

J. Garnacho-Montero
J. Madrazo-Osuna
J. L. García-Garmendia
C. Ortiz-Leyba
F. J. Jiménez-Jiménez
A. Barrero-Almodóvar
M. C. Garnacho-Montero
M. R. Moyano-Del-Estad

Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients

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J. Garnacho-Montero (✉) ·
J. L. García-Garmendia · C. Ortiz-Leyba ·
F. J. Jiménez-Jiménez ·
A. Barrero-Almodóvar ·
M. C. Garnacho-Montero ·
M. R. Moyano-Del-Estad
Intensive Care Unit, Hospital
Universitario Virgen Del Rocío,
41013 Sevilla, Spain
E-mail: jgmrji@arrakis.es
Phone: +34-95-492 48 32
Fax: +34-95-501 34 73

J. Madrazo-Osuna
Department of Clinical Neurophysiology,
Hospital Universitario Virgen Del Rocío,
41013 Sevilla, Spain

J. Garnacho-Montero
Florencio Quintero 18, 6°C,
41009 Sevilla, Spain

Abstract Objective: To determine risk factors and clinical consequences of critical illness polyneuropathy (CIP) evaluated by the impact on duration of mechanical ventilation, length of stay and mortality.

Design: Inception cohort study.

Setting: Intensive care unit of a tertiary hospital.

Patients: Septic patients with multiple organ dysfunction syndrome requiring mechanical ventilation and without previous history of polyneuropathy.

Interventions: Patients underwent two scheduled electrophysiologic studies (EPS): on the 10th and 21st days after the onset of mechanical ventilation.

Results: Eighty-two patients were enrolled, although nine of them were not analyzed. Forty-six of the 73 patients presented CIP on the first EPS and 4 other subjects were diagnosed with CIP on the second evaluation. The APACHE II scores of patients with and without CIP were similar on admission and on the day of the first EPS. However, days of mechanical ventilation [32.3 (21.1) versus 18.5 (5.8); $p = 0.002$], length of ICU and hospital stay in patients discharged alive from the ICU as well as in-hospital mortality were greater in patients with CIP (42/50, 84% versus 13/23, 56.5%;

$p = 0.01$). After multivariate analysis, independent risk factors were hyperosmolality [odds ratio (OR) 4.8; 95% confidence intervals (95% CI) 1.05–24.38; $p = 0.046$], parenteral nutrition (OR 5.11; 95% CI 1.14–22.88; $p = 0.02$), use of neuromuscular blocking agents (OR 16.32; 95% CI 1.34–199; $p = 0.0008$) and neurologic failure (GCS below 10) (OR 24.02; 95% CI 3.68–156.7; $p < 0.001$), while patients with renal replacement therapy had a lower risk for CIP development (OR 0.02; 95% CI 0.05–0.15; $p < 0.001$). By multivariate analysis, CIP (OR 7.11; 95% CI 1.54–32.75; $p < 0.007$), age over 60 years (OR 9.07; 95% CI 2.02–40.68; $p < 0.002$) and the worst renal SOFA (OR 2.18; 95% CI 1.27–3.74; $p < 0.002$) were independent predictors of in-hospital mortality.

Conclusions: CIP is associated with increased duration of mechanical ventilation and in-hospital mortality. Hyperosmolality, parenteral nutrition, non-depolarizing neuromuscular blockers and neurologic failure can favor CIP development.

Keywords Critical illness polyneuropathy · Multiple organ dysfunction syndrome · Sepsis · Electromyography · Muscle relaxants · Mechanical ventilation

Introduction

Diverse patterns of neuromuscular disorders can explain acquired weakness in critically ill patients [1]. However, critical illness polyneuropathy (CIP) is the most precisely defined neuromuscular complication in ICU patients. This entity was described by Bolton et al. in 1984 and is characterized by primary axonal degeneration of the motor and sensory nerve fibers accompanied by degeneration of the skeletal muscles as a result of their denervation [2]. The leading features of this complication are generalized weakness, arreflexia and delayed weaning from mechanical ventilation.

Critical illness polyneuropathy occurs in septic patients, particularly those who develop multiple organ dysfunction syndrome (MODS). However, other types of critically ill patients can also present this complication [3]. The incidence rate ranges from 50 to 80% depending on the group of critically ill patients evaluated and the timing of the electrophysiologic study (EPS) [4, 5, 6]. The precise causes of this polyneuropathy are still unknown. Previous studies have failed to reveal specific vitamin or nutritional deficiencies as well as toxic factors [7]. Malnutrition, hyperalimentation, hyperosmolar states and certain drugs, especially aminoglycosides and neuromuscular blocking agents (NMBAs), have been postulated as causes that might contribute to CIP development in small series and case reports [8]. Several studies excluded patients with previous potential risk factors of peripheral nerve disease such as cancer, alcoholism or diabetes mellitus, which may influence risk factor analysis.

Critical illness polyneuropathy is a well-recognized cause of muscular weakness and has been described in patients with difficult weaning from the ventilator. Data from prospective studies are contradictory because CIP and other neuromuscular diseases produced weaning failure and prolonged mechanical ventilation [9], although a cohort study did not find an increase in duration of mechanical ventilation in patients with CIP compared to those without [10].

An even more controversial topic is the impact of CIP on the outcome of critically ill patients [11]. Thus, whether CIP increases ICU stay or mortality has not been proved. Although a greater ICU mortality has been reported in patients with CIP, this finding could be explained by a higher severity of illness, rather than by a specific contribution of CIP to a poor outcome [5]. The relationship between CIP and in-hospital mortality has not been evaluated. Given these facts, we conducted an inception cohort study in a homogeneous group of septic patients with MODS that evaluated all convincing demographic, biologic, clinical and therapeutic variables that could be implicated in CIP development, in an attempt to identify potential risk factors. Our goals were to identify risk factors associated with CIP devel-

opment in this group of patients and to establish the clinical consequences of CIP, as evaluated by the impact on duration of mechanical ventilation, nosocomial infection rate, length of stay and mortality.

Materials and methods

Hospital

This is a prospective study carried out in the Intensive Care Unit of the Hospital Virgen del Rocío in Sevilla, a 40-bed medical-surgical unit in a large urban hospital with teaching accreditation. Annually, 1800 critically ill patients are admitted.

Patients

From November 1996 to March 1999, all patients with sepsis following American College of Chest Physicians/ Society of Critical Care Medicine criteria [12] and MODS were followed, but only those who required mechanical ventilation for more than 10 days were enrolled in this study. We defined MODS as the presence of two or more organ dysfunctions. Pulmonary dysfunction was defined as hypoxemia with $\text{PaO}_2/\text{FIO}_2$ below 300 in the absence of heart failure. Coagulation dysfunction was defined as platelet count less than $100,000/\text{mm}^3$. Liver dysfunction was defined as a total bilirubin level greater than 2 mg/dl. Acute cardiovascular dysfunction was defined as hypotension, mean arterial pressure (MAP) below 70 mmHg, despite administration of fluid for intravascular volume expansion, requiring the use of vasoactive drugs at any dose. Central nervous system dysfunction was defined as coma with Glasgow Coma Score (GCS) 12 or less excluding the effect of sedative drugs. Acute renal dysfunction was defined as serum creatinine level greater than 2 mg/dl or a doubling of the admission creatinine level in the case of pre-existing renal disease.

Exclusion criteria were: age younger than 18 or older than 80 years, pregnancy, previous history of neuromuscular disease, cirrhosis or end-stage renal disease and patients infected with human immunodeficiency virus. Routinely the patient or, most frequently, close relatives were interrogated about signs and symptoms of pre-existing neuromuscular disease and excluded from the study if previous symptoms were reported. Written consent was obtained from patients' relatives.

At admission to ICU (the first 24 h), severity of the illness and the calculated expected mortality were evaluated by the Acute Physiology and Chronic Health Evaluation (APACHE) II score [13]. The APACHE II scores on the days of the EPS were also noted. Failure of organs and severity of MODS were evaluated by the Sequential Organ Failure Assessment (SOFA) scale at admission and during the subsequent clinical course [14]. All patients received standard supportive treatment including surgical treatment of the focus if necessary, fluid resuscitation, vasoactive drugs and antimicrobial therapy, which was chosen by the physician in charge of the patient. The decision to initiate renal replacement therapy and the election of conventional hemodialysis or continuous venovenous hemofiltration was made by the physician in charge of the patient and always as part of the management of acute renal failure following current recommendations. A biocompatible membrane was always used.

Patients were fed by the enteral route using a polymeric formula (25–30 kcal/kg). If the gut could not be used, total parenteral nutrition (TPN) was administered: nitrogen intake 1.4 ± 0.2 g amino acids/kg-day with a calorie/nitrogen ratio of 1/130 and 60% of calo-

ries as glucose and 40% as fat. The type of fat, long-chain triglycerides (LCT; Intralipid 20%, Pharmacia and Upjohn, Madrid, Spain) or a mixture of medium- and long-chain triglycerides (MCT/LCT; Lipofundin 20%, B. Braun, Madrid, Spain) was chosen by the physician in charge of the patient.

The patients included in this protocol were followed up until death or hospital discharge.

Study design

All patients underwent scheduled EPS (see below). Daily, laboratory tests included: complete blood count, pH, blood glucose, sodium, potassium, phosphorus, creatinine, creatine phosphokinase (CPK) and osmolality. Serum magnesium levels were measured twice a week. On the days of the EPS, the following parameters were measured: albumin, pre-albumin, transferrin, cholesterol, triglycerides, zinc and copper. These variables were measured using a standard hospital auto-analyzer. The following variables were noted: age, sex, dates of admission and discharge from the ICU and the hospital, underlying diseases (diabetes mellitus, neoplasm and alcohol abuse) following previous definitions [15] and source of sepsis.

Detailed information of different factors from the admission to the ICU was also recorded: bacteremia, failure of organs and severity evaluated by SOFA scale choosing the worst values from the admission to the ICU, metabolic disturbances, persistent shock (MAP < 70 mmHg more than 12 h), hemorrhagic shock (major bleeding causing hypotension), renal replacement therapy, enteral nutrition, TPN and the type of intravenous lipid emulsion and drugs such as aminoglycosides, metronidazole, corticosteroids and NMBAs. If aminoglycosides were used, serum concentrations were measured. The type of medication employed and total doses were noted. The duration of mechanical ventilation was also recorded. Extubation or spontaneous ventilation through a tracheotomy marked the end of mechanical ventilation.

Metabolic disorders were defined if they persisted for more than 24 h: severe acidemia (blood pH < 7.2), hyperglycemia (glycemia above 250 mg/dl), hypernatremia (sodium level above 150 mEq/l), hyperosmolality (serum osmolality above 325 mosmol/kg), hypo-osmolality (serum osmolality below 260 mosmol/kg), hypokalemia (potassium level below 2.5 mEq/l), hypophosphatemia (phosphorus level below 1.5 mEq/l), hypomagnesemia (magnesium level below 1 mmol/dl), hypermagnesemia (magnesium level above 3 mmol/dl).

Nosocomial infections were also recorded. Ventilator-associated pneumonia diagnosis required the radiographic appearance of a new and persistent pulmonary infiltrate and at least two of the following criteria: temperature higher than 38°C or lower than 35.5°C, leukocytosis above 12,000 cells/mm³ or leukopenia below 4,000 cells/mm³ and purulent bronchial secretions. The final diagnosis was made by clinical criteria, although a bronchoscopy with protected brush was carried out to obtain microbiologic documentation [16]. Catheter-related bloodstream infection was diagnosed when the same strain was isolated in blood cultures and in the semi-quantitative culture of a catheter segment (yielding > 15 colonies) or if there was a clear clinical response after withdrawal of the catheter and if no primary site other than the intravascular catheter could be identified. Diagnosis of bacteremia of unknown origin was confirmed by at least one positive blood culture without another site simultaneously infected with the same microorganism.

Electrophysiologic studies

These studies were performed in the ICU on days 10 and 21 after the onset of mechanical ventilation. The same investigator (JMO), who was unaware of the patient's medical condition, carried out all these studies. The techniques employed, connection of electrodes and characteristics of the stimulations were those that are routinely used in any neurophysiologic laboratory. Measurement of the potentials was made from peak to peak. All the studies were undertaken at the bedside with a transportable apparatus (Nicolet Compass Portabook).

The study included the measurement of sensory and motor nerve conduction, calculation of the conduction velocities, amplitude and shape of the potentials, measurement of the distal latencies and repetitive nerve stimulation at 3 Hz to exclude neuromuscular transmission defects. The EPS protocol included nerve conduction studies of median, peroneal and tibial nerves measuring compound muscle action potential (CMAP) of the musculus abductor pollicis brevis (APB), musculus extensor digitorum brevis (EDB) and musculus flexor hallucis (FH). In addition, sensory nerve action potential (SNAP) and velocity conduction of the sural nerve and the sensory median nerve were recorded. Except in the case of the sural nerve, the nerve conduction studies were performed orthodromically using surface electrodes. The lower limit of normal for nerve conduction velocities was 50 m/s in the upper limbs or 40 m/s in the lower limbs. A SNAP of less than 12 µV and a CMAP of less than 8 mV for APB, less than 5 mV for EDB and less than 6 mV for FH were deemed abnormal.

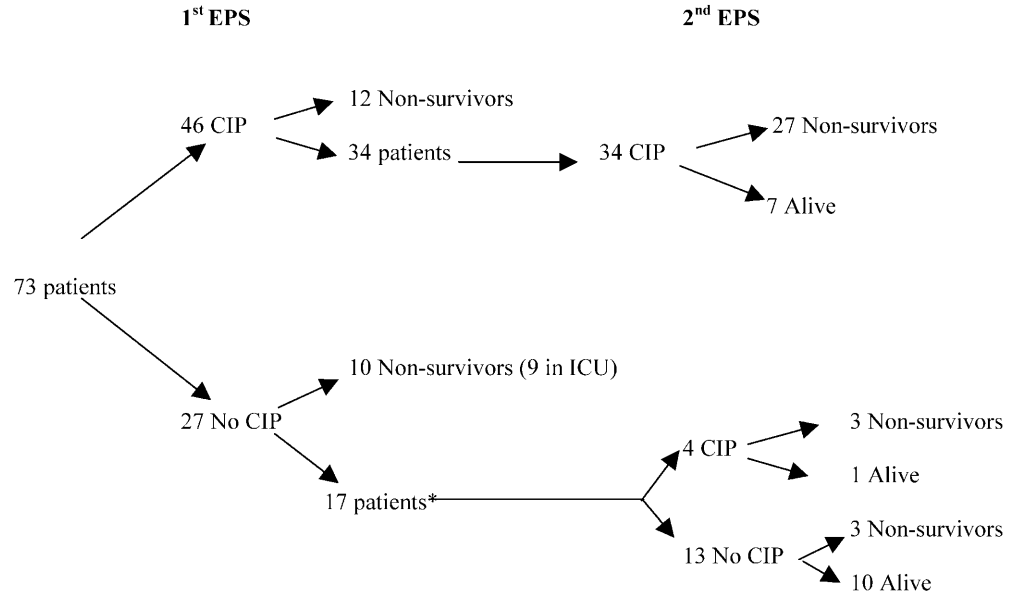
Signs of denervation, such as fibrillation potentials and positive waves in the muscles, were also sought using needle electromyography in deltoid, quadriceps femoris, first dorsal interosseus, extensor digitorum brevis and tibialis anterior muscle. There were at least four insertions per muscle. CIP was diagnosed when signs of acute axonal injuries were present: reduction in CMAP and SNAP amplitudes with minor change in conduction velocities and distal latencies in combination with fibrillation potentials in at least one of the explored muscles [17].

Statistical analysis

Patients were classified as CIP patients or no-CIP patients, depending on the results of the first and second EPSs. First, results were analyzed in regard to the presence of CIP in the first EPS, using only data obtained from the ICU admission to the day of the first EPS. Subsequently, all patients were analyzed considering the presence of CIP with combined data from both EPSs and the variables collected between first and second EPSs were used. Those patients with no CIP in the first EPS and CIP in the second EPS were included in the CIP patients group in the second analysis. All patients that fulfilled criteria for CIP in the first evaluation were also diagnosed as having CIP on the second examination.

Univariate analysis was accomplished using two-sample unpaired *t*-test for parametric continuous variables after correction for equality of variance (Levene's test), U-Mann Whitney test for non-parametric continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables. Statistical significance was considered when *p* was less than 0.05. Multivariate analysis using logistic regression analysis was used to evaluate the independent contribution of variables, including those with significance levels of *p* less than 0.10 in univariate analysis and others with clinical relevance. The model was constructed using a forward stepwise method with the likelihood ratio test. The presence of collinearity in the model was evaluated using the tolerance and variance inflation factor analysis followed by testing the condition in-

Fig. 1 shows the evolution of the patients enrolled in this study (EPS electrophysiologic study, CIP critical illness polyneuropathy, ICU intensive care unit) * Three of these patients had been discharged from the ICU before the second evaluation. In these cases, the second electrophysiologic study was performed in the general ward



dices. No condition index greater than 15 was found, so the variance proportions were not examined. The odds ratio (OR) and the corresponding 95% CI for each variable were also calculated [18].

To evaluate the impact of CIP on the length of stay, length of mechanical ventilation, nosocomial infections and mortality, when appropriate univariate and multivariate analyses were performed, controlled by other variables. The data were collected and analyzed with SPSS 9.0 software package.

Results

Eighty-two patients were enrolled, although nine of them were not analyzed: four had incomplete EPSs due to different technical problems, three presented elevated CPK levels (> 1000 U/l) and two were prematurely transferred to other hospitals. Primary diagnoses were: abdominal sepsis (41), pneumonia (19), urosepsis (4), mediastinitis (3), sepsis of unknown origin (2), soft tissue infection (2) and others (2). The diagnostic approach and evolution of the patients are depicted in Fig. 1. The neurophysiologic data are summarized in Table 1.

Forty-six of these 73 patients [63% (95% CI 51–74)] presented CIP on the first EPS (Fig. 1). Ten of the 27 subjects (37%) without CIP on the first EPS died before the second evaluation (mean 5 days). Seventeen patients without CIP on the first EPS were therefore evaluated 3 weeks after the onset of mechanical ventilation. Four of them without previous signs of CIP were diagnosed as having CIP, while the remainder had no signs of acute axonopathy. Twelve of the 46 patients with CIP died before the second evaluation. The rest showed very similar results to the first EPS in the second one,

that confirmed the diagnosis. Thus, 50 patients with CIP were compared with the other 23 patients without CIP and these results are shown. In addition, when the same analysis was performed comparing only the results of the first EPS (46 patients with CIP and 27 with no CIP), the risk factors for CIP and the impact on clinical variables were the same.

Patients in the two groups had comparable ages, APACHE II scores and calculated expected mortality in the first 24 h. On the day of the first EPS, APACHE II and SOFA scores were similar for the two groups. However, APACHE II scores of the second EPS were significantly higher in patients with CIP [11.5 (8.2) vs 6.9 (8.8); *p* = 0.04]. Previous in-hospital stays [median (range)] were almost identical [2 (0, 73) vs 1 (0, 118); *p* = 0.70] and days in ICU before mechanical ventilation [1 (0, 9) vs 1 (0, 10); *p* = 0.94].

Serum peak CPK levels were similar in the two groups [290.1 (261.7) vs 243.1 (201.4)]. Moreover, serum levels of albumin, pre-albumin, transferrin, total cholesterol, triglycerides, zinc and copper were reduced in both groups but without significant differences. Patients with CIP exhibited typical signs of acute axonopathy: reduced CMAP and SNAP with normal conduction velocities and distal latencies as well as active denervation in muscles.

Univariate analyses of the risk factors for CIP are shown in Tables 2 and 3. None of the underlying diseases analyzed was a risk factor for CIP development. By multivariate logistic regression analysis, five factors were independently associated with CIP development (Table 4). The predicted sensitivity of the model was 74% and the specificity 88%. When the analysis was performed using data obtained from the ICU admission

Table 1 Results of electrophysiologic studies (EPS) Results are mean (SD) (CIP critical illness polyneuropathy)

Nerve	Amplitude (mV/ μ V)		Velocity (m/s)	
	CIP	No CIP	CIP	No CIP
First EPS				
Median, motor	7.4 (4.4) ^a	10.9 (4.3)	53.1 (4.8) ^a	51.2 (4.1)
Median, sensory	11.9 (4.7) ^b	13.7 (6.2)	51.2 (4.8) ^b	48.3 (3.5)
Tibial	3.1 (2.1) ^c	10 (2.1)	46.5 (5.8) ^c	45.9 (6.1)
Peroneal	2.2 (2.0) ^d	8.1 (3.2)	44.1 (4.5) ^d	43.7 (5.6)
Sural	10.1 (4.3) ^e	15.6 (2.1)	43.9 (4.7) ^e	42.4 (6.8)
Second EPS				
Median, motor	5.8 (5) ^f	11.8 (4.4)	55.8 (3.8) ^f	52.7 (4.9)
Median, sensory	10.6 (1.8) ^a	13.9 (3.8)	50.7 (3.7) ^a	50.2 (2.9)
Tibial	2.8 (2.0) ^a	10.1 (2.2)	46.0 (3.9) ^a	44.9 (6.1)
Peroneal	1.6 (2.0) ^b	7.6 (2.4)	43.5 (6) ^b	44.7 (5)
Sural	9.6 (5) ^g	14.6 (4.5)	44.1 (6.3) ^g	41 (5.8)

^a No response in 2 patients^b No response in 8 patients^c No response in 6 patients^d No response in 20 patients^e No response in 10 patients^f No response in 1 patient^g No response in 7 patients**Table 2** Univariate analysis of risk factors for CIP (continuous variables) (CIP critical illness polyneuropathy, EPS electrophysiologic study, RRT renal replacement therapy, SOFA Sequential Organ Failure Assessment, CNS central nervous system)

	CIP (<i>n</i> = 50)		No CIP (<i>n</i> = 23)		<i>p</i>
	Mean	SD	Mean	SD	
Age (years)	61.5	14.0	61.9	12.2	0.92
APACHE II admission	17.5	6.9	17.7	4.8	0.94
Expected mortality	37.8	22.9	35.2	18.7	0.64
APACHE II EPS 1	18.5	5.0	18.2	5.5	0.81
APACHE II EPS 2	11.5	8.2	6.9	8.8	0.04
SOFA EPS 1	11.8	4.2	10.6	5.0	0.29
Worst SOFA					
Renal	2.6	1.2	2.6	1.6	0.77
Cardiovascular	3.4	1.0	3.3	0.9	0.25
Coagulation	1.3	1.4	1.2	1.1	0.98
CNS	2.9	1.2	2.2	0.5	0.04
Respiration	3.2	0.4	3.3	0.5	0.30
Liver	1.6	1.3	1	1.1	0.06

to the first EPS and considering the presence of CIP only on this first EPS, univariate and multivariate analysis of risk factors were exactly the same with small differences in OR.

Nine patients with CIP received NMBAs: vecuronium was used in six patients (total dose ranged from 95 to 708 mg) and atracurium in three cases (total dose ranged from 1520 to 5040 mg). Only one patient without CIP on the first evaluation had received a muscle relaxant (1610 mg atracurium). The rest of the patients did not receive NMBAs at all.

Length of mechanical ventilation was significantly higher in patients who had developed CIP [32.3 (21.1) days vs 18.5 (5.8) days; $p = 0.002$]. By multiple regression analysis, the presence of CIP and ventilator-associated pneumonia were the variables associated with length of mechanical ventilation. Thus, the effects of the diagnosis of CIP and ventilator-associated pneumonia on the length of mechanical ventilation were mean increases of 11.6 days (95% CI 2.6–20.5; $p = 0.012$), and 12.9 days (95% CI 4.4–21.4; $p = 0.003$), respectively.

In relation to the acquisition of nosocomial infections, only primary bacteremia was more frequent in patients with CIP (Table 5). Overall ICU and hospital lengths of stay were similar for the two groups. However, when only patients discharged alive from the ICU were analyzed [median (range)], length of ICU [53 (19,218) days vs 32 (12,107) days; $p = 0.03$] and hospital stays [93 (22,372) days vs 41 (20,231) days; $p = 0.01$] were significantly higher in patients with CIP.

Intensive care unit mortality was similar in the two groups (33/50, 66% vs 12/23, 52.2%; $p = 0.26$) whereas in-hospital mortality was significantly higher in patients with CIP (42/50, 84% vs 13/23, 56.5%; $p = 0.01$). Using multivariate analysis, CIP (OR 7.11; 95% CI 1.54–32.75; $p < 0.007$), age more than 60 years (OR 9.07; 95% CI 2.02–40.68; $p < 0.002$) and the worst renal SOFA (OR 2.18; 95% CI 1.27–3.74; $p < 0.002$) were determined independent predictors of in-hospital mortality.

Table 3 Univariate analysis of risk factors for CIP (categorical variables) (*CIP* critical illness polyneuropathy, *EPS* electrophysiologic study, *RRT* renal replacement therapy, *SOFA* Sequential Organ Failure Assessment, *CNS* central nervous system, *LCT* long-chain triglycerides, *NMBAs* neuromuscular blocking agents)

	CIP (<i>n</i> = 50)		No CIP (<i>n</i> = 23)		<i>p</i>
	Number	%	Number	%	
Diabetes mellitus	10	20	3	13	0.74
Alcohol abuse	11	22	3	13	0.53
Neoplasm	5	10	4	17.4	0.45
Bacteremia	14	28	4	17.4	0.33
Acidemia	13	26	7	30.4	0.69
Persistent shock	21	42	8	34.8	0.56
Hemorrhagic shock	7	14	3	13	1.00
Hypo-osmolality	1	2	1	4	0.53
Hyperosmolality	33	66	11	47.8	0.14
Hyperglycemia	15	30	7	30.4	0.97
Hypernatremia	18	36	5	21.7	0.19
Hypokalemia	10	20	3	13	0.74
Hypophosphatemia	8	16	2	8.7	0.49
Hypomagnesemia	4	8	1	4.3	1.00
Hypermagnesemia	4	8	2	8.7	1.00
RRT	10	20	11	47.8	0.025
SOFA CNS more than 2	38	76	10	43.5	0.007
Parenteral nutrition	27	54	10	43.5	0.40
Lipids	21	42	8	34.8	0.56
LCT	18	36	5	21.7	0.22
Enteral nutrition	28	56	15	62.5	0.46
Aminoglycosides	21	42	10	43.5	0.91
Metronidazole	6	12	5	21.7	0.31
Corticosteroids	7	14	4	17.4	0.73
NMBAs	9	18	1	4.3	0.16

Table 4 Risk factors associated with critical illness polyneuropathy development: multivariate analysis (*NMBAs* neuromuscular blocking agents)

	Odds ratio	95% CI	<i>p</i> value
Hyperosmolality	4.8	1.05–24.38	0.046
Parenteral nutrition	5.11	1.14–22.88	0.02
Use of NMBAs	16.32	1.34–199	0.0008
Neurologic failure ^a	24.02	3.68–156.7	0.001
Renal replacement therapy	0.02	0.05–0.15	0.001

^a GCS below 10

Discussion

Critical illness polyneuropathy has a high incidence in this homogeneous group of septic patients and we demonstrate that several ICU-acquired factors favor CIP development. Moreover, CIP hinders weaning and is associated with higher in-hospital mortality. This higher mortality is not attributable to underlying conditions or illness severity because patients with and without ICU-acquired polyneuropathy had comparable severity scores not only at admission to the ICU (APACHE II score), but also on the day of the first EPS (APACHE II and SOFA scores). Moreover, CIP is an independent predictor of in-hospital mortality. Thus, the risk of hospital mortality was more than 7 times as great among patients that developed CIP

compared with patients who did not exhibit this complication.

We are aware that a case-control design would be more adequate to address this issue but the difficulty of obtaining controls makes it almost unattainable for a single institution. Studies have failed to demonstrate a clear relationship between CIP and mortality and the poor outcome of these patients was explained by the severity of the underlying MODS [5, 10]. In our patients MODS severity was evaluated by the SOFA scale that has been validated as an instrument to discriminate survivors from non-survivors in a large group of critically ill patients [19].

Those patients who presented this complication had a longer duration of mechanical ventilation. In fact, although conflicting data have been published [5, 9, 10], CIP was initially described as a factor that hindered weaning processes [7, 20]. Moreover, CIP can be initially undetected and may cause ICU readmission due to acute neuromuscular respiratory failure after ICU discharge in patients successfully weaned [21]. Recently, Zifko et al. [22] showed that limb conduction parameters did not correlate with the length of mechanical ventilation or the duration of stay in the ICU in 62 patients with the diagnosis of CIP. Our series is the first to report that CIP significantly lengthens hospital stay in those patients discharged alive from the ICU. This finding is of extraordinary importance in view of the economic burden that it represents.

Table 5 Infection rates in critical illness polyneuropathy (CIP) and no CIP patients. Results are mean (standard deviation) (VAP ventilator-associated pneumonia, CRBI catheter-related bloodstream infection)

	CIP <i>n</i> = 50	No CIP <i>n</i> = 23	<i>p</i>
VAP	0.50 (0.65)	0.27 (0.46)	0.18
CRBI	0.28 (0.50)	0.23 (0.43)	0.74
Primary bacteremia	0.29 (0.61)	0.05 (0.21)	0.06
VAP density rate (episodes/100 days of stay)	1.33 (2.04)	1.14 (2.20)	0.41
CRBI density rate (episodes/100 days of stay)	0.76 (1.86)	1.13 (2.46)	1.00
Primary bacteremia density rate (episodes/100 days of stay)	0.77 (1.81)	0.00 (0.00)	0.02

The etiology of CIP is uncertain. Bolton considers that sepsis and MODS are characterized by profound disturbances of the microcirculation that affect all organ systems and afflict the central and peripheral nervous system. In this context, inflammatory mediators or certain toxins can gain access and induce neuronal injury [17]. Our results confirm the common association of CIP and severe encephalopathy [4, 22]. In fact, both are considered parts of the neurologic dysfunction occurring in patients with MODS. Although the moment of appearance has not been clearly determined, a recent study in patients with systemic inflammatory response syndrome or sepsis demonstrates that electrophysiologic signs of CIP are present as early as 2–5 days after admission to the ICU [23].

At present, no effective therapy is available to prevent or treat CIP. Treatment consists largely of supportive care and rehabilitation. Consequently, the identification of risk factors for CIP is essential and should lead to the application of strategies in order to prevent this complication. Hypernatremia, hyperglycemia and azotemia, alone or combined, accounted for the majority of the hyperosmolar states. However, none of these disorders by itself was associated with CIP whereas, in the multivariate analysis, patients with hyperosmolality had a higher risk of suffering this neurologic complication. The relationship between CIP and hyperosmolality has been reported previously [24, 25]. However, Witt et al. found no relationship between serum osmolality and CIP, although this variable was measured on only three occasions from admission to ICU [4]. In contrast, these authors observed higher levels of glycemia in those patients with CIP, while Berek et al. [6] found that neither hyperglycemia nor hyperosmolality was associated with CIP.

Recently, anecdotal reports have linked CIP with the administration of TPN and the cessation of nutritional support diminished the duration and severity of this

complication [26, 27]. These authors considered that the deleterious effects of refeeding or the use of intravenous lipid emulsions with high amounts of polyunsaturated fatty acids (PUFA) were the causes of this axonopathy. In our series, neither the use of LCT nor MCT/LCT (with a substantial reduction of PUFA content) was a risk factor for CIP. TPN is associated with diverse metabolic derangements such as hyperglycemia, hypernatremia and hypertonicity. These disorders may worsen disturbances in microcirculation already occurring in sepsis and MODS. Hence, our data suggest that TPN should be used with caution because it may contribute to the occurrence of CIP in septic patients with MODS.

The use of renal replacement therapy was a protective factor for CIP development in the multivariate analysis. In contrast, in a group of cardiac surgical patients the use of renal replacement therapy was more frequent in those diagnosed with CIP, although the incidence of sepsis and the severity of the process were significantly higher than in the control group [28]. Since the number of patients with renal failure and the severity of this process were similar in the two groups, the likely explanation of our finding is that the use of renal replacement therapy allows for the control of metabolic disturbances or is a means of eliminating a low-molecular toxic agent that might be implicated in CIP development [29].

A chief concern of all clinicians is to avoid, if possible, toxic drugs that could be implicated in the acquisition of CIP. Thus, aminoglycosides [5, 10] have been linked with this, but others failed to confirm this relationship [4]. In our analysis, the use of these antibiotics or corticosteroids was not associated with CIP development, whereas the administration of NMBAs was a strong risk factor. Previous studies showed no relationship between the use of NMBAs and the incidence of CIP, although these drugs were used rarely and in low doses in these studies [4, 9].

Different entities can explain neurophysiologic abnormalities in critically ill patients after the use of NMBAs [30]. Prolonged neuromuscular blockade due to alterations in drug clearance and an acute motor neuropathy have been associated with muscle relaxants [31, 32, 33], although this relationship has been disputed recently [1]. We were very careful in the appraisal of all patients, evaluating persistent neuromuscular blockade by repetitive nerve stimulations and sensory abnormalities. On the other hand, we do not state that the use of NMBAs is a prerequisite for CIP development even though the administration of these agents can probably hasten or worsen an underlying axonopathy.

Necrotizing myopathy affects patients that have received high doses of corticosteroids and NMBAs, particularly following admission for acute severe asthma [34, 35], although a similar clinical picture has been described in critically ill septic patients [36]. In both cases, a marked elevation of serum CPK level is observed.

Moreover, in critically ill patients diverse types of myopathy can be present in patients with or without neurophysiologic criteria of CIP [37]. Nevertheless, in our study serial measurements of CPK were only slightly elevated (three patients who had markedly increased CPK concentrations were excluded from the analysis) and necrotizing myopathy was confirmed by muscle biopsy (data not shown). We did not systematically perform muscle biopsy, so we cannot evaluate the contribution of myopathy. This can be a limitation of our study, but many previous studies have exclusively used EPS and, in fact, CIP can be diagnosed with certainty by EPS performed in the ICU [11].

In summary, our results confirm that, in this selected group of septic patients, CIP is habitually associated

with neurologic failure and different ICU-acquired factors directly influence the development of CIP. A strict control of serum osmolality is advisable and an overzealous use of NMBAs should be avoided in these patients. This complication is associated with an increase in duration of mechanical ventilation and in-hospital mortality. Future investigations should evaluate if strategies designed to avoid or minimize precipitants can prevent the appearance or severity of this serious and frequent complication.

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