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Critical illness polyneuropathy in multiple organ dysfunction syndrome and weaning from the ventilator

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Abstract *Background:* Acute axonal polyneuropathy has been found in patients with multiple organ dysfunction syndrome. This 'critical illness polyneuropathy' (CIP) has been associated with difficult weaning from the ventilator in retrospective studies.
Objective: To test the hypothesis that CIP is related to the degree and number of organ dysfunctions, and to weaning problems.
Design: Prospective study of 18 months.
Setting: A multidisciplinary intensive care unit in a general hospital.
Subjects: Thirty-eight patients under 75 years of age who had been mechanically ventilated for more than 7 days, without previous signs of or risk factors for polyneuropathy.
Measures: Organ dysfunctions were quantified using a dynamic scoring system (0–12 points). Electromyography studies were performed during mechanical ventilation to identify patients with and without CIP.
Results: CIP was present in 18 out of 38 patients and associated with an increased organ dysfunction score (5.3 ± 1.8 vs. 3.6 ± 1.5; $p = 0.003$) and number of organs involved [median (range): 4 (3–5) vs. 2 (1–4); $p = 0.009$], in particular cardiovascular ($p = 0.003$), renal ($p = 0.04$), and hematopoietic failure ($p = 0.04$). Patients with polyneuropathy were ventilated longer, but this was not clearly due to more difficult weaning [median: 16.5 (1–48) vs. 9.5 (1–38) days; $p = 0.26$]. Polyneuropathy was present in 2 of 4 patients with normal weaning.
Conclusions: Axonal polyneuropathy is related to the severity of multiple-organ-dysfunction syndrome. Its presence does not necessarily implicate difficult weaning from artificial ventilation.

Key words Polyneuropathy – Critically ill – Multiple organ dysfunction syndrome – Mechanical ventilation – Weaning – Intensive care – Electromyography

Introduction

Multiple organ dysfunction syndrome (MODS) is an important cause of death in the general intensive care unit (ICU). The syndrome was recognized in the 1970s after life-sustaining techniques had become successful [1]. Even now, mortality from MODS is over 50% [2]. MODS is precipitated by the inflammatory response to an overwhelming insult such as severe trauma or sepsis [3, 4], the release of large amounts of anti-inflammatory mediators interrupting various physiological systems [5].

In the 1980s, an acute polyneuropathy was described in MODS and sepsis [6–13]. Critical illness polyneuropa-

thy (CIP) is the name Bolton et al. [14] gave to this polyneuropathy that is characterized by a generalized dysfunction of nerve axons. It can be diagnosed by electromyography (EMG), which is also the most important means to differentiate CIP from the classical example of acute polyneuropathy, the Guillain-Barré syndrome.

CIP has hitherto only been found in patients on respiratory support. In one prospective study, CIP occurred in 70% of those patients when sepsis or MODS was present [15]. The cause of CIP is still unknown; originally, malnutrition [6] and long-term pharmacological blockade of the neuromuscular synapse [8] were implicated. Currently, it is postulated that CIP is a toxic side effect of the inflammatory response, which also causes other organ failures in MODS [11, 15, 16]. Confusion remains, because CIP has also been described in a few patients without MODS [17, 18].

We have previously shown that CIP causes rehabilitation difficulties [19]. In the early observations, CIP was related to difficult weaning from artificial ventilation [18, 20, 21], possibly due to denervation of inspiratory muscles [22]. In the critically ill, the prolonged need for ventilatory support contributes to morbidity and mortality during hospitalization [23], and CIP may in this way exert a negative influence on prognosis.

All these concepts are based mainly on retrospective studies. In a prospective study, we tested the two hypotheses that CIP is associated with the presence and degree of MODS, and with prolonged weaning from the ventilator.

Materials and methods

Study design

From July 1991 until January 1993, we studied all patients under 75 years of age who were on mechanical ventilation for more than 7 days. All examinations were done in our ICU, which is a 16-bed multidisciplinary unit for medical and surgical patients in a general community hospital. Patients were screened for the presence of polyneuropathy by EMG. Excluded were those patients (1) who were suspected of preexisting polyneuropathy because they had a diagnosis of diabetes mellitus, alcohol abuse, HIV infection, renal disease, or had used neurotoxic medication; (2) reported distal weakness, numbness, paresthesias or radicular pain before the onset of critical illness; (3) who had generalized conduction slowing in their EMG but no evidence for acute axonal damage. Included patients were then separated into two groups, one without polyneuropathy, and one with signs of an acute axonal polyneuropathy [16]. These two groups, referred to as 'without CIP' and 'with CIP', were evaluated for the presence of MODS and sepsis, and the severity of their disease was quantified afterwards. The mean duration of mechanical ventilation and weaning was calculated for both groups. Routine laboratory examinations during the study included serum levels of vitamins B_1 and B_{12}, thyroid-stimulating hormone, phosphate, magnesium, and creatine kinase. The protocol was approved by the ethical committee of our hospital. Informed consent was obtained from the patient or a close relative.

EMG

In our experience, in most cases an early reliable diagnosis of CIP is very difficult clinically and will depend on nerve conduction studies and concentric needle examinations (both referred to as 'EMG'). EMG is necessary for characterization of polyneuropathy before a diagnosis of CIP can be made [14, 16]. EMGs were performed after 7–9 days of mechanical ventilation, after 3 weeks, and after 2 months if the patient was still in the ICU. The EMG protocol included nerve conduction studies of the median, tibial, peroneal, and sural nerves, preferably on the right side, with assessment of nerve conduction velocity and amplitudes of the compound muscle and sensory nerve action potentials at distal and proximal supramaximal stimulation (see [19]). Concentric needle examinations were performed in the m. abductor pollicis brevis, m. interosseus I, m. flexor hallucis brevis, and m. tibialis anterior. If fibrillations or sharp positive waves were found in any of these, the contralateral side and other muscles were studied. Decrement studies were done to evaluate neuromuscular transmission in patients on vecuronium for more than 2 days. In all patients, skin temperatures were above 31 °C. Studies were conducted in the ICU with a transportable Mystro Medelec MS20 apparatus (Vickers Healthcare Co.).

Criteria for CIP

A diagnosis of CIP was made when signs of acute and diffuse axonal dysfunction were present, defined as both the presence of abnormal spontaneous muscle activity in more than one muscle group in more than one extremity, in combination with diminished action potential amplitudes in at least two muscles or nerves. Polyneuropathy characterized by generalized conduction slowing only was not considered to be CIP. We refer to a previous report for the exact normal values [19].

MODS severity

The maximum APACHE II score during the first 24 h in the ICU [24] was calculated. For day-to-day monitoring of complications, a scoring method was used based on the system devised by Goris et al. [3] (see Table 1), and validated by others [25, 26]. The only difference is that we omitted the central nervous system from the original set of organs to be evaluated, because artificial paralysis or sedation often precluded assessment of consciousness. A patient was scored every day using bed chart, medical record, and laboratory data.

Weaning

Methods of mechanical ventilatory support included controlled and (synchronized) intermittent mandatory ventilation, mostly with positive end-expiratory pressure, pressure support, and continuous positive airway pressure ventilation. Weaning trials started when neuromuscular transmission studies were normal. Each day, we examined whether patients could contribute to their own ventilation. When this led to successful respiratory efforts for 2 days or more, this was taken as the start of weaning. Extubation or unassisted ventilation through a tracheostomy marked the end of weaning. Patients who died during ventilatory support were excluded from the weaning analysis.

Table 1 Organ dysfunction scoring system (adapted from Goris et al. [3]). *MV* Mechanical ventilation, *PEEP* positive end-expiratory pressure ventilation, FIO_2 fraction of inhaled oxygen, *BP* blood pressure, *SGPT* alanine aminotransferase, *GGT* γ-glutamyl transferase, *PT* prothrombin, *WBC* white blood count

Organ	Score	
Lung	0	No MV
	1	MV, PEEP ≤ 10 cmH_2O and/or $FIO_2 \leq 0.4$
	2	MV, PEEP > 10 cmH_2O and/or $FIO_2 > 0.4$
Heart	0	Unsustained normal BP
	1	Periods of hypotension requiring volume loading to keep BP > 100 mmHg, or dopamine/dobutamine HCl ≤ 10 µg/kg per minute i.v., or nitroglycerin ≤ 20 µg/min i.v.
	2	Periods of hypotension < 100 mmHg, dopamine/dobutamien HCl > 10 µg/kg per minute i.v., nitroglycerin > 20 µg/min i.v. or adrenalin i.v.
Kidney	0	Creatinine < 240 µmol/l
	1	Creatinine ≥ 240 µmol/l
	2	Hemodialysis or peritoneal dialysis
Liver	0	SGPT < 50 U/l, bilirubin < 35 µmol/l, and GGT < 100 U/l
	1	SGPT > 50 U/l, GGT > 100 U/l, 35 µmol/l ≤ bilirubin ≤ 100 µmol/l, and PT < 20%
	2	Bilirubin > 100 µmol/l
Blood	0	Normal WBC and platelets
	1	Platelets $< 50 \times 10^9$/l and/or 30×10^9/l ≤ WBC < 60×10^9/l
	2	Hemorrhagic diathesis or WBC < 2.5×10^9/l or ≥ 60×10^9/l
Gut	0	Normal
	1	Acalculous cholecystitis, stress ulcer or paralytic ileus
	2	Bleeding from stress ulcer with transfusion of blood > 2 U/24 h, or necrotizing enterocolitis or pancreatitis, and/or spontaneous gallbladder perforation

Medication

Vecuronium bromide (Norcuron, Organon), a nondepolarizing neuromuscular drug, was used for intubation (0.1 mg/kg). In half of the patients (19/38, 11 of whom had CIP), this was followed by a maintenance dose of 0.03 mg/kg per hour or more until the patient stopped breathing spontaneously. The administration was interrupted daily to see if the patient could be ventilated without paralyzation. As a sedative, intravenous midazolam (Dormicum, Roche) was used (0.25 – 1 mg/kg per day). All patients on mechanical ventilaton received subcutaneous calcium heparin, sucralfate and selective gut decontamination (amphotericin B, colistin sulfate and norfloxacin) through a nasogastric tube.

Statistical analysis

A two-sided Student's *t*-test (corrected for unequal variances) was used to study differences between the means of several variables in the group with and without CIP. χ^2 and Fisher's exact 2×2 tests were used to study proportional differences. The nonparametric Mann-Whitney U-test was employed for total number of organ dysfunctions, time to maximum MODS score, and weaning days. Only resulting two-sided p values < 0.05 were considered statistically significant.

Results

From July 1991 until January 1993, 78 patients younger than 75 years were ventilated for more than 7 days. Excluded were two patients with Guillain-Barré syndrome, four with thiopental-induced coma, and six with possible preexisting polyneuropathy. Among 66 eligible patients, reliable EMG recordings could not be obtained in 22 because of severe edema, artificial paralysis until death, limb amputation, or lack of informed consent. In six of the remaining 44 patients, EMG studies revealed polyneuropathy that was not considered to be CIP (see Materials and methods section). This left 38 patients for our analysis.

Association between CIP and MODS

Eighteen of 38 patients studied eventually developed CIP. They were compared with the other 20 patients without polyneuropathy. Indications for admission were about the same in both groups: abdominal surgery in 11 patients (6 without, 5 with CIP), thoracic surgery in 3 (2 vs. 1), primary infection or sepsis in 9 (4 vs. 5), polytrauma in 5 (2 vs. 3), cardiac resuscitation in 6 (3 vs. 3), intracerebral hematoma in 2 (1 in each group), and 2 status asthmaticus (in the non-CIP group).

Patients in both groups had comparable age and sex distributions and similar APACHE II scores in the first 24 h (Table 2). After the first day, patients with CIP had failure of more organ systems and reached the nadir of complications at a later moment. CIP did not develop in patients who had only pulmonary failure (Table 3). We found a higher prevalence of cardiovascular, renal, and hematopoietic complications in patients with CIP. Hypotension requiring aggressive treatment was present in all CIP patients. The overall mortality was 32% in our series (12/38) and tended to be higher in CIP patients (Table 2).

Several factors were studied which have been implicated in polyneuropathy in the ICU (Table 2). Tendencies but no clear differences were found in duration of vecuronium and midazolam administration. Only the association with i.v. aminoglycoside use reached significance. Of 14 patients who received i.v. aminoglycosides (mainly gentamicin), 11 had CIP; apart from three of the latter, they all had clinical sepsis [4]. Three patients received high-dose corticosteroids (one without CIP), but none developed severe myopathy.

Sepsis was present in 47% (18/38) of cases at any time during mechanical ventilation. Positive blood cultures included Gram-positive bacteria in 13 patients (*Staphylococcus epidermidis* and *Enteroccus faecalis*), Gram-negative bacteria in four patients, and *Candida albicans* in one patient. Mean levels of albumin, magnesium, vitamins B_1 und B_{12}, and thyroid-stimulating hormone were the same in both patient groups.

Table 2 Characteristics of 38 patients with and without critical illness polyneuropathy (*CIP*) on mechanical ventilation for more than 7 days

	No CIP	CIP	*p*
Number	20	18	
Males	14 (70%)	12 (67%)	0.83[a]
Mean age (years)	54.7 ± 17.3	58.5 ± 17.0	0.49[b]
Mean number of ventilation days	20.3 ± 10.9	33.6 ± 19.8	0.02[b]
Mean APACHE II in first 24 h	23.1 ± 6.8	21.9 ± 9.1	0.66[b]
Mean maximal MODS score	3.6 ± 1.5	5.3 ± 1.8	0.003[b]
Median number (range) of days to reach maximum MODS score	1 (1 – 2)	4.5 (2 – 9)	0.002[c]
Median number (range) of different organs involved (max. 6)	2 (1 – 4)	4 (3 – 5)	0.009[c]
Sepsis syndrome	8 (40%)	10 (56%)	0.34[a]
Number of deaths in the ICU	4 (20%)	8 (44%)	0.11[a]
Median number (range) of days on			
Vecuronium	0.5 (0 – 16)	2 (0 – 17)	0.18[b]
Midazolam	6.5 (0 – 29)	9.5 (0 – 27)	0.25[b]
I.v. aminoglycosides	0 (0 – 11)	4 (0 – 9)	0.04[b]

[a] χ^2
[b] Student's *t*-test
[c] Mann-Whitney U-test

Table 3 Involvement of different organ system dysfunctions as defined in Table 1 in patients with and without critical illness polyneuropathy (*CIP*)

Organ involved	No CIP	CIP	*p*[a]
Lung	20 (100%)	18 (100%)	1.00
Heart	12 (20%)	18 (100%)	0.003
Kidney	4 (13%)	10 (56%)	0.04
Liver	8 (40%)	12 (67%)	0.12
Blood	3 (15%)	9 (50%)	0.04
Gut	9 (43%)	8 (44%)	0.74

[a] Fisher's Exact test

CIP and weaning

Twenty-eight patients were successfully weaned from the ventilator. Two of them, both with CIP, died later, but were included in the weaning analysis. Of these 28 patients, those with CIP were ventilated longer, but this difference was not clearly explained by more prolonged weaning (Table 4). Two of the 4 patients with a weaning period of 30 days or more had CIP. Both had preexisting chronic obstructive pulmonary disease (COPD) that probably accounted for difficult weaning as in one of the two patients without CIP. The fourth patient, without CIP, had been unconscious for a long time after removal of an intracranial hematoma; prolonged weaning in his case seemed to be due to central respiratory depression. In these four patients who took longer than a month to come off the ventilator, weaning started after 1 – 10 days of ventilation, with 1 – 4 days on vecuronium. Exclusion of all five patients with COPD (Table 4) did not strengthen the association between CIP and number of weaning days ($p = 0.42$). Uncomplicated weaning was defined as coning off the ventilator within 2 days after the first weaning attempt. We found two patients with CIP and two without CIP who did not have any weaning difficulties. These four patients had been on controlled ventilaton for 7 – 10 days before weaning and had received vecuronium for 1 – 4 days.

Discussion

Although polyneuropathy seems prevalent in a high number of patients on prolonged mechanical ventilation, very few prospective studies on CIP are available [15, 27]. Some proposals for a pathophysiological theory of CIP have been based on retrospective studies [16]. The latest of these links CIP with MODS and the massive release of inflammatory mediators. However, recent efforts to find an immunological factor [28] and an experimental treatment based on a presupposed immunotoxic origin [29], have been unsuccessful. Equally uncertain and even less studied is the association between CIP and ventilation weakness. Much selection bias may have entered case descriptions, because the early idea of a cause-effect relationship seemed attractive.

In our prospective study, we took great care to define, within a cohort of critically ill patients on mechanical ventilation, a group with unequivocal CIP and one without any polyneuropathy. We are aware that this meant the exclusion of the majority of eligible patients. This was thought necessary while addressing these basic questions.

Polyneuropathy and MODS

In our study, CIP was strongly associated with multiple organ dysfunctions, confirming an earlier study [15]. CIP did not develop in patients without MODS, and the likelihood of CIP increased with the severity of MODS. This supports the view that the peripheral nervous system is yet

Table 4 Ventilation and weaning in 28 patients successfully weaned from the ventilator. *CIP*, Critical illness polyneuropathy; *COPD*, chronic obstructive pulmonary disease

	No CIP	CIP	*p*
n	16	12	–
Severe respiratory failure[a]	12 (75%)	11 (92%)	0.25[b]
COPD	3 (19%)	2 (17%)	0.89[b]
Median number (range) of days on ventilator until weaning	7.5 (1–30)	11.5 (6–48)	0.03[c]
Median number (range) of weaning days	9.5 (1–38)	16.5 (1–48)	0.26[c]
Phosphate (mmol/l)	1.00±0.20	0.84±0.37	0.25[d]

[a] Maximum lung score 2 on scoring scale (Table 1)
[b] χ^2
[c] Mann-Whitney U-test
[d] Student's *t*-test

another locus for organ failure. All CIP patients had early cardiovascular instability and received antihypotensive medication, but not all CIP patients had sepsis. CIP seemed further associated with renal and hematopoietic failure. It is possible, however, that this is an artifact of the scoring method used. Overall hospital mortality corresponded well with the expected mortality from mean APACHE scores [24]. Mortality was twice as high in patients with CIP, but this is probably due to a more complicated course, indicated by the higher MODS scores.

Obviously, the association of CIP with MODS does not prove that the same pathophysiological mechanisms are involved, as other factors influencing nerve function may accompany MODS. From our study, we conclude that renal failure, depletion of essential constituents like vitamin B, malnutrition, and the use of vecuronium or midazolam, factors all mentioned previously, probably do not account for CIP. There was, however, a link between intravenous use of aminoglycosides and CIP in our study, which may be direct [30] or indirect. Intravenous use of aminoglycosides may be another way of expressing the severity of sepsis and MODS.

CIP and weaning

CIP was recognized 15 years ago in patients who had difficult weaning from artificial ventilation, despite presumptively normal alveolar function. Later, it turned out that polyneuropathy was highly prevalent in such critically ill patients. More recently, muscle disorders [27, 31, 32], encephalopathy [33], effects of medication (vecuronium [34], midazolam [35], corticosteroids [36], aminoglycosides [30]), and hypophosphatemia [37] were recognized as factors influencing weaning. Our study shows that weaning difficulties should not be attributed to CIP too readily. We found an association between total duration of ventilatory support and CIP, but weaning was not convincingly prolonged compared to other patients without CIP who were on long-term assisted ventilation. A more protacted course of illness (due to more severe and extended MODS) is the more likely reason for the difference. Looking at the weaning extremes in our series, we found that very prolonged weaning can be readily explained by factors other than CIP. We also observed that two out of 18 patients (11%) with CIP had no weaning problems at all.

It cannot be concluded from our data that there is no role at all for CIP in ventilation and weaning. Both groups are heterogenous, which limits a comparison of median values. It is possible that some patients without CIP had phrenic nerve axonopathy, which can be demonstrated using diaphragm EMG techniques [38]. Nevertheless, the EMG abnormalities found in inspiratory muscles do not equate with insufficient strength. To establish the latter, one should either correct for all variables that determine pulmonary function apart from diaphragm strength, or directly measure diaphragm strength in all patients. Both approaches are fraught with difficulties. Factors that affect pulmonary performance in the critically ill are diverse, interdependent, and usually coexist. Diaphragm force can only be measured indirectly [39]. One study in which diaphragm function was assessed in seven patients with difficult weaning failed to show a relationship [40]; unfortunately, no EMG information was provided. Even when loss of inspiratory strength is suspected, polyneuropathy, myopathy, fatigue, mechanical factors, or disuse atrophy may account for it.

Our results have two implications. First, physicians should always be alert to finding alternative explanations for difficult weaning, even when CIP is present. Second, difficult weaning is not a good selection criterion for future studies of CIP.

In conclusion, CIP is related to MODS in mechanically ventilated patients. More patients with CIP, than without, die, and they are ventilated longer. There is insufficient evidence, however, that CIP itself is responsible. The clinical importance of CIP in ICU issues remains to be clarified.

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