Strokovni prispevek/Professional article

CRITICAL ILLNESS MYOPATHY IN PATIENTS WITH CENTRAL NERVOUS SYSTEM DISORDERS

MIOPATIJA KRITIČNE BOLEZNI PRI BOLNIKIH Z OKVARO OSREDNJEGA ŽIVČEVJA

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Abstract

Background — *Acute myopathy or neuropathy is a common complication in critically ill patients in intensive care unit. This complication is relatively obvious in patients with primary non-neurological disorder. However, such complication is difficult to notice in patients with primary neurological disorder. The aim of our report is to present four patients with a primary central nervous disease who subsequently developed a secondary peripheral nervous disorder.*

Patients and methods — *The four patients had been admitted to the intensive care unit of the Neurological Department for the acute cerebral disorder. Additionally in the course of disease they had developed clinical signs of either neuropathy or myopathy. One patient was unable to wean from the ventilator. Electrodiagnostic studies and muscle biopsy were performed.*

Results — *Electrodiagnostic studies revealed generalized abnormalities, consistent with both neuropathy and myopathy. The predominant finding in muscle biopsy was a myopathy with moderate to severe myosin filament loss.*

Conclusions — *This report brings two messages. The first is that one should be aware of the possibility of critical illness myopathy/neuropathy also in the neurological intensive care unit. As this peripheral neurological complication is superimposed on primary central neurological disorder, it may be more difficult to notice and to diagnose it clinically. The second message is that electrodiagnostic studies, though mandatory in confirming peripheral lesion, often cannot distinguish between myopathy and neuropathy. As myopathy bears substantially favorable prognosis, a muscle biopsy may be recommended in such cases.*

Key words — *critical illness; intensive care; myopathies; polyneuropathies; electromyography; muscle biopsy*

Izvleček

Izhodišča — *Akutna miopatija ali nevropatija je pogost zaplet pri kritično bolnih v enotah intenzivne terapije. Pomembni dejavniki tveganja za miopatijo in nevropatijo kritične bolezni so sepsa, sindrom sistemskega vnetnega odgovora (angl. systemic inflammatory response syndrome, SIRS), visoki odmerki kortikosteroidov, blokatorji živčnomišičnega prenosa, aminoglikozidi, presaditev jeter/pljuč, jetrna odpoved, večorganska odpoved in elektrolitne ter endokrine motnje. Živčno-mišični zaplet je razmeroma očiten pri bolnikih, ki se zdravijo zaradi primarnih bolezni, ki niso nevrološke. Pri bolnikih s primarno okvaro osrednjega živčevja pa tak zaplet težje prepoznamo. Namen našega poročila je kratka predstavitev štirih kritično bolnih s primarno okvaro osrednjega živčevja, pri katerih se je pojavil sekundarni periferni (živčno-mišični) zaplet.*

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Bolniki in metode *Štirje kritično bolni so bili sprejeti v Center za intenzivno terapijo Nevrološke klinike zaradi akutne okvare osrednjega živčevja (dva s subarahnoidno krvavitvijo, eden z ishemično okvaro ponsa, eden s hipofiznim tumorjem in krvavitvijo v tumor). Ob sprejemu v enoto intenzivne terapije so bili vsi bolniki nezavestni, rabili so mehansko predihavanje, izraženi so bili znaki okvare zgornjega motoričnega nevrona. Sledili so zapleti, ki niso bili nevrološki: okužbe, sepsa, hemodinamska nestabilnost, akutna ledvična odpoved, akutna odpoved nadledvične žleze in akutna endokrina odpoved trebušne slinavke. Srednja starost bolnikov je bila 62,5 let, razpon starosti pa od 49 do 76 let.*

Prvi bolnik je v prvih dneh po sprejemu pridobil nekaj hotenih gibov, vendar se je peti dan po sprejemu v enoto intenzivne terapije pojavila ohlapna tetraplegija. Ostali bolniki so ostali negibni, vendar pa se je spastičnost spremenila v ohlapnost, miotatični refleksi niso bili več izvabljivi. Pri eni bolnici se je okoli petnajstega dne po sprejemu v enoto intenzivne terapije povrnila zavest, ni pa bil mogoč odklop od mehanskega ventilatorja. Nihče od bolnikov ni imel predhodne živčno-mišične bolezni. Pri vseh bolnikih smo pomislili na novo pridobljeno prizadetost perifernih živcev ali mišic. Napravili smo elektromiografsko preiskavo (EMG) in mišično biopsijo.

Rezultati *EMG je pokazala generalizirane abnormnosti, ki so v skladu tako z miopatijo kot nevropatijo. Latence vala M so bile normalne in amplitude nizke, valovi F so bili odsotni, motorične prevodne hitrosti so bile normalne ali mejne, amplitude senzoričnih akcijskih potencialov pa normalne. Koncentrična igelna EMG je odkrila številne fibrilacijske potenciale v vseh pregledanih mišicah. Motoričnih enot ni bilo mogoče oceniti zaradi odsotnosti hotene aktivnosti. Prevladujoča sprememba v mišični biopsiji je bila zmerna do izrazita izguba miozinskih filamentov.*

Zaključki *Prvo sporočilo je, da se moramo zavedati možnosti miopatije in nevropatije kritične bolezni tudi pri bolnikih s primarno okvaro osrednjega živčevja v nevroloških intenzivnih enotah. Ker gre za periferni nevrološki zaplet, ki se nacepi na primarno okvaro osrednjega živčevja, ga težje opazimo in diagnosticiramo. Drugo sporočilo je, da elektrofiziološke preiskave, čeprav neobhodne, pogosto ne morejo razlikovati med nevropatijo in miopatijo. Ker je dolgoročna napoved izida pri miopatiji kritične bolezni boljša kot pri nevropatiji, je v takih primerih indicirana mišična biopsija.*

Ključne besede *kritična bolezen; intenzivna terapija; miopatija; polinevropatija; elektromiografija; mišična biopsija*

Introduction

An acute paralysis of limb and respiratory muscles is increasingly being recognised in critically ill patients since its first description in 1977.[1] It is due to either critical illness polyneuropathy (CIP) or critical illness myopathy (CIM); CIP and CIM are *common* in patients who stay on mechanical ventilation for more than one week, and present as limb weakness and difficulty in weaning from the ventilator.[2] CIM is the most common cause of critical care related weakness.[3] Important risk factors are sepsis, systemic inflammatory response syndrome, high dose corticosteroids, use of neuromuscular blockers, aminoglycosides, liver/lung transplant, liver failure, multi-organ failure, and electrolyte and endocrine disturbances.[4] Due to the complex situation of critical illness, it is difficult to assess a patient by clinical neurological examination alone. Electrophysiological studies are necessary, and sometimes muscle biopsy is needed.[5] CIM and CIP may also be encountered in patients with pre-existing severe acute lesions of brain admitted to the Neurological Intensive Care Unit. In such patients a clinical recognition of CIM and CIP is further hindered by a pre-existing neurological disease.

Patient presentation and methods

We report on a group of four patients admitted to the intensive care unit for central nervous system disorders, and with attributes of the critical illness, who subsequently developed generalized limb flaccidity (signs of lower motor neuron lesion), which replaced previous spasticity (upper motor neuron lesion). One patient in addition was unable to wean from the ventilator. Basic clinical features of our patients are summarised in Table 1.

None of patients was given corticosteroid or sedative agents. The patients were unconscious on admission and mechanically ventilated. Patient 1 regained some voluntary movements soon after the admission, but on the fifth day of the intensive care unit stay, he developed flaccid tetraplegia. Patients 2, 3 and 4 remained immobile but generalised flaccidity replaced previous spasticity and myotatic reflexes became unobtainable. Around the 15th day of the intensive care unit stay, when patient 2 regained consciousness, she was in addition unable to wean from the ventilator. None of patients had a known pre-existing disorder of lower motor neuron or muscle.

Table 1. *Basic clinical features in our patients.*
Tab. 1. *Osnovni klinični podatki pri naših pacientih.*

Pt	Age (years)	Gender	Primary neurological illness	Non-neurological complication	Neuromuscular blocking agents	Days before considering CIM/CIP
	Starost (leta)	Spol	Primarna nevrološka bolezen	Zaplet, ki ni nevrološki	Blokatorji živčno-mišičnega prenosa	Dnevi do upoštevanja CIM/CIP
1	61	M	Pontine ischaemic infarct	Sepsis Acute renal failure Haemodynamic instability	pancuronium 8 mg, 5 days	5
		M	Ishemični infarkt ponsa	Sepsa Akutna ledvična odpoved Hemodinamska nestabilnost	pankuronium 8 mg, 5 dni	
2	76	F	Hypophyseal tumor with haemorrhage	Acute adrenal and endocrine pancreatic insufficiency	pancuronium 4 mg, 3 days	14
		Ž	Hipofizni tumor s krvavitvijo	Akutna nadledvična in endokrina odpoved trebušne slinavke	pankuronium 4 mg, 3 dni	
3	64	F	Subarachnoidal haemorrhage	Pneumonia	pancuronium 4 mg, 5 days	14
		Ž	Subarahnoidna krvavitev	Pljučnica	pankuronium 4 mg, 5 dni	
4	49	M	Subarachnoidal haemorrhage	Purulent meningitis Pneumonia	pancuronium 4 mg, 3 days vecuronium 4 mg, 4 days	15
		M	Subarahnoidna krvavitev	Gnojni meningitis Pljučnica	pankuronium 4 mg, 3 dni vekuronium 4 mg, 4 dni	

Pt – patient, M – male, F – female, CIM - critical illness myopathy, CIP - critical illness polyneuropathy
Pt – bolnik, M – moški, Ž – ženska, CIM - miopatija kritične bolezni, CIP - nevropatija kritične bolezni

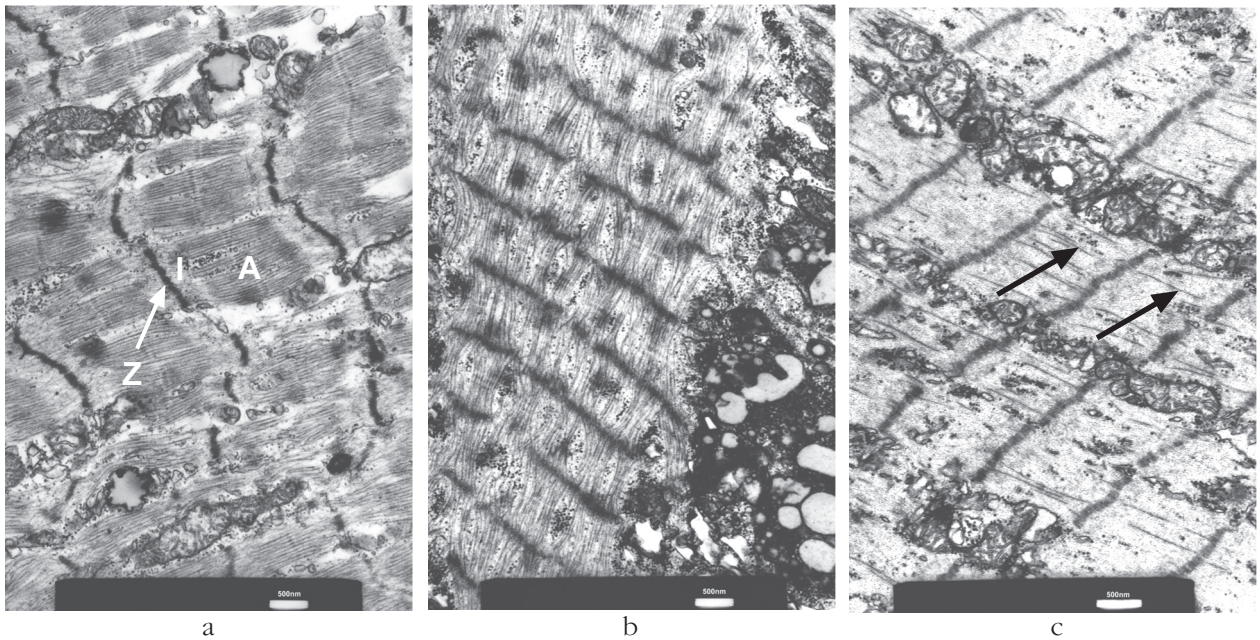
Nerve conduction studies (NCS) and concentric needle electromyography (CNEMG) were performed on the Medtronic Keypoint system, using techniques described elsewhere.[6] NCS were performed on median, ulnar, peroneal, tibial and sural nerves, and CNEMG in one proximal and one distal leg muscle.
Forceps muscle biopsy of the anterior tibial (patients 1, 2 an 3) or biceps brachii muscles (patient 4), opposite the site examined with CNEMG, was performed one day after NCS and CNEMG. Part of the biopsied material was frozen in liquid nitrogen for routine histological, histochemical and immunohistochemical reactions;[7] the other part was fixed in 5% glutaraldehide, embedded in Epon 812 and examined by a Jeol transmission electron microscope.

Results

The highlights of NCS in patients were as follows: normal latencies and low amplitudes of compound muscle action potentials (0.3–3.3 mV in median nerve and 0.3–0.7 mV in tibial nerve), absence of F-wave, borderline or normal motor conduction velocities (48 – 55 m/s in median nerve and 36–49 m/s in tibial nerve), and normal sensory nerve action potentials (7–15 μV in median nerve and 3–4 μV in sural nerve).
Concentric needle EMG revealed diffuse and abundant fibrillation potentials in all examined muscles in all patients, while motor unit potentials (MUP) could not be assessed due to the absence of voluntary contraction.
In all patients, muscle morphology revealed a slightly increased number of macrophages in the endomysium and single atrophic angular slow and fast fibres, while small group atrophy of slow fibres was present in patients 1 and 2 and small group atrophy of both fibre types in patient 4. Single necrotic fibres were only found in the biopsy specimen of patient 4.
Ultrastructural examination revealed diffuse severe loss of myosin filaments in patient 2 (Figure 1c) and moderate loss in patients 1 and 3. Patient 4 had areas with a moderate degree of myosin loss (Figure 1b), exchanging with areas of normal sarcomeric structure (Figure 1a).

Discussion

CIM or CIP is a common complication in critically ill patients in intensive care unit.[2] This complication is relatively obvious in patients with primary non-neurological disorder. However, such complication is difficult to notice in patients with primary central neurological disorder. A new generalised involvement of peripheral nerves or muscles was considered when previously spastic patient developed flaccid weakness and absent myothatic reflexes, and weaning from mechanical ventilator could not be achieved. Failure to wean from the ventilator is often the initial presentation of neuromuscular weakness in the intensive care unit or accompanies limb weakness.[4] The recognition of neuromuscular complication was facilitated by the fact that our patients were not sedated or pharmacologically paralysed on a permanent basis. Furthermore, all had developed serious systemic and infectious complications (Table 1) known to be risk factors for CIM or CIP.[4]
To confirm neuromuscular complication electrodiagnostic studies were performed. The highlight of NCS



a b c

Figure 1. *Typical muscle morphology observed in our patients with critical illness myopathy. (a) Normal sarcomeric structure, patient 4. Z = Z-line, I = I band (actin filaments), A = A band (myosin and actin filaments). (b) Abnormal sarcomeric structure due to moderate myosin filament loss, patient 4. (c) Abnormal sarcomeric structure due to severe, nearly complete myosin filament loss in patient 2; black arrows point to remaining myosin filaments.*

Sl. 1. *Tipična morfologija mišičnine pri naših bolnikih z miopatijo kritične bolezni. (a) Normalna zgradba sarkomere, bolnik 4. Z = črta Z, I = pas I (aktinski filamenti), A = pas A (miozinski in aktinski filamenti). (b) Abnormna zgradba sarkomere zaradi zmerne izgube miozinskih filamentov, bolnik 4. (c) Abnormna zgradba sarkomere zaradi izrazite, skoraj popolne izgube miozinskih filamentov pri bolnici 2; črni puščici kažeta na preostale miozinske filamente.*

findings was a motor abnormality consistent with either CIM or CIP. The most outstanding abnormalities were low amplitude of CMAP and absence of F-wave. A low amplitude of CMAP is consistent with functional loss of generators of the compound electrical muscle response, i.e. muscle fibres. This may be brought about by the loss of either axons or muscle fibres. With a relatively short duration of disease (5 – 15 days), an abnormal spontaneous activity on CNEMG is an argument for myopathy, since it would need more time to evolve in the case of axonal lesion. A pattern of recruitment of MUPs and analysis of MUP parameters might help in differentiation between CIM and CIP but there was no voluntary contraction in our patients. NCS and CNEMG could not therefore reliably differentiate between myopathy and neuropathy.

An interesting feature was the absence of F-waves. It is too easy to assign it to myopathy, and probably also erroneously. However, if myopathy is not the reason for this, is it then the consequence of the axonal lesion? An absence of F-waves is ordinarily taken as a sign of a conduction block along the length of the peripheral nerve. In an individual patient with flaccid paralysis and respiratory weakness, this might evoke the suspicion of acute inflammatory demyelinating poliradiculoneuropathy (Guillain-Barre Syndrome) or CIP. However, Taniguchi and co-workers[8] and others[9] demonstrated that F-waves recorded in healthy subjects showed a progressive decrease in persistence and amplitude after prolonged muscle relaxation. It seems to be a consequence of rest induced suppression of the excitability of the anterior horn cells. An absence of F-waves, therefore, might itself be just a consequence of the inactivity of a critically ill patient.

Muscle biopsy was performed to differentiate between CIM and CIP. Since CIM has better long-term prognosis than CIP,[10] differential diagnosis is important to predict long-term outcome.

The outstanding pathologic feature in all patients was moderate or severe myosin loss (Figures 1b, and 1c) which is characteristic pathomorphological abnormality in CIM.[3] Angular slow and fast fibres and even small group atrophy, also observed in the biopsies of three of our patients, are usually considered to be chronic neuropathic signs.[7] The time interval between the appearance of the clinical signs and biopsy is too short for chronic neuropathic signs to appear. We therefore consider that these signs might represent neuropathic indicators of other causes (radiculopathy and/or concomitant diabetes mellitus in elderly patients might well be the cause). Surprisingly, all our patients had an increased number of macrophages in the endomysium, which could not normally be detected in CIM, although some authors have described it.[11] Electrodiagnostics and biopsy together predominantly showed signs of CIM.

Muscle biopsy is useful for the demonstration of characteristic myopathic alterations with myosin loss and is important with respect to prognosis but it takes time. A more specific bedside test must be sought. One such method is muscle membrane excitability testing,[12] which still awaits assessment and confirmation. A 48-hour test to quantify the myosin/actin ratio on electrophoresis might also be a promising method for diagnosing CIM.[13]

Conclusions

Critical illness neuromuscular disorder may also complicate severe *central* nervous system disease. Due to the primary neurological condition, commonly paralytic by itself, it is difficult to recognise newly developed neuromuscular disease in such patients. Diagnosing it necessitates careful day to day examinations and an *awareness* of this entity. A new generalised involvement of peripheral nerves or muscles should be considered when previously spastic patient develops flaccid weakness and absent myothatic reflexes. Electrodiagnostic evaluation confirms neuromuscular involvement but may not accurately enough differentiate between neuropathy and myopathy. Muscle biopsy is useful for the demonstration of characteristic myopathic alterations with myosin loss and may be indicated with respect to prognosis, since CIM has better long-term prognosis than CIP.

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Arrived 2009-02-16, accepted 2009-06-11