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

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, areflexia 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 therapeutical 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 development 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 Seville, a 40-bed medical-surgical unit in a large urban hospital with teaching accreditation. Annual, 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 PaO2/FiO2 below 300 in the absence of heart failure. Coagulation dysfunction was defined as platelet count less than 100,000/mm3. 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 caloric/nitrogen ratio of 1/130 and 60% of calo-