

Associazione di Neurofisiopatologia del Nord-Est, Treviso 17 Aprile 2004

DIAGNOSTICA NEUROFISIOLOGICA nelle
URGENZE NEUROLOGICHE ed in TERAPIA INTENSIVA

Neuropatie e Miopatie acute nel paziente in condizioni critiche

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Occurrence of neuromuscular abnormalities in prospective cohort studies

NJ Witt et al	Chest 1991; 99:176	70.0 % (30) of patients with sepsis and MOF
AR Spitzer et al	Muscle Nerve 1992; 15: 682	86.0 % (13) of patients with MV > 14 days
JH Cackley et al	Intensive Care Med 1993; 19: 323	95.6 % (22) of patients with CU stay > 7 days
FSS Leijten et al	JAMA 1995; 274: 122	58.0 % (29) of patients with MV > 7 days
K Berek et al	Intensive Care Med 1996; 22: 849	81.8 % (18) of patients with sepsis and MOF
N Latronico	Lancet 1996; 347:1579	100.0% (24) of patients with coma, prolonged sepsis
JH Cackley et al	Intensive Care Med 1998; 24: 801	84.0 % (37) of patients with CU stay > 7 days
M.A.C.J. De Letter et al	J Neuroimmunol 2000; 106: 206	32.6 % (32) of patients with MV > 2 days
M Tepper et al	Neth J Med 2000; 56: 211	76.0 % (19) of patients with sepsis
A Dushchik et al	Intensive Care Med 2001; 27: 686	57.0 % (16) of patients with MV > 3 days
J Gamado-Montem et al	Intensive Care Med 2001; 27: 1288	68.5 % (50) of patients with sepsis
B De Jonghe et al	JAMA 2002; 288:2859-2867	25.3 % (95) of patients with MV > 7 days
N Latronico	Submitted	30.4 % (92) of patients with predicted 30% risk of MOF

Program

- Pathophysiology
- Clinical signs
- Outcome
- Critical illness myopathy, critical illness polyneuropathy, or both?
- Conclusions



Pathophysiology

- Cellular dysoxia and hibernation: The stunned peripheral nerve
- Cytokines, adhesion molecules and coagulation
- Insulin deficiency and hyperglycemia

Critical illness myopathy and neuropathy

N. Latronico, et al.
Lancet 1996; 347:1579

Acutely ill comatose patients were enrolled if they :

- had only minimal movements or complete paralysis in response to painful stimulation;
- had reduced or absent deep-tendon reflexes;
- maintained normal or at least unchanged brainstem reflexes

Inclusion Criteria Fulfilled?

ENG-EMG

Abnormal ?

Muscle biopsy
peroneus brevis muscle

Nerve biopsy
sural nerve

14 normal nerve
8 axonal neuropathy



N Latronico et al. Lancet 1996; 347: 1579-82

The stunned peripheral nerve

Functional impairment

It is tempting to speculate, that sepsis-related nerve failure caused an early impairment of axonal transport and transmembrane potential, a finding easily documented by electrophysiological but not by histological studies.

Structural impairment

With persisting sepsis, the energy supply or use is not restored and histological alterations ensue. Necropsy findings of anterior-horn chromatolysis, a centripetal response to axonal degeneration, reinforces this hypothesis.

N Latronico et al. Lancet 1996; 347: 1579-82

The stunned peripheral nerve

Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction

Hotchkiss RS, et al.
Crit Care Med 1999; 27:1230

A fundamental question that remains unresolved despite these extensive histologic studies is the primary mechanism responsible for patient death in sepsis.

Although apoptosis and necrosis were present in many organs, the extent of cell death was not, in general, sufficient to cause organ failure.

The absence of histologic evidence of cell death sufficient to explain the morbidity/mortality of sepsis suggests that other as yet unrecognized mechanisms may be involved in the pathogenesis of the disorder.

The stunned peripheral nerve

Down-regulation or "hibernation" of the cell

The response of many cells including cardiac myocytes to stress includes a shift to fetal gene expression and may be an attempt to revert to a *lower energy-using state* and avoid death.

The cell does only enough to keep alive and does not perform other whole-organ functions.

An analogy is found in the setting of myocardial infarction and "stunned" myocardium.

Hotchkiss R S, et al. Crit Care Med 1999; 27:1230

The stunned peripheral nerve

... [Hotchkiss and col] describe a net divergence between in vivo evidence of organ failure and absence of histologic evidence of substantial organ damage.

Their fascinating hypothesis that in situations of energy failure, the cells may try to revert to a low energy state and avoid death seems to be operating on in the neuromuscular system.

Latronico N. Crit Care Med 2000; 28:3375

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Pathophysiology

✦ Cellular dysoxia and hibernation: The stunned peripheral nerve

⇒

✦ Cytokines, adhesion molecules and coagulation

✦ Insulin deficiency and hyperglycemia

Cytokines, adhesion molecules and coagulation

Enhanced expression of E-selectin on the vascular endothelium of peripheral nerve in critically ill patients with neuromuscular disorders

Fenzi F, Latronico N, Refatti N, Rizzuto N.
Acta Neuropathol (Berl) 2003; 106:75

Immunohistochemical data provide first evidence that an increased expression of E-selectin, a marker of endothelial-cell activation, takes place in both epineurial and endoneurial vessels of septic patients.

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athophysiology

- ✦ Cellular dysoxia and hibernation: The stunned peripheral nerve
- ✦ Cytokines, adhesion molecules and coagulation
- ➡ ✦ Insulin deficiency and hyperglycemia

Insulin deficiency and hyperglycemia

Peripheral nerve function in sepsis and multiple organ failure

NJ Witt, et al.
Chest 1991; 99:176

A peripheral nerve function index showed statistically significant negative correlations with the time in the critical care unit, and the **serum glucose value**; the serum albumin level showed a positive correlation.

Insulin deficiency and hyperglycemia

Intensive insulin therapy in critically ill patients

Van den Berghe G, et al.
New Engl J Med 2001; 345:1359

Systematic EMG screening on a weekly basis in 363 patients

The incidence of critical illness polyneuropathy was reduced by 44%.

There was a positive, linear correlation between the risk of polyneuropathy and the mean blood glucose level, both in patients with conventional and intensive insulin treatment.

The risk of having CIP with conventional insulin treatment was more than double that of intensive insulin treatment.

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ajor clinical findings

Neuropathy involves both sensory and motor nerves

The most striking clinical finding is muscle wasting and paralysis

Paresis acquired in the intensive care unit. A prospective multicenter study.

De Jonghe B, et al.
JAMA 2002; 288: 2859

All consecutive ICU patients without preexisting neuromuscular disease who underwent mechanical ventilation for 7 or more days were screened daily for awakening

Patients with severe muscle weakness on day 7 were considered to have ICU acquired paresis (ICUAP)



Medical Research Council - MRC

- | | |
|---|--|
| 0 | complete paralysis |
| 1 | minimal contraction |
| 2 | active movement with gravity eliminated |
| 3 | weak contraction against gravity |
| 4 | active movement against gravity and resistance |
| 5 | normal strength |

3 muscle groups in each of the upper and lower limbs
each muscle group score ranges from 0 (paralysis) to 5 (normal muscle strength)
overall score from 0 to 60

MRC < 48: significant weakness

Paresis acquired in the intensive care unit.

A prospective multicenter study.

De Jonghe B, et al.

JAMA 2002; 288: 2859

All consecutive ICU patients without preexisting neuromuscular disease who underwent mechanical ventilation for 7 or more days were screened daily for awakening.

The incidence of ICUAP was **25.3%**



Major clinical findings

Neuropathy involves both sensory and motor nerves

The most striking clinical finding is muscle wasting and paralysis

The neuromuscular respiratory system is not spared

Critical illness polyneuropathy.

A complication of sepsis and multiple organ failure

Zochodne DW, et al.

Brain 1987; 110: 819

Failure to wean from the ventilator and limb weakness prompted neurological referral



Major clinical findings

Neuropathy involves both sensory and motor nerves

The most striking clinical finding is muscle wasting and paralysis

The neuro-muscular respiratory system is not spared

Cranial nerves are usually (not invariably) spared

Limb paralysis usually becomes clinically evident over the first 2-3 ICU weeks



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The role of polyneuropathy in motor convalescence after prolonged mechanical ventilation

FSS Leijten et al.

JAMA 1995; 274: 1221

In 29 of 50 patients (58%), who were receiving mechanical ventilation for more than 7 days, an EMG diagnosis of polyneuropathy was made in the ICU.

Of nine patients with delays beyond 4 weeks, eight had polyneuropathy, five of whom had persistent motor handicap after 1 year.

Critical illness polyneuropathy.

A 2-year follow-up study in 19 severe cases

M. de Seze, et al.

Eur Neurol 2000; 43: 61-69

Two patients died within 2 months, 11 recovered completely, 4 remained quadriplegic and 2 remained quadriparetic

Persistent neuromuscular and neurophysiologic abnormalities in long-term survivors of prolonged critical illness

Fletcher, S. N.

Crit Care med 2003; 31: 1012-1016

Neurophysiologic evidence of chronic partial denervation of muscle consistent with previous critical illness polyneuropathy is almost invariable and can be found up to 5 yrs after intensive care unit discharge in >90% of these long-stay patients.

Challenges in the care of the acutely ill

J F Bion, J E Heffner

Lancet 2004; 363: 970-977

Australian hospitals have extended intensive care services and personnel into hospital wards by creating medical emergency teams.

The UK has outreach care provided by critical-care-trained nurses for patients admitted to the wards.

Better integration should also extend into post-hospital recovery. We are only just beginning to identify the safety issues of post-discharge care, though we know that the physical consequences of critical illness persist.

"It may seem a strange principle to enunciate as the very first requirement in a hospital that it should do the sick no harm."

Florence Nightingale. *Notes on hospitals* (London, 1859)

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Multicenter Italian CRIMYNE study

Acute myopathy and neuropathy developing in critically ill patients represent the failure of the neuromuscular system in patients with multi-organ dysfunction syndrome

The odds ratio for having a critical illness myopathy and neuropathy for patients who have a multi-organ dysfunction syndrome is 4.58 (C.I. 95% 1.64 – 12.81).

Multi-organ dysfunction syndrome should be sought in patients suspected to have acute myopathy or neuropathy

Latronico N et al. 2004 Submitt

Acute myopathy of intensive care: clinical, electromyographic, and pathologic aspects

David Lacomis et al.

Ann Neurol 1996; 40:645

Fourteen critically ill patients had an acute thick filament myopathy due to corticosteroid treatment.

Acute myopathy of intensive care

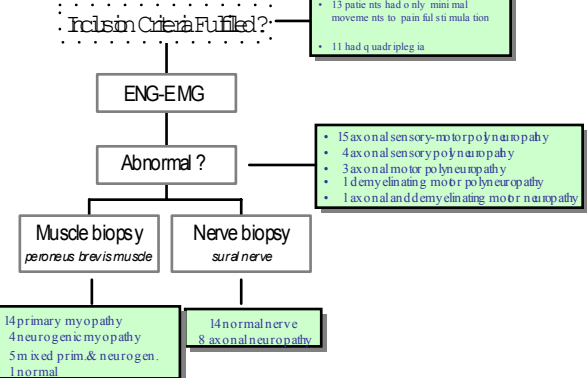
N. Latronico

Ann Neurol 1997; 42:131

7 of 14 had sepsis or severe sepsis or even septic shock
4 had fulminant hepatic failure and 1 had graft rejection
Did they not have a systemic inflammatory response syndrome?

Clinicians should not forget that these patients are always critically ill with catastrophic events on admission and multiple organ dysfunctions during the clinical course, rather than simply patients receiving high-dose corticosteroids.

Is Inclusion Criteria Fulfilled?



N Latronico et al. Lancet 1996; 347: 1579-82

Neuromuscular alterations in the critically ill patient: critical illness myopathy, critical illness neuropathy, or both?

N. Latronico

Intensive Care Med 2003; 29:1411–1413

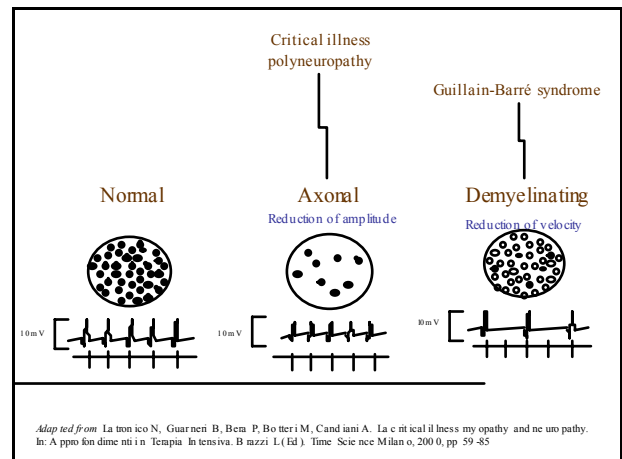
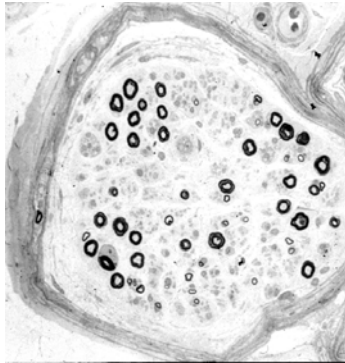
It is important to emphasize that, if the patient fails volitionally to activate his/her muscles, ENG-EMG diagnosis is invariably CIP, even if an acute myopathy is ongoing.

We coined the alarming acronym CRIMYNE (crime means "crime" in Italian) to emphasize that CIM and CIP often coexist.

Direct muscle stimulation combined with standard ENG-EMG, can make a differential diagnosis between myopathy and neuropathy

Conclusions

- Pathophysiology: energy problem at cellular level; MODS
- Clinical signs: muscle weakness and paralysis
- Outcome: CIM better than CIP
- Critical illness myopathy, critical illness polyneuropathy, or both? Both in the acute stage; CIP at a later stage



Do you not have an EMG machine?

Critical illness weakness syndrome

A weak patient

Pre-conditions

Sepsis
MODS
Mechanical ventilation
(Plus normal phosphate, potassium, and magnesium)

Exclusion criteria

Weakness before/causing admission
Cranial nerve signs
Autonomic dysfunction
Lateralizing signs/hyperreflexia
Relaxants in the last 48 hours/abnormal TOF response

Morris C, Trinder JT. Electrophysiology adds little to clinical signs in critical illness polyneuropathy and myopathy. Crit Care Med. 2002;30(2):62