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Critically ill polyneuropathy: electrophysiological studies and differentiation from Guillain-Barré syndrome

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SUMMARY A polyneuropathy of varying severity has been observed in association with sepsis and critical illness in 15 patients. Since clinical evaluation is often difficult, electrophysiological studies provided definitive evidence for polyneuropathy. These revealed reductions in the amplitudes of compound muscle and sensory nerve action potentials, the most marked abnormality. Near-nerve recordings confirmed such reductions for sensory fibres. Needle electromyography revealed signs of denervation of limb muscles. Phrenic nerve conduction and needle electromyographic studies of chest wall muscles suggested that the polyneuropathy partially explained difficulties in weaning patients from the ventilator, an early clinical sign. No defect in neuromuscular transmission was demonstrated, despite the use of aminoglycoside antibiotics in some patients. In those who survived the critical illness, clinical and electrophysiological improvement occurred. The 15 critically ill polyneuropathy patients were compared with 16 Guillain-Barré syndrome patients observed during the same period. The analysis showed that the two polyneuropathies are likely to be separate entities that can be distinguished in most instances by the predisposing illness, electrophysiological features and cerebrospinal fluid results.

Critical illness arises when sepsis and multi-organ dysfunction complicate the course of a primary illness or injury. The pathophysiology, incidence and clinical features of the dysfunction of the various organs are only now being clarified, and despite modern methods of management the mortality rate is at least 60%.[1]

Little is known of the effects on the nervous system. Varying degrees of coma occur in approximately 10% of patients.[1] We have recently described the clinical and pathological features of 12 cases of "septic encephalopathy".[2] Attention to the peripheral nervous system has been limited to studies of metabolic disturbances of skeletal muscle, a potential cause of respiratory muscle fatigue.[3-6] This may be one of the major reasons for ventilatory assistance during the course of critical illness.

The peripheral nerves are also affected. In the last seven years we have observed a polyneuropathy, at times severe, which has complicated the course of critical illness. We have named it critically ill polyneuropathy (CIP). Unexplained difficulty in weaning the patient from the ventilator, reduced deep tendon reflexes and weakening of spontaneous or reflex-induced limb movements were early clinical signs.[7-9] In the setting of critical illness these signs were difficult to elicit, but electrophysiological investigation provided the definitive evidence of polyneuropathy.

This report, therefore, documents the electrophysiological findings in 15 such patients, emphasising their role in arriving at an initial diagnosis and of documenting the subsequent course of the polyneuropathy. It also compares these patients with 16 patients who had Guillain-Barré syndrome and were investigated and treated in our hospital during the same period, since it is important to distinguish these

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Table 1 *Clinical data on septic and critically ill patients*

Patient	*Age (yr)*	*Sex*	*Primary illness*	*Severity of polyneuropathy*	*Course of polyneuropathy*	*Outcome of patients*
1	56	F	Lactic acidosis	Severe	Improved	Recovered
2	56	F	Empyema	Severe	Improved	Recovered
3	66	M	Obstructive lung disease	Moderate	Improved	Death
4	58	F	Pneumonia	Severe	Improved	Death
5	49	M	Acoustic neuroma surgery	Moderate	Improved	Recovered
6	66	M	Obstructive lung disease	Mild	Unchanged	Death
7	72	M	Obstructive lung disease	Mild	Unchanged	Death
8	74	M	Aortic aneurysm surgery	Mild	Improved	Death
9	65	F	Pneumonia	Severe	Improved	Recovered
10	75	F	Hip surgery	Moderate	Worsened	Death
11	72	F	Pancreatitis	Mild	Improved	Recovered
12	67	F	Obstructive lung disease	Mild	Worsened	Death
13	57	M	Bacterial endocarditis	Severe	Worsened	Death
14	83	F	Endometrial cancer	Mild	Unchanged	Death
15	62	F	Septic hip joint	Mild	Improved	Recovered

Table 2 *Clinical data on Guillain-Barré syndrome patients*

Patient	*Age (yr)*	*Sex*	*Primary or predisposing illness*	*Complicating illnesses*	*Severity of polyneuropathy*	*Outcome of polyneuropathy*
1	74	F	Asian influenza innoculation	None	Mild	Improved
2	61	M	Upper respiratory infection	Respiratory and autonomic failure Pneumonia	Severe	Improved
3	25	M	Acute stomatitis	None	Mild	Improved
4	61	M	Upper respiratory infection	Respiratory and autonomic failure	Severe	Improved
5	44	F	Upper respiratory infection	None	Moderate	Improved
6	42	F	Upper respiratory infection	None	Moderate	Improved
7	58	M	Upper respiratory infection	Urinary retention	Moderate	Improved
8	59	F	Influenza innoculation	Respiratory and autonomic failure, pulmonary embolus, syndrome of inappropriate antidiuretic hormone release	Severe	Improved
9	19	M	None	None	Mild	Improved
10	90	M	Influenza	Respiratory and autonomic failure, pneumonia, multiple organ failure	Severe	Improved
11	28	F	None	None	Moderate	Improved
12	61	M	Influenza	None	Moderate	Improved
13	35	M	Upper respiratory infection	Respiratory and autonomic failure, pneumonia, encephalopathy, pulmonary emboli	Severe	Improved
14	42	M	Gastrointestinal infection	None	Moderate	Improved
15	49	F	None	Respiratory and autonomic failure Pneumonia, sepsis	Severe	Improved
16	27	M	Upper respiratory infection	None	Severe	Improved

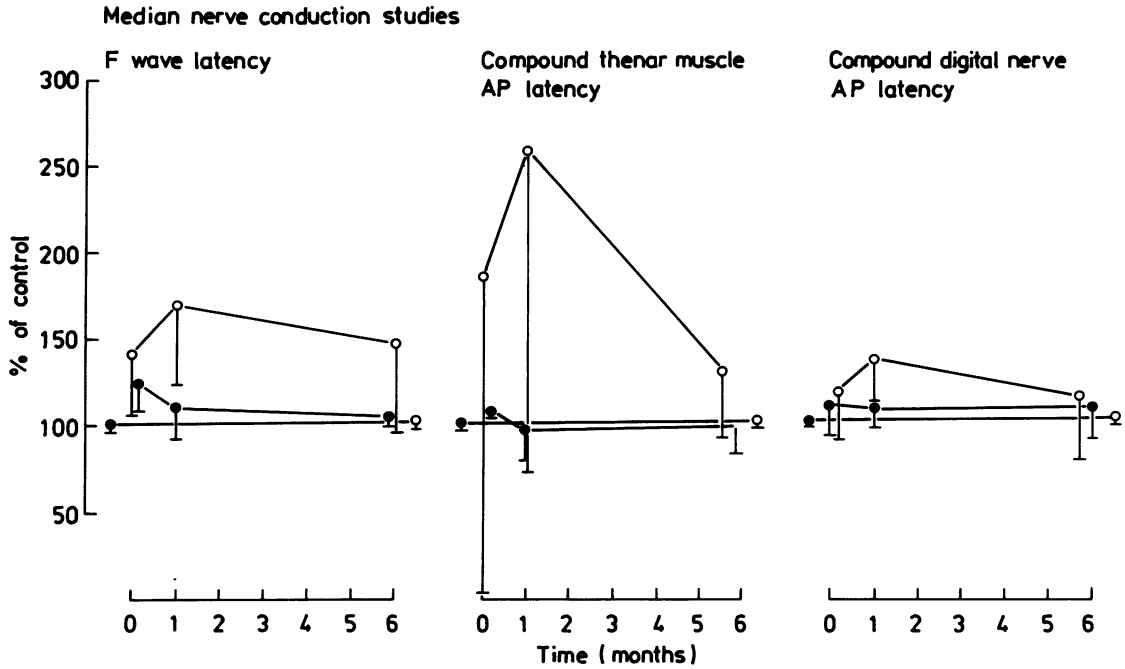

Fig 1 *The maximum speed of impulse conduction (mean − SD) in CIP (●) and Guillain-Barré syndrome (○) patients. This remained near normal in CIP patients, but was considerably slowed in Guillain-Barré syndrome patients, roughly correlating with the course of the polyneuropathy. Note marked prolongation of compound thenar muscle AP latency, suggesting predominant demyelination of distal motor fibres. Partly because of large standard deviations, F wave latencies at zero and one month were the only values that were statistically different between the two groups ($p < 0.05$). (AP means action potential. Months refers to time after first electrophysiological study).*

two neuropathies, each potentially occurring as complications of infection, surgery, and trauma.

Methods

Between 1977 and 1983, 15 CIP and 16 Guillain-Barré syndrome patients (tables 1 and 2) were observed at Victoria Hospital. Both types of polyneuropathies were identified and graded as: mild (electrophysiological abnormalities present with normal or equivocally abnormal neurological signs); moderate (muscle weakness of moderate severity and reduced or absent deep tendon reflexes); severe (severe muscle weakness, absent deep tendon reflexes and signs of severe denervation (grade 3 to 4 spontaneous activity of needle electrode study of muscle). All severe Guillain-Barré syndrome patients required assisted ventilation. The electrophysiological criteria for abnormality were: reductions below two standard deviations in the amplitude of compound action potentials from either muscle or sensory nerve

Table 3 *Control median nerve conduction results (mean ± SD)*

	CIP (15 subjects)	*Guillain-Barré syndrome (16 subjects)*
Motor conduction velocity (Elbow—Wrist)	55·3 ± 3·7 m/s	58·8 ± 2·7 m/s
Motor distal latency	3·6 ± 0·8 ms	3·7 ± 0·6 ms
Thenar compound muscle action potential amplitude	10·0 ± 2·6 mV	11·4 ± 3·3 mV
Sensory conduction velocity (Elbow—Wrist):		
Females	56·6 ± 5·4 m/s	60·8 ± 4·5 m/s
Males	57·1 ± 3·0 m/s	62·9 ± 5·6 m/s
Sensory distal latency:		
Females	2·5 ± 0·3 ms	2·6 ± 0·5 ms
Males	2·5 ± 0·2 ms	2·5 ± 0·4 ms
Digital compound nerve action potential amplitude:		
Females	21·3 ± 9·6 μV	34·7 ± 12·6 μV
Males	18·7 ± 11·8 μV	24·9 ± 10·5 μV
F wave latency	28·2 ± 2·0 ms	27·9 ± 2·3 ms
Hand temperatures	32·1 ± 0·9°C	32·1 ± 0·9°C

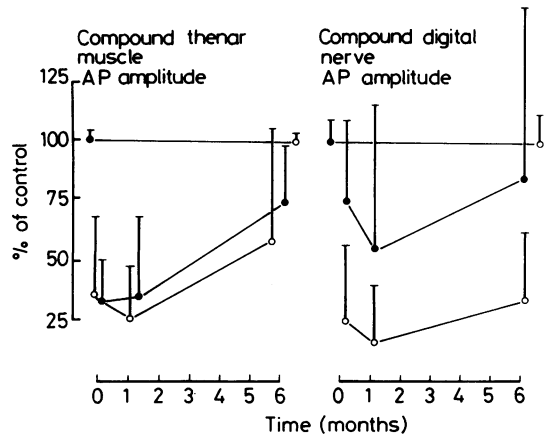

Fig 2 *Mean amplitudes (+ SD) of compound action potentials (AP) in CIP (●) and Guillain-Barré syndrome (○) patients. Values were more depressed in Guillain-Barré syndrome patients, but returned towards normal in both groups at 6 months.*

and abnormal spontaneous activity in muscles of at least two limbs.

The CIP patients were identified according to the above criteria for polyneuropathy and that they were both suffering from sepsis and critically ill. Sepsis was defined as septicaemia or a focus of infection with systemic effects, and critical illness meant significant involvement of two or more major organs. The first four of the CIP patients were reported previously.[9]

The Guillain-Barré syndrome patients were selected during the same period on the basis that they were all adults (over 18 years of age), that the polyneuropathy had run a monophasic course (since all CIP patients had run a monophasic course) and that they conformed to Asbury's criteria for the diagnosis of Guillain-Barré syndrome.[10]

In both groups, initial clinical and EMG examinations were performed within one month of admission to hospital. It was possible to perform follow-up examination at approximately one month and 6 months after the first examination, on seven CIP and ten Guillain-Barré syndrome patients. Patients were lost to follow-up because of death of CIP patients, early recovery and discharge of Guillain-Barré syndrome patients, or transfer to another hospital.

Electrophysiological tests were performed on both groups according to standard procedures using surface electrodes for nerve conduction studies and concentric needle electrodes for electromyography.[9] Surface temperatures were measured on the palm and dorsum of the foot. Septic patients had limb temperatures that were higher than control subjects or Guillain-Barré syndrome patients. Thus, each median nerve conduction value was corrected to a palmar skin temperature of 32·1°C (a control value for our laboratory), using correction factors previously established in our laboratory appropriate to either control subjects or persons with a polyneuropathy.[11,12] The correction factors per 1°C were: F wave latency, normal: 0·64, neuropathy: 1·52 ms; CMAP latency, normal: 0·28, neuropathy: 0·23 ms; CSAP latency, normal: 0·09, neuropathy: 0·10 ms; CMAP amplitude, normal: 0·25, neuropathy: 0·11 mV; CSAP amplitude, normal: 1·96, neuropathy: 0·84 μV. All values in table 3 and figs 1 and 2 are temperature-corrected. A control subject was chosen who matched each CIP or Guillain-Barré syndrome patient for age and sex. All patients' nerve conduction values were expressed as a percentage of the control value. The analysis of digital CSAP amplitudes was performed separately for each sex, since these amplitudes are normally greater in females than males.[13] The lower amplitudes for digital compound nerve action potentials in Guillain-Barré syndrome are likely due to their younger age compared to CIP patients (mean of 48 vs 65 years).

After the above data had been assembled, the CIP and Guillain-Barré syndrome groups were compared graphically and by the two sample *t* test of significance.

Needle electromyographic studies were carried out in selected proximal and distal muscles of both upper and lower limbs and from the external oblique and external intercostal muscles at the fifth interspace. Abnormal spontaneous activity was graded on a scale of 0 (normal) to 4. Brief trains of positive waves or fibrillation potentials induced by needle movement or occurring in only one area of the muscle were simply described and not given a grade. More definitive activity was graded as: grade 1: trains of positive waves or fibrillation potentials in at least two areas of the muscle; grade 3: trains of such waves in all areas of the muscle; grade 4: abundant such activity in all areas of muscle. The amount of motor unit potential activity (number of units recruited by voluntary contraction) was graded on a scale of 4 (normal) to 0 (absent). Initial and serial needle electrode studies were invariably performed on the vastus lateralis muscle, and the findings were recorded on tape.

Other electrophysiological studies were carried out in a further 10 CIP patients studied in 1983 and 1984; five had evidence of polyneuropathy. Tests for defects in neuromuscular transmission on these patients were made by stimulating either the median or ulnar nerve at the wrist and recording from the thenar or hypothenar eminences, respectively. Trains of six supramaximal stimuli were delivered at rates of 3 and 20 Hz. The patients were too ill to contract voluntarily their muscles maximally, so effects after exercise could not be evaluated. Near-nerve needle electrode recordings from the sural nerve were also carried out. For these studies, the sural nerve was stimulated at the calf and the needle electrodes were inserted in a bipolar arrangement near the sural nerve at the ankle. The responses to 64 stimuli were averaged on a Nicolet 1170 averager.

The cerebrospinal fluid was examined in all Guillain-Barré syndrome patients and 12 CIP patients within one month of onset of the polyneuropathy. It was measured by a Dupont automatic clinical analyser. The cell count was performed manually using a counting chamber.

Results

General observations on critically ill patients

The mean age of the patients was 65 (49–83) years, nine females and six males. They presented with a variety of primary illnesses (table 1) which, within hours, deteriorated to a state of critical illness

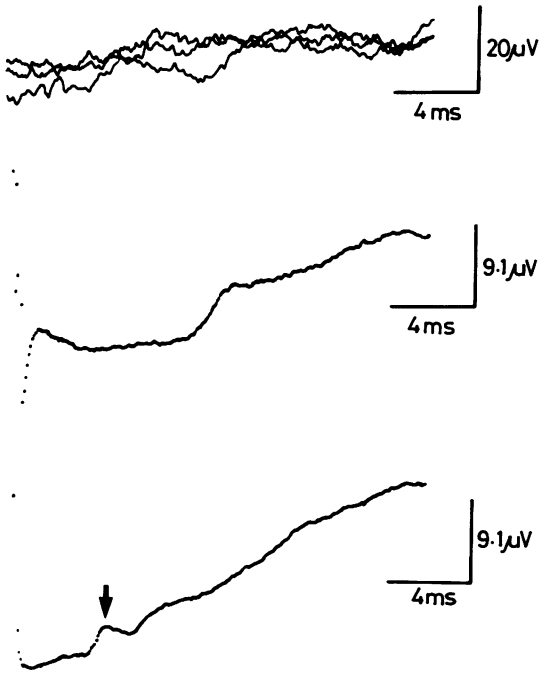

Fig 3 *Sural nerve recordings in a 64-year-old-man who had a moderately severe critically ill polyneuropathy. With surface electrodes at the ankle and stimulating electrodes at mid-calf, no CSAP was recorded after three stimuli (upper figure) or after 64 stimuli had been averaged (middle figure). However, a low voltage CSAP (↓), 3·4 μV, at maximal conduction velocity of 38·8 m/s, was demonstrated with a near nerve recording of 64 averaged responses (lower figure), consistent with partial axonal degeneration of the sural nerve. (The low voltage, later response in the middle figure arose from muscle, not sural nerve; foot skin temperature was 31·9°C).*

requiring early ventilatory assistance and admission to the critical care unit. All were septic and a variety of organisms were cultured from various sites in the body, including the blood. At least two major organ systems were involved but none of the patients who recovered had severe or persisting dysfunction of either liver or kidney. Intensive treatment was given, including nasogastric tube feedings and total parenteral nutrition. Episodes of septic shock, occurring in most patients, were managed by pressor drugs and blood transfusions. Multiple antibiotics were given but no patient consistently received any one type or group of antibiotics and most received both penicillin and aminoglycosides. The serum albumin and absolute lymphocyte counts were depressed in all patients. Careful analysis of our records has not shown any particular antibiotics to be responsible for the polyneuropathy or that the institution of total parenteral nutrition was associated with recovery. Nine of the 14 patients ulimately died but in none of these patients did polyneuropathy appear to be a major reason for death.

Clinical features of critically ill polyneuropathy

The polyneuropathy usually began within one month of admission to the critical care unit. Difficulty weaning the patient from the ventilator as the critical illness was beginning to subside, the development of weakness of the limbs and reduced deep tendon reflexes, were early clinical signs. However, in mild or

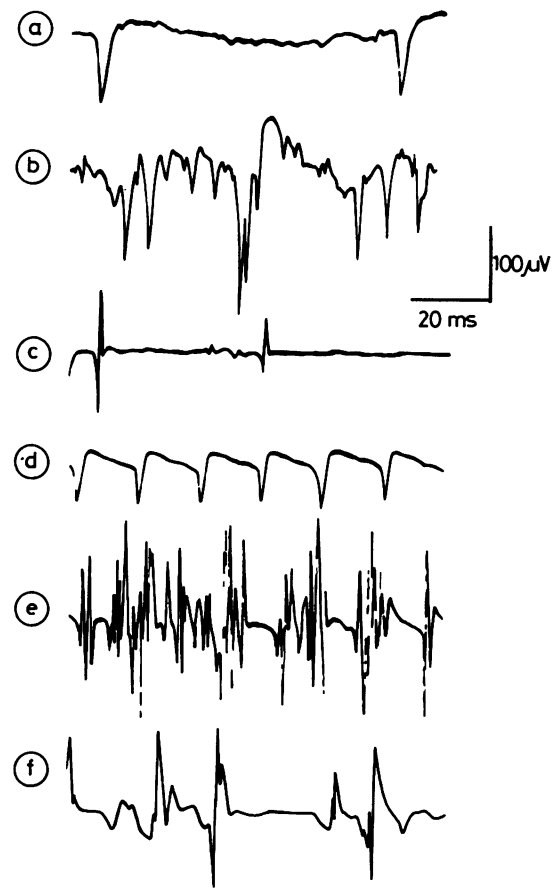

Fig 4 *Selected examples of needle electrode findings in skeletal muscle in the acute phase of critically ill polyneuropathy. Positive waves (a), at times profuse (b), and fibrillation potentials (c) in resting muscle, and motor unit potentials (f) on voluntary activation which were decreased in number, slightly polyphasic, but of relatively normal size, are all findings that are consistent with recent denervation. The reason for the high incidence of myotonic (d) or complex repetitive discharges (e) (seven patients) is speculative. (Note the frequently changing composition of the complex repetitive discharge, an atypical feature).*

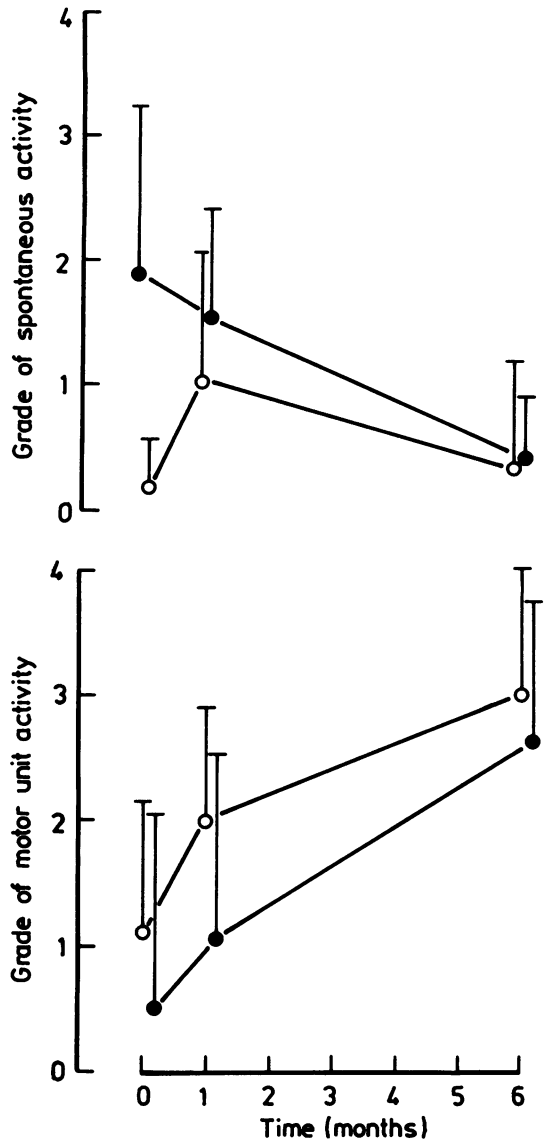

Fig 5 *Concentric needle electrode activity (+ SD) in the quadriceps muscle of CIP (●) and Guillain-Barré syndrome (○) patients. The results were more abnormal in distal and lower limb muscles. The abnormal spontaneous activity consisted mainly of positive sharp waves and fibrillation potentials, 7 CIP patients also exhibiting complex repetitive discharges and myotonic discharges. The magnitude of the abnormalities correlated with the degree of denervation and reinnervation of muscle. Note the relative lack of denervation of muscle in Guillain-Barré syndrome initially, even though few motor units were recruited on voluntary contraction, consistent with predominant demyelination.*

moderate cases, these signs were often equivocal. In cases of severe neuropathy, limb movements were very weak or absent, but head, facial, tongue and jaw movements were relatively preserved (except for some weakness of facial muscles in three cases). Sensory symptoms and signs were milder and, when testable, consisted of varying degrees of stocking and glove loss to all modalities. Autonomic dysfunction was not evident on routine clinical examination. All signs were most marked in the legs and distal parts of the limbs. The polyneuropathy was severe in five, moderate in three, and mild in seven patients.

Clinical and electrophysiological follow-up in eight showed improvement in the polyneuropathy. Of those who failed to improve, the polyneuropathy was unchanged in three while it worsened in two. The mortality rate in the last group was highest, six of seven patients dying. In the group whose polyneuropathy improved, only three of eight patients died.

Recovery occurred over a matter of months. It was longest for those who had the most severe neuropathies, and in these patients, mild, residual clinical signs remained.

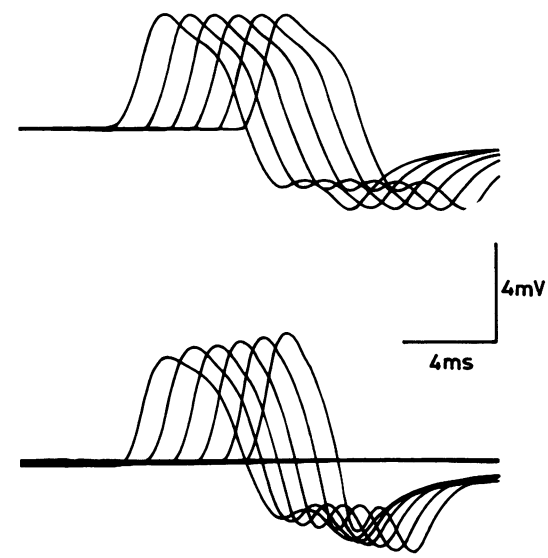

Fig 6 *Repetitive ulnar nerve stimulation studies, recording from hypothenar muscles, in a 43-year-old man, septic and critically ill, on aminoglycoside antibiotics, but with no clinical or electrophysiological evidence of polyneuropathy. Upper figure shows no change in hypothenar CMAP at stimuli of 3 Hz. Lower figure, stimuli at 20 Hz, shows an apparent incrementing response, but this is "pseudofacilitation," since the CMAP area did not change. Thus, no defect in neuromuscular transmission was demonstrated.*

Electrophysiological features of critically ill polyneuropathy

In comparing CIP patients to controls, the most marked and the only statistically significant ($p < 0.02$) nerve conduction abnormality was a reduction in the amplitudes of CMAP and CSAP (figs 1 and 2), which was greatest for muscle (fig 2). Measurements of motor and sensory conduction velocities, distal latencies, and F wave latencies were only mildly abnormal (fig 1).

The pattern of results for common peroneal and sural nerve conduction studies were similar to median nerve, except the reductions in CMAP and CSAP amplitudes were even more marked; the CSAP was absent from the sural nerves of seven patients and from the CMAP of the EDB muscle in three patients. To find out if the CSAP amplitudes were absent as a result of tissue oedema increasing the distance between surface recording electrode and the underlying nerve, near nerve recordings were carried out in a further 10 critically ill patients, five of whom had polyneuropathy. The response was absent with surface electrodes in seven patients but was recorded at low voltage but normal latency with averaged, near nerve recordings in four of these patients (fig 3) amplitude 3·3 (2·6–3·9) μV, but was still absent in three patients. We concluded these seven patients probably had axonal degeneration of their sural nerves, even though just five met the criteria (in *Methods*) for polyneuropathy.

Phrenic nerve conduction studies in 10 of the 15 patients revealed the response over the diaphragm was absent in three, all of whom had a severe polyneuropathy. In the remaining patients, the latencies were not significantly prolonged, as one would expect in a purely axonal degeneration. In our experience, the amplitude of the CMAP from the diaphragm is normally too variable to be usefully interpreted.

The most striking abnormalities were observed on needle electrode study of skeletal muscle (figs 4 and 5). These studies showed typical findings of acute denervation. In resting muscle, fibrillation potentials and positive waves were present, being both numerous and continuous in severe denervation. Unusual spontaneous activity had a high incidence, myotonic discharges being recorded in five patients and complex repetitive discharges in two patients. Needle electromyography was performed unilaterally on the external oblique and external intercostal muscles in 12 of 15 patients. Positive waves and fibrillation potentials were recorded in four of these patients, all having a severe polyneuropathy.

Repetitive nerve stimulation studies on a further 10 patients failed to reveal a defect in neuromuscular transmission, although five of these patients, all on aminoglycoside antibiotics, exhibited the phenomenon of "pseudofacilitation" at rapid rates of stimulation (fig 6).

Thus, the above findings point to a primary degeneration of motor and sensory peripheral nerves supplying the limbs and respiratory system.

Follow-up electrophysiological studies, performed at least once in 11 patients, were commensurate with clinical observations regarding the course of the polyneuropathy (table 1). Patients who improved while showing little change in the initially minimal derangements of speed of impulse conduction, demonstrated a rise in conduction velocities, a decrease in distal latencies, and in particular a rise in the amplitudes of compound muscle and nerve action potential amplitudes at six months (fig 2). Needle electrode studies revealed a gradual disappearance of abnormal spontaneous activity and a reappearance of motor unit potentials (fig 5), many of which were initially polyphasic, consistent with reinnervation of muscle. The time course of this reinnervation and the clinical recovery, itself, was unusually rapid, suggesting the distal parts of peripheral nerves had been predominantly affected and, hence, the distance for reinnervation was not great.

Neuropathological findings in critically ill polyneuropathy

Necropsy studies of the peripheral and central nervous systems were carried out in Patients 3, 4, 5, 9, 13, and 14, the first three of these patients having been previously reported.[9] The results for the last three patients were similar. The findings were consistent with a moderate to severe, primary, axonal polyneuropathy affecting sensory and motor fibres, particularly distal fibres. No significant inflammatory change was seen. In Patients 3 and 4, there was evidence of nerve fibre regeneration. Muscles showed acute denervation atrophy, but Patient 3 showed features suggestive of an additional primary muscle change. However, the central nervous system was spared, indicating this condition was confined to the peripheral nervous system.

Comparison of critically ill polyneuropathy and Guillain-Barré syndrome

The clinical data on both groups are shown in tables 1 and 2. It can be seen that they were similar in sex and severity of polyneuropathy. However, the Guillain-Barré syndrome patients tended to be younger (mean of 48 vs 65 years). However, in CIP patients the polyneuropathy was noted at the peak of critical illness and sepsis, in most instances within a month of admission to the critical care unit. In Guillain-Barré syndrome patients there were the usual predisposing illnesses (influenza innoculation in two, transient infection in 11, and no predisposing cause in three)

which had disappeared before onset of polyneuropathy. In CIP there were many complicating illnesses which began before the onset of polyneuropathy, consistent with sepsis and critical illness, whereas in Guillain-Barré syndrome, complications such as respiratory and autonomic failure, pneumonia, occurred after the polyneuropathy had developed.

The severity of the polyneuropathy was similar in the two types. However, it improved in all Guillain-Barré syndrome patients, but in CIP patients was improved in six, was unchanged in four and progressed in three.

Necropsy of six CIP patients revealed a primary axonal degeneration of motor and sensory fibres with sparing of the central nervous system. None of the Guillain-Barré syndrome patients died or had nerve or muscle biopsy.

In electrophysiological studies, the various measurements of the speed of impulse conduction (F wave latency, compound thenar muscle action potential latency, and compound digital nerve action potential latency (fig 1)) revealed values for CIP that were near normal, consistent with a purely axonal degeneration, and there was little change in these values in follow-up. However, Guillain-Barré syndrome patients, initially and particularly at one month, showed considerable slowing of impulse conduction in motor and sensory fibres. This tendency was most marked in distal motor fibres, as exemplified by the markedly prolonged compound thenar muscle action potential latency. During the six months of follow-up, the Guillain-Barré syndrome abnormalities tended to return towards normal. The amplitudes of compound thenar muscle and compound digital nerve action potentials were considerably reduced initially in both types of polyneuropathy (fig 2), although to a greater degree in Guillain-Barré syndrome, and more so for compound muscle action potentials. In follow-up, there was partial resolution in both types of polyneuropathies. A comparison of the amplitude and shape of compound action potentials on proximal stimulation as compared with distal stimulation revealed no evidence of conduction block or action potential dispersion in critically ill polyneuropathy, whereas these were present in eight of 16 Guillain-Barré syndrome patients.

At the time of the initial study, needle electromyographic studies in CIP patients revealed relatively abundant abnormal spontaneous activity, consistent with denervation atrophy of muscle (fig 5). Such activity was minimal in Guillain-Barré syndrome patients, consistent with a mainly demyelinating polyneuropathy. At one month, there was more electrophysiological evidence of denervation atrophy of muscle in the Guillain-Barré syndrome patients, indicating a degree of associated axonal degeneration. The number of motor unit potentials firing on attempted voluntary contraction was markedly depressed in both neuropathies, but with recovery in both the number of motor unit potentials recruitable with voluntary contraction progressively improved.

The cerebrospinal fluid revealed only mild elevations in CIP patients, mean 45·3 $\pm$ 34·4, but much more marked elevations in Guillain-Barré syndrome patients, mean 109·1 $\pm$ 79·1 mg/dl. The difference of the means was statistically significant using a two sample t test ($p = 0{\cdot}025$).

Discussion

Critically ill polyneuropathy

Between 1977 and 1981, we observed five patients who suffered from this unusual polyneuropathy.[9] Just as they were recovering from their critical illness, there was an inexplicable difficulty in weaning them from the ventilator. Deep tendon reflexes previously present were now reduced, and the limbs appeared flaccid and weak. While the face was mildly weak, muscles of the eyes, tongue, and jaw were relatively strong. Electrophysiological studies were consistent with a primary axonal degeneration of motor and sensory fibres and acute denervation of muscle. Follow-up revealed early improvement, although three patients later died of causes presumably unrelated to the polyneuropathy. Necropsy disclosed a primary axonal degeneration of peripheral nerves with sparing of the central nervous system.

Detailed analysis of the records of these five patients failed to uncover the aetiology.[9] There was no evidence of heavy metal poisoning, porphyria, viral infection, or specific vitamin deficiency. All patients received antibiotics, often in various combinations, and all received aminoglycosides, but blood levels of this group of antibiotics were not significantly elevated and a search of the literature has failed to reveal polyneuropathy as a complication of such treatment. Depressed levels of blood albumin and lymphocytes and observed improvement after the institution of total parenteral nutrition suggest, but do not prove, nonspecific nutritional deficiency as the cause. Since all patients were septic, bacterial toxin was a possible aetiological factor. However, the only specific toxins known to affect the peripheral nervous system are *Legionella pneumophilia* and *Corynebacterium diphtheriae*, neither of which were cultured in these patients. Nonetheless, the nonspecific effects of sepsis, which appear to be widespread and as yet poorly understood,[34] may have had an effect on the peripheral nervous system. Finally, Guillain-Barré syndrome has been a well-documented complication

of severe infection and trauma.[14] However, the unremarkable cerebrospinal fluid protein levels (see *Results*), the electrophysiological and necropsy findings of a primary, axonal degeneration of peripheral nerve, and the lack of significant inflammatory change in peripheral nerves, all argue against this diagnosis.

Preliminary reports from two other centres describe severe neuromuscular disease associated with critical illness. Roelofs *et al*[15] reported four patients who developed a severe, reversible, purely motor, neuropathy in association with sepsis and severe respiratory insufficiency. Rivner *et al*[16] described four patients who developed a similar motor neuropathy, presumably as a complication of severe, hypotensive shock.

The detection of 10 new patients between 1981 and 1983 in our hospital resulted from increased clinical awareness and, particularly, more frequent ordering of electrophysiological studies.[7 8] Critically ill patients who were noted to have difficulty in weaning from the ventilator and an unexplained weakness of limb muscles with relative sparing of the face on voluntary or reflex induced movements, were suspected of having a polyneuropathy. However, as already emphasised, these signs were often equivocal.

All patients were transported to the EMG laboratory while still on a ventilator and receiving various forms of supportive care. Nerve conduction studies revealed findings typical of a primary axonal degeneration of motor and sensory fibres. Peripheral sensory nerve and muscle compound action potential amplitudes were considerably decreased and the velocity of impulse conduction was normal or mildly slowed. The amplitude reductions were not due to limb oedema (which would move the surface recording electrode away from the nerve,[17] since near nerve recordings have shown amplitudes in such patients remain low or absent) (fig 3). Needle electromyography provided definitive evidence of denervation of muscle. There were numerous fibrillation potentials and positive sharp waves in proximal and distal limb, and intercostal muscles. The latter, coupled with abnormalities of phrenic nerve conduction, strongly implicated denervation of respiratory muscles, both chest wall and diaphragm, as the cause of difficulty in weaning from the ventilator. Repetitive nerve conduction studies failed to reveal a defect in neuromuscular transmission, even in patients who had received aminoglycosides (fig 6).

In addition to signs of acute denervation of muscle, needle electrode studies revealed unusual spontaneous activity, and myotonic and complex repetitive discharges in the muscles of seven patients. None of these patients had clinical evidence of either myotonia or muscle stiffness. Both types of discharges have been recorded in a wide variety of both primary muscle diseases and states of chronic denervation.[18] This finding, in conjunction with a marked lowering in the amplitude of the compound muscle action potential, suggests a predominant involvement of motor axons. However, sensory fibres are also involved. The CSAP was significantly lower than control values (fig 1) and morphological examination of purely sensory nerves has shown a primary axonal degeneration.[9]

Follow-up electrophysiological studies were consistent with peripheral nerve axonal regeneration. This regeneration occurred within a few weeks in the milder cases, but even in severe polyneuropathy the period of recovery was earlier than one would have expected if there had been marked proximal axonal degeneration. These observations suggest that the degeneration and regeneration involved distal nerve fibres predominantly.

Thus, electrophysiological findings have proven to be of crucial importance in detecting and following the course of the polyneuropathy which complicates the course of critical illness. One explanation for a puzzling deterioration, or failure to improve, in a patient's condition, has been provided and with such knowledge the patient can be managed more intelligently. Intensive treatment should continue, and should include ventilatory assistance as necessary, as well as the institution or continued use of total parenteral nutrition. Active physiotherapy should be prescribed to prevent joint contractures and pressure sores, which are particularly prone to develop in critically ill patients who also have a polyneuropathy. Follow-up electrophysiological studies will indicate whether or not the polyneuropathy is improving. Moreover, with the ability of electrophysiological studies to clearly identify this type of polyneuropathy, it may be possible in the future, with more intensive prospective investigations, to discover the precise aetiology.

Comparison of critically ill polyneuropathy and Guillain-Barré syndrome

On purely clinical grounds it was difficult to distinguish CIP from Guillain-Barré syndrome. In both, the polyneuropathy ran a monophasic course, the onset being relatively acute, with subsequent improvement occurring in most instances. The clinical features were also similar since there was evidence of muscle weakness in all four limbs, occasionally involving facial muscles and frequently involving the muscles of respiration; the deep tendon reflexes became depressed or absent, and there was some evidence of distal sensory impairment. The predisposing causes were, however, different. CIP invariably

occurred at the peak of critical illness and sepsis, but in Guillain-Barré syndrome there was a brief period of recovery following a relatively minor illness or innoculation. Finally, the prognosis was poorer in CIP, three patients failing to show improvement in the polyneuropathy, whereas all Guillain-Barré syndrome patients improved.

Electrophysiological differences also distinguished the two types of polyneuropathies. In CIP these features were typical of a primary axonal degeneration of motor and sensory nerves:[19] a relative preservation of the speed of impulse conduction, reduction in the amplitudes of muscle and sensory compound action potential amplitudes, no evidence of conduction block, and abundant spontaneous activity on needle electromyography of muscle, consistent with denervation atrophy. Alternatively, Guillain-Barré syndrome patients showed considerable prolongation of impulse conduction, particularly distally, evidence of dispersed compound action potentials or of conduction block, and much less abnormal spontaneous activity in muscle, as one would see in a predominantly demyelinating polyneuropathy.[10 19 20] The cerebrospinal fluid protein showed statistically significant higher levels in Guillain-Barré syndrome than in critically ill polyneuropathy, a further method of distinguishing the two polyneuropathies.[21] Therefore, these two polyneuropathies are almost certainly separate entities that can be distinguished from one another by the above studies in most cases. However, the relatively large standard deviations in electrophysiological and cerebrospinal fluid results in both groups indicates significant variation and there may be difficulties in distinguishing between the two neuropathies in some instances. However, patients who develop polyneuropathy, mild or severe, at the peak of critical illness or sepsis, have electrophysiological features typical of a primary degeneration of motor and sensory fibres, and have a relatively normal cerebrospinal fluid protein, likely have CIP. While the aetiology of CIP remains uncertain, a purely axonal degeneration is more suggestive of a toxic or metabolic disturbance[22-24] than of inflammatory or immune-mediated demyelination.

It was instructive to compare the two neuropathies from the point of view of electrophysiology. In critically ill polyneuropathy, motor and sensory fibres likely degenerate in a random manner, some faster conducting fibres being preserved, accounting for a relatively normal speed of maximum impulse conduction (fig 1). However, the fall-out of these fibres causes reduction in muscle and sensory compound action potential amplitude (fig 2), with no evidence of dispersion of the compound action potential, or of conduction block. This pattern, as already noted is characteristic of a primary axonal degeneration.[19]

The electrophysiological findings in Guillain-Barré syndrome are consistent with a primary segmental demyelination in which even the fastest conducting fibres are involved and there is slowing of the maximum rate of impulse conduction. Disproportionate slowing of conduction in some fibres results in a dispersion of the compound action potential. Severe demyelination results in conduction block in which compound action potential areas are larger on distal stimulation than on proximal stimulation. One explanation for the reduced CMAP and SNAP amplitudes (fig 2) is the possibility that the demyelination predominantly affected the distal portions of the nerve fibres, beyond the conventional point of distal stimulation.[25] This possibility is supported by the fact that, initially, needle electromyography revealed little evidence of denervation atrophy of muscle (fig 5), including distal muscles such as the first dorsal interosseus of the hand and the extensor digitorum brevis of the foot. The increased spontaneous activity at one month indicated a degree of axonal damage had developed. Indeed, in three of our Guillain-Barré syndrome patients, impulse conduction was not particularly slowed and spontaneous activity was more abundant in muscle, indicating the main pathology was axonal degeneration.

This pattern of nerve conduction and needle electrode abnormality in Guillain-Barré syndrome is consistent with observations by others. McLeod[20] observed similar marked prolongation of distal motor latency and reductions in CSAP amplitudes. The prolonged F wave latencies were similar to Kimura's patients.[26] Brown and Feasby[25] performed several techniques and analyses which allowed them to conclude that reduced CMAP amplitude was due to the combination of conduction block and denervation atrophy. By stimulating beyond the conventional point of distal stimulation, that is the median nerve in the palm and peroneal nerve in the foot, they were able to produce a further rise in amplitude, strongly suggesting the presence of a distal block.

In both CIP and Guillain-Barré syndrome, electrophysiological abnormalities gradually returned towards normal after the first month, consistent with axonal regeneration and segmental demyelination, respectively. In CIP, the degree of clinical and electrophysiological recovery was surprisingly rapid, suggesting axonal degeneration and regeneration were predominantly distal. In both groups, residual clinical and electrophysiological abnormalities were present at 6 months, indicating recovery had been incomplete.

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