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IEVA SEREIKĖ

CRITICAL ILLNESS NEUROMUSCULAR ABNORMALITY AFTER PROLONGED TREATMENT IN THE INTENSIVE CARE UNIT

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Scientific supervisor – prof. dr. Dalius Jatužis (Vilnius University, Biomedical sciences, medicine – 06B).
Scientific consultant – prof. dr. Michel R. Magistris (Geneve University, Biomedical sciences, medicine – 06B).

The defence of the dissertation will be held at the open meeting of the Defence Board.
Chairman:
Prof. dr. Rūta Mameniškienė (Vilnius University, Biomedical Sciences, Medicine – 06B).
Members:
Prof. dr. Saulius Ročka (Vilnius University, Biomedical Sciences, Medicine – 06B);
Prof. dr. Pranas Šerpytis (Vilnius University, Biomedical Sciences, Medicine – 06B);
Prof. dr. Antanas Vaitkus (Lithuanian University of Health Sciences, Biomedical Sciences, Medicine – 06B);
Prof. dr. Grzegorz Kozera (Collegium Medicum in Bydgoszcz, Biomedical Sciences, Medicine – 06B).

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Address: 2 Santariskiu St, Vilnius, Lithuania.

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IEVA SEREIKĖ

ILGAI INTENSYVIOSIOS TERAPIJOS SKYRIUJE GYDYTŲ LIGONIŲ KRITINIŲ BŪKLIŲ NEURORAUMENINIS PAŽEIDIMAS

Daktaro disertacija

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Mokslinis vadovas – prof. dr. Dalius Jatužis (Vilniaus universitetas, biomedicinos mokslai, medicina – 06B).
Mokslinis konsultantas – prof. dr. Michel R. Magistris (Ženevos universitetas, biomedicinos mokslai, medicina – 06B).

Disertacija ginama viešame disertacijos Gynimo tarybos posėdyje.
Pirmininkė – prof. dr. Rūta Mameniškienė (Vilniaus universitetas, biomedicinos mokslai, medicina – 06B).
Nariai:
Prof. dr. Saulius Ročka (Vilniaus universitetas, biomedicinos mokslai, medicina – 06B);
Prof. dr. Pranas Šerpytis (Vilniaus universitetas, biomedicinos mokslai, medicina – 06B);
Prof. dr. Antanas Vaitkus (Lietuvos sveikatos mokslų universitetas, biomedicinos mokslai, medicina – 06B);
Prof. dr. Grzegorz Kozera (Bydgoščiaus Medicinos kolegija, biomedicinos mokslai, medicina – 06B).

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ABBREVIATIONS

APACHE II	Acute Physiology and Chronic Health Assessment II
CI	Confidence interval
CIM	Critical illness myopathy
CINMA	Critical illness neuromuscular abnormality
CIP	Critical illness polyneuropathy
CTS	Carpal tunnel syndrome
DL	Distal latency
EMG	Electromyography
ENMG	Electroneuromyography
ICU	Intensive care unit
MV	Mechanical ventilation
MOFS	Multiple organ failure syndrome
MUAP	Motor unit action potential
NCS	Nerve conduction studies
NCV	Nerve conduction velocity
OR	Odds ratio
SAPS	Simplified Acute Physiology Score
SD	Standard deviation
SOFA	Sequential Organ Failure Assessment

INTRODUCTION

Critical illness neuromuscular abnormality (CINMA) is the most common cause of muscle weakness in the intensive care unit. Neuromuscular complications during critical illness can present as critical illness polyneuropathy (CIP) and critical illness myopathy (CIM). The term "critical illness" describes the patients, who are treated in the intensive care unit (ICU) with sepsis and (or) multiple organ failure syndrome (MOFS), leading to a severe condition of the patient. Now this term is no longer used due to uncertainty.

For the first time, CINMA was described in 1984. Ch. Bolton and colleagues in 1977–1981 observed 5 patients who experienced limb weakness during treatment in the ICU. Although the reasons of admission to ICU were diverse, all 5 patients developed respiratory failure syndrome, sepsis and MOFS. Clinical examination revealed weakness of the proximal and distal limb muscles, loss of deep tendon reflexes and sensory impairment. Electroneuromyography (ENMG) studies were performed, and motor and sensory axonal fiber damage was confirmed. Three patients had autopsy examination performed, and moderate to severe primary axonal motor and sensory polyneuropathy was proven. Also, muscle fiber degeneration was observed, both due to denervation and primary muscle fiber damage. Probable causes of polyneuropathy (such as Guillain-Barre syndrome, diabetes mellitus, lack of vitamins, toxins, etc.) have been excluded, and the nerve damage was associated with sepsis. So Ch. Bolton used the term "critical illness polyneuropathy" for the first time.

In the last decade of the 20^{th} century, a series of publications on myopathy, which manifested in the ICU, appeared. Most of the cases were attributed to treatment with the corticosteroids and neuromuscular blocking agents. Myopathy in patients with critical illness is referred as acute quadriplegic myopathy, acute necrotizing myopathy in the ICU, myopathy of large fibers, acute corticosteroid-induced myopathy, acute myopathy induced by hydrocortisone, acute myopathy associated with severe asthma, acute corticosteroid and pancuronium-associated myopathy. All of these names represent one syndrome, which may be called CIM.

There is increasing evidence that polyneuropathy and myopathy occur at the same time. Clinical and histological tests show, that nerves and muscles can be damaged at a time - at the same time decreased muscle fibre excitability, reflecting myopathy, and

primary axonal motor and sensory neuropathy can be detected. It might be challenging to differentiate polyneuropathy and myopathy in the ICU setting. Clinical neurological examination may be equivocal: it is impossible to assess patients' complaints, sensory disturbances cannot be evaluated, and assessment of muscle strength is inaccurate. ENMG studies are not readily available in the ICU, and the results depend on the timing of investigation and patients' comorbidities. These studies are time consuming and require both skilled staff and expensive equipment. Muscle or nerve biopsies are rarely performed, as the results of the histologic tests do not change the treatment options. As it might be impossible to differentiate polyneuropathy and myopathy, such terms as CINMA, CRIMYNE (*CRitical Illness MYopathy and/or NEuropathy*) or CINM (critical illness neuromyopathy) can be used.

The frequency of this condition varies from 11 % to 100 % of patients treated in the ICU. Usually this condition presents as bilateral flaccid weakness with or without sensory abnormalities, hyporeflexia and muscle atrophy, as well as difficulty in weaning from the mechanical ventilation. Involvement of motor and sensory nerve fibers has been documented, as well as muscle fiber atrophy.

Multiple risk factors are related with the development of CINMA, but their contribution remains questionable.

The interest in the ICU acquired weakness has increased significantly. This has been undoubtedly influenced by the achievement of the intensive therapy, allowing patients to survive most serious conditions. During the last 30 years, a number of both prospective and retrospective studies have been carried out to improve the understanding of nerve and muscle damage in critical conditions. At present, the exact frequency of this problem remains unknown, as the risk or pathophysiological factors. There is the lack of sufficient data on the manifestation, prophylaxis, treatment and outcome of the disease.

THE AIM OF THE STUDY

The purpose of this study was to evaluate frequency, features and factors, associated with the development of CINMA in patients after prolonged treatment in the ICU using clinical and electrophysiological tests, and to evaluate the symptoms and the factors associated with the unfavourable outcome 6 months after discharge from the ICU.

THE OBJECTIVES OF THE STUDY

1. To determine the incidence of CINMA in patients after prolonged treatment in the ICU.
2. To identify clinical and electrophysiological signs of CINMA.
3. To identify the risk factors associated with the development of CINMA after prolonged treatment in the ICU.
4. To evaluate clinical and electrophysiological signs of CINMA after 6 months after discharge from ICU.
5. To evaluate factors associated with the unfavourable outcomes of CINMA.

SIGNIFICANCE AND SCIENTIFIC NOVELTY OF THE STUDY

Complex assessment of patients after prolonged treatment in the ICU was performed – complaints and neurological signs were evaluated, and a comprehensive neurophysiological examination was performed. Based on the modern diagnostic criteria, a neuromuscular damage associated with a critical illness was confirmed. Patients were examined twice: after treatment in the ICU and at follow-up after 6 months after discharge. More than 100 patients were studied. We have also identified the most sensitive and specific clinical and neurophysiological signs of CINMA.

In Lithuania there are no studies analysing neuro-muscular symptoms and electrophysiological changes and their course in patients undergoing long-term treatment in the intensive care unit. Also these studies are lacking worldwide.

Based on the results of the study, we identified, that neuromuscular weakness related to critical illness is a common complication of long-term treatment in the ICU. The identification of CINMA allows predicting the duration of treatment in the intensive care unit and outcomes. We may be able in the future to recommend the most appropriate treatment for the best recovery of function of nerves and muscles.

MATERIALS AND METHODS OF THE STUDY

After approval of Lithuanian Bioethics Committee we have studied patients after prolonged treatment in the medical-surgical ICU in Vilnius University Hospital Santariškių klinikos. Each participant agreed in writing to participate in the investigation by signing the Informed consent form.

Selection of patients, inclusion and non-inclusion criteria

105 patients after prolonged treatment in the ICU and 96 control subjects, selected by age and gender, without peripheral nervous system or muscle disease, were studied. Data from the electrophysiological examinations of the control group were used to calculate the absolute values of nerve impulse conduction parameters (sensory and motor nerve response amplitudes, distal latencies and nerve impulse conduction velocities) as reference values.

The duration of long-term treatment in the ICU was determined by calculating the average duration of treatment in the ICU (average with one standard deviation, 5 + 2 days, i. e., 7 days and more). The subjects met the inclusion criteria and did not meet any exclusion criteria.

Inclusion criteria:

1. Subjects, who were treated in the ICU 7 days or longer.
2. Subjects elder than 18 years of age.

Exclusion criteria:

1. A subject does not meet any inclusion criteria.
2. A subject with primary mental illness.
3. A subject does not agree to participate in the investigation and does not sign the Informed consent form.

All patients underwent clinical neurological examination, nerve conduction studies (NCS) and needle electromyography (EMG) twice: on the day of the discharge from ICU and at follow-up at least 6 months after the first examination. All subjects were contacted by phone and invited for follow-up visit. We used the same examination protocol during both visits. The neurological and neurophysiological examination of patients was performed by the author of this work.

General data. The following data were assessed: age, gender, duration of the treatment in the ICU, duration on MV (the duration of the invasive or non-invasive MV, hours), duration of sedation and analgesia (hereinafter referred to as the duration of sedation) (the duration, when an infusion of the drug in order to sedate or reduce pain, is administered, hours).

In order to determine the extent of a person's organ function or rate of failure, SOFA (Sequential Organ Failure Assessment) system was used. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal

and neurological systems. The worst data from the first and last day of treatment in the ICU were used. A greater than 0 SOFA score is considered a failure of the organ system. The maximum number of SOFA is 24. MOFS was diagnosed if SOFA score was 6 and more at the time of admission to ICU. In order to classify the severity of disease SAPS 3 (Simplified Acute Physiology Score 3) and APACHE II (Acute Physiology and Chronic Health Assessment II) were used. The severity of the organ system failure was evaluated by the same physician, who was instructed to perform these assessments.

Clinical neurological investigation. All subjects were examined using a routine protocol for the symptoms and signs of neuropathy and myopathy.

In order to assess symptoms of CINMA, subjects were asked six questions about sensory symptoms (pain, numbness and anaesthesia in arms and legs) and two questions about motor symptoms (weakness in arms and legs). If the answers to the two questions about the sensory symptoms were positive, the patient was considered as having symptoms of sensory neuropathy. If the answer to one of the two questions about motor symptoms was positive, the patient was considered as having symptoms of motor neuropathy.

Objective signs of neuropathy were evaluated by the clinical neurological sensory, motor and tendon reflex examination. We assessed the pain, touch, vibration, and position senses in all four extremities. We studied the pain sensation with a needle. The sensation of pain was evaluated as normal, decreased (hypalgesia) or absent (analgesia). The sense of touch was assessed with a ball of wool. It was considered as normal, decreased (hypoesthesia) or absent (anesthesia). The sense of vibration was examined camerton of 128 Hz at the distal phalanx of the index in hand and hallux in foot. The sense of vibration was scored from 0 to 8. It was considered as normal, if score was 7 and higher in hands, and 6 and higher in feet. The position sense was evaluated by moving the distal phalanx of the index in hand and hallux in foot. Position sensory impairment was present if the patient could not indicate the direction of the joint movement.

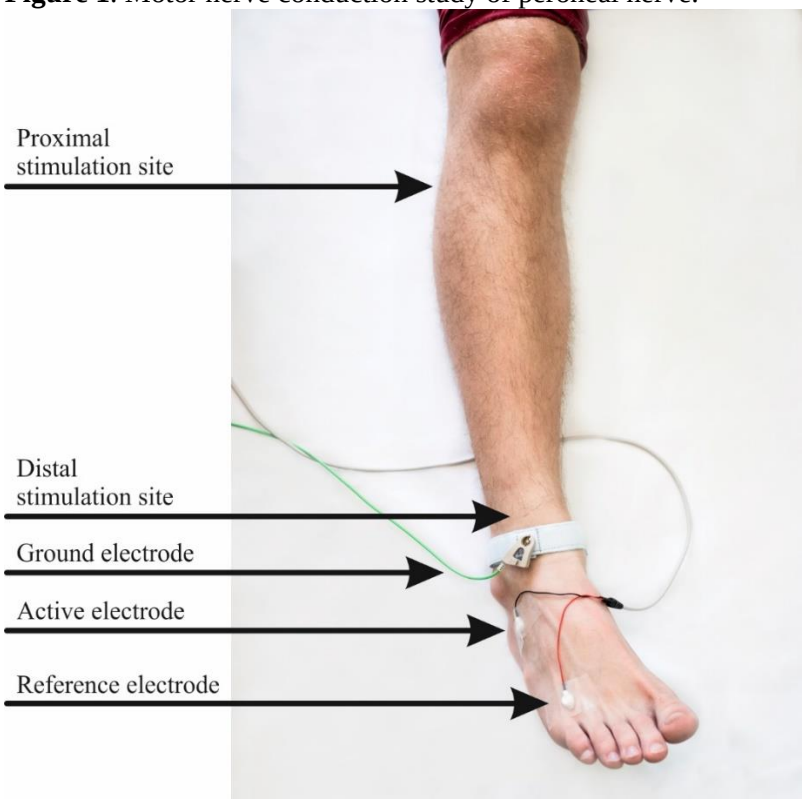
We examined deep tendon reflexes (biceps, carporadial, patellar and ankle jerk) in all limbs. Deep tendon reflexes were considered as normal, decreased or unobtainable. Muscle strength was evaluated using Medical Research Council (MRC) scale, according to B. de Jonghe's method. We evaluated the strength of 3 muscle groups in each extremity (forearm flexion and extension, wrist flexion, hip flexion and extension, foot dorsal flexion). Each muscle group score ranges from 0 (paralysis) to 5 (normal muscle strength),

and the overall score from 0 to 60. An MRC score ≤ 48 indicated significant muscular deficit, whereas an MRC score 49 or higher was considered a very mild weakness or normal. Patients with MRC score 0 or 1 and 2 (range 0–24) were defined as having tetraplegia. Patients with an MRC score between 24 and 48 were defined having tetraparesis. We also evaluated for the presence of muscle wasting in proximal and distal parts of arms and legs.

All clinical signs were considered as signs of polyneuropathy only if they occurred bilaterally.

NCS and EMG. Neurophysiological studies were performed with Nihon-Kohden device Neuropack II. All patients had conventional orthodromic motor and antidromic sensory nerve conduction studies on median, ulnar, common peroneal motor, tibial and sural nerves. Nerves were tested unilaterally in arms, and bilaterally in legs. All motor nerves were tested using surface electrodes; median and ulnar sensory fibers were tested using ring electrodes, sural nerve – using surface electrodes. The example of motor nerve NCS is shown in figure 1.

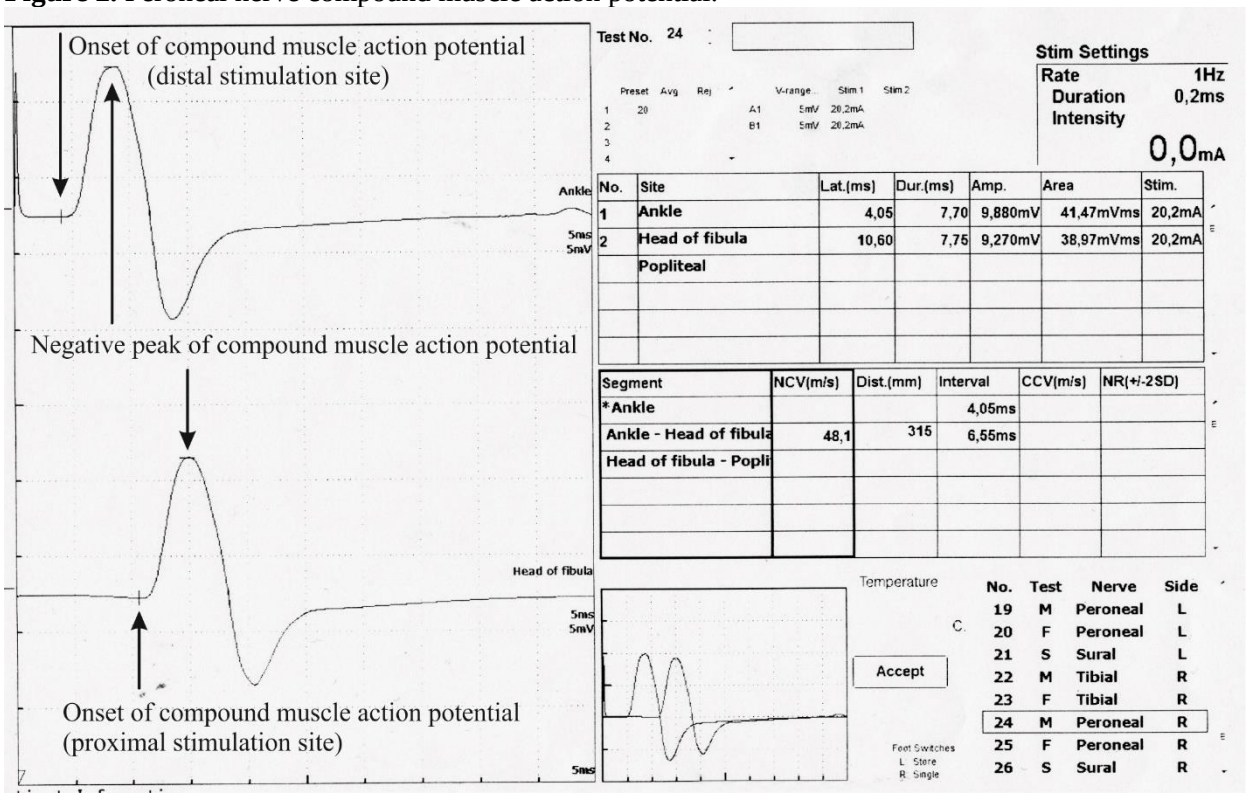
Figure 1. Motor nerve conduction study of peroneal nerve.



Notes. The photo shows distal stimulation site over the dorsum of the foot near the ankle, 7 cm from the active electrode, over the belly of extensor digitorum brevis muscle, and proximal stimulation site at the head of fibula

Results of nerve conduction velocity (NCV), distal latency (DL), compound muscle action potential amplitudes (CMAP, from the baseline to the negative peak) and sensory nerve action potential amplitudes (SNAP, from the baseline to the negative peak) were compared to age and gender correlated normal values established in our laboratory. The example of compound muscle action potential is shown in figure 2.

Figure 2. Peroneal nerve compound muscle action potential.



Needle EMG examinations were performed with a monopolar needle electrode and included deltoid, rectus femoris, anterior tibial and abductor pollicis brevis muscles. The presence of spontaneous activity, as demonstrated by fibrillation potentials and positive sharp waves, was stated as present or absent. The number and morphology of motor unit potentials was estimated by visual and auditory means.

Diagnostic criteria for CINMA and grouping of subjects.

Diagnosis of polyneuropathy. The diagnosis of polyneuropathy was made based on the diagnostic criteria for distal symmetric polyneuropathy, proposed by the American Academy of Neurology. These criteria include both clinical and electrophysiological features of polyneuropathy. The probability of distal symmetric polyneuropathy is estimated from the highest (4 points) to the lowest (1 point). The polyneuropathy was diagnosed if the probability was scored 3 and 4 points. If the probability of polyneuropathy

was 0 to 2 points, the patient was considered to have no polyneuropathy. The minimal electrophysiological criteria for polyneuropathy were changes in at least two different nerves' responses (at least one of the nerves - the sural nerve). Responses were considered as abnormal, if their value was below or above the mean and the two standard deviations of control groups response values. Values of the nerve response parameters are presented in Table 1.

Table 1. Values of the nerve responses, considered as abnormal.

		Amplitude	**DL (ms)**	**NCV (m/s)**
Motor nerves	Median	< 4,0 mV	> 4,0	< 48,3
	Ulnar	< 4,9 mV	> 3,8	< 50,0
	Peroneal	< 2,7 mV	> 4,6	< 40,4
	Tibial	< 3,8 mV	> 4,3	< 40,0
Sensory nerves	Median	< 15,2 μV	> 3,7	< 48,1
	Ulnar	< 12,4 μV	> 3,5	< 47,7
	Sural	< 5,4 μV	-	< 39,7

Notes. Normal values were established based on the nerve conduction studies of the control group. Amplitude and NCV was considered as abnormal if the value was below than the mean – 2 SD. A DL was considered as abnormal if the value was above the mean + 2 SD. mV – millivolts. μV – microvolts. DL – distal latency. ms – milliseconds. NCV – nerve conduction velocity. m/s – meters per second.

Diagnosis of CIP. The diagnosis of CIP was made if these criteria were present: 1. The patient was critically ill; 2. Limb weakness or difficulty weaning from ventilation after non-neuromuscular causes were excluded; 3. Electrophysiological evidence of axonal motor and sensory polyneuropathy. CIP was diagnosed if no signs of an old neurogenic injury were detected on the NCS and EMG or other possible causes of polyneuropathy (diabetes mellitus, renal impairment, alcohol abuse etc.) were excluded.

Diagnosis of myopathy. Myopathy was diagnosed based on the clinical (proximal and/or distal limb weakness, with or without muscular atrophy changes in the absence of sensory impairment) and EMG studies. An electrophysiological diagnosis of myopathy was made on the basis criteria proposed by American Association of Electrodiagnostic Medicine. Myopathy-specific changes were considered as short duration, low-amplitude and polyphasic motor unit potentials with or without spontaneous activity in proximal and/or distal muscles.

Diagnosis of CIM. The diagnosis of CIM was made if these criteria were present: 1. Patient was critically ill; 2. Limb weakness or difficulty weaning from ventilation after non-neuromuscular causes were excluded; 3. Needle EMG with short duration, low amplitude motor unit potentials, with or without fibrillation potentials.

Diagnosis of mononeuropathy (median, ulnar or peroneal nerve damage) was confirmed by NCS based on routine methods.

Grouping of study subjects. The subjects were divided into two groups: 1. Patients with CINMA – if diagnosis of CIP and/or CIM was made; 2. Patients without CINMA. Certain signs of peripheral nerve or muscle damage could be detected in this group, but they were not diagnosed with CINMA as they did not met the diagnostic criteria for neuromuscular damage.

Statistical analysis. Data were analysed using statistical software package SPSS (version 20.0) and R-commander. The distribution of normality of continuous variables was tested with Kolmogorov-Smirnov or Shapiro-Wilk compatibility criteria. Continuous variables were expressed as mean ± SD or median values with 25–75% quartiles. Two independent groups were compared by Student's t-test when normally distributed or by Mann-Whitney test for non-normally distributed. When comparing more than two groups (patients with CINMA, patients without CINMA and control group), a non-parametric Kruskal-Wallis test was used and a post hoc analysis was performed by pairwise comparison of the groups. For two dependent samples, a t-test for dependent samples or a non-parametric Wilcoxon sign test was used. Paired measurements were compared using non-parametric McNemar test.

Categorical variables were expressed as frequencies and percentages. For comparison between two categorical variables chi-squared test or Fisher exact test was used. Multivariate logistic regression analysis (development of CINMA as dependent variable) was performed using backward stepwise model. Odds ratio and 95% confidence intervals (CI) are given.

The specificity and sensitivity of clinical and neurophysiological tests was analysed using ROC (*receiver operator characteristic*) curves and AUC (*area under curve*). Scores ranged from 0.5 to 1.0 with higher values indicating a better predictive model. For each nerve, the best cut-off value for the specific amplitude was determined by identifying the value that maximized the optimal sensitivity and specificity.

The binary multivariate logistic regression (forward-stepwise) method was used to identify the factors that predict CINMA. The logistic regression model included factors that significantly influenced the development of CINMA in the univariate analysis. Odds ratio (OR) and 95% confidence intervals (CI) are given.

RESULTS

General characteristics of the subjects. The sample consisted of 105 patients, treated in the ICU for 7 days and longer. 9 (8,6 %) subjects were diagnosed with neuromuscular impairment not related to critical illness: in 4 cases it was caused by diabetes mellitus, in 3 cases – by alcohol abuse, and in 2 cases – by blood disorder. The data of these subjects were not included in the further analysis. Data of 96 subjects were used. Baseline patients' characteristics are shown in table 2.

Table 2. Baseline patients' characteristics.

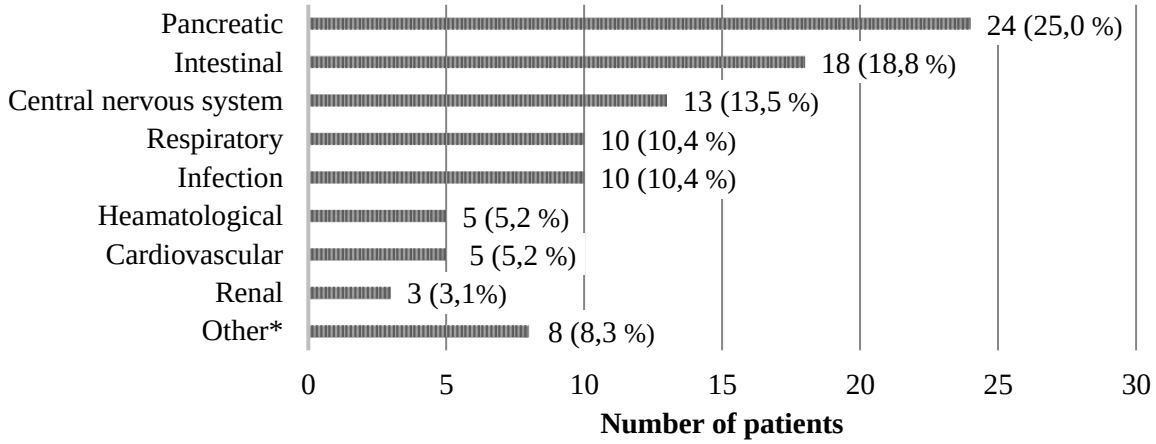
	Subjects (n = 96)
Gender, male (percent)	54 (56,3 %)
Age, years°	51,86 ± 16,79 (19–85)
Duration of the treatment in the ICU, days°	19,44 ± 13,59 (7–79)
Duration of MV, hours	208 (86–421)
Duration of sedation, hours	115 (48–215)
First ICU day APACHE II score, points	16,50 (12–21)
First ICU hour SAPS 3 score, points	56 (50–65)
First ICU day SOFA score, points	7 (4–9)
MOFS during first ICU day	58 (60,4 %)
Sepsis during treatment in the ICU	34 (35,4 %)
Last ICU day SOFA score, points	2 (2–3)
MOFS during last ICU day	5 (5,2 %)

Notes. Quantitative variables are given as median and 25-75 % percentiles. Categorical values are given as absolute value and percent. °, age and treatment in duration of the treatment in ICU duration is given as mean with standard deviation and minimal-maximal values. APACHE II – *Acute Physiology and Chronic Health Evaluation* scale. ICU – intensive care unit. MOFS – multiple organ failure syndrome. MV – mechanical ventilation. n – number of patients. SAPS 3 – *Simplified Acute Physiology Score*. SOFA – *Sequential Organ Failure Assessment*.

Mechanical lung ventilation was not applied for 13 patients (13,5 %), 25 patients did not require sedation (26,0 %).

Most of the patients' causes of admission to the ICU were pathologies of therapeutic profile - 65 (67,7 %); 16 (16,7 %) patients had urgent surgical pathology; 15 (15,6 %) – elective surgical pathology. The causes of admission to ICU are given in figure 3.

Figure 3. Causes of disorders of 96 patients, treated in the intensive care unit.



Notes. *This group included patients with gynaecological (n = 1), metabolic (n = 2), liver (n = 2) disorders, and with mixed pathology (n = 3).

The majority of subjects were hospitalized to the ICU due to pancreatic or intestinal disorders (42 patients, 43,8 %).

The control group for electrophysiological data consisted of 96 healthy individuals from 18 to 84 years, 52 men and 44 women. Control group did not differ significantly from study subjects according to age and gender (table 3).

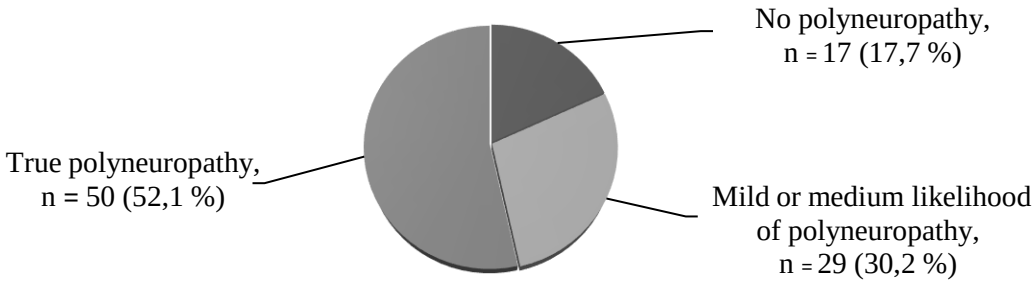
Table 3. Characteristics of study subjects and control group.

	Study subjects (n = 96)	**Control group (n = 96)**	**p value**
Gender, male (percent)	54 (56,3 %)	52 (54,2 %)	0,91
Age, years	51,86 ± 16,79 (19–85)	50,82 ± 12,41 (18–84)	0,54

Notes. Age is given as mean with standard deviation and minimal-maximal values. Gender is given as absolute value and percent. n – number of patients.

Diagnosis of CINMA. Based on the diagnostic criteria of distal symmetrical polyneuropathy, 50 individuals (52,1 %) were diagnosed with polyneuropathy (likelihood of polyneuropathy scored 3 and 4). 17 patients had no symptoms nor signs of polyneuropathy (likelihood of polyneuropathy scored 0). The distribution of patients according to the likelihood of polyneuropathy is shown in figure 4.

Figure 4. The distribution of patients according to the likelihood of polyneuropathy.

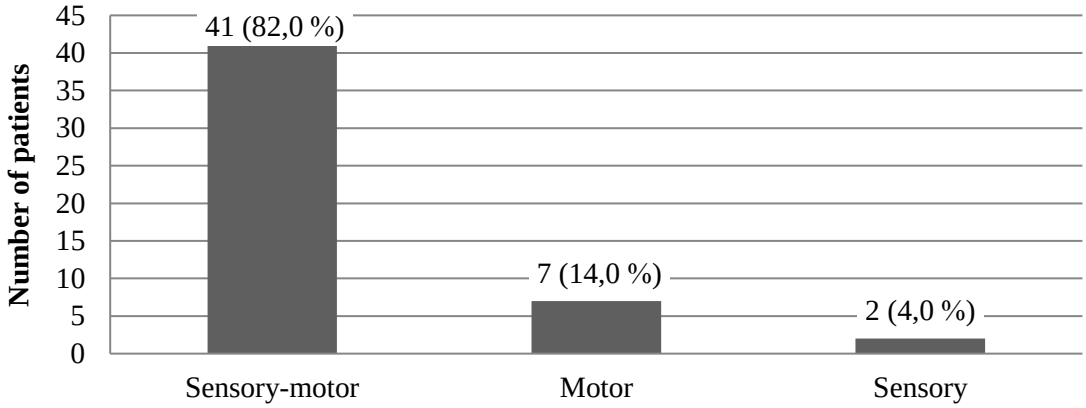


Notes. n – number of patients.

50 patients (52,4 %), with the likelihood of polyneuropathy 3 or 4, were diagnosed with CINMA. 46 subjects (47,6 %) were not diagnosed with CINMA, as they did not meet the diagnostic criteria for neuropathy or myopathy.

Symptoms and signs of CINMA. All patients with CINMA were diagnosed with polyneuropathy (100,0 %). In all cases neuropathy was axonal. The distribution of polyneuropathy based on nerve fiber involvement is shown in figure 5.

Figure 5. Distribution of polyneuropathy based on nerve fiber involvement.



Notes. Percent value from all subjects with polyneuropathy (n = 50).

All 50 patients had signs of neuropathy in legs, 36 patients (72,0 %) had the signs also in arms. Myopathy was diagnosed in 12 cases (24,0 %), but only with obvious clinical and neurophysiological signs of polyneuropathy.

Symptoms of CINMA. 34 (68,0 %) patients with CINMA had complaints related to neuromuscular involvement. 10 patients (21,7 %) without CINMA reported such complaints ($p < 0,001$). The results of analysis of complaints are given in table 4.

Table 4. Frequency of complaints, expressed by patients with and without critical illness neuromuscular abnormality.

Complaint		**Patients with CINMA (n = 50)**	**Patients without CINMA (n = 46)**	**p value**
Pain	Arms	1 (2,0 %)	1 (2,2 %)	1
	Legs	2 (4,0 %)	0	0,43
Numbness	Arms	8 (16,0 %)	1 (2,2 %)	0,06
	Legs	9 (18,0 %)	1 (2,2 %)	0,001
Anaesthesia	Arms	1 (2,0 %)	0	1
	Legs	1 (2,0 %)	0	1
Weakness	Arms	25 (50,0 %)	10 (21,7 %)	0,004
	Legs	31 (62,0 %)	10 (21,7 %)	< 0,001

Notes. CINMA – critical illness neuromuscular abnormality. n, number of subjects.

10 patients (20,0 %) with CINMA and 1 (2,2 %) patient without CINMA reported sensory disturbances (p = 0,006). 33 (66,0 %) patients with CINMA admitted having weakness, as did 10 (21,7 %) patients without CINMA (p < 0,001). All patients reported of sensory disturbances only in conjunction with limb weakness.

Most frequently patients with CINMA complained about weakness in legs and arms, and numbness in legs.

Signs of CINMA. In order to determine the objective sings of CINMA, we evaluated the findings of neurological examination of both patients with and without CINMA.

Sensory impairment. Sensory impairment was detected in 45 patients (90,0 %) with CINMA and in 24 patients (52,2 %) without CINMA (p < 0,001). The distribution of sensory impairment is presented in table 5.

Table 5. Sensory impairment in patients with and without critical illness neuromuscular abnormality.

Sensory impairment		Patients with CINMA (n = 50)	Patients without CINMA (n = 46)	p value
Pin prick	Arms	4 (8,0 %)	0	0,12
	Legs	4 (8,0 %)	1 (2,2 %)	0,36
Light touch	Arms	4 (8,0 %)	0	0,12
	Legs	9 (18,0 %)	2 (4,3 %)	0,06
Vibration sense	Arms	34 (68,0 %)	9 (19,6 %)	< 0,001
	Legs	42 (84,0 %)	20 (43,5 %)	< 0,001
Joint position sense	Arms	7 (14,0 %)	1 (2,2 %)	0,6
	Legs	14 (28,0 %)	1 (2,2 %)	< 0,001

Notes. CINMA – critical illness neuromuscular abnormality. n – number of subjects.

The most frequent sensory abnormality in CINMA group was impaired sense of vibration in legs and arms, and impaired position sense in legs.

Changes of tendon reflexes. 39 (78,0 %) persons with CINMA had abnormal (decreased or absent) deep tendon reflexes, as only 10 persons (21,7 %) without CINMA (p < 0,001) (table 6).

Table 6. Decreased or absent deep tendon reflexes in patients with and without critical illness neuromuscular abnormality.

Tendon reflexes	Patients with CINMA (n = 50)	Patients without CINMA (n = 46)	p value
Biceps	3 (6,0 %)	0	0,24
Carporadial	7 (14,0 %)	0	0,01
Knee	20 (40,0 %)	1 (2,2 %)	< 0,001
Ankle	39 (78,0 %)	9 (19,6 %)	< 0,001

Notes. CINMA – critical illness neuromuscular abnormality. n – number of subjects.

39 (78,0 %) patients had bilaterally abnormal ankle jerks, in 20 (40,0 %) patients ankle jerks were unobtainable. 32 (64,0 %) patients with CINMA had abnormal

tendon reflexes in legs, 7 (14,0 %) patients – also in arms. 1 patient without CINMA had bilaterally normal ankle jerks, but knee reflexes were decreased. This patient had no other complaints related to neuromuscular involvement, her vibration sense in legs was impaired, but NCS were normal. In this case decreased knee reflexes were considered as clinically insignificant finding.

Patients with CINMA significantly more frequently had decreased or absent carporadial, knee and ankle reflexes as patients without CINMA.

Muscle strength. The average muscle strength in patients with CINMA was 52,12 ± 6,30 (35–60), in patients without CINMA 57,3 ± 6,7 (30–60) (the difference was statistically significant, $p < 0,001$). 2 patients without CINMA had hemiparesis, caused by upper motor neuron damage. The data of these patients were excluded from the analysis of muscle strength (table 7).

Table 7. Muscle strength of patients with and without critical illness neuromuscular abnormality.

Muscle strength	**Patients with CINMA (n = 50)**	**Patients without CINMA (n = 44)**	**p value**
Overall average muscle strength	52,12 ± 6,30	58,61 ± 3,20	< 0,001
Score < 24 (tetraplegia)	0	0	1
Score 24-48 (tetraparesis)	17 (34,0 %)	2 (4,5 %)	0,003
Score 49-59 (mild paresis)	24 (48,0 %)	9 (20,5 %)	0,003
60 (normal strength)	9 (18,0 %)	33 (75,0 %)	< 0,001

Notes. CINMA – critical illness neuromuscular abnormality. n – number of subjects.

Tetraplegia was not present in any subject, but 17 (34,0 %) patients had reduced muscle strength (tetraparesis), and it was significantly more frequent in patients with CINMA ($p = 0,003$). 9 patients with CINMA (18,0 %) had normal muscle strength. The distribution of muscle weakness in proximal and distal parts of the extremities is shown in table 8.

Table 8. The distribution of muscle weakness in patients with and without critical illness neuromuscular abnormality.

Muscle weakness		**Patients with CINMA (n = 50)**	**Patients without CINMA (n = 44)**	**p value**
Arms	Proximal	30 (60,0 %)	9 (20,5 %)	< 0,001
	Distal	24 (48,0 %)	5 (11,4 %)	< 0,001
Legs	Proximal	36 (72,0 %)	6 (13,6 %)	< 0,001
	Distal	32 (64,0 %)	3 (6,8 %)	< 0,001

Notes. CINMA – critical illness neuromuscular abnormality. n – number of subjects.

Muscle weakness was observed more frequently in legs than in arms, with similar distribution in proximal and distal parts.

Muscle wasting. Muscle wasting was noted in 21 (42%) patient with CINMA compared to 4 (8,7 %) patients without CINMA ($p < 0,001$). In patients with CINMA, muscle atrophy was more frequent in distal parts of arms and legs (table 9).

Table 9. The distribution of muscle wasting in patients with and without critical illness neuromuscular abnormality.

Muscle wasting		**Patients with CINMA (n = 50)**	**Patients without CINMA (n = 46)**	**p value**
Arms	Proximal	8 (16,0 %)	2 (4,3 %)	0,09
	Distal	13 (26,0 %)	2 (4,3 %)	0,004
Legs	Proximal	10 (20,0 %)	3 (6,5 %)	0,06
	Distal	18 (36,0 %)	2 (4,3 %)	< 0,001

Notes. CINMA – critical illness neuromuscular abnormality. n – number of subjects.

The clinical neurological examination revealed, that CINMA presents with sensory impairment (impaired vibration sense in arms and legs and impaired joint position sense in legs), decreased or absent deep tendon reflexes (carporadial, knee and ankle jerk) and motor impairment (decreased muscle strength in proximal and distal parts of extremities and muscle wasting in distal parts of the limbs).

Electrophysiological signs of CINMA. In order to identify the most significant electrophysiological signs of CINMA we compared the results of NCS and EMG in patients with CINMA, without CINMA, and in healthy subjects of the control group. We identified the most sensitive and specific electrophysiological criteria of CINMA.

Electrophysiological signs of polyneuropathy were detected in 50 (100,0 %) patients with CINMA and in 6 (13,0 %) patients without CINMA. These 6 subjects with electrophysiological signs of neuromuscular damage were not assigned to the CINMA group as they did not have other (clinical) criteria of neuromuscular involvement.

Out of 96 subjects examined, 6 (6,3 %) patients had electrophysiological features of the median nerve entrapment at wrist (carpal tunnel syndrome, CTS): 2 patients with CINMA and 4 patients without. 7 (7,3 %) patients had electrophysiological signs of ulnar nerve entrapment at the elbow (cubital tunnel syndrome): 3 patients with CINMA and 4 patients without CINMA. Signs of myopathy were detected in 12 patients (12,5 %), but only in the presence of peripheral nerve damage.

Results of NCS. Within CINMA group, in two cases median nerve response was not included in the analysis due to CTS and in 3 cases ulnar nerve response was excluded due to cubital tunnel syndrome. In patients without CINMA group, the median and ulnar nerve responses of 4 patients were excluded due to CTS and cubital tunnel syndrome

respectively. The prevalence of mononeuropathies was not statistically significantly different between patients with CINMA and without CINMA (CTS, p = 0,42; cubital tunnel syndrome, p = 0,47).

The results of the NCS studies in patients with CINMA are given in Table 10.

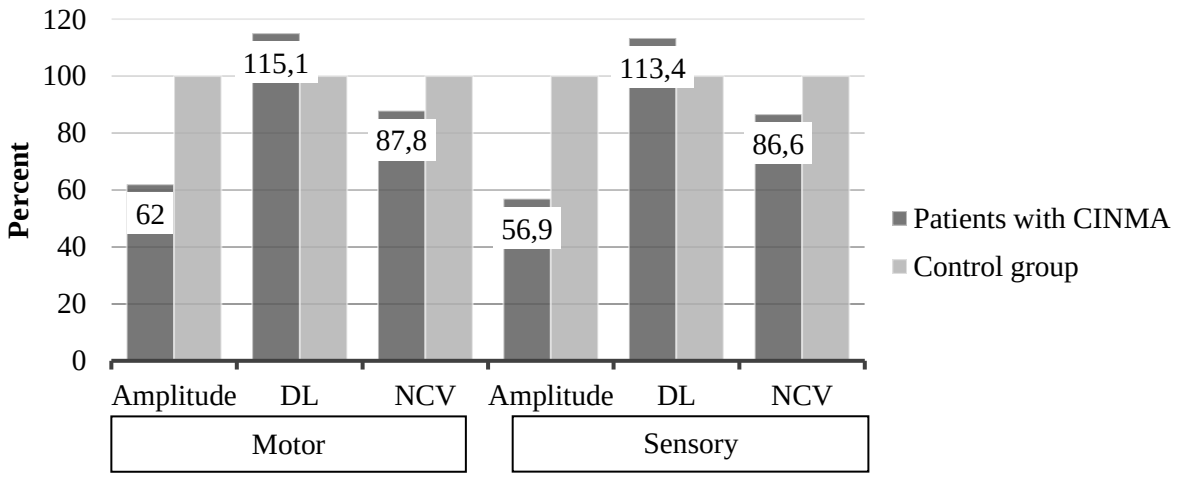
Table 10. The results of nerve conduction studies of patients with critical illness neuromuscular abnormality.

		Number of examined nerves	Normal response	Abnormal response	Absent response
Motor nerves	Median	48	29 (60,4 %)	19 (39,6 %)	0
	Ulnar	47	36 (76,6 %)	11 (23,4 %)	0
	Peroneal	100	18 (18,0 %)	53 (53,0 %)	29 (29,0 %)
	Tibial	100	46 (46,0 %)	36 (36,0 %)	18 (18,0 %)
Sensory nerves	Median	48	27(56,3 %)	20 (41,7 %)	1 (2,1 %)
	Ulnar	47	27 (57,4 %)	19 (40,4 %)	0
	Sural	100	28 (28,0 %)	2 (2,0 %)	70 (70,0 %)

We identified, that the most commonly affected were the nerves of legs: motor peroneal and tibial and sensory sural.

Median nerve. The results of comparison of median nerve parameters in patients with CINMA and control group is given in Figure 6.

Figure 6. Comparison of mean values of median nerve response parameters of patients with critical illness neuromuscular abnormality and the control group.



Notes. CINMA – critical illness neuromuscular abnormality. DL – distal latency. NCV – nerve conduction velocity.

The greatest difference was observed in median nerve CMAP and SNAP amplitudes: CMAP on average consisted 62,0 % of the control groups' mean CMAP, SNAP – 56,9 %. Results of comparison among patients' with CINMA, patients' without CINMA and control group of median nerve are given in Table 11.

Table 11. Comparison of motor and sensory responses of median nerve among patients with critical illness neuromuscular abnormality, patients without critical illness neuromuscular abnormality and control group subjects.

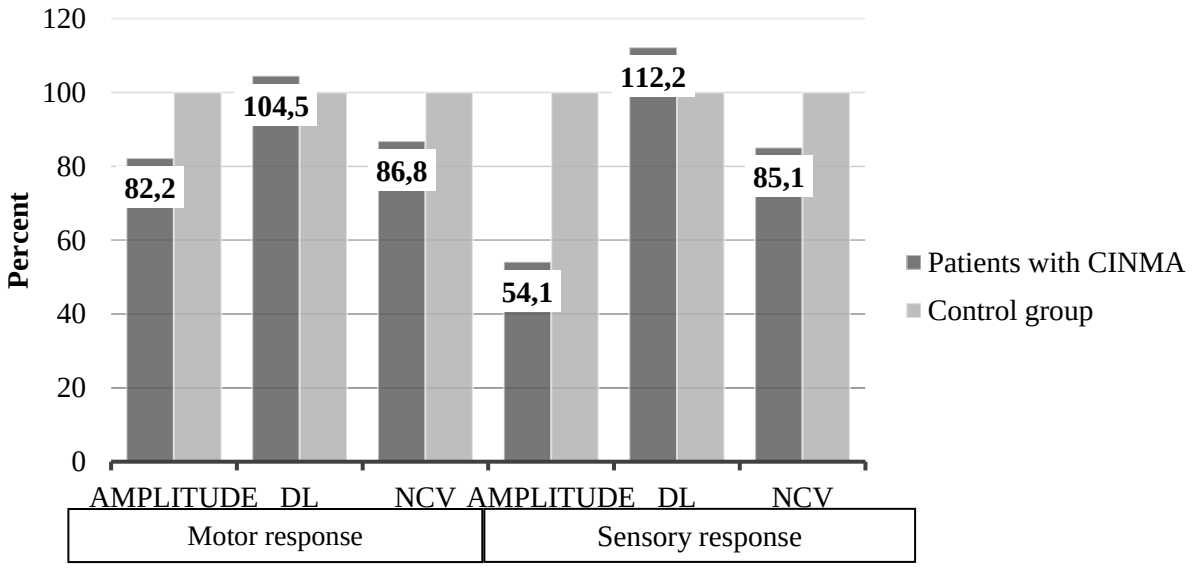
	Patients with CINMA (n = 48)	**Patients without CINMA (n = 42)**	**Control group (n = 96)**	**p value**	***post hoc***
Group number	**I**	**II**	**III**		
CMAP					
Amplitude (mV)	4,84 ± 2,12	6,08 ± 2,52	7,81 ± 2,68	χ^2 = 38,42; < 0,001	I < II < III
DL (ms)	3,97 ± 0,45	3,65 ± 0,51	3,45 ± 0,29	χ^2 = 38,09; < 0,001	I > II, III II = III
NCV (m/s)	49,13 ± 4,30	52,78 ± 4,20	55,95 ± 3,91	χ^2 = 64,81; < 0,001	I < II < III
SNAP					
Amplitude (μV)	19,30 ± 10,24	32,45 ± 12,32	33,95 ± 12,53	χ^2 = 44,23; < 0,001	I < II, III II = III
DL (ms)	3,63 ± 0,40	3,30 ± 0,34	3,20 ± 0,26	χ^2 = 35,67; < 0,001	I > II, III II = III
NCV (m/s)	46,90 ± 5,91	51,12 ± 5,18	54,16 ± 3,79	χ^2 = 44,34; < 0,001	I < II < III

Notes. Results are given as mean and standard deviation. n – number of nerve response, when the response was present. CINMA – critical illness neuromuscular abnormality. CMAP – compound muscle action potential. DL – distal latency. mV – millivolts. μV – microvolts. ms – milliseconds. NCV – nerve conduction velocity. m/s – meters per second. SNAP – sensory nerve action potential.

All parameters of both CMAP and SNAP of median nerve in patients with CINMA were statistically significantly worse compared with both patients without CINMA and subjects of control group.

Ulnar nerve. The results of comparison of ulnar nerve parameters in patients with CINMA and control group is given in Figure 7.

Figure 7. Comparison of mean values of ulnar nerve response parameters of patients with critical illness neuromuscular abnormality and the control group.



Notes. CINMA – critical illness neuromuscular abnormality. DL – distal latency. NCV – nerve conduction velocity.

The greatest difference was observed in ulnar nerve SNAP amplitudes: mean SNAP on average consisted 54,1 % of the control group. Results of comparison among patients' with CINMA, patients' without CINMA and control group of ulnar nerve are given in Table 12.

Table 12. Comparison of motor and sensory responses of ulnar nerve among patients with critical illness neuromuscular abnormality, patients without critical illness neuromuscular abnormality and control group subjects

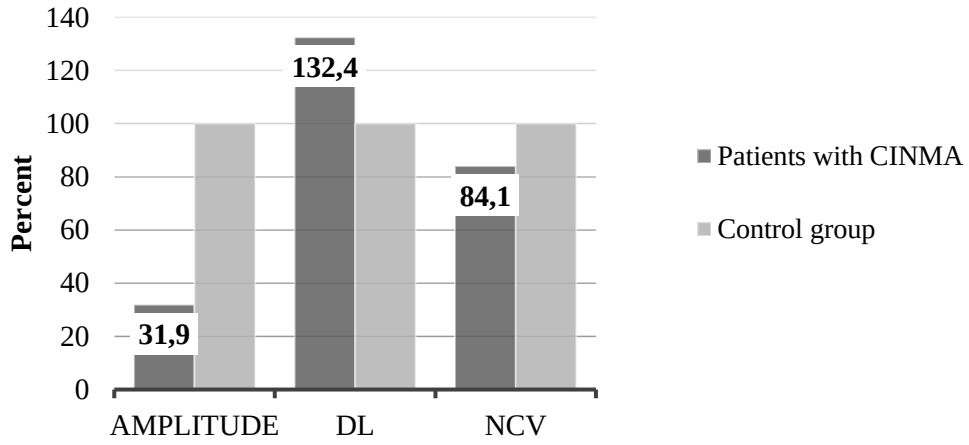
	Patients with CINMA (n = 47)	**Patients without CINMA (n = 42)**	**Control group (n = 96)**	**p value**	***post hoc***
Group number	**I**	**II**	**III**		
CMAP					
Amplitude (mV)	6,02 ± 1,73	7,32 ± 1,79	8,03 ± 2,36	χ^2 = 22,41; <0,001	I < II, III II = III
DL (ms)	3,03 ± 0,48	2,89 ± 0,40	2,90 ± 0,35	χ^2 = 3,26; 0,20	-
NCV (m/s)	50,75 ± 4,75	55,14 ± 4,90	58,46 ± 4,61	χ^2 = 55,55; <0,001	I < II < III
SNAP					
Amplitude (μV)	16,17 ± 9,22	25,17 ± 12,06	29,89 ± 11,75	χ^2 = 46,27; <0,001	I < II, III II = III
DL (ms)	3,23 ± 0,42	2,87 ± 0,29	2,88 ± 0,28	χ^2 = 26,49; <0,001	I > II, III II = III
NCV (m/s)	45,76 ± 6,05	52,04 ± 4,85	53,75 ± 3,75	χ^2 = 53,38 <0,001	I < II, III II = III

Notes. Results are given as mean and standard deviation. n – number of nerve response, when the response was present. CINMA – critical illness neuromuscular abnormality. CMAP – compound muscle action potential. DL – distal latency. mV – millivolts. μV – microvolts. ms – milliseconds. m/s – meters per second. NCV – nerve conduction velocity. SNAP – sensory nerve action potential.

Patients with CINMA had significantly worse ulnar CMAP parameters, except DL, compared to both patients without CINMA and control groups. The parameters of ulnar SNAP in patients with CINMA were worse compared to both patients without CINMA and control group.

Peroneal nerve. The results of comparison of peroneal nerve parameters in patients with CINMA and control group is given in Figure 8.

Figure 8. Comparison of mean values of peroneal nerve response parameters of patients with critical illness neuromuscular abnormality and the control group.



Notes. CINMA – critical illness neuromuscular abnormality. DL – distal latency. NCV – nerve conduction velocity.

The mean peroneal CMAP amplitude was 31,9 % that of control group. Results of comparison among patients' with CINMA, patients' without CINMA and control group of peroneal nerve are given in Table 13.

Table 13. Comparison of motor responses of peroneal nerve among patients with critical illness neuromuscular abnormality, patients without critical illness neuromuscular abnormality and control group subjects.

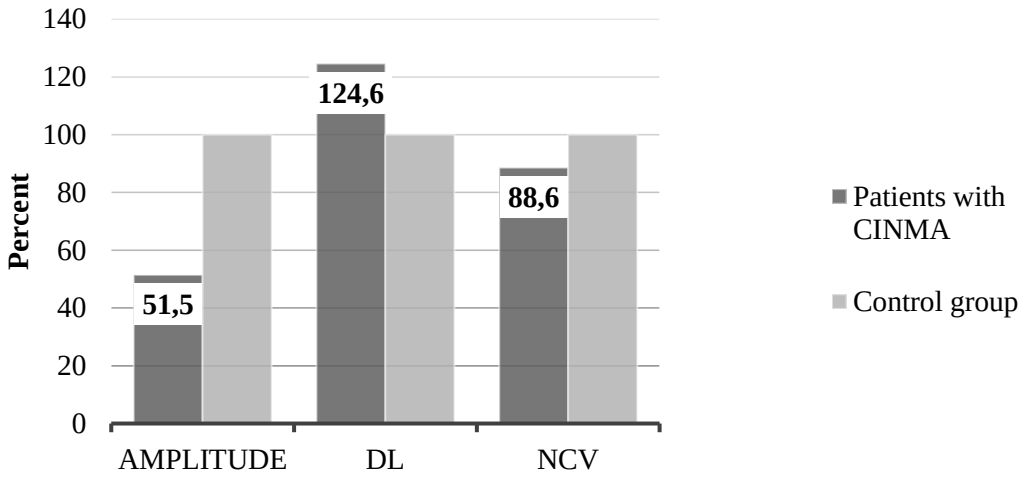
	Patients with CINMA (n = 71)	**Patients without CINMA (n = 92)**	**Control group (n = 96)**	**p value**	***post hoc***
Group number	**I**	**II**	**III**		
Amplitude (mV)	1,73 ± 1,27	4,30 ± 1,63	5,42 ± 1,59	χ^2 = 127,04; < 0,001	I < II < III
DL (ms)	4,70 ± 0,81	3,91 ± 0,71	3,55 ± 0,50	χ^2 = 81,27; < 0,001	I > II > III
NCV (m/s)	39,43 ± 4,17	43,54 ± 2,88	46,86 ± 3,57	χ^2 = 105,38; < 0,001	I < II < III

Notes. Results are given as mean and standard deviation. n – number of nerve response, when the response was present. CINMA – critical illness neuromuscular abnormality. DL – distal latency. mV – millivolts. m/s – meters per second. ms – milliseconds. NCV – nerve conduction velocity.

All parameters of peroneal nerve CMAP were significantly worse comparing to patients without CMAP and control group.

Tibial nerve. Results of comparison of tibial nerve parameters in patients with CINMA and control group are given in Figure 9.

Figure 9. Comparison of mean values of tibial nerve response parameters of patients with critical illness neuromuscular abnormality and the control group.



Notes. CINMA – critical illness neuromuscular abnormality. DL – distal latency. NCV – nerve conduction velocity.

The mean tibial CMAP amplitude was 51,5 % that of control group. Results of comparison among patients' with CINMA, patients' without CINMA and control group of peroneal nerve are given in Table 14.

Table 14. Comparison of motor responses of tibial nerve among patients with critical illness neuromuscular abnormality, patients without critical illness neuromuscular abnormality and control group subjects.

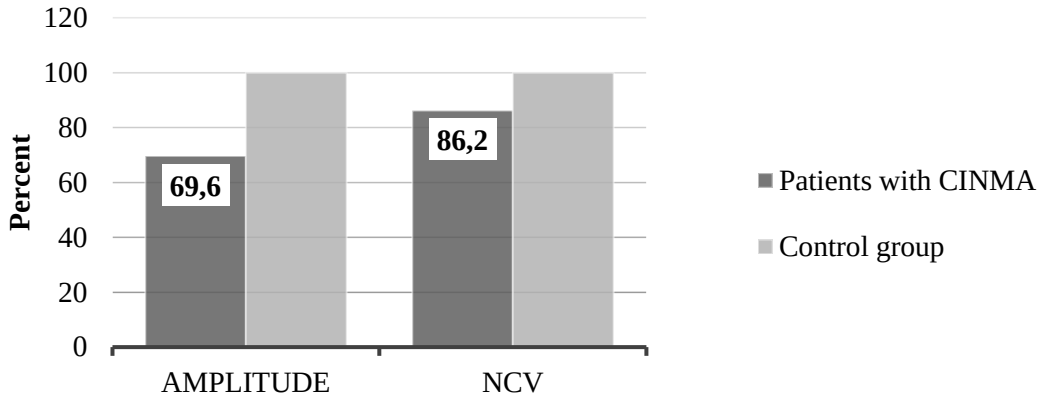
	Patients with CINMA (n = 82)	**Patients without CINMA (n = 92)**	**Control group (n = 96)**	**p value**	***post hoc***
Group number	**I**	**II**	**III**		
Amplitude (mV)	4,78 ± 3,32	9,39 ± 3,27	9,28 ± 3,26	χ^2 = 77,40; < 0,001	I < II, III II = III
DL (ms)	4,41 ± 0,94	3,84 ± 0,55	3,54 ± 0,39	χ^2 = 52,71; < 0,001	I > II > III
NCV (m/s)	40,96 ± 5,22	44,51 ± 3,71	46,22 ± 3,87	χ^2 = 46,73; < 0,001	I < II < III

Notes. Results are given as mean and standard deviation. n – number of nerve response, when the response was present. CINMA – critical illness neuromuscular abnormality. DL – distal latency. mV – millivolts. ms – milliseconds. m/s – meters per second. NCV – nerve conduction velocity.

All parameters of peroneal nerve CMAP were significantly worse compared to patients without CINMA and control group. Pairwise comparison revealed, that peroneal CMAP amplitude was not significantly different between patients without CINMA and control group.

Sural nerve. The results of comparison of sural nerve parameters in patients with CINMA and control group is given in Figure 10.

Figure 10. Comparison of mean values of sural nerve response parameters of patients with critical illness neuromuscular abnormality and the control group.



Notes. CINMA – critical illness neuromuscular abnormality. NCV – nerve conduction velocity.

The mean sural SNAP amplitude was 69,6 % that of control group. Results of comparison among patients' with CINMA, patients' without CINMA and control group of sural nerve are given in Table 15.

Table 15. Comparison of sensory responses of sural nerve among patients with critical illness neuromuscular abnormality, patients without critical illness neuromuscular abnormality and control group subjects.

	Patients with CINMA (n = 30)	**Patients without CINMA (n = 86)**	**Control group (n = 96)**	**p value**	***post hoc***
Group number	**I**	**II**	**III**		
Amplitude (μV)	11,11 ± 5,17	14,88 ± 6,75	15,96 ± 6,47	χ^2 = 15,12; 0,001	I < II, III II = III
NCV (m/s)	40,33 ± 5,50	44,36 ± 4,81	46,77 ± 4,37	χ^2 = 36,76; < 0,001	I < II < III

Notes. Results are given as mean and standard deviation. n – number of nerve response, when the response was present. CINMA – critical illness neuromuscular abnormality. μV – microvolts. m/s – meters per second. NCV – nerve conduction velocity.

Patients with CINMA sural SNAP amplitude and NCV were statistically significantly worse compared to those without CINMA and control group subjects.

Based on NCS, we identified, that patients with CINMA had significantly lower amplitudes of CMAPs and SNAPs in both arms and legs. The greatest reduction of amplitude was that of peroneal CMAP and ulnar SNAP.

Results of EMG. EMG study was performed on 95 subjects, 1 patient without CINMA refused from this study.

Spontaneous activity. Spontaneous activity (fibrillations and (or) positive sharp waves) was detected in 26 patients (27,1 %): 25 (50,0 %) with CINMA and one without (2,2 %) ($p < 0,001$). The distribution of spontaneous activity in patients with and without CINMA is shown in Table 16.

Table 16. Spontaneous activity in patients with critical illness neuromuscular abnormality and without critical illness neuromuscular abnormality

Muscle	Patients with CINMA (n = 50)	Patients without CINMA (n = 45)	p value
Deltoid	3 (6,0 %)	0	0,25
Abductor pollicis brevis	12 (24,0 %)	1 (2,2 %)	0,002
Rectus femoris	6 (12,0 %)	0	0,03
Anterior tibial	21 (42,0 %)	0	< 0,001

Notes. CINMA – critical illness neuromuscular abnormality. n – number of subjects.

In patients with CINMA spontaneous activity was observed in 42 muscles (21,0 % of total muscles examined). Spontaneous activity was statistically significantly more frequent in distal muscles.

Motor unit action potentials. 12 patients (24,0 %) with CINMA had short duration, polyphasic MUAPs (myopathic type), and 9 patients (18,0 %) – large, long duration potentials (neurogenic type). The analysis of MUAPs is presented in Table 17.

Table 17. Motor unit action potentials in patients with critical illness neuromuscular abnormality and without.

Muscle	Normal MUAPs	Myopathic MUAPs	Neurogenic MUAPs
Patients with CINMA (n = 50)			
Deltoid	42 (84,0 %)	6 (12,0 %)	2 (4,0 %)
Abductor pollicis brevis	45 (90,0 %)	2 (4,0 %)	3 (6,0 %)
Rectus femoris	41 (82,0 %)*	2 (4,0 %)	7 (14,0 %)
Anterior tibial	32 (64,0 %)*	9 (18,0 %)*	9 (18,0 %)*
Patients without CINMA (n = 45)			
Deltoid	43 (95,6 %)	2 (4,4 %)	0
Abductor pollicis brevis	44 (97,8 %)	0	1 (2,2 %)
Rectus femoris	43 (95,6 %)	1 (2,2 %)	1 (2,2 %)
Anterior tibial	43 (95,6 %)	0	2 (4,4 %)

Notes. MUAP – motor unit action potential. CINMA – critical illness neuromuscular abnormality. n – number of subjects. * – statistically significant difference between patients with CINMA and without CINMA.

We identified, that patients with CINMA more frequently had abnormal MUAPs as compared with patients without CINMA. Both myopathic and neurogenic changes were more frequent in distal muscles.

The value of clinical and electrophysiological tests diagnosing CINMA. To identify the diagnostic value of clinical and electrophysiological tests diagnosing CINMA, we calculated sensitivity, specificity and AUC of various parameters (Table 18).

Table 18. Sensitivity and specificity of clinical and neurophysiological examination.

		Sensitivity, % (CI)	Specificity, % (CI)	AUC
Clinical signs	Neuropathic symptoms	68,2 (55,1–80,9)	78,3 (66,3–90,2)	0,731
	Decreased or absent ankle reflexes	76,4 (64,2–87,8)	82,6 (71,7–93,6)	0,793
	Decreased distal sensation	90,3 (81,7–98,3)	47,8 (33,4–62,3)	0,689
	Tetraparesis (muscle strength ≤ 48)	34,0 (22,4–47,9)	91,3 (79,7–96,6)	0,627
	Distal muscle atrophy	45,4 (28,3–55,7)	100 (100–100)	0,710

ENMG changes	Abnormal NCS	100 (100–100)	87,1 (77,2–96,7)	0,935
	Spontaneous activity on EMG	50,0 (36,6–63,4)	97,8 (88,7–99,6)	0,739

Notes. CI – confidence interval. ENMG – electroneuromyography. NCS – nerve conduction studies. EMG – electromyography. AUC – *area under curve*.

The most sensitive method to diagnose CINMA is to detect changes on NCS (sensitivity 100 %), but some clinical features (distal muscle atrophy and tetraparesis) have a higher specificity. The best diagnostic accuracy (sensitivity and specificity ratio) has abnormal NCS.

To determine the diagnostic accuracy for each single nerve, we constructed individual ROC curves. The best amplitude cut-off value and the resulting sensitivities and specificities for all of the nerves are displayed in table 19.

Table 19. Accuracy of each nerve amplitude for the diagnosis of CINMA

		Sensitivity, % (CI)	**Specificity, % (CI)**	**AUC**	**Cut-off value**
Motor nerves	Median	58,0 (43,2–71,8)	54,3 (39,0–69,1)	0,625	5,00 mV
	Ulnar	62,0 (47,2–75,3)	58,7 (43,2–73,0)	0,668	6,47 mV
	Peroneal	79,5 (63,5–90,7)	82,6 (68,6–92,2)	0,932	2,27 mV
	Tibial	79,1 (64,0–90,0)	73,9 (58,9–85,7)	0,834	6,13 mV
Sensory nerves	Median	70,2 (55,1–82,7)	69,6 (54,2–82,3)	0,770	22,71 μV
	Ulnar	68,8 (53,7–81,3)	67,4 (52,0–80,5)	0,821	17,30 μV
	Sural	62,6 (35,4–84,8)	68,9 (53,4–81,8)	0,694	9,30 μV

Notes. CI – confidence interval. AUC – area under curve. mV – millivolts. μV – microvolts.

The motor nerve with the best diagnostic accuracy was the peroneal nerve (cut-off value 2,27 mV). Sensory nerve with the best diagnostic accuracy was ulnar nerve.

Factors, associated with CINMA. The comparison between patients with CINMA and without is given in Table 20.

Table 20. The comparison of data of patients with and without critical illness neuromuscular abnormality.

	Patients with CINMA (n = 50)	**Patients without CINMA (n = 45)**	**p value**
Gender, male (percent)	29 (58,0 %)	25 (54,3 %)	0,84
Age, years°	56,50 ± 16,60 (19–85)	46,83 ± 15,67 (19–72)	0,004
Duration of the treatment in the ICU, days°	24,06 ± 16,32 (7–79)	14,41 ± 7,09 (7–35)	0,001
Duration of MV, hours	282,00 (132,50–601,00)	151,50 (64,50–272,50)	0,006
Duration of sedation, hours	139,50 (76,50–285,75)	89,00 (42,00–169,50)	0,05
First ICU day APACHE II score, points	18,50 (13,75–23,25)	13,50 (11,00–18,25)	0,001
First ICU hour SAPS 3 score, points	60,50 (52,00–75,50)	53,50 (48,00–59,25)	0,007
First ICU day SOFA score, points	8 (4–9)	6 (3–8)	0,04
MOFS during first ICU day	32 (64,0 %)	24 (52,2 %)	0,26
Sepsis during treatment in the ICU	29 (58,0 %)	18 (39,1 %)	0,07
Last ICU day SOFA score, points	2 (2–4)	2 (2–3)	0,27
MOFS during last ICU day	5 (10,0 %)	0	0,08

Notes. Quantitative variables are given as median and 25-75 % percentiles. Categorical values are given as absolute value and percent. ° – age and treatment in the ICU duration is given as mean with standard deviation and minimal-maximal values. APACHE II – *Acute Physiology and Chronic Health Evaluation* scale. CINMA – critical illness neuromuscular abnormality. ICU – intensive care unit. MOFS – multiple organ failure syndrome. MV – mechanical ventilation. n – number of patients. SAPS 3 – *Simplified Acute Physiology Score*. SOFA – *Sequential Organ Failure Assessment*.

Patients with CINMA were 10 years older (p = 0,004), they were treated in the ICU 10 days longer (p = 0,001) and they were on mechanical ventilation 8 days longer (p = 0,006) compared to the patients without CINMA. Patients with CINMA had higher admission SOFA, APACHE II and SAPS 3 scores.

Mechanical lung ventilation was not applied to 13 patients (5 with CINMA and 8 without CINMA, p = 0,29). 25 patients did not require sedation (12 with CINMA and 13 without CINMA, p = 0,64).

In order to identify factors, associated with CINMA, possible risk factors were identified by univariate logistic regression analysis (Table 21).

Table 21. The results of binary univariate logistic regression analysis (dependent variable – critical illness neuromuscular abnormality).

Factor	Odds ratio	95 % CI	p value
Gender, male	0,86	0,38–1,93	0,72
Age	1,04	1,01–1,07	0,006
Duration of the treatment in the ICU	1,08	1,03–1,13	0,002
Duration of MVs	1,00	1,00–1,01	0,003
Duration of sedation, hours	1,00	1,00–1,01	0,04
Admission APACHE II score	1,14	1,06–1,24	0,001
First ICU hour SAPS 3 score	1,07	1,02–1,11	0,002
Admission SOFA score	1,15	1,01–1,31	0,04
MOFS during first ICU day	1,63	0,72–3,69	0,24
Last ICU day SOFA score	1,34	0,98–1,83	0,065
Surgery during ICU	2,52	0,99–6,36	0,05
Tracheostomy	0,50	0,21–1,17	0,11
Renal replacement therapy	5,91	1,82–19,16	0,003

Notes. APACHE II – *Acute Physiology and Chronic Health Evaluation* scale. CI – confidence interval. ICU – intensive care unit. MOFS – multiple organ failure syndrome. MV – mechanical ventilation. n – number of patients. SAPS 3 – *Simplified Acute Physiology Score*. SOFA – *Sequential Organ Failure Assessment*.

We have identified that older age, longer treatment in the ICU duration, longer duration of MV, longer sedation, worse status, defined by APACHE II, SAPS 3 and first day SOFA scores, and renal replacement therapy is associated with development on CINMA.

The binary multivariate logistic regression (forward-stepwise) method was used to identify the factors that predict CINMA. The results are given in Table 22.

Table 22. The results of binary logistic regression analysis (dependent variable – critical illness neuromuscular abnormality).

Risk factor	b	Odds ratio	95% CI	p value
Age	0,044	1,05	1,01 –1,08	0,006
Duration of treatment in the ICU	0,092	1,1	1,04 –1,16	0,001
Admission APACHE II score	0,131	1,14	1,04 – 1,25	0,006
Intercept	-6,025	0,002		<0,001

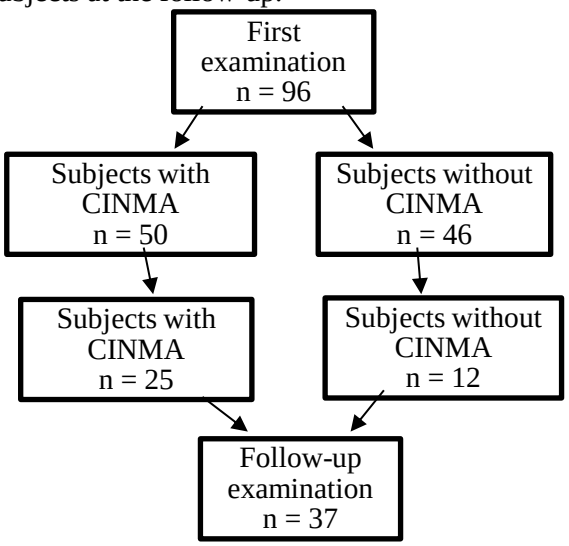
Notes. APACHE II – Acute Physiology and Chronic Health Evaluation scale. CI – confidence interval. ICU – intensive care unit.

The multivariate logistic regression analysis showed that risk factors independently associated with CINMA were older age, longer duration of the treatment in the ICU and severity of illness during ICU admission (estimated by the APACHE II score).

Outcomes of CINMA. Of the 96 individuals included in the analysis, 10 (10,4 %) died. Three people died in the hospital after discharge from ICU (3,1 %), all of these patients had been diagnosed with CINMA. The remaining 7 persons died within 6 months after discharge from hospital – 4 patients with CINMA and 3 patients without CINMA. There was no statistically significant difference in mortality between patients with CINMA and without CINMA – 7 (14,0 %) and 3 (6,5 %), p = 0,23.

Follow-up examination. 37 patients (38,5 % of all subjects or 43,0 % of the survivors) arrived for a follow-up examination after more than 6 months (median 236 days) after discharge from ICU. Figure 11 shows a chart of the subjects, who came for follow-up.

Figure 11. Chart of subjects at the follow-up.



Notes. n – number of subjects. CINMA – critical illness neuromuscular abnormality.

Out of 50 patients with CINMA, 25 (50,0 %) subjects came for a follow-up. 12 (26,1 %) out of 46 patients without CINMA also came for follow-up. Table 23 presents data of subjects who came for follow-up.

Table 23. Data of patients at follow-up.

	Subjects (n = 37)
Gender, male (percent)	25 (67,6 %)
Age, years°	55,28 ± 16,55 (19 – 85)
Duration of the treatment in the ICU, days°	18,46 ± 12,58 (7 – 58)
Duration of MV, hours	204 (72,5 – 414)
Duration of sedation, hours	108,5 (46,25 – 153,50)
First ICU day APACHE II score, points	18 (12 - 24)
First ICU hour SAPS 3 score, points	60 (48,5 – 73,5)
First ICU day SOFA score, points	7 (4 – 10,5)
MOFS during first ICU day	17 (43,6 %)
Last ICU day SOFA score, points	2 (2 – 3,5)
MOFS during last ICU day	4 (10,3 %)

Notes. Quantitative variables are shown as median and 25-75 percentiles. Categorical values are shown as absolute value and percent. ° – age and treatment in the ICU duration is shown as mean with standard deviation and minimal-maximal values. APACHE II – *Acute Physiology and Chronic Health Evaluation* scale. ICU – intensive care unit. MOFS – multiple organ failure syndrome. MV – mechanical ventilation. n – number of patients. SAPS 3 – *Simplified Acute Physiology Score*. SOFA – *Sequential Organ Failure Assessment*.

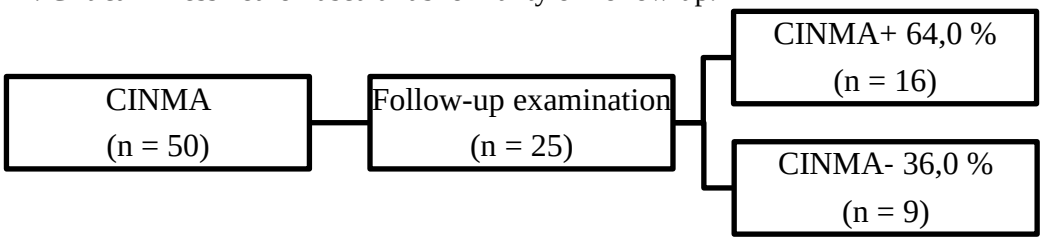
Mechanical lung ventilation was not applied for 5 patients (13,5 %), 13 patients did not require sedation (35,1 %).

Based on the diagnostic criteria of distal symmetrical polyneuropathy, during follow-up 16 (43,2 %) were diagnosed with polyneuropathy. 21 (56,8 %) did not fulfil criteria of polyneuropathy. None of the patients were diagnosed with new polyneuropathy, which developed after discharge from ICU. All subjects had axonal polyneuropathy. No cases of myopathy were identified on follow-up.

Of the 16 patients who still had polyneuropathy, 14 (87,5 %) had both sensory and motor impairment, 1 (6,25 %) patient had motor polyneuropathy and sensory polyneuropathy was also diagnosed in 1 (6,25 %) patient. All patients had polyneuropathy in legs, and 8 (50,0 %) also in arms.

Of the 25 subjects who had CINMA on ICU discharge, 16 (64,0 %) still were diagnosed with polyneuropathy on follow-up, and 9 patients (36,0 %) recovered (Figure 12).

Figure 12. Critical illness neuromuscular abnormality on follow-up.

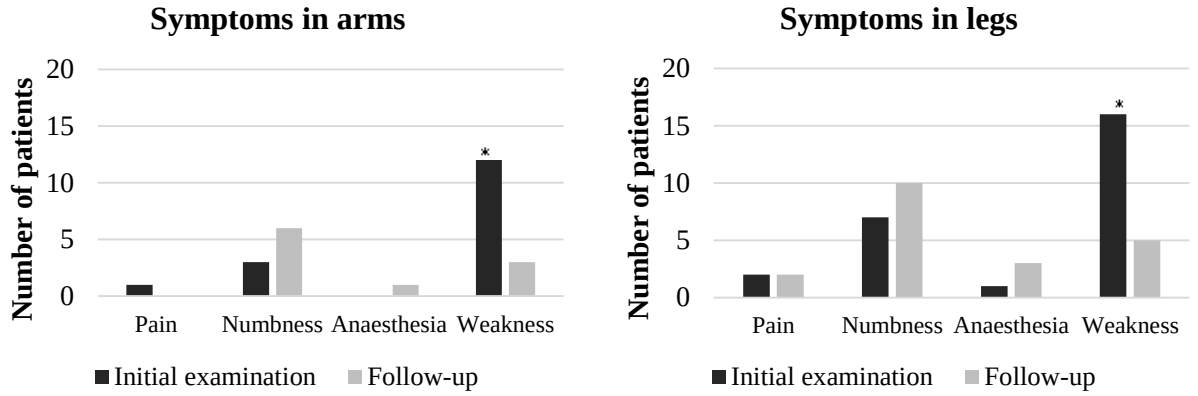


Notes. n – number of subjects. CINMA – critical illness neuromuscular abnormality.

Signs and symptoms of CINMA at follow-up. In order to find out which symptoms of CINMA had changed after discharge from ICU, we compared the findings of clinical neurological examination of patients who developed CINMA and came for follow-up visit (n = 25).

Symptoms of CINMA at follow-up. At follow-up 8 (32,0 %) patients had complaints related to neuromuscular involvement. 6 (24,0 %) patients admitted having sensory symptoms, 6 (24,0 %) reported weakness. Compared to the first study, there was no statistically significant difference in the number of patients who had complaints – 17 (68,0 %) during first examinations and 8 (32,0 %) at follow-up (p = 0,21) (Figure 13).

Figure 13. Complaints, expressed by patients with critical illness neuromuscular abnormality at discharge from intensive care unit and at follow-up.



Notes. * – statistically significant difference between initial examination and follow-up.

At follow-up patients most frequently reported numbness in arms and legs. Patients with CINMA less often complained about weakness in the extremities at follow-up compared to ICU discharge, but no significant difference was observed in sensory complaints.

Sensory impairment at follow-up. At follow-up sensory impairment was detected in 18 patients (72,0 %), during discharge from ICU – in 22 patients (88,0 %) (p = 0,22) (Table 24).

Table 24. Sensory impairment in patients with critical illness neuromuscular abnormality at discharge from intensive care unit and at follow-up.

Sensory impairment		**Patient with CINMA at ICU discharge (n = 25)**		
		Initial examination	**Follow-up**	**p value**
Pin prick	Arms	4 (16,0 %)	0	0,125
	Legs	3 (12,0 %)	3 (12,0 %)	1
Light touch	Arms	3 (12,0 %)	1 (4,0 %)	0,625
	Legs	5 (20,0 %)	5 (20,0 %)	1
Vibration sense	Arms	19 (76,0 %)	7 (28,0 %)	<0,001
	Legs	21 (84,0 %)	18 (72,0 %)	0,45

Joint position sense	Arms	5 (20,0 %)	0	0,06
	Legs	11 (44,0 %)	6 (24,0 %)	0,06

Notes. CINMA – critical illness neuromuscular abnormality. ICU – intensive care unit. n – number of patients.

The only sensory impairment that improved after discharge from ICU was sense of vibration in arms.

Changes of deep tendon reflexes at follow-up. During initial examination 18 (72,0 %) patients had tendon reflexes changes, at follow-up – 16 (64,0 %) (p = 0,5) (Table 25).

Table 25. Decreased or absent deep tendon reflexes in patients with critical illness neuromuscular abnormality at discharge from intensive care unit and at follow-up.

Deep tendon reflexes	**Patient with CINMA at ICU discharge (n = 25)**		
	Initial examination	**Follow-up**	**p value**
Biceps	1 (4,0 %)	0	1
Carporadial	3 (12,0 %)	0	0,25
Knee	7 (28,0 %)	5 (20,0 %)	0,774
Ankle	18 (72,0 %)	16 (64,0 %)	0,5

Notes. CINMA – critical illness neuromuscular abnormality. ICU – intensive care unit. n – number of subjects.

There were not statistically significant changes comparing initial and follow-up examinations.

Muscle strength at follow-up. The average muscle strength of patients with CINMA statistically significantly improved: during initial examination it was assessed to be 52,76 ± 5,99 (38–60), at follow-up 58,76 ± 2,82 (50–60) (p < 0,001). The average improvement of muscle strength was of 6,00 points (Table 26).

Table 26. Muscle strength in patients with critical illness neuromuscular abnormality at discharge from intensive care unit and at follow-up.

Muscle strength	**Patient with CINMA at ICU discharge (n = 25)**		
	Initial examination	**Follow-up**	**p value**
The overall average muscle strength	52,76 ± 5,99	58,76 ± 2,82	< 0,001
Score < 24 (tetraplegia)	0	0	1
Score 24-48 (tetraparesis)	6 (24,0%)	0	0,03
Score 49-59 (mild paresis)	14 (56,0%)	7 (28,0%)	0,14
60 (normal strength)	5 (20,0%)	18 (72,0%)	< 0,001

Notes. CINMA – critical illness neuromuscular abnormality. ICU – intensive care unit. n – number of subjects.

At follow-up no patients with tetraparesis were identified. The overall muscle strength statistically significantly improved (p < 0,001). The distribution of muscle weakness between proximal and distal parts of extremities during initial and follow-up examinations is given in table 27.

Table 27. The distribution of muscle weakness in patients with critical illness neuromuscular abnormality at discharge from intensive care unit and at follow-up.

Muscle weakness		Patient with CINMA at ICU discharge (n = 25)		
		Initial examination	Follow-up	p value
Arms	Proximal	12 (48,0 %)	1 (4,0 %)	0,001
	Distal	11 (44,0 %)	1 (4,0 %)	0,002
Legs	Proximal	17 (68,0 %)	2 (8,0 %)	< 0,001
	Distal	12 (48,0 %)	4 (16,0 %)	0,021

Notes. CINMA – critical illness neuromuscular abnormality. ICU – intensive care unit. n – number of subjects.

Muscle strength has significantly improved in both arms and legs.

Muscle wasting at follow-up. At the follow-up 5 patients (20,0 %) had muscle atrophy. Comparing with the first study (muscle atrophy was observed in 10 patients (40,0 %), there was no statistically significant difference (p = 0,18) (table 28).

Table 28. The distribution of muscle wasting in patients in patients with critical illness neuromuscular abnormality on discharge from intensive care unit and at follow-up.

Muscle wasting		Patient with CINMA at ICU discharge (n = 25)		
		Initial examination	Follow-up	p value
Arms	Proximal	3 (12,0 %)	1 (4,0 %)	0,63
	Distal	5 (20,0 %)	3 (12,0 %)	0,69
Legs	Proximal	4 (16,0 %)	2 (8,0 %)	0,63
	Distal	9 (36,0 %)	5 (20,0 %)	0,29

Notes. CINMA – critical illness neuromuscular abnormality. ICU – intensive care unit. n – number of subjects.

There was no statistically significant differences in muscle atrophy between two studies.

Clinical neurological examination revealed, that at follow-up muscle strength improves significantly, but sensory impairment, tendon reflexes and muscle atrophy do not change.

Electrophysiological changes at follow-up. The ENMG studies were performed on 37 individuals who arrived to follow-up visit. 2 (5,4 %) patients had electrophysiological features of the median nerve entrapment at wrist. 2 (5,4 %) had electrophysiological signs of ulnar nerve entrapment at the elbow. In these cases same mononeuropathies were diagnosed on initial examination. No new cases of mononeuropathy or polyneuropathy have been identified.

Results of NCS. All 25 patients with CINMA had NCS performed at follow-up. In two cases median nerve response was not included in the analysis due to CTS and in 2 cases ulnar nerve response was excluded due to cubital tunnel syndrome. Results of follow-up NCS are given in Table 29.

Table 29. The results of follow-up nerve conduction studies of patients with critical illness neuromuscular abnormality.

		Number of examined nerves	Normal response	Abnormal response	Absent response
Motor nerves	Median	23	20 (87,0 %)	3 (13,0 %)	0
	Ulnar	23	21 (91,3 %)	2 (8,7 %)	0
	Peroneal	50	17 (34,0 %)	25 (50,0 %)	8 (16,0 %)
	Tibial	50	30 (60,0 %)	11 (22,0 %)	9 (18,0 %)
Sensory nerves	Median	23	14 (60,9 %)	7 (30,4 %)	2 (8,7 %)
	Ulnar	23	12 (52,2 %)	10 (43,5 %)	1 (4,3 %)
	Sural	50	8 (16,0 %)	33 (66,0 %)	25 (50,0 %)

We identified, that at follow-up most commonly affected remained the nerves of legs: motor peroneal and sensory sural.

Median nerve. The comparison of median CMAP and SNAP at initial visit and follow-up is given in Table 30.

Table 30. Comparison of motor and sensory responses of median nerve at discharge from intensive care unit and at follow-up.

	Initial examination (n = 23)	Follow-up (n = 23)	p value*
CMAP			
Amplitude (mV)	4,69 ± 1,83	5,75 ± 2,22	0,002
DL (ms)	4,11 ± 0,84	4,07 ± 1,26	0,70
NCV (m/s)	48,88 ± 3,99	48,43 ± 5,68	0,83
SNAP			
Amplitude (μV)	17,28 ± 8,77	18,57 ± 8,87	0,36
DL (ms)	3,56 ± 0,35	3,67 ± 0,66	0,99
NCV (m/s)	47,37 ± 5,85)	47,03 ± 7,09	0,69

Notes. Results are given as mean and standard deviation. n – number of nerve responses, when the response was present. CMAP – compound muscle action potential. DL – distal latency. mV – millivolts. μV – microvolts. m/s – meters per second. ms – milliseconds. NCV – nerve conduction velocity. SNAP – sensory nerve action potential.

Median CMAP amplitude has statistically significantly improved (p = 0,002). Mean increase was 1,06 mV (22,6 %). Median SNAP did not change significantly.

Ulnar nerve. The comparison of ulnar CMAP and SNAP at initial visit and follow-up is given in Table 31.

Table 31. Comparison of motor and sensory responses of ulnar nerve at discharge from intensive care unit and at follow-up.

	Initial examination (n = 23)	Follow-up (n = 23)	p value*
CMAP			
Amplitude (mV)	5,65 ± 2,17	6,72 ± 1,59	0,004
DL (ms)	3,07 ± 0,48	3,28 ± 0,54	0,27
NCV (m/s)	50,15 ± 4,49	51,24 ± 3,74	0,20
SNAP			
Amplitude (μV)	13,89 ± 8,82	15,53 ± 8,92	0,23
DL (ms)	3,48 ± 0,89	3,23 ± 0,63	0,29
NCV (m/s)	43,69 ± 7,68	46,26 ± 7,33	0,06

Notes. Results are given as mean and standard deviation. n – number of nerve responses, when the response was present. CMAP – compound muscle action potential. DL – distal latency. mV – millivolts. μV – microvolts. m/s – meters per second. ms – milliseconds. NCV – nerve conduction velocity. SNAP – sensory nerve action potential.

Ulnar CMAP amplitude statistically significantly improved (p = 0,004). Mean increase was 1,07 mV (19,0 %). Ulnar SNAP did not change.

Peroneal nerve. The comparison of peroneal CMAP at initial visit and follow-up is given in Table 32.

Table 32. Comparison of motor responses of peroneal nerve at discharge from intensive care unit and at follow-up.

	Initial examination (n = 50)	**Follow-up (n = 50)**	**p value**
Amplitude (mV)	1,72 ± 1,26	2,41 ± 1,54	<0,001
DL (ms)	4,79 ± 0,83	4,67 ± 1,04	0,34
NCV (m/s)	39,61 ± 4,35	41,37 ± 3,33	0,07

Notes. Results are given as mean and standard deviation. n – number of nerve responses, when the response was present. DL – distal latency. mV – millivolts. ms – milliseconds. m/s – meters per second. NCV – nerve conduction velocity.

Peroneal CMAP amplitude statistically significantly improved (p < 0,001), mean increase was 0,69 mV (40,1 %).

Tibial nerve. The comparison of tibial CMAP at initial visit and follow-up is given in Table 33.

Table 33. Comparison of motor responses of tibial nerve at discharge from intensive care unit and at follow-up.

	Initial examination (n = 50)	**Follow-up (n = 50)**	**p value**
Amplitude (mV)	5,21 ± 3,75	5,64 ± 2,91	0,36
DL (ms)	4,25 ± 0,76	3,95 ± 0,71	0,14
NCV (m/s)	40,31 ± 4,58	41,78 ± 3,76	0,27

Notes. Results are given as mean and standard deviation. n – number of nerve responses, when the response was present. mV – millivolts. DL – distal latency. ms – milliseconds. NCV – nerve conduction velocity. m/s – meters per second.

Tibial CMAP did not change significantly.

Sural nerve. The comparison of sural SNAP at initial visit and follow-up is given in Table 34.

Table 34. Comparison of sensory responses of sural nerve at discharge from intensive care unit and at follow-up.

	Initial examination (n = 50)	**Follow-up (n = 50)**	**p value**
Amplitude (μV)	11,06 ± 5,73	12,05 ± 4,10	0,40
NCV (m/s)	38,38 ± 4,62	40,76 ± 4,66	0,052

Notes. Results are given as mean and standard deviation. n – number of nerve response, when the response was present. μV – microvolts. ms – milliseconds. NCV, nerve conduction velocity. m/s, meters per second.

Sural SNAP did not change significantly.

Results of EMG. EMG at follow-up was performed in 8 (32,0 %) patients. Spontaneous activity was detected in 3 (12,0 %) patients, at initial visit in 6 (24,0 %) patients. Myopathic changes were not detected. All 8 patients had signs of reinervation.

Neurophysiological studies revealed, that on follow-up the only amplitudes of median, ulnar and peroneal CMAP improved significantly.

Factors, associated with the outcome of CINMA. We analysed factors, related with unfavourable outcome of CINMA. Results are given in Table 35.

Table 35. Factors, associated with critical illness neuromuscular abnormality diagnosis at follow-up.

Variable	CINMA+ (n = 16)	CINMA- (n = 21)	p value
Gender, male (percent)	13 (81,2 %)	12 (57,1 %)	0,17
Age, years°	60,44 ± 19,36 (19 – 85)	51,71 ± 14,01 (19 – 68)	0,04
Duration of the treatment in the ICU, days°	22,00 ± 14,01 (7–58)	16,48 ± 11,52 (7–45)	0,83
Duration of MV, hours	230 (156 - 405)	157 (22 – 444,5)	0,25
Duration of sedation, hours	109 (88 – 143)	68 (29,5 – 209,5)	0,53
First ICU day APACHE II score, points	21 (18 – 28,5)	17 (11,5 – 20)	0,006
First ICU hour SAPS 3 score, points	61,5 (55 – 79,75)	58 (47 – 65)	0,06
First ICU day SOFA score, points	9,5 (4 – 12,75)	6 (3 – 9)	0,06
MOFS during first ICU day	10 (62,5 %)	6 (28,6 %)	0,05
Last ICU day SOFA score, points	2 (2 – 4)	2 (2 – 3,5)	0,62
MOFS during last ICU day	2 (12,5 %)	1 (4,8 %)	0,57

Notes. Quantitative variables are shown as median and 25-75 percentiles. Categorical values are shown as absolute value and percent. ° – age and treatment in the ICU duration is shown as mean with standard deviation and minimal-maximal values. APACHE II – *Acute Physiology and Chronic Health Evaluation* scale. CINMA – critical illness neuromuscular abnormality. ICU – intensive care unit. MOFS – multiple organ failure syndrome. MV – mechanical ventilation. n – number of patients. SAPS 3 – *Simplified Acute Physiology Score*. SOFA – *Sequential Organ Failure Assessment*.

Patients, who had CINMA at follow-up, were on average 9 years older (mean age respectively 60,44 and 51,71, p = 0,037) and they had higher admission APACHE II score (respectively 21 and 17, p = 0,006).

CONCLUSIONS

1. Critical illness neuromuscular abnormality is a common complication after long-term treatment in the intensive care unit.
2. Critical illness neuromuscular abnormality presents with sensory disturbances, changes in tendon reflexes, motor disorders, and electrophysiological changes of axonal polyneuropathy and myopathy.

3. Risk factors related to the occurrence of critical illness neuromuscular damage after long-term treatment in the intensive care unit are older age, longer treatment in the intensive care unit duration and more severe condition at the admission.
4. One-third of patients recover after half a year after leaving the intensive care unit.
5. An unfavourable prognosis may be associated with older age and severity of condition at the admission to the intensive care unit.

LIST OF PUBLICATIONS AND PRESENTATIONS

Publications

1. Klimašauskas A, **Sereikė I**, Klimašauskienė A, Bakšienė R, Šipylaitė J. Pre-ICU quality of life as a predictor of post-ICU mortality in patients with critical illness polyneuropathy. Medicina (Kaunas) 2017; 53 (accepted manuscript). Straipsnis „ISI Web of Science“.
2. Klimašauskas A, **Sereikė I**, Klimašauskienė A, Kėkštas G, Ivaškevičius J. The impact of medical conditions on the quality of life of survivors at discharge from intensive care unit. Medicina (Kaunas) 2011; 47 (5): 270-277. Straipsnis „ISI Web of Science“.
3. **Sereikė I,** Jatužis D, Klimašauskienė A, Klimašauskas A. The value of clinical investigation and electroneuromyography in diagnosing critical illness neuromuscular abnormality after prolonged treatment in the intensive care unit. Seminars in Neurology. 2017; 21 (71): 15-22.
4. **Sereikė I**, Klimašauskienė A, Jatužis D, Klimašauskas A. Unanswered question about critical illness neuromuscular abnormality. Seminars in Neurology 2014; 18 (62): 255–261.
5. Klimašauskas A, **Sereikė I**, Klimašauskienė A, Ivaškevičius J. Influence of neuromuscular disroder on the quality of life in case of long-term ICU treatment. Seminars in Neurology 2011; 15 (47): 31-37.

Presentations

1. **Sereikė I**, Klimašauskienė A, Klimašauskas A, Jatužis D. The price for surviving critical illness. International conference ,,Evolutionary Medicine: Perspectives in Understanding Health and Disease, 27-30 May 2014, Vilnius, Lithuania.

2. **Sereikė I,** Klimašauskienė A, Klimašauskas A, Budrys V. Clinical and electrophysiological signs and symptoms of critical illness neuromuscular abnormality. 7th Baltic Congress of Neurology, May 9-12, 2012, Tartu, Estonia.

Theses

1. Klimašauskas A, **Sereikė I,** Klimašauskienė A, Šipylaitė J. Pre-ICU quality of life as predictor of post-ICU mortality in patients with critical illness neuromuscular abnormality. 33rd Congress of Scandinavian Society of Anaesthesiology and Intensive Care Medicine, 10-12 June, 2015, Reykjavik, Iceland.
2. **Sereikė I,** Klimašauskienė A, Klimašauskas A, Budrys V. Critical illness neuromuscular abnormality after long-term treatment in intensive care unit. 7th Baltic Congress of Neurology, May 9-12, 2012, Tartu, Estonia.
3. **Sereikė I,** Budrys V, Klimašauskienė A, Klimašauskas A. Peripheral nerve damage after treatment in intensive care unit. The 14th Congress of the European Federation of Neurological Societies, September 25-28, 2010, Geneva, Switzerland.
4. **Sereikė I,** Klimašauskienė A, Klimašauskas A. Peripheral nerve damage after treatment in intensive care unit. 6th Baltic Congress of Neurology, May 5-8, 2009, Vilnius, Lithuania.
5. **Sereikė I,** Klimašauskienė A, Klimašauskas A. Clinical and electrophysiological signs of critical illness neuropathy. 6th Baltic Congress of Neurology, May 5-8, 2009, Vilnius, Lithuania.

CURRICULUM VITAE

Ieva Sereikė

Education

2013–2017 doctoral studies at the Vilnius University, Faculty of Medicine.

2004–2008 neurology resident in Vilnius University, Faculty of Medicine.

1997–2003 Vilnius university, Faculty of medicine (studies of medicine).

1997 graduated Vilnius Naujininkų secondary school.

Professional experience

Since 2008 junior research associate at the Clinic of Neurology and Neurosurgery in the Faculty of Medicine of Vilnius University.

Since 2008 neurologist at the Vilnius University hospital Santaros klinikos, Centre of Neurology.

2007–2008 assistant at the Vilnius University hospital Santaros klinikos, Centre of Neurology.

Research interests

Fields of interest include clinical neurophysiology, electroneuromyography and evoked potentials studies, transcranial magnetic stimulation, diagnostic and treatment options for multiple sclerosis, peripheral nervous system and muscle diseases.

Since 2008 performs. I. Sereikė contributed to the fact that in 2009 in Vilnius University hospital Santaros klinikos visual evoked potentials were introduced to everyday practice. On the initiative of I. Sereikė and the efforts made by the Centre of Neurology transcranial magnetic stimulation as diagnostic toll was introduced.

Heads students research projects in the area of interest. Gives lectures on physicians training courses. Gives presentation on peripheral nervous system disorders and clinical neurophysiology, attends local and international conferences, and is constantly developing in the area of interest.

SUMMARY IN LITHUANIAN

ILGAI INTENSYVIOSIOS TERAPIJOS SKYRIUJE GYDYTŲ LIGONIŲ KRITINIŲ BŪKLIŲ NEURORAUMENINIS PAŽEIDIMAS

Įvadas

Kritinių būklių neuroraumeninis pažeidimas (KBNRP) yra dažniausia raumenų silpnumo, pasireiškiančio intensyviosios terapijos skyriuje (ITS) priežastis. Neuroraumeninės komplikacijos esant kritinėms būklėms gali pasireikšti kaip kritinių būklių polineuropatija (KBP) arba kritinių būklių miopatija (KBM). Daugėja duomenų, kad polineuropatija ir miopatija esant kritinėms būklėms pasireiškia kartu. Atskirti polineuropatiją nuo miopatijos ITS sudėtinga dėl kelių priežasčių. Klinikinis neurologinis ištyrimas gali būti neinformatyvus: paciento apklausti neįmanoma, tiriant neurologiškai jutimų sutrikimai nevertinami, o raumenų jėgos įvertinimas netikslus. ENMG tyrimas nėra plačiai prieinamas ITS, jo rezultatai priklauso nuo atlikimo laiko (atliekant tyrimą per anksti, pakitimų gali dar nebūti), gretutinių ligų (jau anksčiau buvęs nervų ar raumenų pažeidimas dėl cukrinio diabeto, alkoholizmo ir pan.). Šis tyrimas užima daug laiko, subtiliems pakitimams gali prireikti specialių įgūdžių reikalaujančių metodų (pvz., KBM tiksliau nustatoma atliekant tiesioginę raumens stimuliaciją, o tai nėra įprastinis metodas, todėl kol kas taikomas tik moksliniuose tyrimuose). Raumens ar nervo biopsija, įtariant KBM ar KBP, atliekama retai, bent jau dėl to, kad tyrimas yra invazinis ir jo rezultatas iš esmės nepakeičia gydymo taktikos. Taigi, nesant galimybių atskirti miopatijos ir polineuropatijos, tokie terminai kaip KBNRP (kritinių būklių neuroraumeninis pažeidimas), CRIMYNE (kritinių būklių miopatija ir (ar) neuropatija, angl. *CRitical Illness Myopathy and/or NEuropathy*) ar KBNM (kritinių būklių neuromiopatija) yra visiškai tinkami. Nuo pirmųjų aprašymų susidomėjimas ITS įgytu silpnumu reikšmingai išaugo. Tam įtakos neabejotinai turėjo intensyviosios terapijos ir medicinos pasiekimai,

leidžiantys išgyventi sunkiausios būklės pacientams. Per 30 metų atlikta nemažai tiek perspektyvinių, tiek retrospektyvinių tyrimų, leidusių geriau suprasti per kritines būkles pasireiškiantį nervų ir raumenų pažeidimą. Šiuo metu dar nėra nustatytas tikslus šios problemos dažnis, nežinomi rizikos ir patofiziologiniai veiksniai, nėra pakankamai duomenų apie ligos pasireiškimą, profilaktiką, gydymą ir išeitis.

Darbo tikslas

Nustatyti kritinių būklių neuroraumeninio pažeidimo dažnį pacientams, ilgai gydytiems intensyviosios terapijos skyriuje, įvertinti šio pažeidimo klinikinius bei elektrofiziologinius požymius, nustatyti simptomų dinamiką bei veiksnius, susijusius su nepalankia išeitimi, praėjus 6 mėnesiams po išvykimo iš intensyviosios terapijos skyriaus.

Darbo uždaviniai

1. Nustatyti kritinių būklių neuroraumeninio pažeidimo dažnį pacientams, ilgai gydytiems intensyviosios terapijos skyriuje.
2. Nustatyti klinikinius ir elektrofiziologinius kritinių būklių neuroraumeninio pažeidimo požymius.
3. Nustatyti rizikos veiksnius, susijusius su kritinių būklių neuroraumeninio pažeidimo išsivystymu po ilgo gydymo intensyviosios terapijos skyriuje.
4. Įvertinti kritinių būklių neuroraumeninio pažeidimo klinikinių ir elektrofiziologinių pokyčių dinamiką po 6 mėnesių išvykus iš intensyviosios terapijos skyriaus.
5. Įvertinti veiksnius, susijusius su nepalankia ilgalaike kritinių būklių neuroraumeninio pažeidimo išeitimi.

Praktinė darbo reikšmė ir originalumas

Lietuvoje ir pasaulyje nėra atlikta perspektyvinių tyrimų, analizuojančių pacientų po ilgo gydymo intensyviosios terapijos skyriuje neuroraumeninius simptomus ir elektrofiziologinius pokyčius bei jų dinamiką. Taip pat nėra atlikta tyrimų apie ilgalaikio gydymo ITS reikšmę nervų ir raumenų pažeidimo atokioms išeitims. Tikimės, kad mūsų tyrimo rezultatai papildys jau atliktų tyrimų duomenis, susijusius su KBNRP klinikiniais ir neurofiziologiniais simptomais, padės laiku ir tiksliai diagnozuoti šią būklę pacientams, ilgai gydytiems ITS, bei ateityje leis skirti tinkamiausias gydymo bei profilaktikos priemones.

Remdamiesi tyrimo rezultatais, nustatėme, kad kritinių būklių neuroraumeninis pažeidimas yra dažna ilgo gydymo intensyviosios terapijos skyriuje komplikacija.

Nustačius neuroraumeninį silpnumą galima prognozuoti gydymo intensyviosios terapijos skyriuje trukmę, ilgalaikes išeitis bei rekomenduoti tinkamiausią gydymą, kad kuo geriau atsikurtų įvairios funkcijos. Pacientus vertinome atsižvelgdami į perspektyvą ir išanalizavome veiksnius, susijusius su kritinių būklių neuroraumeninio pažeidimo pasireiškimu bei nepalankia jo išeitimi. Įvertinome kritinių būklių neuroraumeninio pažeidimo dažnį po ilgo gydymo ITS, taip pat apibendrinome šio sutrikimo klinikinius bei elektrofiziologinius požymius. Identifikavome jautriausius ir specifiškiausius klinikinius bei elektrofiziologinius žymenis, leisiančius anksti įtarti neuroraumenininį pažeidimą. Įrodėme, kad ilgas gydymas yra susijęs su KBNRP bei kad sveikimas po šio susirgimo yra ilgalaikis procesas.

Tiriamieji ir tyrimo metodika

Tyrimas atliktas Vilniaus universiteto Medicinos fakulteto Neurologijos ir neurochirurgijos klinikos Neurologijos centre, Vilniaus universiteto ligoninės Santariškių klinikų Neurofiziologinių tyrimų kabinete. Tiriamieji atrinkti iš Vilniaus universiteto ligoninės Santariškių klinikų I reanimacijos ir intensyviosios terapijos skyriaus pacientų. Tyrime dalyvavo 105 asmenys, ilgai gydyti ITS, ir 96 kontrolinės grupės tiriamieji, atrinkti pagal amžių ir lytį, nesirgę periferinės nervų sistemos ar raumenų ligomis. Kontrolinės grupės asmenų elektrofiziologinių tyrimų duomenys naudoti apskaičiuojant nervinio impulso laidumo rodiklių normalias vertes absoliučiais skaičiais. Ilgo gydymo ITS trukmė nustatyta apskaičiavus vidutinę gydymo I reanimacijos ir intensyviosios terapijos skyriuje kalendoriniais metais (vidurkis su vienu standartiniu nuokrypiu, 5 + 2 paros – t. y. 7 paros ir ilgiau). Klinikinio tyrimo protokolą patvirtino Lietuvos bioetikos komitetas. Į tyrimą įtraukti abiejų lyčių asmenys, ilgai (7 paras ir ilgiau) gydyti ITS.

Tiriamuosius asmenis ištyrėme neurologiškai bei neurofiziologiškai du kartus: išvykimo iš ITS dieną ir pakartotinai, praėjus ne mažiau nei 6 mėnesiams po pirmojo ištyrimo.

Klinikinis neurologinis ištyrimas. Tiriamiesiems pateikėme šešis klausimus apie jutiminius (skausmą, tirpimą ar nejautrą rankose ir kojose) bei du klausimus apie motorinius (silpnumą rankose ir kojose) simptomus. Objektyvūs neuropatijos požymiai vertinti atlikus klinikinį neurologinį jutimų, motorikos ir refleksų tyrimą. Vertinome skausmo, švelnaus prisilietimo, vibracijos ir padėties jutimus visose galūnėse. Tyrėme šiuos sausgyslių refleksus: dvigalvio raumens (*m. biceps brachii*), žastinio-stipininio

raumens (*m. brachioradialis*), kelio girnelės ir Achilo. Refleksai vertinti kaip normalūs, susilpnėję ar negauti. Vertinome 3 raumenų grupių jėgą kiekvienoje galūnėje (dilbio tiesimas ir lenkimas, riešo tiesimas, klubo lenkimas ir tiesimas, pėdos lenkimas). Raumenų jėga vertinta nuo 0 (nėra raumens susitraukimo) iki 5 (normali jėga) balų pagal MRC (angl. *Medical Research Council Scale for Muscle Strength*) skalę. Bendra raumenų jėga vertinta pagal B. de Jonghe metodą. Vertinant pagal šį metodą, kiekvienos raumenų grupės jėgos įvertinimas sumuojamas, bendra balų suma gali svyruoti nuo 0 iki 60. Jei bendra raumenų jėga < 24 balai, būklė vertinta kaip tetraplegija, jei ≤ 48 balai – tetraparezė, 49-59 balai – lengva tetraparezė, 60 balų - normali raumenų jėga. Įvertinome raumenų atrofijų buvimą rankų ir kojų proksimalinėse (žastuose ir šlaunyse) bei distalinėse (plaštakose ir pėdose) dalyse. Visi klinikiniai požymiai vertinti kaip polineuropatijos požymiai tik tuomet, jei pasireiškė abiejose kūno pusėse.

Neurofiziologinis ištyrimas. Neurofiziologinio tyrimo metu atlikome elektroneurografiją (ENG) ir adatinę elektromiografiją (EMG). ENG tyrimą atlikome remiantis įprasta metodika, stimuliuojant motorinius nervus ortodromiškai, sensorinius nervus - antidromiškai. Vertinome vidurinio (*n. medianus*) ir alkūninio (*n. ulnaris*) nervų motorines ir jutimines skaidulas vienoje pusėje, kojose – abipus bendrąjį šeivinį (*n. peroneus communis*), blauzdinį (*n. tibialis*) ir blauzdos odos (*n. suralis*) nervus. Visos motorinės skaidulos tirtos paviršiniais elektrodais, vidurinio ir alkūninių nervų jutiminės skaidulos – žiediniais elektrodais, odos blauzdos nervo jutiminės skaidulos paviršiniais elektrodais. Suminio raumens veikimo potencialo (SRVP, nuo izolinijos iki negatyvaus piko), jutiminio nervo veikimo potencialo (JNVP, nuo izolinijos iki negatyvaus piko), nervo laidumo greičio (NLG) rodikliai lyginti su atitinkamo amžiaus normalios vertėmis, nustatytomis mūsų laboratorijoje. EMG metodu tyrėme šiuos raumenis vienoje kūno pusėje: rankoje deltinį (*m. deltoideus*), trumpąjį atitraukiamąjį rankos nykščio raumenį (*m. abductor pollicis brevis*), kojoje tiesųjį šlaunies raumenį (*m. rectus femoris*) ir priekinį blauzdos raumenį (*m. tibialis anterior*). Tyrimas atliktas koncentriniu adatiniu elektrodu. Kiekvienas šių raumenų adatiniu elektrodu tirtas bent 4 taškuose. Registruotas aktyvumas raumens ramybės metu (vertintas spontaninis aktyvumas, yra arba nėra) ir nedidelio įtempimo metu (vertinti motorinio vieneto veikimo potencialai, MVVP, normalūs, miopatinio tipo ar neurogeninio tipo).

KBNRP diagnostikos kriterijai. Polineuropatijos diagnozė suformuluota remiantis diagnostiniais distalinės simetrinės polineuropatijos kriterijais, pasiūlytais JAV neurologų akademijos. KBP diagnozuota tuomet, jei buvo šie kriterijai: 1. Pacientas serga kritiškai sunkia liga. 2. Galūnių silpnumas ar sunkumas atjungiant nuo dirbtinės plaučių ventiliacijos, atmetus su neuroraumeniniu pažeidimu nesusijusias priežastis. 3. Elektrofiziologiniai aksoninės motorinės ir sensorinės polineuropatijos požymiai. KBP nustatyta, jei atliekant ENMG tyrimą nenustatyta seno neurogeninio pažeidimo požymių, arba jei nerasta paūmėjimo požymių, bei atmesta kita galima polineuropatijos priežastis (cukrinis diabetas, lėtinis inkstų pažeidimas, lėtinis alkoholizmas ir kt.). KBM diagnozuota, jei buvo šie kriterijai: 1. Pacientas serga kritiškai sunkia liga. 2. Galūnių silpnumas ar sunkumas atjungiant nuo dirbtinės plaučių ventiliacijos, atmetus su neuroraumeniniu pažeidimu nesusijusias priežastis. 3. Atliekant adatinę EMG nustatyti trumpi, žemos amplitudės miopatiniai MVVP, su spontaniniu aktyvumu ar be jo.

Tiriamųjų grupės. KBNRP diagnozė suformuluota tuomet, jei buvo nustatoma KBP ir (ar) KBM. Tiriamuosius suskirstėme į dvi grupes: 1. Pacientai, kuriems nustatytas KBNRP (priskirti pacientų su KBNRP grupei) – tiriamajam nustatyta KBP ir (ar) KBM. 2. Pacientai, kuriems nenustatytas KBNRP (priskirti pacientų be KBNRP grupei). Šios grupės tiriamiesiems galėjo būti nustatomi kai kurie periferinių nervų ar raumenų pažeidimo požymiai, tačiau jie nepriskirti KBNRP grupei, nes neatitiko diagnostinių klinikinių ir elektrofiziologinių polineuropatijos kriterijų.

Rezultatai

Tiriamąją imtį sudarė 105 pacientai, gydyti ITS 7 paras ir ilgiau. Iš jų 9 pacientams nustatytas su kritine būkle nesusijęs lėtinis neuroraumeninis pažeidimas. Darbe analizuoti 96 asmenų duomenys Pakartotiniam ištyrimui, praėjus daugiau nei 6 mėnesiams (nuo pirmojo tyrimo, atvyko 37 asmenys (38,5 % nuo visų tiriamųjų arba 43,0 % nuo likusių gyvų tiriamųjų). Didžiąją tiriamųjų dalį sudarė pacientai, hospitalizuoti į ITS dėl kasos ar žarnyno pažeidimo (42 pacientai, 43,8 %). 50 asmenų (52,1 %) nustatyta polineuropatija. Miopatija nustatyta 12 pacientų, tačiau tik kartu su periferinių nervų pažeidimu. Visiems pacientams nustatyta aksoninio tipo polineuropatija. Dažniausiai nustatyta sensomotorinė polineuropatija – 41 pacientui. 7 pacientams nustatyta motorinė polineuropatija. Jutiminė neuropatija diagnozuota 2 pacientams. Įvertinę klinikinio neurologinio ištyrimo duomenis nustatėme, kad KBNRP dažniausiai pasireiškia jutimų

sutrikimais (sutrikęs vibracinis rankų ir kojų jutimas bei padėties jutimo sutrikimas kojose), sausgyslių refleksų pokyčiais (sumažėjęs ar išnykęs rankų žastinio-stipininio raumens sausgyslės ir kojų kelio girnelės bei Achilo sausgyslės refleksai), motorikos sutrikimais (galūnių raumenų jėgos sumažėjimu proksimaliai ir distaliai bei distalinių galūnių dalių raumenų atrofijomis).

Elektrofiziologinių polineuropatijos kriterijų nustatyta 50 (100,0 %) asmenų pacientų su KBNRP grupėje bei 6 (13,0 %) asmenims pacientų be KBNRP grupėje. Šie 6 asmenys, turėję elektrofiziologinių neuroraumeninio pažeidimo požymių, nepriskirti pacientų su KBNRP grupei, nes jiems nebuvo nustatyta kitų (klinikinių) polineuropatijos požymių. Nustatėme, kad KBNRP grupėje dažniausiai pakinta kojų nervų atsakai: šeivinio ir blauzdinio nervų motoriniai bei blauzdos odos jutiminiai. Įvertinę EMG tyrimo rezultatus, nustatėme, kad pacientams su KBNPR statistiškai reikšmingai dažniau nustatyta spontaninio aktyvumo, dažniausiai priekiniame blauzdos raumenyje. Taip pat priekiniame blauzdos raumenyje aptikta pakitusių (miopatinio ar neurogeninio tipo) motorinio vieneto veikimo potencialų. Nustatyta, kad jautriausias metodas diagnozuojant KBNRP yra pakitęs ENG tyrimas (jautrumas – 100 %), tačiau kai kurie klinikini rodikliai (atrofija distalinėse galūnių ir tetraparezė) pasižymi didesniu specifiškumu. Mažiausiai jautrus yra spontaninio aktyvumo nustatymas EMG tyrimo metu. Geriausiu diagnostiniu tikslumu pasižymi sumažėjusi šeivinio nervo motorinio atsako amplitudė. Jutiminis nervas, pasižymėjęs geriausiu diagnostiniu tikslumu - sumažėjusi alkūninio nervo atsako amplitudė.

Nagrinėjant KBNRP rizikos veiksnius, nustatėme, kad pacientų su KBNRP ir be KBNRP pasiskirstymas pagal lytį statistiškai reikšmingai nesiskyrė ($p = 0,837$), tačiau reikšmingai skyrėsi pagal vidutinį amžių – pacientai su KBNRP buvo vidutiniškai 10 metų vyresni (vidutinis amžius 56,50 m. ir 46,83 m. $p = 0,004$). Pacientai su KBNRP vidutiniškai 10 parų ilgiau gydyti ITS ($p = 0,001$) bei jiems vidutiniškai 9 paromis ilgiau taikyta DPV (401,73 val. lyginant su 190,53 val.; $p = 0,006$) lyginant su pacientais be KBNRP. Šių pacientų būklė pagal APACHE II, SAPS 3 ir SOFA skales pirmąją gydymo ITS parą buvo statistiškai reikšmingai sunkesnė (atitinkamai 1,5, 5 bei 8 balais), tačiau išvykimo iš ITS dienos SOFA skalės balai statistiškai reikšmingai nesiskyrė. Nustatėme,

kad KBNRP rizikos veiksniai yra vyresnis amžius, ilgesnė gydymo ITS trukmė bei blogesnė būklė vertinant pagal APACHE II skalę.

Iš 96 asmenų, kurių duomenys įtraukti į analizę, mirė 10 (10,4 %). 3 asmenys mirė ligoninėje po iškėlimo iš ITS (3,1 %) – visiems šiems pacientams buvo nustatytas KBNRP. Likę 7 asmenys mirė per 6 mėnesius po iškėlimo iš ITS – 4 pacientai su KBNRP bei 3 pacientai be KBNRP. Statistiškai reikšmingo skirtumo pagal mirštamumą tarp pacientų su KBNRP ir be KBNRP grupių nenustatyta – 7 (14,0 %) ir 3 (6,5 %), p = 0,23.

Pakartotinai išsitirti iš 50 pacientų su KBNRP atvyko 25 (50,0 %). Iš 46 pacientų be KBNRP į pakartotinį tyrimą atvyko 12 (26,1 %). per pakartotinį tyrimą 16 (43,2 %) pacientų nustatyta polineuropatija. 21 (56,8 %) ši patologija nenustatyta. Iš 25 asmenų, kuriems per pirmąjį tyrimą nustatytas KBNRP, 16 (64,0 %) per pakartotinį tyrimą išliko KBNRP požymių, 9 pacientai (36,0 %) pasveiko. Nei vienam pacientui nenustatyta naujos, po išvykimo iš ITS atsiradusios polineuropatijos. Visiems pacientams pakartotinio, taip pat kaip ir pirmojo tyrimo metu, nustatyta aksoninio tipo polineuropatija. Miopatija pakartotinio tyrimo metu nenustatyta nei vienam pacientui.

Iš 16 tiriamųjų, kuriems per pakartotinį tyrimą nustatyta polineuropatija, 14 pacientų (87,5 %) aptiktas jutiminių ir motorinių nervų skaidulų pažeidimas, 1 (6,25 %) pacientui nustatyta motorinė polineuropatija. Jutiminė polineuropatija taip pat diagnozuota 1 pacientui (6,25 %). Visiems pacientams pažeidimas pasireiškė kojose, 8 (50,0 %) kartu ir rankose.

Įvertinę klinikinio neurologinio ištyrimo rezultatus nustatėme, kad vidutiniškai per 8 mėnesius išvykus iš ITS, pacientams, kuriems buvo nustatytas KBNRP, statistiškai reikšmingai pagerėja raumenų jėga, tačiau jutimų sutrikimai, sausgyslių refleksai bei raumenų atrofija statistiškai reikšmingai nepakinta. Įvertinę neurofiziologinio tyrimo rezultatus, nustatėme, kad išvykus iš ITS statistiškai reikšmingai pagerėja vidurinio, alkūnino ir šeivinio nervų SRVP amplitudės. Pacientai, kuriems pakartotinio tyrimo metu nustatėme KBNRP, buvo vidutiniškai devyneriais metais vyresni (vidutinis amžius 60,44 ir 51,71, p = 0,037) ir jų būklė gydymo ITS metu buvo sunkesnė vertinant pagal APACHE II skalę (atitinkamai 23,56 ir 16,14, p = 0,006).

Išvados

1. Kritinių būklių neuroraumeninis pažeidimas yra dažna ilgo gydymo intensyviosios terapijos skyriuje komplikacija.
2. Kritinių būklių neuroraumeninis pažeidimas pasireiškia jutimų sutrikimais, sausgyslių refleksų pokyčiais, motorikos sutrikimais bei elektrofiziologiniai pokyčiais, būdingais aksoninei polineuropatijai ir miopatijai.
3. Rizikos veiksniai, susiję su kritinių būklių neuroraumeninio pažeidimo pasireiškimu po ilgo gydymo intensyviosios terapijos skyriuje, yra vyresnis amžius, ilgesnė gydymo intensyviosios terapijos skyriuje trukmė bei sunkesnė būklė.
4. Praėjus pusei metų po išvykimo iš intensyviosios terapijos skyriaus pasveiksta trečdalis pacientų.
5. Nepalankios kritinių būklių neuroraumeninio pažeidimo išeitys gali būti siejamos su vyresniu amžiumi ir sunkesne būkle hospitalizuojant į intensyviosios terapijos skyrių

Praktiniai pasiūlymai

1. Kadangi vis daugiau pacientų išgyvena kritines ligas, svarbu, kad intensyviosios terapijos gydytojai, šeimos gydytojai, neurologai, reabilitologai, taip pat slaugytojos ir kineziterapeutai žinotų apie kritinių būklių neuroraumeninį pažeidimą, jo priežastis ir klinikinius požymius.
2. Vyresniems, sunkesnės būklės ir ilgiau ITS skyriuje gydytiems pacientams tikslinga atidžiai vertinti periferinių nervų ir raumenų pažeidimo požymius, ir juos nustačius, nukreipti neurologo konsultacijai.
3. Išvykstant iš intensyviosios terapijos skyriaus rekomenduojame įvertinti raumenų atrofiją distalinėse galūnių dalyse bei Achilo refleksus abipus. Nustačius šiuos požymius, tikslinga neurologo konsultacija siekiant įvertinti pažeidimo lokalizaciją, atmesti kitas neuroraumeninio pažeidimo priežastis bei esant galimybei atlikti elektroneuromiografijos tyrimą.
4. Atliekant elektroneurografiją tikslinga vertinti šeivinio nervo atsaką. Nustačius šio nervo suminio raumens veikimo potencialo amplitudę, mažesnę nei 2,27 mV, tikslingas išsamesnis ištyrimas dėl polineuropatijos.
5. Tikslinga informuoti pacientą, kad pasireiškus kritinių būklių neuroraumeninio pažeidimo požymių, sveikimas gali užtrukti ilgiau nei 6 mėn. Sveikimas priklauso nuo būklės sunkumo gydant ITS bei paciento amžiaus.

6. Rekomenduojame nukreipti visus pacientus, kurie buvo ilgai gydyti ITS, neurologo konsultacijai praėjus 6 mėnesiams po išvykimo iš ligoninės siekiant įvertinti polineuropatijos simptomus ir požymius, esant reikalui atlikti detalius neurofiziologinius tyrimus, patvirtinančius diagnozę