Neuromuscular paralysis in the intensive care unit

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ABSTRACT

Objectives: To determine the features, causes, risk factors and outcome of acquired neuromuscular paralysis in critically ill patients.

Methods: Retrospective review of all confirmed cases of acquired polyneuropathy and myopathy examined by our Neurology service in the Intensive Care Unit (ICU), at King Fahad National Guard Hospital, Riyadh, Kingdom of Saudi Arabia over a period of 5 years. All patients had comprehensive electrophysiological studies and one third had muscle and nerve biopsies.

Results: Thirty cases were included, 8 cases of polyneuropathy, 15 cases of myopathy and 7 cases of mixed neuropathy and myopathy. Absent deep tendon reflexes and absent sensory potential on nerve conduction studies were significantly suggestive of neuropathy. The level of creatine phosphokinase was not of great diagnostic value. Most polyneuropathy and myopathy cases had passed through a stormy ICU course with sepsis and multiorgan failure. The use of high doses of steroids was more associated with myopathy. Seven patients died in ICU, the others were discharged to the wards after a mean ventilation period of 40 days. One patient became chronic ventilator dependent.

Conclusions: From this series and available literature, it seems that symptomatic myopathy is more frequent than polyneuropathy and some risk factors are common for both (sepsis and multiorgan failure) while the use of steroids is more associated with ICU myopathy. Treating sepsis and stopping corticosteroids results in the improvement of most of the cases.

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Generalized weakness in critically ill patients is increasingly recognized as a frequent complication in intensive care units (ICU) and a common cause of prolonged ventilator dependency.[1-3] Sepsis, multi-organ failure and the use of some drugs such as corticosteroids, neuromuscular blocking agents and aminoglycosides have been strongly implicated in the ICU paralysis syndromes, but the pathophysiology of these disorders is poorly understood.[1-6] Most neuromuscular syndromes occurring in ICU setting belong to one of 2 groups: critical illness myopathy and critical illness polyneuropathy. Another rare group is the occurrence of prolonged neuromuscular blockade.[7] The distinction may be difficult in a particular patient, not only in obtaining a good history as physical examination is difficult in ICU patients, but also as these entities often overlap. Meticulous electrodiagnostic studies, muscle and nerve histopathological evaluation are often needed to establish a precise diagnosis.[2,8] Over the last 5 years, we examined 30 cases of ICU neuromuscular paralysis which are described in this paper.

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Methods. The charts of all adult ICU patients for the Neurology service was consulted for weakness or difficulty to wean from the ventilator at King Fahad National Guard Hospital, Riyadh, Kingdom of Saudi Arabia (KSA) from June 1997 to June 2002 were reviewed. Patients with central neurological causes of weakness or previously identified peripheral causes were excluded. It was carried out by radiological evaluation (computed tomography [CT] scan or magnified resonance imaging [MRI]) of the brain and electroencephalogram (EEG), if needed, of which 15 patients (50%) required CT scan or MRI. Demographic data, physical findings, details of the illness and drug therapy, results of electrophysiological studies, laboratory and biopsy results and potential risk factors associated with critical illness polyneuropathy or myopathy were reviewed. All patients had a comprehensive neurological examination and electrophysiological studies, including motor and sensory conduction, needle electromyogram (EMG) examination in the upper and lower limbs and repetitive stimulation test. Eleven patients had nerve and muscle biopsies, however, on the rest of the patients, muscle biopsy was either refused by the family or the primary caring physician. In few patients, clinical improvement was noticeable at the time of neurological consultation; hence, muscle biopsy was not requested. Electromyogram criteria for neuropathy were the presence of widespread signs of denervation, namely, fibrillations and positive sharp waves and decreased amplitude or absence of sensory potentials and compound muscle actions potentials. Neurogenic recruitment pattern was very helpful for the diagnosis of neuropathy when seen. Unfortunately, most of the patient with neuropathy were severe and most of those patients on motor units were recorded. The presence of typical myopathic units was the main EMG criteria for the diagnosis of myopathy. When both myopathic and neuropathic features coexisted, whether on muscle biopsy or EMG studies, the case was considered as mixed neuromyopathy. Chi-square test was used as statistical analysis.

Results. From the 35 originally selected patients, 5 were excluded: one woman was diagnosed with nemaline rod myopathy that became obvious after she was admitted to ICU for another problem and 4 patients were diagnosed with motor neuron disease. The remaining 30 patients had a critical polyneuropathy and myopathy illnesses. They constituted 1.2% of ICU admissions in the same period of which 15 were men and 15 were women with a mean age of 55 years (range 18-81 years). Fifteen (50%) were diagnosed with myopathy (mean age of 50 years), 8 (27%) with polyneuropathy (mean age of 55 years) and 7 (23%) with a mixed disorder (mean age of 57 years). The main clinical, electrophysiological and biochemical findings in the 3 groups are shown in **Table 1**. Abnormal sensory potentials (p=0.0001), the absence of myopathic units (p=0.0003) or the presence of denervation potentials (p=0.0007) and the absence of deep tendon reflexes (p=0.0003) were strongly associated with polyneuropathy. Serum creatine phosphokinase (CPK) was elevated in only 27% of the myopathic cases and its elevation was not enough to diagnose myopathy (p=0.1). The highest value did not exceed 10,000 u/l. All patients, except 2 (93%) had sepsis and 23 (77%) had multiple organ failure. Other associated risk factors were bronchial asthma in 18 cases, corticosteroids

Table 1 - Clinical, electrophysiological and biological findings.

Clinical and laboratory findings	Neuropathy N=8 n (%)	Myopathy N=15 n (%)	Mixed N=7 n (%)
Absent tendon reflexes	7 (87)	5 (33)	3 (43)
Absent sensory potentials	7 (87)	1 (7)	1 (14)
Denervation potentials	8 (100)	4 (27)	3 (43)
Myopathic units	0*	12 (86)*	5 (71)
Elevated CPK	0	(27%)	3 (43)

*2 no units, CPK - Creatinine phosphokinase

Table 2 - Associated risk factors.

Risk factors	Neuropathy N=8 n (%)	Myopathy N=15 n (%)	Mixed N=7 n (%)	Total N=30 n (%)
Sepsis	8 (100)	13 (86)	7 (100)	**28 (93)**
Multiorgan failure	8 (100)	11 (73)	4 (57)	**23 (77)**
Steroids	3 (37)	12 (80)	3 (43)	**18 (60)**
Bronchial asthma	2 (25)	8 (53)	1 (14)	**11 (36)**
Aminoglycosides	5 (62)	8 (53)	5 (71)	**18 (60)**

use in 18 cases and the use of aminoglycosides in 11 cases. Two patients had liver transplant and were on heavy immunosuppressive regimen. The association of risk factors with each of the 3 entities is shown in **Table 2**. The use of steroids was significantly associated with myopathy (p=0.004). There were no associations with the other risk factors. Nerve and muscle biopsies revealed a non-specific myopathy in 9 of 11 cases and a mixed condition (axonal neuropathy with myopathy) in the other 2 cases. There were perfect correlation between electrophysiological studies and pathological results.

Seven patients (23%) died in the ICU as compared to 20% deaths from all causes over the same period. Four of them belonged to the polyneuropathy group (50%) while 2 died in the myopathy group (13%) (p=0.056). All other patients were ultimately weaned from ventilator after a mean duration of 40 days (range 14-120 days), except one who became chronic ventilator dependent. There was no significant difference in the duration of ventilation between the survivors of the 3 groups (means 38, 41 and 42 days).

Discussion. The main findings in our study was the relative rarity of ICU related neuromuscular weakness, the preponderance of myopathy over polyneuropathy, the relative high frequency of mixed cases and the absence of neuromuscular junction disorders in this series. The frequency of this disorder was most likely underestimated because only referred patients were included. It is very possible that we were not consulted for the mild cases and also for those patients who were very sick and died before the attempt of weaning them from mechanical ventilation. The optimal prospective study of the epidemiology of the neuromuscular disorders occurring in the ICU has yet to be performed. All of the studies available in the literature are limited by incomplete electrophysiology or other pitfalls. In 2 prospective studies published,[9,10] the frequency of nerve dysfunction after severe sepsis and multiorgan failure has reached up to 70%. Most of these cases were however, detected by electrophysiological study and were clinically asymptomatic. Lacomis et al[11] published perhaps the largest series of ICU related symptomatic neuromuscular disorders studied by electrophysiology and muscle biopsy to determine the neuromuscular cause of weakness. From their 92 patients, 42% had ICU acquired myopathy, 13% had axonal polyneuropathy and 2% prolonged neuromuscular blockade. The other 43% had pre-existing diseases revealed or worsened by their ICU stay (acute lateral sclerosis, myasthenia, neuropathies and so forth). It is however surprising that no mixed cases were found in that series, while those constituted approximately a quarter of our cases. On the other hand, our findings were similar that ICU myopathies were more frequent than neuropathies. We also found, that absent deep tendon reflexes and sensory potentials on conduction studies are significantly associated with polyneuropathy, while CPK level did not appear to be a significant diagnostic tool.

Sepsis was present in almost all of our patients (93%), suggesting that it is a major risk factor for both polyneuropathies and myopathies occurring in ICU setting. In a recent paper, Hund[12] advocated the idea that most of these syndromes are in fact complications of sepsis. This was previously postulated by Bolton[13] who speculated that the factors responsible for the systemic effects of sepsis, namely, release of tumor necrosis factor, histamines and arachidonic acid metabolites, activation of the complement and cell adhesion systems and formation of free radicals may also cause axonal damage. In this view, the peripheral nerve is just another organ system that fails during sepsis.

The pathophysiology of ICU myopathy or sepsis associated myopathy is more complex as at least 3 pathological types have been described: 1) a diffuse non-necrotizing "cachectic" myopathy, a myopathy with selective loss of thick filaments and an acute necrotizing myopathy.[12] The first non-necrotizing category is the most common and often associated with polyneuropathy. It is often designated in the literature as "critical illness myopathy". Histopathological changes include variations of muscle fibers size, fiber atrophy and angulation, centralized nuclei and so forth. There are no inflammatory cells and serum CPK is often normal.[12] All our cases in which a muscle biopsy was carried out belonged to this group. The "thick filament myopathy" has been more associated with the use of corticosteroids for severe asthma or organ transplant. In many cases, neuromuscular blocking agents have been used as well.[12] The hallmark is the absence of thick (myosin) filaments on electron microscopy.[14] It seems that glucocorticoid treatment and sepsis stimulate muscle proteolysis and this process is amplified by muscle inactivity from neuromuscular blockade.[15] The third category, the necrotizing myopathy, is quite rare. Some ICU patients develop prominent myonecrosis that can even lead to rhabdomyolysis.[16] This category seems also associated with the use of corticosteroids and neuromuscular blockers.

In conclusion, this series and the available published data suggest that symptomatic acquired myopathy in ICU patients is more frequent than symptomatic polyneuropathy and that mixed cases are also common. Both myopathy and polyneuropathy share common risk factors, namely, sepsis and multiorgan failure. Corticosteroid usage is however, more associated with myopathy. The death rate in our patients was similar to the other

ICU patients and all the survivors, except one, were ultimately weaned from ventilator. This suggests that most of these patients improve when the offending risk factors, namely, sepsis, multiorgan failure and corticosteroids usage do not exist.

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