of Guillain-Barré syndrome*Features required for the diagnosis*

- Progressive motor weakness of more than one limb (excluding Miller-Fisher syndrome)
- Areflexia
- Disease course less than 4 weeks
- There should be no evidence of:
 - hexacarbon abuse, organophosphate poisoning, severe hypophosphataemia, diphtheria, polio, botulism, Japanese encephalitis virus, vasculitis, localised spinal cord lesion, porphyria, lead intoxication

Features strongly supportive of the diagnosis

- Relative symmetry
- Mild sensory signs or symptoms
- Facial nerve or other cranial nerve involvement
- Initial absence of fever
- Acellular CSF and elevation of CSF protein 1 week after onset of motor symptoms
- Electrophysiological evidence of demyelination.

* CSF = Cerebrospinal fluid

Electromyogram. Nerve conduction studies can determine whether or not there is a neuronal disorder and an electromyogram will distinguish between a demyelinating disorder and an axonal degeneration (although both may occur with severe form of Guillain-Barré syndrome).

Identification of a cause. While *Campylobacter*, cytomegalovirus, Epstein-Barr virus, mumps, herpes simplex virus, hepatitis A virus, or mycoplasma infections may precipitate Guillain-Barré syndrome, therapies directed against these agents have not been shown to be of benefit, and therefore their culture or serology are often not performed. Serology to detect HIV antibody may be performed in all 'at risk' patients. Investigation to exclude SLE, hexacarbon abuse, porphyria, diphtheria, polio, Japanese encephalitis virus, botulism, organophosphate poisoning, lead intoxication and severe electrolyte disturbance (e.g. hypokalaemia, hyperkalaemia, hypermagnesaemia, hypophosphataemia) are performed. A nerve biopsy is usually only required if a chronic relapsing polyneuropathy is suspected.

Treatment

Monitoring in an intensive care unit is required, as up to 30% of patients with Guillain-Barré syndrome require mechanical ventilation (increasing in patients who have rapid disease progression).²⁰ Endotracheal intubation or tracheostomy are performed if the vital

capacity is less than 800 - 1000 mL, a bulbar palsy is present or the patient is unable to cough and clear respiratory secretions.

Immunotherapy (intravenous immune globulin or plasmapheresis) should be initiated as soon as possible as it is no longer effective if initiated 2 or more weeks after the onset of motor symptoms. Gamma globulin is recommended (in the absence of contraindications) rather than plasmapheresis for patients with severe Guillain-Barré syndrome (e.g. those who are unable to walk > 5 m unaided), on the grounds of equivalent efficacy, similar cost, greater convenience, and ease of administration.^{21,22}

Gamma globulin

Daily infusion of pooled gamma globulin (0.4 g/kg/day) for five days (i.e. total dose of 2.0 g/kg over 5 days), if given within the first two weeks of the onset of the disease, is as effective as plasma exchange,²³ although one study reported high rates of relapse or progression.²⁴ Complications associated with intravenous gamma globulin occur in up to 5% of patients (particularly in those who have a selective IgA deficiency) and include flushing, fever, rigors, cough, chest pain, urticaria, anaphylaxis, seizures, aseptic meningitis and acute renal failure.²⁵

A randomised multicenter trial of 383 adult patients with Guillain-Barré syndrome comparing plasmapheresis, immunoglobulin and combined treatments (i.e. plasmapheresis followed by gamma globulin) during the first two weeks after onset of neuropathic symptoms found that plasmapheresis and immunoglobulin had equivalent efficacy and that the combined treatment did not confer a clinically significant advantage when compared to either plasmapheresis or gamma globulin alone.^{22,26} However, as there was a trend towards faster recovery of unaided walking in a subgroup in one study (i.e. those with complete neurophysiological data),²⁶ one review recommended combined therapy (e.g. plasmapheresis followed by gamma globulin) for severely ill patients.²⁷

A second course of immunoglobulin (i.e. 0.4 g/kg/day for 5 days) has been reported to be beneficial in patients in whom there was a continued deterioration or no response after 14 - 21 days to therapy.²⁸

Plasmapheresis

Plasmapheresis is recommended for all patients with severe Guillain-Barré syndrome (e.g. those who are unable to walk 5 m unaided) in whom gamma globulin is contraindicated. It must be performed early in the course of the disease (i.e., within 2 weeks of the onset of symptoms) and before ventilation is required, because treatment started after ventilation, is often less

effective.^{17,29} Plasmapheresis shortens the duration of ventilation (from 48 - 24 days) and the time to walk unaided (from 85 - 53 days).^{17,30} It may also halt the progression of the disease.³¹

Five plasma exchanges are performed on alternate days (in one large study four exchanges conferred greater benefit compared with two exchanges but six exchanges conferred no greater benefit compared with four exchanges).³² On each occasion 40 - 50 mL/kg of plasma are removed and replaced, half by 0.9% saline and half by a 5% albumin in 0.9% saline solution. The replacement regimen using albumin is as effective as a regimen using fresh frozen plasma and has been found to have fewer undesirable side effects.^{31,33} The complications associated with plasma exchange include, replacement fluid problems (e.g. hypervolaemia, hypovolaemia, anaphylaxis), venous access problems (e.g. bleeding, infection, pneumothorax) and hypoglobulinaemia problems (e.g. increasing the risk of infection, a bleeding diathesis, and a reduction in pseudocholinesterase).³⁴

Pain relief

Moderate to severe pain is a common and early symptom in up to 80% of patients.³⁵ It includes paraesthesia, dysaesthesia, axial and radicular pain, myalgia, meningism, joint pain and visceral discomfort.³⁶ Correct positioning and splinting of paralysed limbs can alleviate muscle and joint pains, and mattresses and pads to reduce trauma to pressure areas may also be helpful.^{36,37} Neuritic pain may respond to paracetamol, carbamazepine (200 mg 8-hourly),³⁸ tricyclic antidepressants (amitriptyline 75 mg at night), topical capsaicin (0.075% 6-hourly - particularly for superficial burning pain),³⁹ or quinine sulphate,⁴⁰ although the 'restless leg syndrome' and severe limb pain which is often severe during the resolution of the disease often requires oral, parenteral or epidural opiate analgesia (i.e. methadone 10 mg-6-hourly, morphine 1-4 mg i.v. hourly, or epidural morphine 2 mg nocte⁴¹) to provide relief.^{35,36} Gabapentin, from 900 mg to 3600 mg daily, has also been used successfully for neuritic pain.⁴²

General care of an unconscious patient

Physiotherapy for passive leg movement, splinting of ankles and wrists to prevent contractures, eye, mouth and pressure point care, fluid, electrolyte and nutritional care, prophylaxis for pulmonary embolism and acute stress ulceration, skilled nursing to counter depression and an inability to effectively communicate, are also required.^{43,44}

Other therapy

Up to 40% of patients treated with immunotherapy

show no clear improvement, thus other therapies have been proposed, including;

Interferon-β. Interferon-β 1a (6 mIU subcutaneously on alternate days for 16 days) has been reported to be successful in the management of a patient unresponsive to plasma exchange.⁴⁵

CSF Filtration. In one prospective controlled clinical trial of 37 patients with Guillain-Barré syndrome daily cerebrospinal fluid filtration (30 - 50 mL of CSF filtered and replaced 5 to 6 times through a sterile filter designed to remove cells, bacteria, endotoxins, immunoglobulins and inflammatory mediators) for 5 - 15 consecutive days was as effective as plasmapheresis.⁴⁶

Corticosteroids. Corticosteroids are of no benefit in patients with uncomplicated Guillain-Barré syndrome.⁴⁷ They may also cause recovery to be slower and the beneficial effect of plasma exchange may be negated.⁴⁸ However, corticosteroids and immunosuppressants in association with plasmapheresis may be of benefit in the 3% of patients who progress to a chronic relapsing polyneuropathy.^{11,31,48} In a recent open study of 25 patients with Guillain-Barré syndrome, an infusion of pooled gamma globulin (0.4 g/kg/day) and 0.5 g methylprednisolone intravenously daily for five days, resulted in a greater improvement after 4 weeks when compared with the results from a previously reported group of 74 patients treated with pooled gamma globulin only.⁴⁹

Prognosis

For a patient who does not require ventilation, the prognosis for complete recovery is good. For patients who present with a diarrhoeal illness, are elderly (i.e. above 40 years), require ventilation and have axonal degeneration, neuronal recovery is generally slower and often incomplete.⁵⁰ In most series, 19 - 28% of patients have a persistent motor defect after 1 year.^{13,15,51} The mortality associated with Guillain-Barré syndrome, even in a major teaching hospital, is up to 10%, and is usually caused by a cardiac arrhythmia due to the associated autonomic defects,^{13,52} or uncontrolled sepsis.¹⁵

POLYNEUROPATHY AND MYOPATHY IN THE CRITICALLY ILL

The differential diagnosis of an ascending motor polyneuropathy in the critically ill patient (Table 2) includes central nervous system diseases, polyneuropathies (e.g. Guillain Barré syndrome, critical illness polyneuropathy, distal motor axonopathy), neuromuscular diseases (e.g. myasthenia gravis, Eaton-Lambert syndrome), dysregulation of acetylcholine receptors (e.g. characterised by succinylcholine hyperkalaemia associated with burns, etc), myopathies (e.g. critical

illness myopathy, neuromuscular junction blockers and corticosteroids in asthma, thyrotoxicosis, polymyositis), nutritional and electrolyte abnormalities (e.g. hypokalaemia, hypophosphataemia), ischaemic and reperfusion injuries and disuse and immobilisation atrophies.^{53,54}

Table 2. Differential diagnosis of an ascending motor polyneuropathy

Guillain Barré syndrome
Critical illness polyneuropathy
Myasthenia gravis, Eaton-Lambert syndrome
Chronic relapsing inflammatory polyneuropathy
Polymyositis, dermatomyositis
Motor neurone disease
Poliomyelitis, progressive post-poliomyelitis muscular atrophy
Japanese encephalitis virus infection
Botulism
Diphtheria
Tick paralysis
Rabies
Spinal cord disease
transverse myelitis, spinal tumour, anterior spinal artery syndrome, spinal arteriovenous malformation
Toxins
lead toxicity, hexacarbon abuse, organophosphate toxicity, cantharidin poisoning
Drugs
nitrofurantoin, perhexiline, dapsone
Pontine infarction
Central pontine myelinolysis
Acute porphyria
Electrolyte disturbances
hypermagnesaemia, hypophosphataemia hypokalaemia, hyperkalaemia

Critical illness polyneuropathy and myopathy often exist together in critically ill patients,⁵⁵ and are probably caused by a small number of activated leucocytes that infiltrate skeletal muscle and produce pro and anti-inflammatory cytokines.⁵⁶ Electromyography and nerve conduction studies are required to establish the diagnosis and to treat appropriately critically ill patients with motor dysfunction, whereas muscle biopsy is only needed to properly classify the disorder.⁵⁷ As a neuropathy and myopathy often coexist and as muscle biopsies are only required for diagnosis rather than for management, the motor dysfunction characteristic of the critically ill patient is sometimes known as critical illness polyneuropathy and myopathy (CIPNM). Some would even prefer to call both disorders critical illness

myopathy,⁵⁸ particularly as myopathic changes are more common than polyneuropathic changes.⁵⁹

Critical illness polyneuropathy

A motor polyneuropathy known as critical illness polyneuropathy (CIP) may occur in critically ill patients, causing a predominantly proximal muscle weakness with reduced tendon reflexes (although, unlike Guillain-Barré syndrome where the tendon reflexes are absent, in critical illness polyneuropathy the tendon reflexes are often preserved⁶⁰). The disorder is caused by an axonal degeneration of both motor and sensory fibres with preservation of the myelin sheath and no evidence of a neuronal lymphocytic infiltrate that can be seen with Guillain-Barré syndrome. The cerebrospinal fluid protein level is normal, and cranial nerve and autonomic functions are usually preserved; all of which distinguish the disorder from the Guillain Barré syndrome (the latter may also be precipitated by an acute illness).⁶¹⁻⁶³ Distal motor axonopathy is probably a variant of critical illness polyneuropathy. It has the clinical and electrophysiological features of a myopathy with the distal involvement of motor axons producing "myopathic" motor unit potentials.⁵⁵

Neuromuscular junction blockade in a critically ill patient may be caused by prolonged use of neuromuscular blockers, aminoglycosides, hypermagnesaemia, coexistent myasthenia gravis or Eaton-Lambert syndrome. These patients retain peripheral nerve sensation, and peripheral nerve stimulation studies may be used to confirm the presence of neuromuscular junction blockade, distinguishing them from critical illness polyneuropathy.⁶⁴

Critical illness polyneuropathy is diagnosed by electromyography and nerve conduction studies, in the absence of other causes (e.g. neurotoxic agents including metronidazole, perhexiline, vincristine and organophosphate poisoning and B₁₂ deficiency).⁶⁵⁻⁶⁷ The cause is unknown, although neurotoxic effects from prolonged elevation of proinflammatory cytokines (e.g. tumor necrosis factor- α , interleukin-1, interleukin-2 and interleukin-6), platelet activating factor, arachidonic acid, free oxygen radicals and proteases may play a role.⁶⁸

Apart from treatment of the underlying cause of sepsis, there is no specific treatment for the neuropathy (e.g. intravenous immunoglobulin does not alter the course of CIP c.f. Guillain-Barré syndrome⁶⁹). However, one study reported a 44% reduction in the incidence of CIP in mechanically ventilated critically ill patients who received intensive insulin therapy to maintain the blood glucose level between 4.4 – 6.1 mmol/L.⁷⁰

Recovery from critical illness polyneuropathy

usually occurs over weeks to months depending on the severity of the disease. In some patients (particularly those with a greater body weight loss, a long ICU stay and long duration of sepsis),⁷¹ the weakness may persist.

Critical illness myopathy

The acutely ill patient may develop an acquired myopathy due to an associated acute (e.g. trauma, alcoholic rhabdomyolysis, polymyositis, hypokalaemia, hypophosphataemia) or chronic (e.g. thyrotoxicosis, Cushing's disease) disease. However, a characteristic acute generalised myopathy (i.e. acute quadriplegic myopathy⁷² or acute necrotising myopathy⁷³) has also been described in critically ill patients particularly in the presence of two of the three following conditions:⁷⁴⁻⁷⁶

- 1) treatment with a nondepolarising neuromuscular blocking agent,
- 2) treatment with high dose glucocorticoids (e.g. acutely ill asthmatic patient) and
- 3) severe sepsis.

It is suggested that the elevation of skeletal glucocorticoid receptors produced by the denervation or sepsis in association with elevated levels of tumor necrosis factor- α , enhances skeletal muscle catabolism.⁷⁷ A muscle biopsy commonly shows muscle fiber atrophy that predominantly involves fast twitch fibres.^{77,78}

These patients retain peripheral nerve sensation, and peripheral nerve stimulation and nerve conduction studies distinguish them from polyneuropathy or neuromuscular junction syndromes. There is often an elevation of plasma creatine phosphokinase, particularly in patients with an acute necrotising myopathy. Electromyography will reveal diagnostic abnormal skeletal muscle potentials and muscle biopsy will reveal loss of thick myosin filaments and degrees of muscle fibre atrophy and necrosis. In critical illness, disuse (i.e. cachectic) myopathy also contributes to muscle wasting.⁵⁵

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