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Neuromuscular complications of sepsis

C.F. Bolton

University of Western Ontario, Victoria Hospital, London, Ontario, Canada

Abstract. Sepsis and multiple organ failure are major problems in medical and surgical intensive care units. Critical illness polyneuropathy occurs in 70% of these patients. Difficulty in weaning from the ventilator is an early sign. Electrophysiological studies are necessary to establish the diagnosis; these studies show an axonal degeneration of peripheral nerve fibres. Recovery occurs in weeks or months, depending upon severity. Muscle biopsy reveals denervation atrophy. Sepsis itself does not induce a neuromuscular transmission defect, but neuromuscular blocking agents may increase the severity of critical illness polyneuropathy. If steroids are used in addition to neuromuscular blocking agents, a severe myopathy may result. Other effects on muscle are cachectic myopathy and panfascicular muscle fibre necrosis. A variety of combinations of these conditions may affect the same patient. Only well-designed prospective studies will determine the true effect of these medications on the neuromuscular system in septic patients.

Introduction

The septic syndrome has been recently defined by Bone [1] as evidence of infection, increased respiratory rate, increased heart rate, elevated or reduced body temperature and evidence of multiple organ failure. It occurs in 20%–50% of patients in major medical or surgical critical care units [2] and is a common occurrence in the general wards or tertiary care hospitals. In the last 15 years, critical illness polyneuropathy has been defined [3–8] and has been shown to occur in 70% of patients with this syndrome [8]. The muscle, however, may also be involved [7, 8], possibly in more than one way. Moreover, there have recently been a number of reports which have implicated neuromuscular blocking agents and possibly steroids as being causes of neuropathy [9–14], myopathy [15–18] and prolonged neuromuscular blockade [19] in patients in critical care units. Neuromuscular blocking agents may be used in patients in critical care units to facilitate ventilation. Because of concern over extended paralysis seemingly induced by these agents, it has been recommended that their use be limited [20]. While this recommendation seems reasonable, it is my view that sepsis may play a more predominant role in the paralysis than is generally recognised. This paper will review methods of diagnosing and managing the complex neuromuscular conditions associated with sepsis.

Critical illness polyneuropathy

Critical illness polyneuropathy is associated with a typical series of events as sepsis affects the nervous system [21]. Within a matter of hours after onset of infection, an encephalopathy often develops which is diffuse and, at times, severe [22] (Fig. 1). As the sepsis is being successfully treated and the encephalopathy resolving, a difficulty in weaning from the ventilator is observed. Clinical signs of polyneuropathy may be absent in over half of the patients. If present, symptoms consist of varying degrees of weakness of the limbs and reduced or absent deep tendon reflexes. Sensory testing is relatively unreliable in these patients. Deep painful stimulation to a distal extremity, by pressing the nailbed, is a good method of observing the degree of clinical weakness. In polyneuropathy, with this manoeuvre, it will be noted that the limb movements are weak or absent, whereas there is strong facial grimacing. Prolonged neuromuscular blockade is often characterised by weakness of cranial as well as limb muscles, and therefore this manoeuvre may occasionally differentiate between polyneuropathy and neuromuscular blockade.

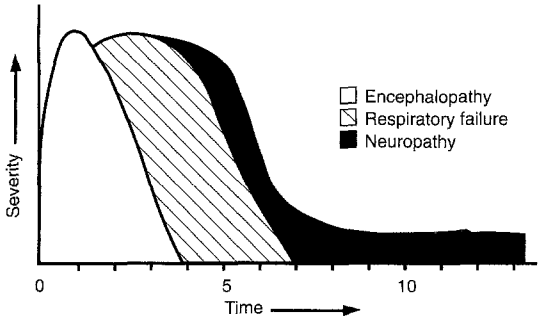

Fig. 1. The typical series of neurological complications after the onset of the septic syndrome. The time course may vary from weeks to months.

Clinical examination is often unreliable; electrophysiological studies must, therefore, be utilised to diagnose the polyneuropathy [23]. The first sign is a reduction in the muscle compound action potential amplitude which occurs within five days of axonal damage. After 1–3 weeks, fibrillation potentials and positive sharp waves appear in the muscle as signs of denervation. The motor unit potentials (if the patient is able to recruit them) may have a normal appearance or may be somewhat reduced in amplitude and polyphasic, suggesting an associated primary myopathy [7, 8]. The sensory compound action potential amplitude may be reduced or absent as a result of the polyneuropathy, or it may be reduced simply as the result of tissue oedema removing the recording surface electrode away from the underlying nerve. Near nerve recordings may disclose a very low amplitude potential of normal latency, consistent with a primary axonal degeneration of sensory fibres and, in general, electrophysiological findings point to a primary axonal degeneration of peripheral nerve fibres [5]. Morphological studies of peripheral nerve have confirmed this type of degeneration, and there is no evidence of inflammation, such as that which may occur in immune-mediated neuropathies [7]. Muscle biopsy shows scattered, atrophic fibres, typical of acute denervation, or grouped atrophy, typical of more long-standing denervation. In a few patients, there may be scattered necrosis of muscle fibres, suggesting an associated primary myopathy secondary to the sepsis [7].

The mechanism of critical illness polyneuropathy is not known. Witt et al. [8] conducted a prospective study of 43 patients to examinine a number of variables that might cause the polyneuropathy. A significant relationship to time in the critical care unit and levels of blood glucose and albumin was observed (Fig. 2), suggesting that polyneuropathy is directly related to the sepsis and multiple organ failure. We have speculated that a disturbance of the microcirculation to the peripheral nerve in the brain may be a basic mechanism [8, 21].

Because of the often associated denervation of muscle secondary to the critical illness polyneuropathy, it has been difficult to determine if the muscle is primarily involved. In a recent review [23] of muscle biopsies taken from 11 patients with sepsis, where the nature of the muscle weakness was not certain, it was found that varying degrees of denervation atrophy were the predominant change, with little evidence of muscle fibre necrosis. Despite this, we are still suspicious that the muscle is primarily involved, along with other organ systems, in the septic syndrome.

Difficulty in weaning from the ventilator has been a common manifestation of critical illness polyneuropathy. Of 29 patients studied in our unit who had difficulty in weaning from the ventilator that on a clinical basis appeared neuromuscular, 28 were found to have a neuromuscular problem. In addition to standard electrophysiological studies of peripheral nerve and muscle, we performed phrenic nerve conduction and needle electromyography of the diaphragm. The majority of these patients had critical illness polyneuropathy and a few others had evidence of neuromuscular transmission defect, primary myopathy and disorders of central drive due to an associated encephalopathy.

Neuromuscular transmission defects

During retrospective and prospective studies to characterise critical illness polyneuropathy, we performed repetitive nerve stimulation studies and found no evidence for a defect in neuromuscular transmission associated with sepsis [5, 7]. At those times, neuromuscular blocking agents to ease ventilation were uncommonly used and could not be implicated as causing polyneuropathy [8]. The experience of Coronel et al. [24] in France has been similar. In the last 5 years, neuromuscular blocking agents, particularly the shorter-acting ones such as vecuronium, have been used somewhat more frequently in our critical care unit, rarely for prolonged periods of time. We are now observing the occasional patient who has septic syndrome and suddenly develops weakness in the limbs, lasting more than several hours, after a single injection of a neuromuscular blocking agent. Repetitive nerve stimulation studies show the typical decremental response, indicating a neuromuscular transmission defect induced by the drug (Fig. 3). At initial testing in such a patient, the muscle compound action potential is quite low, indicating that in addition to the neuromuscular block, a polyneuropathy is also likely to be present. Denervation potentials then appear in muscle. This suggests that the main problem is critical illness polyneuropathy, with the neuromuscular blocking

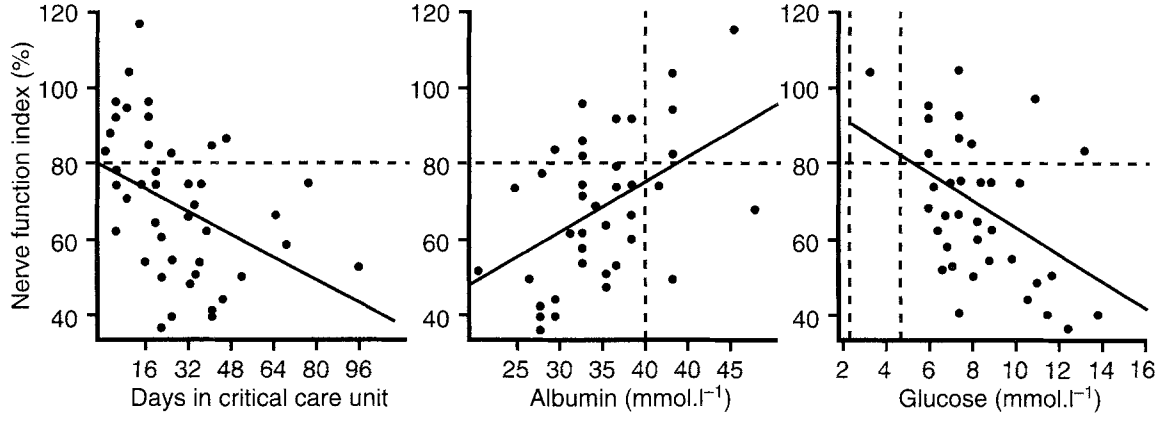

Fig. 2. Peripheral nerve function in 43 patients with the septic syndrome worsened with time in the critical care unit. Such function bore a negative relationship to the serum albumin, possibly secondary to vascular permeability, and a positive one to the blood glucose, possibly secondary to insulin resistance. These relationships are consistent with the polyneuropathy being secondary to the septic syndrome [8].

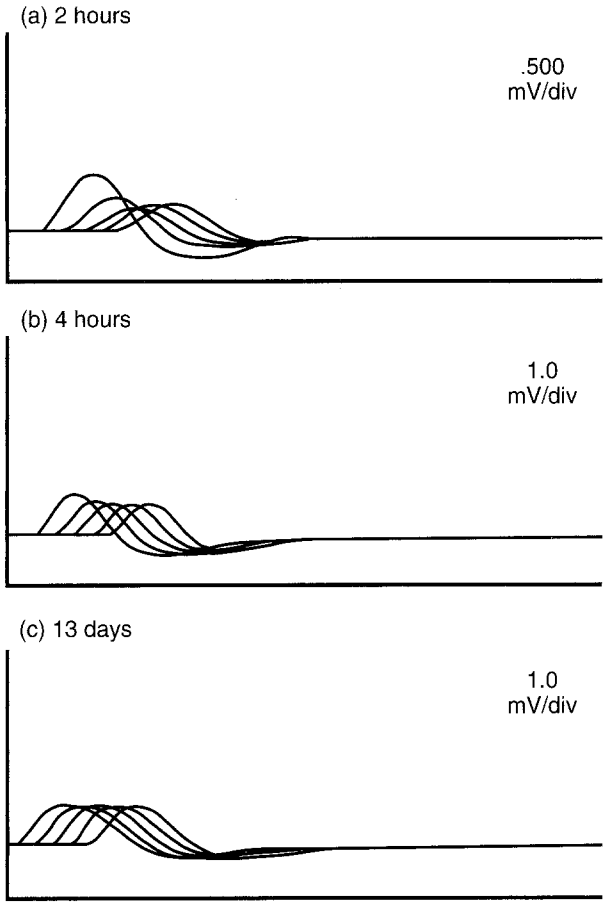

Fig. 3. Critical illness polyneuropathy plus neuromuscular blockade (vecuronium 10 mg i.v.). The patient had had the septic syndrome for six weeks, and weakness after a single injection of vecuronium seemed more severe and prolonged than expected. Repetitive median nerve stimulation with recording from the thenar muscle showed a decremental response, typical of vecuronium-induced block, except in the initial action potential which was quite low. Needle EMG at two and four hours showed EMG signs of denervation which had become more severe at 13 days, when the neuromuscular block had disappeared. We suspect critical illness polyneuropathy was the main cause of weakness in this patient and was probably present before vecuronium was used.

agent simply exacerbating the problem and bringing it to clinical attention.

We have also observed the occasional patient who has had severe, generalised muscular weakness induced by a combination of prolonged treatment with neuromuscular blocking agents and high-dose steroids for acute, severe asthma. Such patients, clinically and electrophysiologically, have findings of a primary myopathy. Sepsis could well be an important, underlying factor in these cases and in other cases reported in the literature.

Therefore, in our experience, and in regard to a number of reports in the literature, there have been two relatively distinct syndromes associated with the use of neuromuscular blocking agents in the critical care unit. Either vecuronium or pancuronium bromide have usually been implicated.

In the first of these [9–14], patients who have sepsis and multiple organ failure are given neuromuscular blocking agents for several days and after this medication is discontinued, the patient is noted to be quadriplegic. There are clinical and electrophysiological signs of a primary axonal degeneration of motor fibres with denervation atrophy of muscle. Repetitive nerve stimulation studies may or may not show a defect in neuromuscular transmission which, if present, is transient. There is elevation of creatinine phosphokinase to moderate or high levels, and muscle biopsy usually shows evidence of denervation and, at times, necrosis. Again, it is possible the predominant factor was sepsis and critical illness polyneuropathy; however, the neuromuscular blocking agent may have had an additive toxic effect.

The second syndrome is where a patient presents with acute, severe asthma that requires the use of high-dose steroids and neuromuscular blocking agents for several days [15–17]. When the patient is taken off these medications, it is noted that there is quadriplegia and difficulty in weaning from the ventilator. While some of the cases have suggested a motor neuropathy, others have indicated the presence of a primary myopathy. Repetitive stimulation studies may or may not show a defect in neuromuscular transmission. Creatinine phosphokinase levels may be considerably elevated. Muscle biopsy shows with certain stains the distinctive features of a loss of structure centrally in muscle fibres. Furthermore, within this area, under electron microscopy, there is a loss of the thick filament (myosin) normally present in muscle [15]. There may also be degrees of denervation atrophy and necrosis. These morphological changes are similar to those that can be induced in experimental animals, where the muscle is experimentally denervated in conjunction with high-dose steroid treatment [25].

It could be argued that these experimental results support the clinical findings. Sepsis may primarily induce a critical illness polyneuropathy resulting in denervation of muscle, and then, with the combination of high-dose steroids and neuromuscular blocking agents, a primary myopathy with its distinctive features. In both of these syndromes, if the patient survives the sepsis, recovery from the neuromuscular problem always occurs, although this may require a number of weeks in more severe cases.

Finally, prolonged weakness induced by these drugs may be purely due to the neuromuscular transmission defect, particularly in the presence of renal failure [19]. Reversal occurs in a matter of hours or days, with no evidence of either neuropathy or myopathy, although systematic studies to exclude neuropathy or myopathy have usually not been performed.

Theories to explain neuromuscular syndromes

While the precise mechanisms of critical illness polyneuropathy and the additional effects of neuromuscular blocking agents and steroids are not known, some speculation is possible. The septic syndrome may be due to a disturbance in the microcirculation of various organs [26, 27]. If this were to affect peripheral nerves, energy depletion would produce the distal axonal degeneration typical of critical illness polyneuropathy [7, 8]. Increased capillary permeability may be a prominent feature of the microcirculatory disturbance. Consequently, potentially toxic substances, such as neuromuscular blocking agents or their metabolites, could gain entry to the endoneural space and cause further direct damage to nerve axons.

These mechanisms may also apply to muscle. Animal experiments show that the effects of steroids on denervated muscle are a thick (myosin) filament loss [25], typical of that seen in human cases [15]. One could speculate in human cases that the muscle

is first denervated by critical illness polyneuropathy, and additionally by neuromuscular blocking agents, with the entry of steroids completing the toxic effect (Fig. 4).

The aforementioned mechanisms theoretically explain the three main types of neuromuscular conditions that have been seen in man:

1. Polyneuropathy due to sepsis alone (critical illness polyneuropathy)
2. Polyneuropathy due to sepsis plus neuromuscular blocking agents
3. Polymyopathy due to sepsis, neuromuscular blocking agents and steroids.

Only prospective studies in man and animals will unravel these complex neuromuscular events.

Primary myopathies

Due to prolonged recumbency in the critical care unit, the commonest primary myopathy in patients with sepsis and multiple organ failure may be cachexia or disuse atrophy of muscle. The EMG and creatinine phosphokinase levels are normal. Muscle biopsy shows Type II fibre atrophy. However, no systematic studies to determine this have yet been made. In our biopsy material, the predominant features have been denervation atrophy [23] secondary to critical illness polyneuropathy.

A rare complication of infection is panfascicular muscle fibre necrosis [28, 29]. In this situation, there is a sudden, generalised weakness of muscles accompanied by marked elevation of creatinine phosphokinase and, occasionally, myoglobinuria. There may or may not be abnormal spontaneous activity on needle EMG of muscle, and muscle biopsy may be normal in the early stages. However, findings of muscle fibre necrosis are evident later on, and in severe cases, panfascicular muscle fibre necrosis is observed. An inflammatory reaction may be secondary to the necrotic muscle fibres. Recovery is usually quite prompt and occurs spontaneously. This condition represents an unusual reaction on the part of muscle to a variety of insulting agents in addition to sepsis, such as acute physical trauma and certain chemicals [28]. As a result of the high incidence of infection and trauma in patients being managed in critical care units, this myopathy may be more common than is recognised.

Investigating muscle weakness in critically ill patients

When investigating muscle weakness in critically ill patients, a review of the history is important, particularly in relation to possible underlying sepsis and the use of medications, such as neuromuscular blocking agents and steroids. The physical examination is difficult due to mechanical ventilation, sedation, vascular lines, etc., and electrophysiological studies are always indicated. Levels of creatinine phosphokinase give some indication of the degree of muscle fibre breakdown. Muscle biopsy may be necessary. The same patient may have combinations of the

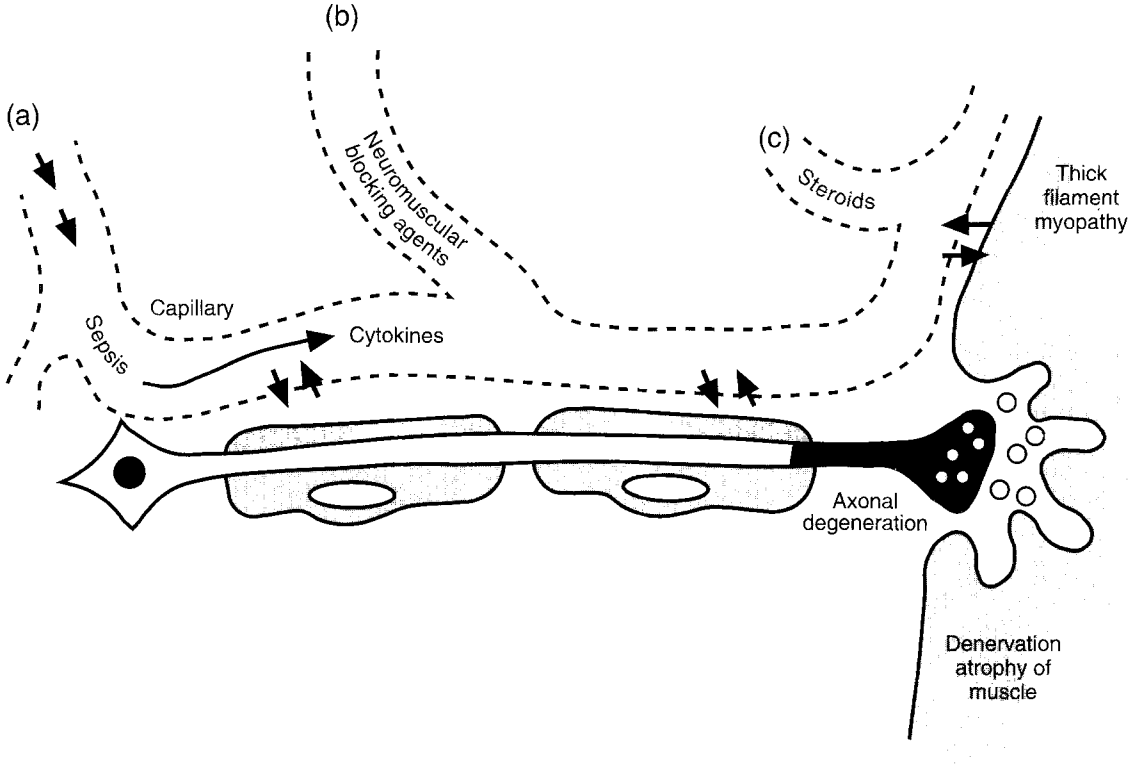

Fig. 4. Theoretical mechanisms of medication-induced neuropathy and myopathy in septic patients. Through the release of cytokines from macrophages, sepsis induces capillary permeability. This and other vascular disturbances may induce endoneurial oedema, hypoxia and, hence, a distal axonal degeneration typical of critical illness polyneuropathy (a). However, the increased capillary permeability may also allow the entry of known toxins, such as neuromuscular blocking agents or their metabolites, which may further induce neuropathy (b). The entry of steroids into muscle may have the additional effect of inducing a myosin filament myopathy (c).

above-described conditions. Many reports currently in the literature lack essential information to determine the true nature of the neuromuscular disorder. In order to do so, clinical examination, electrophysiological testing, measurements of creatinine phosphokinase, and muscle, and at times nerve, biopsies may be necessary and should be performed for research purposes. A summary of how these different neuromuscular syndromes associated with sepsis can be differentiated is shown in Table 1.

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Table 1. Features of neuromuscular disorders in critically ill patients

Condition	Antecedent illness	Clinical features	Electro-physiology	Morphology	Treatment	Prognosis
Critical illness polyneuropathy	Sepsis	Absent, or signs of mainly motor neuropathy	Consistent with a primary axonal degeneration of mainly motor fibres	Primary axonal degeneration of nerve, denervation atrophy of muscle	Treat septic syndrome	Good in 40% who survive sepsis and organ failure
Neuromuscular blocking agents and neuropathy	Sepsis	Acute quadriplegia	Neuromuscular transmission defect and/or axonal motor neuropathy	Normal or denervation atrophy on muscle biopsy	None	Good
Neuromuscular blocking agents, steroids and myopathy	Sepsis?	Acute quadriplegia	Neuromuscular transmission defect and/or myopathy	Thick myosin filament loss	None	Good
Panfascicular muscle fibre necrosis	Transient infection, trauma, etc	Severe muscle weakness, increased creatinine phosphokinase, often myoglobinuria	Positive sharp waves and fibrillation potentials on needle electromyography	Panfascicular muscle fibre necrosis	None, or haemodialysis for myoglobinuria	Good
Cachectic myopathy	Severe systemic illness, prolonged recumbency	Diffuse muscle wasting	Normal	Type II fibre atrophy on muscle biopsy	Physiotherapy, improved nutrition	Good

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Professor C.F. Bolton
University of Western Ontario
Victoria Hospital
375 South Street
London
Ontario
Canada N6A 4G5