The Neurological Complications of Sepsis

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Encephalopathy and polyneuropathy occur in 70% of septic patients. The encephalopathy is diffuse, appears early, is often severe, but reverses quickly with successful treatment of the sepsis. The electroencephalogram is a sensitive indicator of the incidence and severity of the encephalopathy, but computed tomograms of the brain and cerebrospinal fluid findings are unremarkable. Critical-illness polyneuropathy develops later and in association with multiple-organ failure. Recovery is more gradual. Difficulty in weaning from the ventilator is an important early manifestation. Electromyography should be routinely performed to establish the diagnosis. The polyneuropathy is a primary axonal degeneration, predominantly of distal motor fibers. A persistent deficit may eventuate in severe cases. Whether muscle is affected as consistently as brain and peripheral nerve, and by the same process, has not been determined. Medications used in critical care units, notably sedatives and neuromuscular blocking agents, often confuse the clinical picture. The neurological pathophysiology is unknown but current evidence suggests that nervous system dysfunction arises through the same mechanisms as for systemic organs in the septic syndrome.


Sepsis has been a common and frequently fatal illness in humans. It originally meant "putrefaction," the decomposition of organic matter by bacteria and fungi [1]. Its nature in humans is still being debated, but centers on the systemic effects of sepsis, as defined by increased respiratory and heart rate, elevated or depressed body temperature, and inadequate organ perfusion [2] (Table 1). The pathophysiology is complex [3] (Fig 1). During sepsis, bacterial wall components activate the complement system, neutrophils, monocytic cells, endothelial cells, and factor XII of the coagulation cascade. Cell activation involves the release of several cytokines, notably tumor necrosis factor and interleukin-1 (IL-1) and -2 (IL-2), which are important mediators in the septic syndrome. Prominent effects are increased capillary permeability and vasodilatation [3], with resulting disturbances of the microcirculation of various organs. Sepsis remains prevalent in the general wards of major hospitals, and multiple-organ failure may affect 20 to 50% of patients in medical or surgical critical care units [4].

Although briefly described by Bright in 1827 [5] and Osler in 1892 [6], the effects of sepsis on the nervous system have been largely ignored. In recent years the introduction of antibiotics and various methods to treat the systemic effects of sepsis aggressively have allowed patients to either recover or survive for a much longer period, allowing time for its neurological complications to appear and be recognized. Sepsis has profound effects on both the central and the peripheral nervous system.

Septic Encephalopathy

In a prospective study of 69 septic patients by Young and colleagues [7], encephalopathy occurred in 70%, being severe in most. Within hours of a positive finding on blood culture, careful testing revealed impaired attention, concentration, orientation, and writing, but focal signs, seizures, and cranial nerve palsies were rare. Moreover, asterixis, tremor, and multifocal myoclonus, commonly seen in metabolic encephalopathy, were infrequent, while paratonic rigidity was common. Severe encephalopathy, manifesting as delirium and then coma, was evident within 2 weeks of admission to a critical care unit and preceded signs of polyneuropathy (Fig 2).

This neurological picture is almost diagnostic, provided sepsis is clearly present. However, blood cultures may show positive findings in less than half of septic patients [8] and a septic focus may be difficult to find. Moreover, other conditions must always be kept in mind. Foremost among these are infections that affect the nervous system more directly, such as bacterial, fungal, or other meningitides; encephalitis;

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Table 1: Definition of the Septic Syndrome by Bone (2)

1. Clinical evidence of infection
2. Respiratory rate > 20/min; if mechanically ventilated, > 10 liter/min
3. Heart rate > 90/min
4. Temperature > 38.5°C or < 31.1°C
5. Inadequate organ perfusion with one or more of the following:
   a. Partial oxygen pressure (PaO₂)/fraction of inspired oxygen (FiO₂) < 280 without pulmonary or cardiovascular disease
   b. Elevated plasma lactate level
   c. Oliguria—urine output < 0.5 ml/kg of body weight for at least 1 hr

Pathogenesis

Although the pathogenesis of the encephalopathy is not known, we propose a hypothesis that should be testable (see Fig 1).

Since encephalopathy may occur early in the course of sepsis, without direct infection of the brain and without consistent neuropathological change, a reversible "metabolic" mechanism is likely. Endotoxin probably does not directly affect the adult brain, as it does not cross the blood-brain barrier in sufficient concentration to alter function [10]. Early encephalopathy often begins before the failure of other organs and thus is not secondary to other organ failure.

The septic syndrome may occur with noninfectious diseases, particularly severe trauma and burns [11]. Here, the principal mediators are cytokines, chemical messengers released from macrophages and lymphocytes [2]. These produce capillary leakage and tissue edema, interference with microcirculation, increased procoagulant activity, and direct effects on tissue metabolism. These effects can lead to failure of various organs.

It seems reasonable that the brain can also be affected by the same mechanism. Experimentally, the blood-brain barrier becomes leaky in a patchy manner within the first few hours of sepsis [12]. Transport of amino acids across the blood-brain barrier is altered in sepsis [13]. Cytokines may also directly affect brain function. When directly injected into the brain or ventricular system, high doses of IL-1 and IL-2 alter the behavior and EEG in experimental animals [14, 15]. Soporific effects and EEG slowing follow injection of IL-2 into the locus ceruleus; this appears to be due to the activation of opiate receptors which activate the adenylate cyclase system [16]. IL-1 facilitates slow-wave sleep [17] and causes fever by its effect on the hypothalamus [18]. There are likely other sites of action in deep and superficial brain structures. The direct effect of cytokines on brain function may be enhanced by alterations in the blood-brain barrier. Dysfunction of the blood-brain barrier could further alter the chemical milieu of the interstitial fluid including amino acid content, peptides, and hormones. Vasogenic cerebral edema could also interfere with diffusion between brain cells and capillaries. Small areas of infarction could occur as a result of increased procoagulant effect.

The brain could also be affected in a secondary manner after the failure of other organs—liver, kidneys, and general circulation [19].

Neuromuscular Complications

The neuromuscular complications may be quite varied and are difficult to sort out by purely clinical examination. Systematic electrophysiological studies, measurements of creatinine phosphokinase, and examination of a muscle biopsy specimen are helpful diagnostically.
Fig 1. Possible mechanisms for septic encephalopathy and critical-illness polyneuropathy. Arrows pointing to the curved line indicate mechanisms that may apply to both the central and the peripheral nervous system. The lower arrows designate treatments that may affect these systems independently. The heavy arrows highlight the most likely mechanisms. These hypotheses are complex, but involve the infecting organism inducing chemical, microvascular, metabolic, or treatment effects that may act independently or in concert. The release of cytokines from macrophages and thence from T lymphocytes may directly affect the brain or act indirectly on the blood-brain barrier and microcirculation. Such vascular effects are abetted by activation of the complement system and factor XII. The encephalopathy may also be due to the failure of other organs or to direct infection of the brain with the formation of microabscesses. Critical-illness polyneuropathy may be due to disturbances of the microcirculation of peripheral nerve through vascular effects similar to those affecting the brain. Various treatments used in the critical care unit may play an additive role for both the encephalopathy and the polyneuropathy.
Fig 2. The typical course of the nervous system complications of sepsis: encephalopathy, difficulty weaning from the ventilator, and then polyneuropathy. In this severe form the time course was in months, but it could be weeks in milder forms.

(Table 2). The pathophysiology remains speculative (see Fig 1).

Critical-Illness Polyneuropathy
In the last 15 years a polyneuropathy has been observed in critical care units throughout the world. It has been attributed to a variety of causes: gentamycin [20], the muscle relaxant pancuronium bromide [21], Guillain-Barré syndrome [22], pancreatic disease [23], and nutritional disturbance [24]. However, the majority of reports have linked the neuropathy to sepsis and multiple-organ failure (critical illness) [25-32] and a prospective study has established the incidence at 70% [33]. These patients, with major medical, surgical, or traumatic illnesses, will have been in the critical care unit for at least a week and septic encephalopathy [7] may be disappearing (see Fig 2). The earliest sign of polyneuropathy is difficulty in weaning from the ventilator; then distal weakness and reduced deep-tendon reflexes appear. In severe forms, complete quadriplegia and respiratory paralysis occur with relative sparing of the cranial musculature. These clinical signs are evident in only half the patients. Electrophysiological studies, which should be done routinely, will detect the polyneuropathy in the remainder. The electrophysiological signs are those of a pure axonal degeneration, mainly of motor, but also of sensory fibers. Conduction velocities and distal latencies are relatively preserved but compound muscle and sensory action potentials are reduced, and fibrillation potentials and positive sharp waves appear in muscle as shown by needle electromyography. Reduction of the diaphragmatic compound muscle action potential and signs of denervation of the chest wall muscles establish the polyneuropathy as a cause of difficulty in weaning from the ventilator [31, 33].

Comprehensive studies at autopsy and by nerve biopsy have shown the presence of a primary axonal degeneration of motor and sensory fibers, mainly distally, without evidence of inflammation. The only central nervous system manifestation has been central chromatolysis of anterior horn cells, secondary to the axonal degeneration [27, 31]. Thus, for some reason, in contrast to the central nervous system, damage to the peripheral nervous system is more severe, and at times irreparable.

While critical-illness polyneuropathy is the most common polyneuropathy encountered in the critical care unit, other neuropathies occasionally occur and must always be considered. Guillain-Barré syndrome is readily identified by the characteristic antecedent illness and the demyelinating type of polyneuropathy as demonstrated by electrodagnostic studies [29]. Other polyneuropathies may be of metabolic origin, such as thiamine or vitamin E deficiency, pyridoxine abuse, hypophosphatemia, or porphyria; the result of toxicity, particularly antibiotics, metronidazole, aminoglycosides, or penicillin [33]; or a remote effect of carcinoma [34]. Motor neuron disease may present with respiratory insufficiency. A variety of traumatic mononeuropathies [35] are relatively common in the critical

<table>
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<th>Conditions</th>
<th>Incidence</th>
<th>Clinical Features</th>
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<th>Creatinine Phosphokinese</th>
<th>Muscle Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical-illness polyneuropathy</td>
<td>Common</td>
<td>Flaccid limbs, respiratory weakness</td>
<td>Axonal degeneration of motor and sensory fibers</td>
<td>Near normal</td>
<td>Denervation atrophy</td>
</tr>
<tr>
<td>Disuse (cachectic myopathy)</td>
<td>Common (?)</td>
<td>Muscle wasting</td>
<td>Normal</td>
<td>Normal</td>
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</tr>
<tr>
<td>Myositis</td>
<td>Rare</td>
<td>Flaccid weakness, myoglobinuria</td>
<td>Abnormal spontaneous activity in muscle</td>
<td>Markedly elevated</td>
<td>Panfascicular muscle fiber necrosis</td>
</tr>
<tr>
<td>Pyomyositis</td>
<td>Rare</td>
<td>Flaccid limb weakness</td>
<td>Abnormal spontaneous activity in muscle</td>
<td>Markedly elevated</td>
<td>Multiple pyogenic abscesses</td>
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care unit. Thus, the term “ICU neuropathy” should be avoided, and the exact type of neuropathy identified. Moreover, critical-illness polyneuropathy may occur outside the critical care unit, in patients who develop sepsis in the course of severe renal failure [36]. Approximately 50% of patients who have sepsis and multiple-organ failure survive. Those with a mild polyneuropathy recover in a matter of weeks, months for those with more severe forms. Unusually severe neuropathy may not improve [33].

Difficulty in weaning from the ventilator is a common problem in critical care units. It is often attributed to respiratory muscle fatigue [37]. However, critical-illness polyneuropathy may be the most common cause [25, 31, 38], particularly in those patients intractable from ventilator dependence [39]. Knowledge of this phenomenon aids decisions regarding respirator techniques, nursing care, prognosis, and overall management. Moreover, recognition of critical-illness polyneuropathy anticipates the need for physiotherapy, rehabilitation, and other supportive measures as the patient recovers.

There is no evidence that specific methods of treating the septic syndrome, such as the use of inotropic drugs, antibiotics, and parenteral or enteral nutrition, are in any way responsible for the polyneuropathy [31, 33]. In fact, all measures to prevent or treat the septic syndrome are the only current methods of dealing with the polyneuropathy.

Pathophysiology of Critical-Illness Polyneuropathy

The exact cause of critical-illness polyneuropathy is unknown. Retrospective [31] and prospective [33] studies have failed to incriminate a variety of potential causes, including types of primary illness or injury, Guillain-Barré syndrome, medications including aminoglycoside antibiotics and neuromuscular blocking agents, and specific nutritional deficiencies. Sepsis itself is the likely cause [31, 33]. The severity of the polyneuropathy can be quantified from electrophysiological data [33]. It tends to be more severe the longer each patient is in the critical care unit. Sepsis and multiple-organ failure also tend to increase in frequency and severity under similar circumstances [2]. Increasing blood glucose and decreasing serum albumin concentrations correlate with decreasing peripheral nerve function [33]. Both biochemical changes are well-recognized manifestations of the sepsis and multiple-organ failure syndrome.

Recent investigations allow speculation on the basis of this polyneuropathy. The microcirculation of various organs is disturbed in sepsis [33] (see Fig 1). Blood vessels supplying peripheral nerve lack autoregulation [40], rendering them particularly susceptible to such disturbances. Moreover, cytokines that are secreted in sepsis have histamine-like properties that may increase microvascular permeability. The resulting endoneurial edema could induce hypoxia by capillary closure, an increase in intercapillary distance, and other mechanisms. The result would be a primary axonal degeneration [31, 33, 41] which is typical of that seen in critical-illness polyneuropathy.

Neuromuscular Transmission Defects

Repetitive nerve stimulation studies in septic patients have shown no defect in neuromuscular transmission [29, 31]. However, several reports suggested that prolonged treatment with neuromuscular blocking agents may induce a pure, axonal motor neuropathy [21, 42]. Other reports indicated that when these agents are combined with high-dose steroids, a myopathy with thick-filament myosin loss is induced [43]. However, in our view the issue remains unresolved since sepsis was a factor in most, if not all, of these patients. Moreover, steroids and neuromuscular blocking agents were infrequently used in the 49 patients with critical-illness polyneuropathy reported by Bolton and colleagues [31, 33]. Nonetheless, it is possible these agents may contribute to the neuropathy or myopathy associated with sepsis.

Myopathy

It is unlikely that sepsis and multiple-organ failure would spare skeletal muscle, but the impact on muscle function is not well understood and has been difficult to study. Several types of primary myopathy have been proposed. The best defined are listed in Table 2.

Respiratory muscle fatigue [37] is often invoked as an explanation for failure to wean patients from mechanical ventilators, but the most frequent cause in studies by Bolton and colleagues has been critical-illness polyneuropathy [31, 44]. Malnutrition has also been cited, but severe muscle weakness does not occur with starvation [45] and patients with anorexia nervosa have normal results on electrophysiological studies [46]. Disuse, while causing type 2 fiber atrophy, is not associated with electrophysiological abnormalities [46] or defects in the muscle content of high-energy phosphate metabolites [47]. However, there is evidence that a catabolic myopathy occurs as a result of the action of IL-1 and tumor necrosis factor [48]. Although the clinical effects are ill defined, several authors have identified defects in high-energy metabolites in patients with respiratory failure, cardiogenic shock, severe congestive failure, and sepsis [49–51].

A syndrome of diffuse myositis may occur during overwhelming infections, with viruses, Escherichia coli, leprospirosis, Legionnaire’s disease, and organisms causing the toxic shock syndrome [52]. Features include diffuse muscle weakness and tenderness, high creatinine phosphokinase levels, and at times, myoglobinuria. Muscle biopsy specimens show panfascicular
necrosis [53]. While this is an uncommon event, not witnessed in prospective studies of 43 patients with sepsis and multiple-organ failure [33], it did occur in 5 patients over 2 years in one intensive care unit (D. Ramsay and D. W. Zochedne, unpublished data, 1991). Even more rarely in overwhelming bacterial infection, muscle may be directly involved by multiple abscesses. The clinical features are similar to those of diffuse myositis [54]. Thus, muscle biopsy should be performed when the diagnosis is in doubt.

In studies of critical-illness polyneuropathy, single-fiber muscle fiber necrosi was seen in several patients [31], raising the possibility that a "septic myopathy" might occur. Such necrosis may cause abnormal spontaneous activity of muscle, indistinguishable from that due to denervation [55]. Also, polyphasic and low-amplitude, brief voluntary motor unit potentials occur in both early reinnervation and primary muscle disease. However, single-fiber necrosis may result from acute denervation [56], and creatinine phosphokinase levels were normal or only mildly elevated in septic patients studied prospectively [33]. Thus, with the high incidence of neuropathy in sepsis, an associated myopathy has been difficult to establish with certainty. Nonetheless, 2 patients with critical-illness polyneuropathy had severe reductions of bioenergetic reserve, as estimated by the phosphocreatine–inorganic phosphate (PCr/Pi) ratio using phosphorus 31 nuclear magnetic resonance spectroscopy of their forearm muscles [47]. The reduction exceeded that expected from denervation in nonseptic patients [47] and paralleled findings in experimental animals [37]. It is conceivable that disturbances of the microcirculation, as in brain and peripheral nerve, could account for the energy depletion (see Fig 1).

Specific Treatment

Methods of treating the septic syndrome directly, such as by using anticycletin/tumor necrosis factor monoclonal antibodies [58], are becoming available and offer hope that the devastating effects of this syndrome on various organs, including the nervous system, can be avoided. It is our view that monitoring the nervous system would be a relatively sensitive method of gauging the clinical effect of such treatment. Electrophysiological measurements of cerebral function by EEG [7, 9] and of peripheral nerve function by electromyographic techniques [33] have shown close correlations with key manifestations of the septic syndrome.

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