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Patterns of neurophysiological abnormality in prolonged critical illness

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Abstract *Objective*: To describe the various patterns of neurophysiological abnormalities which may complicate prolonged critical illness and identify possible aetiological factors.
Design: Prospective case series of neurophysiological studies, severity of illness scores, organ failures, drug therapy and hospital outcome. Some patients also had muscle biopsies.
Setting: General intensive care unit (ICU) in a University Hospital.
Patients: Forty-four patients requiring intensive care unit stay of more than 7 days. The median age was 60 (range 27–84 years), APACHE II score 19 (range 8–33), organ failures 3 (range 1–6), and mortality was 23%.
Results: Seven patients had normal neurophysiology (group I), 4 had a predominantly sensory axonal neuropathy (group II), 11 had motor syndromes characterised by markedly reduced compound muscle action potentials and sensory action potentials in the normal range (group III) and 19 had combinations of motor and sensory abnormalities (group IV). Three patients had abnormal studies but could not be classified into the above groups (group V). All patients had normal nerve conduction velocities. Electromyography revealed evidence of denervation in five patients in group III and five in group IV. There was no obvious relationship between the pattern of neurophysiological abnormality and the APACHE II score, organ failure score, the presence of sepsis or the administration of muscle relaxants and steroids. A wide range of histological abnormalities was seen in the 24 patients who had a muscle biopsy; there was no clear relationship between these changes and the neurophysiological abnormalities, although histologically normal muscle was only found in patients with normal neurophysiology. Only three of the eight patients from group III in whom muscle biopsy was performed had histological changes compatible with myopathy.
Conclusions: Neurophysiological abnormalities complicating critical illness can be broadly divided into three types – sensory abnormalities alone, a pure motor syndrome and a mixed motor and sensory disturbance. The motor syndrome could be explained by an abnormality in the most distal portion of the motor axon, at the neuromuscular junction or the motor end plate and, in some cases, by inexcitable muscle membranes or extreme loss of muscle bulk. The mixed motor and sensory disturbance which is characteristic of 'critical illness polyneuropathy' could be explained by a combination of the pure motor syndrome and the mild sensory neuropathy. More precise

identification of the various neurophysiological abnormalities and aetiological factors may lead to further insights into the causes of neuromuscular weakness in the critically ill and ultimately to measures for their prevention and treatment.

Key words Critical illness · Multiple organ failure · Neuromuscular complications · Sepsis · Drug therapy

Introduction

Critical illness can be complicated by extreme weakness which may delay weaning from mechanical ventilation and prolong subsequent mobilisation. Postulated causes include the persistent effects of muscle relaxants or their metabolites [1], muscle fibre atrophy [2], a peripheral neuropathy [2–5] and a myopathy [2, 6–12], sometimes accompanied by muscle necrosis [9, 10]. A variety of factors may contribute to the development of muscle wasting complicating critical illness but the severe, acute myopathies have often been attributed to the administration of pharmacological doses of steroids, especially in those with acute asthma and when combined with steroid based muscle relaxants [6–8, 11]. 'Critical illness' neuropathy was first described in the early 1980s as a mixed motor and sensory axonal polyneuropathy complicating sepsis or hypotension and occurring in association with the development of multiple organ failure [3–5], but its precise aetiology remains uncertain. An atypical neurological syndrome, characterised by markedly reduced motor activity with little or no sensory involvement has also been described in patients with acute respiratory failure [13, 14] and in surgical patients with evidence of sepsis who required prolonged mechanical ventilation [15]. The aetiology of this 'motor' syndrome, which may occur in those with single organ failure and without objective evidence of sepsis [13, 14], is also unclear, as is its relationship to the acute quadriplegic myopathy with myosin loss which can complicate critical illness [11, 16].

In an attempt to elucidate the nature and aetiology of the neuromuscular abnormalities which may accompany critical illness, we carried out a prospective clinical, neurophysiological and histopathological study of long-stay, mechanically ventilated patients in our intensive care unit (ICU).

Patients and methods

We prospectively studied a mixed population of mechanically ventilated, critically ill patients recruited over a 3-year period, whose sole criterion for entry was duration of ICU stay of 7 days or more. Patients with pre-existing neuromuscular disorders were excluded. In contrast to previous workers, we did not restrict recruitment to patients with sepsis and multiple organ failure [17] nor to those with clinically obvious weakness [3–5]. Informed consent was obtained from the patients or their relatives. The Hospital Ethics Committee approved the protocol.

A clinical examination was performed at the time of patient recruitment and details of weakness and reflexes noted. Because these patients were severely ill, and usually obtunded due to drug therapy or the effects of the underlying condition, we used a simple grading system in which weakness was defined as mild (able to lift limbs against gravity), moderate (able to move limbs with gravity eliminated) or severe (unable to move limbs) according to the subjective assessment of one of the authors (JHC). This assessment preceded the performance of neurophysiological studies, but took place after neuromuscular blocking agents had been stopped and when the patient had become responsive.

Electrophysiological studies were performed using standard techniques. These included median and sural sensory action potential (SAP) amplitudes, compound muscle action potential (CMAP) amplitudes from abductor pollicis brevis (APB), and extensor digitorum brevis (EDB), median and common peroneal motor conduction velocities and concentric needle electromyography in five areas of at least tibialis anterior and biceps brachialis and sometimes rectus femoris muscles also. The lower limit of normal for motor nerve conduction velocities was 50 m/s in the upper limbs or 40 m/s in the lower limbs. A SAP (normal in our laboratory mean 23 μv, range 11–62 μv) of less than 10 μV or less than 5 μV in patients over 70 years old, CMAPs of less than 3.0 mV for APB (normal in our laboratory mean 7.6 mv, range 4.0–12.1 mv), and of less than 1.0 mV for EDB (normal in our laboratory mean 4.5 mv, range 2.7–8.0 mv) were regarded as abnormal. We deliberately set values lower than our normal range in order to ensure that patients were classified on the basis of unequivocal abnormalities. Twelve patients also underwent repetitive nerve stimulation to exclude neuromuscular junction dysfunction.

Muscle biopsies were obtained from the 24 patients in whom there were no contraindications (eg. thrombocytopaenia, coagulopathy, refused consent) under local anaesthetic (5 ml 2% lignocaine), from the vastus lateralis muscle using the percutaneous conchotome technique. Samples were processed by standard techniques [2] and frozen sections were examined after staining, with haematoxylin and eosin, the modified Gomori trichrome method and Periodic Acid Schiff stain. Histochemistry was carried out for ATPase at pH 9.4 and pH 4.6, NADPH-TR and succinic acid dehydrogenase. On the ATPase at pH 9.4 stained section, the fibre type proportion was determined and fibre size was measured by computerised morphometric analysis.

Drug therapy was recorded, with particular emphasis on steroid and muscle relaxant administration. The APACHE II [18] score, an organ failure score [2] and the presence or absence of sepsis (according to our previously published objective criteria) [2] were also noted. In five patients the detailed records for muscle relaxant administration were lost. For the purpose of analysing aetiological factors, these patients were all assumed to have received muscle relaxants for more than 24 h, although the dose and type are uncertain.

The findings were not analysed statistically because of the relatively small numbers in the various groups.

Results

A total of 44 (23 male) long-stay (> 7 days), mechanically ventilated patients was studied. The median age

was 60 (range 27–84) years, and median APACHE II score was 19 (range 8–33). These values are typical of the long-stay population of our ICU. The overall ICU mortality was 18%, with a further two patients dying on the ward after ICU discharge, giving a hospital mortality of 23%. Patients' clinical details are given in Table 1.

Neurophysiological studies were normal in only seven patients (group I). In the remainder, three distinct patterns of neurophysiological abnormality could be identified. Four patients had sensory neuropathy characterised by reduced SAPs, most often affecting the sural nerve and normal CMAPs (group II), while 11 patients had motor syndromes characterised by markedly reduced CMAPs involving both upper and lower limbs and SAPs in the normal range (group III). A further 19 patients had a combination of low CMAPs and low SAPs (group IV). Three had abnormal results but could not be classified with certainty because insufficient data were recorded at the time of study for technical reasons (group V). Nerve conduction velocities were normal (> 50 m/s) in all patients. Electromyography revealed evidence of denervation, such as fibrillation potentials and positive sharp waves, in five patients in group III and five in group IV. Repetitive nerve stimulation revealed no evidence of persistent pharmacological neuromuscular junction blockade in 12 patients in whom these studies were carried out (two from group I, six from group III and four from group IV). The neurophysiological data are summarised in Table 2.

There was a wide range of histological abnormalities in the 24 patients who had muscle biopsy and there was no clear relationship between these changes and the neurophysiological abnormalities (Table 2). The most common abnormality (12 patients) was diffuse atrophy of both fibre types, which was often severe. The next most frequent abnormality was myopathy with fibre atrophy and occasional scattered necrotic fibres, affecting eight patients. Only three of the eight patients from group III in whom muscle biopsy was performed had histological changes compatible with myopathy. Other, rarer features were neurogenic atrophy in three patients and isolated type 2 muscle fibre atrophy in one. Only two patients had normal muscle, and both of these were also normal on neurophysiological examination. No patients had evidence of gross muscle necrosis or inflammatory changes.

The age, APACHE II, organ failure scores, incidence of sepsis and outcome are given for patients in the various groups in Table 3. Overall 64% of the patients fulfilled the predefined objective criteria [2] for the diagnosis of sepsis. There were patients in all groups with only single organ failure and 20% of the study group overall had single organ failure (Table 3). The most common organ failure was respiratory (100%) and more than half the patients (55%) fulfilled the criteria for cardiovascular failure. Other organ failures were less common, but included gastro-intestinal (32%), renal (27%), central nervous system (25%), hepatic (20%) and haematological (18%). Failure of the neuromuscular apparatus diagnosed neurophysiologically occurred in 84% of the patients studied.

Table 1 Clinical details

No.	Age/Sex	Diagnosis
Group I		
1	70 M	Aortobifemoral graft
2	29 M	Multiple trauma
3	27 M	Cocaine overdose
4	65 F	Exacerbation of chronic bronchitis
5	58 M	Exacerbation of chronic bronchitis
6	54 F	Cardiac arrest
7	63 F	Head injury
Group II		
8	70 F	Mitral valve replacement & coronary artery bypass
9	36 M	Peritonitis
10	29 M	Smoke inhalation
11	31 M	Head injury
Group III		
12	72 M	Psoas abscess
13	72 F	Exacerbation of chronic bronchitis
14	59 M	Pneumonia
15	58 M	PE, renal failure, cardiac arrest, ARDS
16	62 F	Peritonitis
17	41 M	Neuroleptic malignant syndrome
18	47 M	Pneumonia
19	43 F	Multiple trauma
20	70 M	Peritonitis
21	70 F	Stroke post carotid endarterectomy
22	47 F	Peritonitis
Group IV		
23	76 M	Aneurysm repair, chronic bronchitis
24	46 F	Heart transplant
25	72 F	Exacerbation of chronic bronchitis
26	56 F	Pneumonia
27	61 F	Peritonitis
28	34 F	Pelvic actinomycosis
29	63 F	Peritonitis
30	70 M	Aortic valve replacement
31	32 M	Smoke inhalation
32	77 F	Peritonitis
33	67 F	Cardiogenic shock
34	84 M	Ruptured aortic aneurysm
35	55 M	Aortic embolus
36	70 F	Renal failure due to amyloidosis
37	55 F	Multiple trauma, fat embolus
38	57 F	Exacerbation of chronic bronchitis
39	65 M	Peritonitis
40	41 M	Head injury
41	62 F	Oesophageal rupture
Group V		
42	64 M	Flail chest
43	33 M	Immunocompromised, pneumonia
44	66 M	Hyperosmolar diabetic coma

Table 2 Summary of neurophysiological data and muscle biopsy findings

Group	No.	Sural SAP (μv)	Adductor pollicis brevis CMAP (mv)	Extensor digitorum brevis CMAP (mv)	Muscle biopsy
I	7	16 (5–22)	4.7 (3.2–6.0)	3.4 (1.1–7.0)	Normal (2) Diffuse fibre atrophy (1)
II	4	3 (0–6)	4.0 (3.4–6.7)	1.5 (1.1–1.9)	Diffuse fibre atrophy (2) Type II fibre atrophy (1)
III	11	12 (6–16)	1.6 (0.4–3.4)	0 (0–0.7)	Diffuse fibre atrophy (3) Neurogenic atrophy (2) Myopathy (3)
IV	19	0 (0–6)	2.4 (0.4–4.0)	0 (0–0.6)	Diffuse atrophy (6) Neurogenic atrophy (1) Myopathy (3)
V	3	18 (14–20)	ND	2.0 (0.6–2.4)	Myopathy (2)

Data presented as median value (range). For normal values see text

Table 3 Age, severity of illness and outcome data according to neurophysiological group

Group	No.	Age	APACHE	Organ failures	Sepsis	Mortality	ICU stay	Post ICU hospital stay
I	7	58 (27–72)	27 (13–33)	3 (1–6)	57	14	21 (15–61)	15 (11–45)
II	4	46 (29–70)	15 (12–19)	2 (1–2)	25	0	17 (13–29)	40 (3–192)
III	11	62 (41–72)	17 (12–29)	3 (1–4)	64	27	33 (8–62)	21 (10–34)
IV	19	61 (32–84)	19 (8–29)	3 (1–6)	68	26	48 (15–93)	40 (1–106)
V	3	57 (33–62)	20 (10–22)	1 (1–3)	66	33	22 (7–25)	10 (10–10)

Data presented either as median (range) or percentages

Patients in all groups received muscle relaxants (Table 4), the only two in use on our unit during the study period being vecuronium and atracurium. All neurophysiological groups included patients who had received large doses of muscle relaxants as well as patients who received none. Muscle relaxants were not used at all in 23 % of the patients, and in others only small bolus doses were used. The largest dose of atracurium (48,200 mg) was given to a patient who developed no abnormality; three patients with the motor syndrome (group III) and three patients with mixed motor and sensory neuropathy (group IV) received no muscle relaxants at all. There were also many patients who received muscle relaxants for less than 24 h of their stay (Table 4).

Overall only 25 % of the patients received corticosteroids and the administration of these agents did not appear to be associated with any particular neurophysiological pattern (Table 4). There were patients in all groups who received a combination of muscle relaxants and steroids (Table 4).

The degree of weakness and reflex abnormality found on clinical examination was variable. Severe weakness was confined to patients in groups III, IV and V, who were tetraparetic with very reduced muscle tone. Many were totally incapable of movement. Weakness affected both the proximal and distal muscle groups. Reflexes were largely normal in groups I and II, whereas they were commonly depressed or absent in groups III, IV and V. Muscles innervated by the cranial nerves were relatively spared.

Discussion

Our observations in this unselected group of long-stay, mechanically ventilated intensive care patients have led us to conclude that neurophysiological abnormalities complicating critical illness can be broadly divided into three types – sensory abnormalities alone (group II), a pure motor syndrome (group III) and a mixed motor and sensory disturbance (group IV). In all cases demyelination was excluded by normal conduction velocities. Patients in group II seemed to be suffering from a predominantly sensory axonal neuropathy, similar to that described in patients with a variety of chronic systemic illnesses, such as diabetes mellitus, in the elderly and in patients given metronidazole. The neurophysiological findings in patients which we have classified as group III, who exhibited an unusual combination of

Table 4 Use of muscle relaxants and steroids according to neurophysiological group

Group	No.	Muscle relaxants	Muscle relaxants for > 24 h	Steroids	Both
I	7	71	71	29	29
II	4	75	75	0	0
III	11	73	36	27	18
IV	19	84	53	32	32
V	3	33	0	66	33

Percentages of patients in each group who received neuromuscular blocking agents, steroids or both

markedly abnormal CMAPs with normal SAPs, are of particular interest since they are not characteristic of a diffuse axonal polyneuropathy. We do not believe that this group of patients, which we have previously reported as having neurogenic weakness [13], can be classified with any certainty as having a conventional neuropathy and would prefer to call this syndrome, which could be explained by an abnormality in the most distal portion of the motor axon, at the neuromuscular junction or the motor end plate, and in some cases by inexcitable muscle membranes or extreme loss of muscle bulk, critical illness motor syndrome (CIMS). Patients reported by Gorson and Ropper [14] as 'acute respiratory failure neuropathy' and by Hund and colleagues [15] had the same neurophysiological abnormality.

The group IV neurophysiological abnormalities were similar to those in group III but with the addition of sensory changes. Findings in these patients are those of "critical illness neuropathy", which we suggest could represent a group of patients with a combination of the pure motor syndrome seen in group III and the group II non-specific mild sensory neuropathy.

Although some patients with CIMS might simply have suffered a dramatic loss of muscle mass such as may occur in a severe myopathy [6, 7], in several of our patients the occurrence of fibrillation potentials and positive sharp waves suggests that myopathy alone is unlikely to account for the neurophysiological abnormalities. Moreover, in those patients who were able to cooperate with voluntary motor unit studies, the features of chronic denervation and re-innervation were observed. Although fibrillations may be seen in inflammatory myositis and in those with severe muscle necrosis, none of the patients in this study or our previous report [2] showed such gross changes on muscle biopsy and myopathy was seen in only three of the eight patients in group III from whom a muscle biopsy was obtained. Muscle necrosis, when present, was limited to occasional single fibres. Clinically our patients had both proximal and distal weakness and in most cases the tendon reflexes were diminished or absent, as observed in many other reports [13–15, 17]. We therefore conclude that, in the majority of cases, the clinical features of this intriguing syndrome cannot be explained solely by a primary muscle disorder, although we recognise that some patients classified as having CIMS may be suffering from an acute quadriplegic myopathy with inexcitable muscle membranes [11, 12, 16] or extreme loss of muscle bulk. In a few patients, therefore, the neurophysiological features of 'critical illness neuropathy' [5, 17], could be explained by a combination of a severe myopathy (with loss of muscle bulk and/or inexcitable muscle membranes) with a sensory axonal neuropathy.

It was not possible to determine the true incidence of neurophysiological abnormalities from this study, since we were not able to study all patients who fulfilled the entry criteria, either because they died or were discharged before they could be studied, or because consent was refused. Nevertheless, the recruited patients were typical of our long-stay patients and approximately 84% showed some abnormality, a similar incidence to that found by Berek et al. [19]. Of the 24 patients who also had muscle biopsies, a variety of abnormalities occurred in 92%. The range of different neurophysiological abnormalities and the variety of histological features seen on muscle biopsy suggests that the aetiology of nerve and muscle disorders complicating critical illness is varied and complex. Certainly there appeared to be no obvious relationship between the abnormalities on neurophysiological testing and muscle histology, although the only two normal muscle biopsies were from patients with normal neurophysiology.

It has previously been suggested that the development of critical illness neuropathy is invariably associated with multiple organ failure and sepsis [5, 17] and there are a number of theoretical arguments in support of such an association. We have shown, however, that peripheral neurological changes may occur in patients who do not fulfil accepted objective criteria for the diagnosis of sepsis, as well as in those with only single organ failure – an observation previously made in three smaller series of patients with respiratory failure [2, 13, 14]. As would be expected in a study of long-stay ICU patients, sepsis and multiple organ failure were common, but did not seem to be a prerequisite for the development of neurophysiological abnormalities. The validity of this observation is compromised, however, by the difficulties associated with the use of strict 'yes or no' objective criteria for the diagnosis of organ failure and sepsis. It has to be acknowledged that many of our patients might have fulfilled less stringent criteria for both mild sepsis or systemic inflammation and borderline organ dysfunction.

It is also widely believed that administration of muscle relaxants is associated with neuromuscular disorders on the ICU [1, 20–22], although the first report of this association [20] was submitted for publication prior to

the first description of critical illness neuropathy [5] and the various myopathies which may complicate severe illness [2, 6, 12]. Possible mechanisms for such an association include the persistent effects of muscle relaxants or active metabolites [1], pharmacological denervation hastening muscle atrophy, some form of slowly reversible damage to the motor end plate or direct neuromuscular damage especially when these agents are used in combination with aminoglycosides [20] or corticosteroids [7]. The steroid components of the muscle relaxants pancuronium and vecuronium have also been implicated as a cause of prolonged weakness due to a variant of steroid myopathy, but this cannot explain a recent report of tetraparesis following atracurium therapy in a patient with severe asthma [21], since atracurium has no steroidal component.

We have shown that neurophysiological abnormalities, including the purely motor syndrome, may occur in those who have never received neuromuscular blocking agents, and that the administration of extremely large doses of muscle relaxants is not necessarily complicated by prolonged motor weakness or neurophysiological changes. Moreover repetitive nerve stimulation excluded persistent pharmacological neuromuscular junction blockade when performed in six patients with CIMS and four with critical illness neuropathy. It seems possible that the abnormalities of neuromuscular function originally ascribed to pancuronium [20] and other muscle relaxants [21, 22] have little or no connection with the administration of these agents and, in such cases, the administration of a muscle relaxant may simply reflect the severity of the underlying disease, particularly the need to ensure adequate ventilation in the early stages of management. Although we try to resist the use of muscle relaxants in critically ill patients, we do not believe that they are as much of a "two-edged sword" as some [22], provided overdose and accumulation of metabolites are avoided and particular care is taken in patients with hepatic or renal impairment [1]. In our study patients with renal failure who required the prolonged use of neuromuscular blocking agents invariably received atracurium, which has no metabolites active at the neuromuscular junction.

Steroid administration did not appear to be associated with any particular neurological or muscle histological feature, nor did the combination of steroid with muscle relaxant administration. We have previously described patients similar to our group III patients who did receive such a combination [13], but another series of similar patients with the same neurophysiological abnormality were not all so treated [14].

Neurophysiological and muscle histological abnormalities are extremely common in long-stay, mechanically ventilated patients and it is important that such patients are not assumed to have irreversible neurological damage, although recovery may be prolonged. The diverse and complex nature of the changes which we have described here, together with previous studies documenting myopathy [6, 7], rhabdomyolysis [8], necrotising myopathy [9, 10], acute quadriplegic myopathy [11, 12, 16] and other muscle and nerve abnormalities [2–5, 13–15, 17, 23] suggest that a single cause is unlikely. In particular, the neurophysiological features of the motor syndrome (group III in our proposed classification) could be caused by various abnormalities of muscle and nerve, either alone or in combination. Neurophysiologically it resembles a well documented motor axonal neuropathy associated with a flaccid acute paralysis [24] and there is evidence that it may be due to a lesion of the terminal motor axons [25]. At the moment we are unable to offer any firm suggestions as to their aetiology. Certainly we cannot consistently implicate steroids or muscle relaxants as predisposing factors. Our findings with respect to muscle relaxants have been supported by other previous studies [15, 23, 26]. It is to be hoped that more precise identification of the various neurophysiological abnormalities may lead to further insights into the causes of neuromuscular weakness in the critically ill and, ultimately, to measures for their prevention and treatment.

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