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REVIEW

Acquired neuromuscular disorders in critically ill patients: a systematic review

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Abstract *Objective*: To summarize the prospective clinical studies of neuromuscular abnormalities in intensive care unit (ICU) patients.
Study identification and selection: Studies were identified through MEDLINE, EMBASE, references in primary and review articles, personal files, and contact with authors. Through duplicate independent review, we selected prospective cohort studies evaluating ICU-acquired neuromuscular disorders.
Data abstraction: In duplicate, independently, we abstracted key data regarding design features, the population, clinical and laboratory diagnostic tests, and clinical outcomes.
Results: We identified eight studies that enrolled 242 patients. Inception cohorts varied; some were mechanically ventilated patients for ≥ 5 days, others were based on a diagnosis of sepsis, organ failure, or severe asthma while others were selected on the basis of exposure to muscle relaxants, or because of participation in muscle biochemistry studies. Weakness was systematically assessed in two of the eight studies, concerning patients with severe asthma, with a reported frequency of 36 and 70 %, respectively. Electrophysiologic and histologic abnormalities consisted of both peripheral nerve and muscle involvement and were frequently reported, even in non-selected ICU patients. In a population of patients mechanically ventilated for more than 5 days, electrophysiologic abnormalities were reported in 76 % of cases. Two studies showed a clinically important increase (5 and 9 days, respectively) in duration of mechanical ventilation and a mortality twice as high in patients with critical illness neuromuscular abnormalities, compared to those without.
Conclusions: Prospective studies of ICU-acquired neuromuscular abnormalities include a small number of patients with various electrophysiologic findings but insufficiently reported clinical correlations. Evaluation of risk factors for these disorders and studies examining their contribution to weaning difficulties and long-term disability are needed.

Key words Critical illness · Neuromuscular abnormalities · Ventilator-dependence · Sepsis · Electromyography · Muscle biopsy

Introduction

Studies about abnormalities of the neuromuscular system complicating critical illness were first published 20 years ago. The initial case report described a 24-year-old woman with asthma who exhibited severe weakness following mechanical ventilation and the administration of hydrocortisone and pancuronium [1]. A case series of five patients with sepsis and paralysis related to polyneuropathy was reported subsequently by

Table 1 CINMA: an anatomic and functional classification (*SIRS* systemic inflammatory response syndrome, *MOD* multiple organ dysfunction, *ARDS* acute respiratory distress syndrome)

Clinical context	Anatomic disorder
• SIRS/MOD	• Sensory-motor axonopathy
• Non-depolarizing neuromuscular blockers, Corticosteroids Asthma, ARDS	• Motor axonopathy Atrophy with myosine loss Muscle necrosis
• SIRS ("necrotizing myopathy of intensive care")	• Muscle necrosis
• Immobilization, coma, malnutrition	• Diffuse type II fiber atrophy
Clinical context	**Functional disorder**
• Non-depolarizing neuromuscular blockers	• Neuromuscular transmission abnormality
• Hypophosphatemia, hyperkalemia, hypokalemia, hypercalcemia, hypermagnesemia	• Muscle cell dysfunction

Bolton and colleagues [2]. Since then the number of retrospective studies [3–6], and editorials [7–9] on this phenomenon have increased considerably. Many narrative reviews [10–13] have also been published, mostly focusing on historical features, specific populations, and/or pathophysiological mechanisms.

Clinicians have suspected that weakness and a variable constellation of physical signs, such as sensory abnormalities and/or decreased deep tendon reflexes may be explained on the basis of neuromuscular disease acquired in the intensive care unit (ICU). Electrophysiologic and histologic examinations have revealed abnormalities involving sensory and/or motor peripheral nerves, the neuromuscular junction, and muscle fibers. A landmark review article published recently [11] outlined the major conditions of critical illness neuromuscular abnormalities (CINMA) (Table 1).

Critical illness polyneuropathy characterized by primary axonal degeneration of motor and sensory fibers is the most common manifestation of CINMA [10]. The weakness tends to occur following prolonged treatment of sepsis and may represent the neural manifestation of multiple organ failure (MOF). The second most fully described syndromes are purely motor deficits comprising muscle atrophy restricted to type II fibers [5, 14], muscle fiber necrosis [15], and even motor axonopathy [16]. These motor syndromes are observed in patients recovering from respiratory failure such as in acute asthma or the acute respiratory distress syndrome (ARDS). High and prolonged doses of corticosteroids and/or non-depolarizing neuromuscular blockers are thought to be strongly associated with these neuromuscular abnormalities, although pathophysiologic mechanisms remain to be established. The remaining conditions are less well described. Necrotizing myopathy associated with rhabdomyolysis revealed by high creatine phosophokinase plasma levels has been described in patients with multiple injuries and severe sepsis [17]. Severe muscle proteolysis has been observed after prolonged immobilization, regardless of the cause of immobilization, and is often worsened by malnutrition [18]. In addition, prolonged neuromuscular blockade [6] or metabolic disturbances such as hypophosphatemia, hypomagnesemia, hypermagnesemia, hypokalemia, and hypocalcemia [19, 20] can precipitate or aggravate weakness. CINMA appears to be a syndrome related to various conditions, rather than a specific disease related to a specific condition.

In whichever context it occurs, CINMA may be responsible for prolonged mechanical ventilation and increased length of ICU stay. Although a search for definitive risk factors, pathophysiologic mechanisms, and preventive interventions will be important in directing future research, determining the clinical spectrum of the disease is the first step in such a research program. The goal of this systematic review was to appraise critically and summarize the prospective clinical studies of ICU-acquired neuromuscular disorders, describing the frequency, clinical features, and outcomes related to critical illness and neuromuscular abnormalities.

Materials and methods

To identify prospective studies, we searched two computerized databases from January 1980 to September 1997. For MEDLINE and EMBASE, we used the following text words and key words: critical care, intensive care, critical illness, neuropathy, polyneuropathy, myopathy, neuromyopathy, neuromuscular, muscular, prospective studies. We had no language restrictions.

The titles (and the abstracts, when available) in the MEDLINE and EMBASE printouts and the reference lists of all primary articles and review articles were reviewed independently in duplicate. Any additional relevant articles were identified and retrieved.

The following selection criteria were applied to the full manuscripts by two of the authors (B.D.J. and D.C.) independently: studies had to enroll critically ill adult patients presenting acquired peripheral nervous system and/or muscular and/or neuromuscular transmission abnormalities, described clinically and/or electrphysiologically and/or histologically, involving limbs and/or respiratory muscle, in prospective cohort studies. A priori, we excluded retrospective studies, case series, and studies concerning central nervous system (CNS) abnormalities. In duplicate, data were abstracted concerning the population, findings on clinical examination, the results of neuromuscular tests, and clinical outcome.

Potential confounding pharmacotherapy which could affect the frequency of CINMA was also extracted: corticosteroids, neuromuscular blockers, aminoglycosides, and metronidazole. The first two types of drugs have been been frequently associated with the occurrence of CINMA in ICU patients with acute asthma or ARDS. The last two are commonly used antibiotics, which are known to worsen neuromuscular transmission in patients with myasthenia gravis (aminoglycosides) or to induce polyneuropathy after prolonged administration (metronidazole). For each study, in-

formation reflecting the validity of the study was also extracted. This included: (1) description of the cohort; (2) time of inclusion of patients in the study; (3) duration of follow-up; (4) whether any clinical or electrophysiologic or histologic examination was initially planned, percentage of patients in whom this examination was performed; (5) comprehensive description of the clinical examination, if any; (6) description of the electrophysiologic examination if any. These criteria are presented for each study in Tables 2 and 3. Because very sparse data concerning risk factors were available in these studies, risk factor could not be comprehensively summarized in this review. Disagreements between reviewers concerning design characteristics and raw data abstraction were resolved by discussion and consensus.

Results

Study identification and selection

The database search yielded seven potentially relevant studies, and reference review yielded an additional two. One study enrolling patients both retrospectively and prospectively, in which it was not possible to distinguish between the two types of patient selection, was excluded [21]. Two case series were also excluded [22, 23], and also one prospective study enrolling exclusively patients with CNS disease [24]. Total agreement was reached regarding study selection.

Study design

Patient characteristics

The characteristics of the eight studies included are reported in Table 2 [25–32]. The sample size of these investigations ranged from 22 to 50. Although some of the same patients were probably reported in different articles [30, 31], the total number of patients reported in these studies was 242, 145 of whom had CINMA (or were suspected of having CINMA) and 97 of whom were controls. Inclusion criteria for patients were mechanical ventilation for > 5 days in three studies [29–31], diagnosis of sepsis or organ failure in two [25, 32], diagnosis of severe asthma [28], exposure to vecuronium [27], or participation in muscle biochemistry studies [26]. Two investigators specified that patients were enrolled in a consecutive manner [28, 30]. Most excluded patients with previous neuromuscular disease [25–27, 30–32], previous central neurologic disease [30–32], or potential risk factors for neuromuscular disease such as diabetes, alcoholism, human immunodeficiency virus, malignancy, and renal failure [27, 30, 31]. Some studies also described the use of pharmacotherapy suspected of impairing neuromuscular function, including neuromuscular blockers, corticosteroids, aminoglycosides, and metronidazole [25, 28–30, 32].

Patient outcomes

Only three of the eight studies included a formal clinical evaluation of CINMA focused on the physical examination in a percentage of patients specified by the investigator (Table 3). All had an initial clinical assessment. Two had unscheduled [27, 28] and one regularly scheduled [32] further evaluations. Electrophysiologic examination was performed systematically in five studies [25, 27, 30–32], and in a subset of patients in two others [28, 29]. Electrophysiologic evaluation generally included sensory and motor nerve conduction studies and needle electromyography (EMG). However, evaluation of neuromuscular transmission was available in only one study [27]. Diaphragmatic EMG was conducted in one study which included phrenic nerve stimulation [25]. Two investigations reported muscle biopsies in all patients [26, 29], but in one other this was only performed in selected patients, mostly because of lack of consent from patients or relatives [28].

Study results

The frequency of weakness in the three cohort studies which specified how many patients were assessed for clinical neurologic function [27, 28, 32] is reported in Table 3. In the two that enrolled patients with asthma and/or who had received vecuronium, the frequency was 70 and 36%, respectively [27, 28]. In the study that enrolled mechanically ventilated patients with MOF it was 60% [32], although only 68% were clinically evaluated. Among the three cohort studies enrolling non-selected ICU patients, none described the frequency of weakness or other clinical parameters, probably because of impaired consciousness in most of the patients. Muscle atrophy was reported in 3/5 patients in whom polyneuropathy was subsequently diagnosed on EMG [27] and in 5/15 in another study [32]. Deep tendon reflexes were reported as decreased or absent in all 15 patients with polyneuropathy in one study [25] and in 5/10 in a second [27].

Electrophysiologic and histologic abnormalities were variable across studies but were generally detectable in the majority of patients (Table 3). In none of the four cohort studies of patients with organ failure were both EMG and muscle biopsy systematically performed. In two studies in which EMG was systematically performed [25, 32], abnormalities were found in 70 and 82% of patients, respectively. The most frequent finding was axonal neuropathy ("critical illness polyneuropathy"). In the two other studies, where muscle biopsy was performed [26, 29], primary muscle disease (atrophy not related to denervation and/or muscle necrosis) was found in 78% of patients and was frequently associated with signs of denervation due to axonopathy [29]. In the two

Table 2 CINMA: study characteristics[a] (*APACHE* Acute Physiology and Chronic Health Evaluation score, *ARDS* Acute Respiratory Distress Syndrome, *CIP* Critical Illness Polyneuropathy, *diag* diagnosis, *EMG* Electromyographic, *HIV* Human Immunodeficiency Virus, *MOF* Multiple Organ Failure, *NR* Not Reported, *SAPS* Simplified Acute Physiology Score, *SIRS* Systemic Inflammatory Response Syndrome)

Study	Enrollment	Patient characteristics	Potential confounding pharmacotherapy
Witt et al. [25]	Inclusion: sepsis + MOF (dysfunction in 2 or more organs) + ventilated > 5 days + age > 16 years Exclusion: previous peripheral neuropathy	n = 43; mean age: 64 years; main diag: lung disease 10, surgery 9, trauma 7, sepsis 6, heart 5, brain 3, miscellaneous 3 (all encephalopathy)	Tobramycin 33, gentamicin 16, vancomycin 13, metronidazole 12, muscle relaxants "rarely used"
Helliwell et al. [26]	Inclusion: selected ICU patients participating in biochemical studies Exclusion: primary muscle disease	n = 31; mean age: NR; main diag: sepsis 19, peripheral vascular disease 5, major trauma 5, poisoning 1, eclampsia 1 (all patients had $\geq$ 1 organ failure)	NR
Kupfer [27]	Inclusion: ventilated patients receiving vecuronium $\geq$ 6 h Exclusion: age > 60, hypotension, sepsis syndrome, MOF, renal or hepatic dysfunction, diabetes, alcoholism, collagen vascular disease, neuromuscular disease, malignancy, HIV, pregnancy	n = 10; mean age: 34 years; main diag: status asthmaticus 8, viral pneumonitis 2	Vecuronium: 10; patients with polyneuropathy: 1352 mg for 7.2 days; without polyneuropathy: 528 mg for 3.8 days (p = 0.04)
Douglass [28]	Inclusion: consecutive severe asthmatic patients with mechanical ventilation	n = 25; mean age: 39 ± 17 years; 492 ± 602 mg vecuronium 2.5 ± 2.5 days paralyzed	Corticosteroids 25, vecuronium 22
Coakley [29]	Inclusion: projected or actual ICU stay > 7 days + $\geq$ 1 organ failure Exclusion: weakness or wasting on admission, coagulopathy	n = 23; mean age: 55 years; mean APACHE: 15.9; main diag: trauma 5, cardiorespiratory arrest 4, chronic airflow limitation 4, miscellaneous 10; during ICU stay: sepsis in 11	Corticosteroids 6, non-depolarizing muscle relaxants 15
Leijten et al. [30]	Inclusion: consecutive medico-surgical ICU patients ventilated > 7 days + age < 75 (no cardiac surgery) Exclusion: preexisting polyneuropathy, Guillain-Barré, thiopental-induced coma, fractures, bilateral leg amputation, severe edema, referral from other hospital after prolonged ventilation, curarization until death	n = 50; mean age: 57 years; mean APACHE: 22.6; main diag: acute or complex, elective surgery 19, infection 12, trauma 9, miscellaneous 10, during ICU stay: sepsis in 21	Vecuronium 2, aminoglycosides 4, prednisolone 10
Leijten et al. [31]	Inclusion: medico-surgical consecutive ICU patients ventilated > 7 days + age < 75 (no cardiac surgery) Exclusion: EMG abnormalities not considered to be CIP, diabetes mellitus, alcohol abuse, HIV infection, renal disease, neurotoxic medication, thiopental-induced coma, artificial paralysis until death, preexisting polyneuropathy, limb amputation	n = 38; mean age: 56 years; mean APACHE: 22.5; main diag: abdominal or thoracic surgery 14, sepsis 9, polytrauma 5, cardiac resuscitation 6, stroke 2, status asthmaticus 2; during ICU stay: sepsis in 18	Vecuronium with intubation 38, continuous infusion 19; aminoglycosides 14, corticosteroids 3
Berek et al. [32]	Inclusion: (sepsis or SIRS) + MOF + age > 16 years Exclusion: previous polyneuropathy, myopathy, central nervous system disease and all preexisting disease which might possibly have been responsible for development of polyneuropathy (diabetes mellitus, alcohol abuse, renal disease, HIV patients . . .)	n = 22; mean age: 51 years; mean SAPS: 14.8; main diag: trauma 15, pancreatitis 3, miscellaneous 4	Neuromuscular blocking agents 0, corticosteroids 0, aminoglycosides: yes but number not reported

[a] Shown here are the inclusion and exclusion criteria used to enroll patients, a description of the population, and pharmacologic co-interventions

Table 3 CINMA: Initial clinical assessment, neuromuscular tests and outcomes (*MV* mechanical ventilation, *DTRs* deep tendon reflexes, *MUP* motor unit potential, *EMG* electromyography, *NA* not applicable, *NMB* neuromuscular blockers, *NR* not reported, *PN* polyneuropathy, *CPK* creatine phosphokinase)

	Witt et al. [25]	Helliwell et al. [26]	Kupfer [27]	Douglass [28]	Coakley [29]	Leijten et al. [30]	Leijten et al. [31]	Berek et al. [32]
Time of initial assessment after ICU admission (days)	20 (5–89)	NR	24 h after discontinuation of NMB	NR	10 (3–37)	7–9 after onset of MV	7–9 after onset of MV	14–28
Initial clinical assessment								
No. (%) of patients clinically evaluated for weakness	NR	NR	10/10 (100)	25/25 (100)	NR	NR	NR	15/22 (68)
No. (%) of patients with weakness	15/?	NR	7/10 (70)	9/25 (36)	NR	NR	NR	9/15 (60)
Weakness severe/moderate/mild	NR	NR	NR	4/2/3	NR	NR	NR	1/4/4
No (%) of patients with muscle wasting	NR	NR	3/10 (30)	NR	NR	NR	NR	5/15 (33)
No. (%) of patients with absent/ reduced DTRs	15/?	NR	5/10 (50)	NR	NR	NR	NR	9/15 (60)
No. (%) of patients with difficulty weaning	15/?	NR	2/10 (20)	NR	NR	NR	NR	NR
Neuromuscular tests								
Standard EMG:								
No. (%) of patients with EMG	43/43 (100)		10/10 (1000)	4/25 (16)	10/23 (43)	50/50 (100)	38/38 (100)	22/22 (100)
Normal	13/43 (30)	NA	5/10 (50)		1/10 (10)	12/50 (24)	20/38 (53)	4/22 (18)
Axonopathy (sensory/motor/sensori-motor)	30/43 (70) (0/0/30)		5/10 (50) (1/4/0)	0	9/10 (90) (0/1/8)	11 (22)	18/38 (47)	16/22 (73) (0/3/13)
Demyelinating	0		0	0	0	7 (14)	NA	0
Mixed	0		0	0	0	11 (22)	NA	2 (9)
Other				4/4 (100)[b]		9 (18)		
Neuromuscular transmission study	NR	NR		NR	NR	NR	NR	NR
No. (%) of patients with NMT study			10/10 (100)					
Abnormalities			2/10 (20)					
MUP	NR	NR	NR	NR		NR	NR	NR
No. (%) of patients with MUP					4/23 (17)			
Myopathic pattern					2/4 (50)			
Muscle biopsy:	NR		NR			NR	NR	NR
No. (%) of patients with biopsy		31/31 (100)		6/25 (24)	23/23 (100)			
Normal		9		0	1/23 (4)			
Denervation atrophy		3		0	4/23 (17)			
Atrophy not related to denervation		12		3 (50)	10/23 (43)[d]			
Necrosis or myopathic pattern		17[a]		3 (50)	8/23 (35)			
Creatine phosphokinase:	NR	NR	NR			NR	NR	NR
No. (%) of patients with CPK measurement				25/25 (100)	15/23 (65)			
No. (%) of patients with CPK > 200 IU/l				19/25 (76)	7/15 (47)			
Mean CPK value (IU/l)				1575 (66–7430)[c]	200 (17–6665)			
Outcomes								
ICU mortality [No. (%)]:								
All patients	20/43 (46)	16/31 (51)	3/25 (12)	NR	5/23 (21)	18/50 (36)	12/38 (32)	7/22 (32)
CINMA patients	NR	NR	3/9 (33)	1/9 (11)	NR	14/29 (48)	8/18 (44)	NR
Non-CINMA patients						4/21 (19)	4/20 (20)	
Duration of ventilation (days):								
All patients	NR	NR	NR	6.6 ± 6.6	NR	NR	NR	NR
CINMA patients	NR	NR	NR	12.9 ± 6.6	NR	25 (8–109)	28 (7–96)	NR
Non-CINMA patients				($p < 0.02$)		20 (8–49)	17 (2–68)	
						$p = 0.03$	NS	

Mean duration of clinical follow-up in survivors	NR	NR	NR	NR	Until ICU discharge	1 year after ICU discharge	NR	3 months
No. (%) of CINMA survivors with clinical sequelae	NR	NR	NR	NR	18/18 (100)	NR	NR	6/15 (40)
Disability: severe/moderate/mild	NR	NR	NR	NR	9/5/4	NR	NR	0/2/4
Duration of CINMA in survivors	NR	NR	In the 2 patients with prolonged NMB: 24–72 h In the 5 patients with PN: 5 days–6 months	NR	NR	3 days–1 year	NR	NR

[a] Total may add up to more than number of patients because some patients had more than one abnormality
[b] Myopathic pattern in all patients
[c] CPK peak occurred 3.6 ± 1.5 days after ICU admission. In 4 patients there was a second peak of CPK occurring 18.5 ± 1.9 days after admission. Those 4 patients exhibited profound muscle weakness
[d] Including 2 patients with type II fiber atrophy

studies enrolling patients with asthma and/or administration of vecuronium [27, 28], the EMG, although not systematically performed, showed only a myopathic pattern in one study [28] and signs of muscle denervation in 50 % of patients in the other [27]. In this last study, prolonged neuromuscular blockade probably accounted for the clinical weakness in 20 % of the patients. In one large cohort study of non-selected ICU patients, in which electrophysiologic examination was systematically performed, 76 % had electrophysiologic abnormalities [30].

Summarizing the clinical outcomes in these studies is difficult because the duration and completeness of follow-up was variable and not reported in detail. Duration of paralysis was reported in two studies [27, 30]. In one enrolling patients with acute asthma [27], the duration of paralysis ranged between 5 days and 6 months, except for two patients with prolonged neuromuscular blockade in whom weakness resolved within 72 h. In the second, performed in an unselected ICU population [30], the duration of weakness ranged from 3 weeks to 1 year. Duration of mechanical ventilation in CINMA patients was available in three studies [28, 30, 31] (mean duration, respectively, 13, 25, and 28 days) with extremes ranging from 1 week to more than 100 days. The duration of mechanical ventilation was significantly longer than in non-CINMA patients in two of those investigations [28, 30]. Length of ICU stay was not reported in any study. Two compared mortality between CINMA and non-CINMA patients (48 vs 19 % [30] and 44 vs 20 % [31]), suggesting that detection of EMG abnormalities could have prognostic value in patients ventilated for more than 7 days.

Discussion

In the eight studies included in this systematic review, diverse patient populations were enrolled. Six studies described patients with sepsis and/or MOF [25, 26, 29, 32] and patients who had previously received neuromuscular blockers and/or corticosteroids [27, 28]. As so many different circumstances can lead to CINMA, more information about frequency of CINMA in non-selected ICU patients would be of interest. However, only two cohort studies [27, 28] were conducted in a non-selected population.

The main clinical feature of CINMA is weakness. Only two cohort studies, enrolling a total of 35 patients and including asthmatic patients who had received corticosteroids and/or neuromuscular blockers, systematically evaluated weakness [27, 28]. Drawing strong conclusions about the frequency of this clinical sign of weakness is thus difficult. The frequency of CINMA in a general ICU population still remains unclear. Large cohort studies are needed to address this issue. Severity

of weakness was described in only one investigation [28], using the categories mild, moderate, or severe.

By contrast, electrophysiologic and/or histologic assessments were performed in all but one study [26]. These studies confirm the high frequency of electrophysiologic abnormalities in selected populations (MOF or asthma), as in non-selected patients. In Leijten et al.'s investigation [30], 76 % of patients mechanically ventilated for more than 5 days had electrophysiologic abnormalities. Correlations with clinical findings were not specified. Although EMG and muscle biopsies were never performed systematically in the same study, unsuspected primary muscle involvement was found in patients with weakness associated with multiple organ dysfunction or sepsis, in which peripheral nerve abnormalities are usually described. This could reflect a direct effect of sepsis on muscle fiber, or of concurrent pathologies such as disuse proteolysis and malnutrition. Conversely, axonal abnormalities may be encountered in patients treated with corticosteroids and neuromuscular blockers in whom primary muscle abnormalities are expected. Thus, no specific electrophysiologic or histologic pattern corresponding to a specific condition was reported.

ICU-acquired axonopathy, although possibly influenced by pre-ICU diseases, can be confidently detected on electrophysiologic examination. This test may be a useful for the diagnosis and could help further epidemiologic studies. However, the importance of peripheral neurologic abnormalities detected when patients are still in a coma, as was frequently the case in these studies, is unclear. Early systematic detection of electrophysiologic abnormalities in ICU patients might have prognostic value, since these abnormalities are associated with a high mortality [30, 31]. However, the difficulty of obtaining electrophysiologic evaluation in ICU patients may preclude this systematic approach in daily practice. The importance of the histologic examination in assessing weakness in the ICU setting also needs to be better understood. Primary muscle involvement is unlikely to be definitively determined without muscle biopsy, but this may be refused because the test is invasive and has no proven therapeutic implications at present.

Two studies comprehensively reported the comparative duration of mechanical ventilation between CINMA and non-CINMA patients [30, 31], showing prolonged mechanical ventilation in CINMA patients, the difference reaching statistical significance in one investigation [30]. However, establishing the potential contribution of CINMA to weaning difficulty is challenging. Only one study cited here described a correlation between limb and respiratory muscle weakness [25]. Superficial diaphragmatic EMG is unreliable [33], needle diaphragmatic EMG is risky in ventilated patients [34], and phrenic nerve stimulation is difficult to perform in many ICUs. These problems may account for the dearth of information concerning the attribution of CINMA to diaphragmatic weakness and delayed liberation from mechanical ventilation. Two cohort studies enrolling patients with MOF reported a comparative mortality between CINMA patients diagnosed on electrophysiologic examination and non-CINMA patients, both of them showing a higher mortality in CINMA patients [30, 31]. Although none of these differences were significant, possibly due to sample sizes that were too small, electrophysiologic diagnosis of CINMA could thus be a risk factor for mortality in ICU patients with MOF. It is not clear whether this finding reflects a higher initial severity of illness in CINMA patients or a specific contribution to mortality. Further large, matched case-control studies could help to address this point.

The optimal type of investigation required to evaluate the natural history of a disease and its impact on patients in the short and long term is a prognosis study. Such studies describe inception cohorts at a similar point in time and follow them prospectively to provide clinical outcome data using specific criteria systematically applied to all patients [35]. Among the prognosis studies cited in this review, the inception cohorts were well described, but the patients were identified at different points in the history of their illnesses. Many were evaluated while comatose, precluding careful evaluation of weakness. The duration of clinical follow-up, when mentionned, was variable but tended to be short, precluding long term assessment of function and survival. Finally, the sample sizes in these studies were small, making confidence intervals around these estimates highly variable. However, individually and in aggregate, these studies have helped to describe the problem of CINMA and have provided useful information for intensivists.

Risk factors for CINMA were not summarized in this review for many reasons. Although six of the studies reported risk factor analysis [25–28, 30, 31], these were mainly performed to explain electrophysiologic or histologic results, but not to predict which factors were associated clinical abnormalities such as weakness or paralysis. Moreover, many studies excluded patients with potential risk factors such as diabetes mellitus, alcohol abuse, or renal failure, possibly leading to a selection bias for risk factor analysis.

Future studies should focus on clinically important problems such as failure to wean from mechanical ventilation and length of ICU stay in the short term, and post-ICU and posthospital disability in the long term. Ideally, reproducible measurements using bedside tests and objective scales should be incorporated at regular intervals. Potential risk factors for weakness should be carefully documented, including dosing of drugs that may exacerbate or cause weakness. Electrophysiologic tests should incorporate studies of neuromuscular transmission to diagnose conditions exacerbated by non-de-

polarizing neuromuscular blockers and aminoglycosides. In patients agreeing to muscle biopsy, histologic examination may be the only way to evaluate accurately muscle involvement, which may be underappreciated by physical or EMG examination.

A consensus conference may be useful in which multidisciplinary experts could explore whether endorsement of a specific classification system would allow readers to make comparisons across studies and facilitate communication among clinicians and scientists. A common set of definitions may also promote multicenter studies, thereby creating a database of sufficient size to generate stable incidence estimates, to identify accurately risk factors, and to determine clinical and economic sequelae. Better understanding of the mechanisms and predictors of CINMA might help to target preventive therapy (e.g., minimizing exposure to paralytic agents) and encourage rigorous evaluation of potential therapeutic interventions (e.g., intensive physiotherapy, including nerve and/or muscle electrostimulation, intravenous immunotherapy [36], and other innovative approaches).

Appendix

The members of the Groupe d'Etude et de Réflexion sur les Neuromyopathies En Reanimation are: Sami Antoun, Jérome Authier, Christian Boyer, Jean Carlet, Gilles D'honneur, Bernard De Jonghe, Isabelle Durand-Zaleski, Edouard Ferrand, Jean-Pascal Lefaucheur, Franck Lagneau, Francine Mesrati, Pierre Moine, Luc Montuclard, Hervé Outin, Benoit Plaud, Jean-Claude Raphael, Dominique Renon, Tarek Sharshar, Gilles Troché.

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