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BRIEF REPORT

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Steroid-induced myopathy in patients intubated due to exacerbation of chronic obstructive pulmonary disease

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Abstract *Objective:* To determine incidence, risk factors and impact on various outcome parameters of the development of acute quadriplegic myopathy in a selected population of critically ill patients. *Setting:* A prospective cohort study carried out in the intensive care unit of a tertiary-level university hospital. *Patients:* All patients admitted due to acute exacerbation of chronic obstructive pulmonary disease who required intubation and mechanical ventilation, and received high doses of intravenous corticosteroids. *Interventions:* A neurophysiological study was performed in all cases at the onset of weaning. Muscular biopsy was taken when the neurophysiological study revealed a myopathic pattern. *Measurements and results:* Twenty-six patients were enrolled in the study. Nine patients (34.6%) developed myopathy. Only seven patients were treated with muscle relaxants. Histology confirmed the diagnosis in the three patients who underwent muscle biopsy. APACHE II score at admission, the rate of sepsis and the total doses of corticosteroids were significantly higher in patients with myopathy compared with those patients that did not develop it. Myopathy is associated with an increase in the duration of mechanical ventilation [15.4 (9.2) versus 5.7 (3.9) days; $p<0.006$], the length of ICU stay [23.6 (10.7) versus 11.4 (7.05) days; $p<0.003$] and hospital stay [33.3 (19.2) versus 21.2 (16.1) days; $p<0.034$)]. Myopathy was not associated with increased mortality. *Conclusions:* In the population under study, severity of illness at admission, the development of sepsis and the total dose of corticosteroids are factors associated with the occurrence of myopathy after the administration of corticosteroids. Myopathy was associated with prolonged mechanical ventilation and in-hospital stay.

Keywords Myopathy · Sepsis · Chronic obstructive pulmonary disease · Corticosteroids · Mechanical ventilation

Introduction

Diverse neuromuscular disorders can explain acquired weakness in critically ill patients: critical illness polyneuropathy (CIP), drug-related neuromuscular junction defects and myopathies [1, 2]. Acute quadriplegic myopathy (AQM) typically affects patients with status asthmaticus [3, 4] requiring mechanical ventilation and the administration of high-dose intravenous corticosteroids and/or non-depolarizing neuromuscular blocking agents (NMBAs). Though the etiology of AQM remains unclear, some studies suggest that the total doses of drugs administered and the duration of muscle relaxation are the main offending factors [4]. Nevertheless, other studies report AQM in patients treated with corticosteroids who did not receive NMBAs or only in small doses [5].

Moreover, other critically ill patients not exposed to these agents can also present this complication [6].

Chronic obstructive pulmonary disease (COPD) is a common disease that may require ICU admission and mechanical ventilation. High doses of corticosteroids and muscle relaxants are frequently used in this situation. So far, there has been no prospective study evaluating the risk factors and the impact on the outcome of AQM in a group of patients admitted to the ICU due to acute exacerbation of COPD.

Our aims were to determine its incidence and the risk factors associated with the development of AQM, and to evaluate the outcome in patients requiring high doses of intravenous corticosteroids, intubation and mechanical ventilation due to acute exacerbation of COPD.

Materials and methods

Description of patients

This is a prospective study carried out in the intensive care unit of the Hospital Virgen del Rocío in Sevilla. We enrolled in the study all patients admitted to the ICU from 1997 to 2000 due to acute exacerbation of COPD requiring mechanical ventilation for more than 48 h and receiving high doses of intravenous corticosteroids. "High doses" were defined as at least 240 mg of methylprednisolone (or the equivalent if another corticosteroid was used) in the first 48 h of admission. All patients met the established criteria for COPD diagnosis [7] and all these patients received at least 240 mg of methylprednisolone. So, none of the ventilated COPD patients were excluded in the same period.

The patient or, most frequently, close relatives were questioned about symptoms of pre-existing neuromuscular disease and candidates were excluded from the study if previous symptoms were reported. Exclusion criteria were: age older than 80 years, cardiac arrest prior to ICU admission, diagnosis of pneumonia at admission to the ICU, cirrhosis, end-stage renal disease and the presence of HIV infection. Written consent was obtained from patients' relatives and the study was approved by the ethics committee of the Hospital Virgen del Rocio.

At admission to ICU, the severity of illness was evaluated by the Acute Physiology and Chronic Health Evaluation (APACHE) II score. All patients were treated with short-term ß$_2$-agonists and intravenous corticosteroids [7], midazolam (Dormicum, Roche, Madrid, Spain) and some patients also received NMBAs.

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

Study design

The factors analyzed were: demographic data, prior history of mechanical ventilation, previous oral corticosteroid therapy, type of medication employed and total doses (corticosteroids, NMBAs and aminoglycosides), metabolic disorders [8] and development of sepsis and/or bacteremia, according to the ACCP/SCCM criteria, during ICU stay [9]. Two types of corticosteroids were employed in this study: hydrocortisone and methylprednisolone.

The duration of mechanical ventilation was recorded and the attending physician assessed daily the patient readiness to be weaned from mechanical ventilation. This was initiated when the attending physician considered that the patient was stabilized and ready to be weaned off the ventilator. Weaning was performed by a 2-h trial of spontaneous breathing following the protocol described by Esteban et al. [10].

Neurophysiological studies

A neurophysiological study was performed at the onset of weaning from mechanical ventilation when the patients were co-operative enough to enable the study of motor unit potentials. The diagnosis of acute myopathy relies on the identification of motor unit action potentials (MUAPs) generated by voluntary efforts. MUAPs were sought using needle electromyography in biceps brachii and deltoid muscles. AQM was diagnosed if small, brief and polyphasic MUAPs characteristic of a myopathic process were obtained and represented at least 20% of all the MUAPs recorded [11].

Muscle biopsy

Muscle biopsy was taken when the neurophysiological study revealed a myopathic pattern. A special written consent was obtained to perform the muscular biopsy. When biopsy was not performed, refusal of permission was the cause. Biopsy of the biceps brachii was carried out following standard surgical procedures. Sections of 5 μm were obtained, stained with haematoxylin-eosin, Gomori trichrome, oil-red O and histo-enzymatic techniques [12] .

Statistical analysis

Comparisons between those patients that developed AQM and those who did not were accomplished using two-sample unpaired *t*-test for parametric continuous variables, 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.

Results

Of the 30 patients enrolled in the study, only 26 were analyzed: two did not complete the neurophysiological study due to technical problems and two other patients were prematurely transferred to another hospital. The neurophysiological evaluation was performed in all cases at the onset of weaning. The median elapsed time (range) between the onset of mechanical ventilation and the neurophysiological evaluation was 6 (2–12) days. Electromyographic features were consistent with AQM in nine patients (34.6%), all of whom exhibited a clinically evident weakness of upper and lower limbs, however only four patients in the no-AQM group showed a clinically evident weakness. Seven patients (four in the AQM group and three in the no-AQM group) were treated with NMBAs (vecuronium). Serum creatine phosphokinase (CPK) levels at admission to the ICU were similar in the two groups [242 (144) IU/l vs 195 (186) IU/l]. Peak CPK levels were significantly higher in patients developing AQM [1414 (1402); range 260–3765 IU/l] than in the other group [252 (161); range 88–625 IU/l] ($p<0.05$). Seven patients developed sepsis during ICU stay and prior to the onset of weaning.

Table 1 Comparisons of factors for acute quadriplegic myopathy (continuous and categorical variables). Results are expressed as mean values (standard deviation) for continuous variables and as number (%) for categorical variables

	AQM (*n*=9)	No AQM (*n*-=17)	*p* value
Age (years)	61.6 (8.7)	65.8 (6.7)	0.185
APACHE II at admission	23.1 (3.5)	14.0 (3.4)	0.000
Hydrocortisone dose (mg)	1694.0 (1509.0)	1176.0 (971.0)	0.380
Methylprednisolone dose (mg)	1310.5 (874.9)	743.8 (387.8)	0.095
Total doses of steroids[a]	1649.5 (842.3)	979.1 (409.1)	0.050
NMBAs dose	13.0 (22.0)	11.0 (29.0)	0.188
Previous corticosteroid	2 (22.2%)	4 (23.5%)	1.000
History of previous mechanical ventilation	1 (11.1%)	1 (5.9%)	1.000
Bacteremia	2 (22.2%)	1 (5.9%)	0.268
Sepsis	6 (66.6%)	1 (5.9%)	0.002
Neuromuscular blockers	4 (44.4%)	3 (17.6%)	0.188
Aminoglycosides	2 (22.2%)	0 (0%)	0.111
Hypokalemia	1 (11.1%)	1 (5.9%)	1.000
Hypophosphatemia	4 (44.4%)	6 (35.2%)	0.692
Hypomagnesemia	0 (0%)	0 (0%)	1.000

AQM acute quadriplegic myopathy, *NMBAs* non-depolarizing neu- romuscular agents, *hypokalemia* potassium level below 2.5 mEq/l for more than 24 h, *hypophosphatemia* phosphorus level below 1.5 mEq/l for more than 24 h, *hypomagnesemia* magnesium level below 1 mmol/dl for more than 24 h
[a] Total doses of steroids were calculated considering that 1 mg of methylprednisolone is equivalent to 5 mg of hydrocortisone

Table 2 Clinical evolution of patients enrolled in the present study

	AQM (*n*=9)	No AQM (*n*=17)	*p*
Duration of mechanical ventilation (days)	15.4 (9.2)	5.7 (3.9)	0.006
Length of ICU stay (days)	23.6(10.7)	11.4 (7.05)	<0.003
Length of hospital stay (days)	33.3 (19.2)	21.2 (16.1)	<0.034
ICU mortality, *n* (%)	3 (33.3%)	3 (17.6%)	0.628
In-hospital mortality	5 (55.5)	4 (23.5%)	0.194

AQM acute quadriplegic myopathy

Comparing patients that developed AQM with those that did not show this complication: APACHE II score at admission, the rate of sepsis and the total doses of corticosteroids were significantly higher in patients with AQM (Table 1). Table 2 shows the impact of AQM on the duration of mechanical ventilation, length of stay and mortality.

Muscle biopsy was performed in three patients with neurophysiological suspicion of AQM that was confirmed by histology in all cases. Histology revealed atrophy affecting predominantly type II myofibers without inflammatory changes, scattered necrosis and loss of myosin thick filaments.

Discussion

Our study shows that one-third of the patients admitted to the ICU due to acute exacerbation of COPD and receiving high doses of corticosteroids developed AQM. We have proved that the total doses of corticosteroids administered, the severity of illness at admission and the occurrence of sepsis are risk factors associated with AQM development. AQM is associated with an increment in the duration of mechanical ventilation and the length of in-hospital stay.

Three previous retrospective studies concluded that AQM might be due to a synergistic effect of corticosteroids and NMBAs, although muscle relaxants were identified as the main insult. Leatherman et al. [3] reported that 29% of the patients receiving corticosteroids in conjunction with NMBAs developed AQM, whereas 0% of the patients that received corticosteroids, but not NMBAs, developed this complication. The other two studies identified NMBAs and the duration of muscle relaxation as independent predictors of AQM [4, 13]. This lack of agreement may be explained by the fact that, in these studies, the diagnosis was made through clinical and laboratory data without systematic neurophysiological evaluation. We admit that the relatively small size of our sample compared with the other studies may explain the fact that NMBAs have not been considered a risk factor for AQM [3, 4, 13].

The contribution of corticosteroids and NMBAs to the development of AQM remains controversial. A recent study has concluded that the use of corticosteroids is an independent risk factor for ICU-acquired paresis [14]. Based on the neurophysiological examination, all the cases included in this study were diagnosed as having axonal neuropathy, but a myopathic pattern was present on the muscular biopsies of all of the patients with clinical weakness lasting for 14 days.

Sepsis is an offending agent in our series. Experimental studies have demonstrated that sepsis affects respiratory muscle function [15, 16]. Latronico et al. [17] showed that most of their patients who developed AQM had not been treated with NMBAs or corticosteroids, but all had suffered from prolonged sepsis. In sepsis, proteolysis is associated with the activation of the ubiquitin-proteasome pathway in skeletal muscle [18]. However, this pathway was not enhanced in the muscular fibers of five septic patients with AQM, although three of them had been exposed to corticosteroids and NMBAs.

Our study shows that severity of illness at admission is associated with the development of AQM. Although Behbehani et al. [4] show that the APACHE II scores are not significantly different in patients with and without myopathy, our findings may be explained by the fact that COPD patients, who are more critical at admission to the ICU, need higher doses of corticosteroids and are prone to develop nosocomial sepsis. The combination of these two factors seems to be strongly involved in the development of AQM.

We admit several limitations to our study. First, given the small number of patients, we were unable to develop a statistical model to identify risk factors independently associated with AQM development. Secondly, the total dose of midazolam was not prospectively recorded and it would have been very helpful to measure certain physiological parameters to guide the weaning process. Third, the length of mechanical ventilation was longer in patients that developed AQM than in those patients that did not develop this complication. Hence, AQM might increase the duration of mechanical ventilation, although we cannot ignore that the prolonged intubation might be a risk factor for AQM development as it increases the period of muscle inactivity [14, 19]. In addition, we did not monitor the real compliance with our weaning protocol and therefore any possible violations of this protocol were not recorded. Consequently, our results should be interpreted with caution because the higher duration of mechanical ventilation observed might be due to different weaning approaches. Finally, some of these patients may also suffer acute polyneuropathy, but this alternative diagnosis was not explicitly evaluated. Despite all these limitations, we consider that this study contributes to our knowledge of AQM in COPD patients.

To sum up, clinicians should not forget that the use of high doses of corticosteroids in acute exacerbation of COPD may contribute to the development of AQM. The present study implies a dose-response and this is essential because other factors identified, such as the development of sepsis and the severity of illness at admission, are hardly modifiable.

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