MEDICINA SPECIALISTICA RIABILITATIVA DELLE CURE CORRELATE

Zaira Symeonidou[1,4], Kassiani Theodoraki[2], Athanasios Chalkias[3], Erifili Argyra[2], Roberto Casale[4]

Critical Illness Polyneuropathy (CIP): a multicenter study on functional outcome

[1] Department of Physical Medicine and Rehabilitation, General Hospital of Attica "KAT", 14561 Athens, Greece

[2] Department of Anesthesiology, Pain Relief and Palliative Care, Aretaieion University Hospital, University of Athens, 11528 Athens, Greece

[3] National and Kapodistrian University of Athens, Medical School, MSc "Cardiopulmonary Resuscitation", Athens, Greece

[4] Department of High Technology Rehabilitation & Pain Rehabilitation Unit, Habilita Care and Research Hospitals, Zingonia di Ciserano (BG), Italy

ABSTRACT. Objective. *To describe the functional recovery of consecutive inpatients with Critical Illness Polyneuropathy (CIP) at the time-point of the discharge from rehabilitation units according to Barthel Index scores. To examine whether age, gender, pre-ICU admission diagnosis, tracheostomy performance, heterotopic ossification development and duration of neuro-rehabilitation treatment are among the prognostic factors that can predict the functional outcome in studied patients.*
Design. *A retrospective observational clinical study from January 2010 to December 2014. Three rehabilitation units in Greece.*
Results. *Sixteen subjects (57.1%) had >60 BI discharge scores, showing a prospect in gaining further independence. Females presented a tendency for better functional outcome vs males (73.8 ± 12.6 vs 58.6 ± 23.4, p=0.082). Respiratory, septic and neurologic patients demonstrated better rates of functional improvement after the rehabilitation process vs cardiac patients (p<0.001, p=0.009 and p=0.019, respectively vs p=0,072). Heterotopic ossification development proved to be an adverse independent prognostic factor of functional outcome (47.8 ± 25.7 vs 68.8 ± 17.7, p=0.023).*
Conclusions. *A proportion of included patients experienced severe disability with poor prospect of further functional development and return to work at the discharge from the rehabilitation units. According to the present study, which is the first that focuses only on CIP and its outcome, specific prognostic factors can be defined. Our results can be used as pilot data for larger studies, so that firmer conclusions can be drawn.*

Key words: Critical illness, Critical illness polyneuropathy, CIP functional outcome, CIP outcome prognostic factors, CIP return to work.

Introduction

Critical Illness Polyneuropathy (CIP) is a major neurological complication among patients with extended stay in Intensive Care Units (ICU). It is characterized as one of the primary causes of ICU-Acquired Weakness and has been strongly associated with prolonged duration of mechanical ventilation and difficulty in weaning from the ventilator. Occurring exclusively in critical care patients, CIP has an impact on delayed discharge from the ICU, whereas post-ICU survivors present serious motor deficits with functional impairment and a defective quality of life.

The entity of Critical Illness Polyneuropathy was first described by Bolton et al. in 1984, in his attempt to explain the noticeable weakness in patients admitted in ICU suffering from sepsis or multi organ failure (1). Since then CIP is described as a motor and sensory polyneuropathy with a primary axonal degeneration of motor and sensory fibers in electrophysiological tests (1-4). Clinically, CIP appears as pronounced limb muscle weakness, with preserved facial musculature contractions sparing and involvement of phrenic nerve (1, 3-7). Reduction or absence of deep tendon reflexes and loss of peripheral sensation usually accompany the syndrome (4, 6, 7).

Several risk factors have been identified for CIP, with sepsis, systemic inflammatory response syndrome (SIRS) and multiple organ failure (MOF) being the most common among them (4, 7-11). However, the exact incidence of CIP is difficult to be measured due to the extensive variability among studied population and the different diagnostic criteria used (8, 9, 12, 13). Available data indicate the existence of CIP at a higher level of 50% in patients with sepsis, MOF and prolonged ICU stay (14). A systematic review of 24 studies in 2007 concluded that the median prevalence of neuromuscular dysfunction in adults suffering from sepsis, MOF or prolonged ICU stay was 46% (95% CI, 43-49%), 7.8% of which had CIP (8, 9, 12).

While prediction of the long-term functional outcome of the dysfunction seems to be a main interest in the literature (8, 10, 12, 13, 15-20), other studies focus on disability conditions that intervene with subjects' productivity and ability to work (21, 22). Taking into consideration that CIP is directly linked to severe disability that hinders the physical ability for employment, in this obser-

vational retrospective study we describe the functional recovery of consecutive inpatients with CIP at the time-point of discharge from rehabilitation units. Moreover, we sought to identify any prognostic factors that can possibly predict the functional outcome of CIP in studied patients. Specifically, we examined the impact of age, gender, underlying disease that led to ICU admission, tracheostomy performance, heterotopic ossification development and duration of neuro-rehabilitation stay on the functional outcome according to the discharge Barthel score.

Methods

Inclusion/Exclusion criteria

In this retrospective study, we analyzed the medical records of all consecutive patients with CIP, who were admitted to one rehabilitation unit of General Hospital of Attica "KAT" and two rehabilitation units of National Rehabilitation Centre, from January 2010 to December 2014. Among a total of 2.238 inpatients that were admitted to the three rehabilitation units during these years, we registered the patients with the diagnosis of CIP, out of which 28 were found eligible for our study.

The inclusion criteria of our research were based on the specific diagnostic criteria for CIP according to the Cochrane Collaboration database: 1) critical illness as a result of multi-organ dysfunction or failure, 2) limb weakness or difficulty in weaning from the ventilator (after exclusion of non-neuromuscular causes), 3) electrophysiological evidence of axonal motor and sensory polyneuropathy, 4) absence of a decremental response on repetitive nerve stimulation (12). Selection of subjects at a working age was defined as an additional inclusion criterion in our study.

The exclusion criteria we settled, aiming to avoid confounders of functional and neuromuscular performance of CIP, were: preexisting neurological deficits (peripheral polyneuropathy or myopathy, Guillain-Barre syndrome, myasthenia Gravis, peripheral nerve lesions due to malposition), cerebral or spinal cord injury or stroke, diseases at high risk of developing neuromuscular dysfunction (hepatic or renal insufficiency, alcohol and drug abuse, HIV infection, diabetes mellitus, vitamin deficiency) and cancer.

Study design

For the needs of our study, variables obtained from medical records of the three Rehabilitation Units included age, gender, diagnoses of ICU admission, duration of ICU treatment, history of tracheostomy performance, heterotopic ossification development, duration of in-hospital rehabilitation program and functional ability at baseline and discharge respectively. Ethical requirements of our study comprised of no namely use of patients' personal information. The study was approved by the common Ethical Research Committee for the three Rehabilitation Units (General Hospital of Attica 'K.A.T.' - license number: 988 & 1424).

History / Physical examination / Functional evaluation

Physical examination appeared common in the three rehabilitation units and comprised of muscle assessment,

deep tendon reflexes, sensory examination and range of joint motion evaluation. Physical examination of muscle strength was based on the Medical Research Council (MRC) scale, with evaluation of arm abductors, elbow flexors and wrist extensors for the upper limb and hip flexors, knee extensors and foot dorsal flexors for the lower limb (7, 18, 23-25). Sensory examination assessed touch, pain, temperature and vibration. In case of limited range of motion in a joint, full imaging scan for heterotopic ossification detection was prepared (26, 27).

Functional ability was evaluated according to the Barthel Index (BI) scale, which quantified dependence in activities of daily living (ADL) (28). Feeding, bathing, grooming, dressing, bowel and bladder care, toilet use, transfers, ambulation and stairs climbing were scored from 0 (total dependence) to 10 or 15 (total independence) (Total range 0-100).

Diagnosis / Electrophysiological testing

According to clinics' archives, all patients underwent electrophysiological evaluation which included motor and sensory nerve conduction studies (NCS) and needle electromyography (EMG) upon admittance to the rehabilitation units. NCS assessed eight motor nerves with the orthodromic method (median, ulnar, common peroneal and tibial nerves, bilaterally) and six sensory nerves with the antidromic method (median, ulnar and common peroneal nerves, bilaterally). Repetitive nerve stimulation was performed from the median nerve and EMG was performed from the deltoid and tibialis anterior muscles for all included patients.

The diagnosis of CIP was based on the decreased compound muscle action potential (CMAP) amplitudes in at least two nerves of different limps, severe depression or absence of sensory nerve action potential (SNAP) amplitudes (in the absence of tissue edema) in NCS, constant response on repetitive nerve stimulation and normal or large motor unit potentials (MUPs) with a reduced recruitment pattern in EMG. As all included patients were able to cooperate during the examination, the differential diagnosis with critical illness myopathy (CIM) was established on the basis of normal SNAPs in NCS and small polyphasic MUPs with early recruitment pattern in EMG (7, 9, 14, 17-19, 29, 30).

Rehabilitation program

Patients of all three units followed an individualized interdisciplinary program based on common principles of rehabilitation of 2 hours' duration per day, 5 days per week. Progressive mobilization in order to achieve a sitting and standing position, range of motion improvement, joint mobilization, strength and balance exercises and gait re-education were applied to each patient, adjusted to their own status. Included subjects also followed a tailored occupational therapy program oriented in regaining gradually independence in activities of daily living, with the aim of self-care improvement. Additionally, clinical psychologists supported patients at least once a week during the rehabilitation procedure, in order to keep a stable psychological status.

Statistical analysis

Parameters were checked for normality of distributions with the Kolmogorov-Smirnov test. Descriptive statistics (frequency distributions) were used to summarize the data. Results are expressed as mean ± SD for numerical data and number (percentages) for categorical data. The parameters age, gender, underlying disease that led to ICU admission, tracheostomy performance, heterotopic ossification development and duration of neuro-rehabilitation stay were used as independent variables in search of any correlation with the functional outcome after in-hospital neuro-rehabilitation treatment (discharge Barthel score). Comparisons of baseline and discharge Barthel scores between groups were performed with the unpaired t-test and one way analysis of variance (ANOVA) while comparisons of baseline and discharge Barthel scores within the same group were performed with the paired t-test. The Pearson product moment correlation coefficient test was used to test the correlation of age and duration of rehabilitation treatment with the discharge Barthel score (outcome variable). Stepwise multiple linear regression analysis was performed in order to adjust for the effect of confounding and to investigate the independent predictive value of variables. A value of $p < 0.05$ was considered as statistically significant. Statistical analysis was performed by the use of SPSS for Windows v.17.0 statistical software (Statistical Package for the Social Sciences, SPSS Inc., Chicago, Ill., USA).

Results

Upon admittance in the Rehabilitation Units none of the included patients had signs of mental status impairment, all were fully oriented in time, place, space and had neither cranial nerve nor autonomic involvement. They presented flaccid weakness of four extremities, with minimal movement or total paralysis and admission MRC sum scores ≤36. Mild hypoesthesia of trunk and limbs was observed. Deep tendon reflexes of upper and lower limbs appeared absent or diminished in all patients. Additionally, all had records of diagnostic laboratory tests (blood cell count, coagulation parameters, glucose, urea, creatinine levels, liver enzymes, Na, K, ferrum, ferritin, B12 and folic acid levels) within the normal limits or with mild and reversible deviations.

From a total of 2.238 patients, 44 (0.02%) were initially selected. Of these, 16 (36%) subjects were excluded because they did not meet the inclusion/exclusion criteria (Figure 1) and finally 28 patients were found completely databased and eligible for our study. Demographic and clinical characteristics are demonstrated in Tables I and II.

Functional ability at admission and discharge from the rehabilitation units was assessed according to the Barthel Index (BI) scale. Admission Barthel scores <40 quantified severe dependency for all patients of this study. A definite improvement due to rehabilitation care was obvious, with mean Barthel scores at admission and discharge differing significantly (15.3 ± 9.1 vs 63.6 ± 21.6, $p < 0.05$) (Table II). Specifically at discharge, three subjects (10.7%) had a high Barthel score (>85), thirteen subjects (46.4%) and seven subjects (25.0%) had medium Barthel scores (60-85 and 40-60 respectively) and five subjects (17.9%) had a low Barthel score (<40) (Figure 2).

Impact of each variable was investigated according to the discharge Barthel scores separately. While two genders did not differ at admission Barthel scores (p=0.242), females presented a trend for better discharge outcomes as compared to males (73.8 ± 12.6 vs 58.6 ± 23.4, p=0.082), which however did not reach statistical significance (Table III).
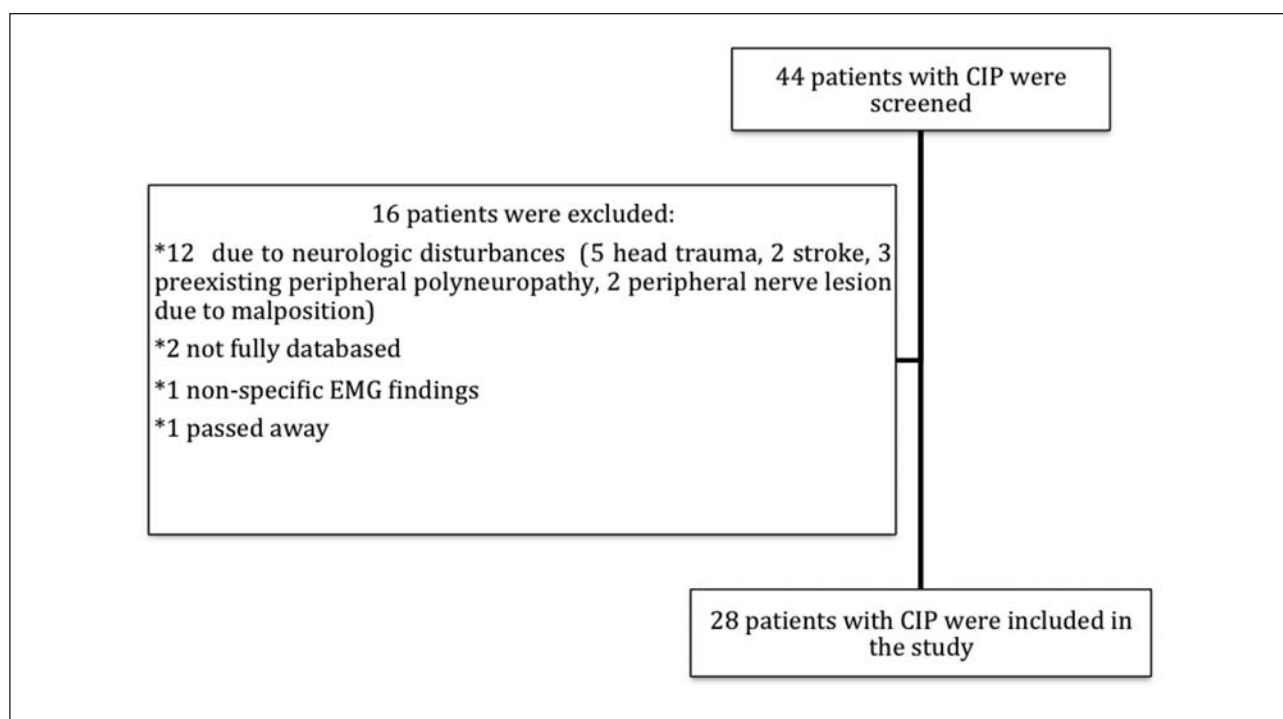

Figure 1. *Patient selection*

**Table I.** *Demographic data and clinical characteristics*

Gender	Male	19 (67.9)
	Female	9 (32.1)
Cause of ICU admission	**Respiratory:**	16 (57.1)
	ARDS	5 (17.9)
	Pneumonia	6 (21.4)
	Exacerbation of COPD	2 (7.1)
	Drowning	1 (3.6)
	Primary pneumothorax	2 (7.1)
	Sepsis: Septic shock	5 (17.9)
	Cardiac:	4 (14.3)
	C.A. due to peri-M.I. arrhythmias	2 (7.15)
	C.A. due to A.F.	2 (7.15)
	Neurologic: Refractory Status Epilepticus	3 (10.7)
Tracheostomy	No	13 (46.4)
	Yes	15 (53.6)
Heterotopic ossification	No	21 (75.0)
	Yes	7 (25.0)

ARDS: Acute Respiratory Distress Syndrome, COPD: Chronic Obstructive Pulmonary Disease, C.A.: Cardiac Arrest, M.I.: Myocardial Infarction, A.F.: Atrial Fibrillation, ICU: Intensive Care Unit

Table II. *Demographic data and clinical characteristics*

	Mean±SD (min-max)
Age	53.6±14.5 (21-79)
ICU length of stay (d)	48.1±29.2 (8-135)
Rehabilitation Unit length of stay (d)	109.4±70.7 (6-282)
Baseline Barthel score	15.3±9.1 (0-35)
Discharge Barthel score	63.6±21.6 (15-95)

ICU: Intensive Care Unit, SD: Standard Deviation, (d): days
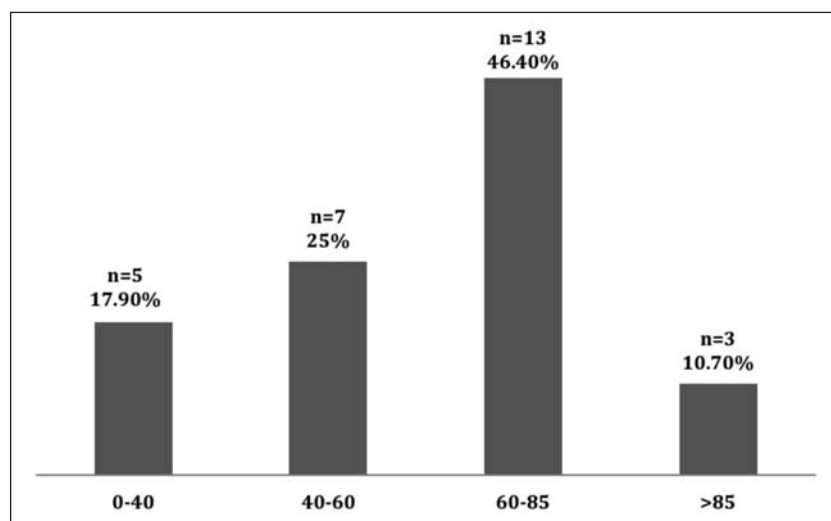
Figure 2. *Discharge Barthel Scores*

Patients presented no significant difference neither at admission (p=0.179) nor at discharge (p=0.186) Barthel scores among four subcategories (respiratory, septic, cardiac and neurologic) of ICU admission aetiologies (Table III). In details, rehabilitation care resulted in a definite functional improvement for patients admitted to the ICU due to respiratory, sepsis and neurologic pathology, according to the comparison of admission to discharge Barthel scores (p<0.001, p=0.009 and p=0.019, respectively). However, in patients with in-hospital cardiac arrest, less functional improvement was noticed, as in this group discharge Barthel scores were not significantly different from admission Barthel scores (p=0.072) (Table IV).

Performance or not of a tracheostomy did not prove to affect the final functional outcome, as patients began from a similar baseline (p=0.829) and presented no significant difference in discharge Barthel scores (p=0.404) (Table III).

Patients who developed heterotopic ossification and those who did not, also began from a similar functional level at admission (p=0.290). However, occurrence of the complication resulted in significantly lower discharge Barthel scores for the afflicted patients (47.8 ± 25.7 vs 68.8 ± 17.7, p=0.023) (Table III).

Regarding the quantitative variables age and duration of rehabilitation treatment, no significant correlation with the final outcome (discharge Barthel score) was demonstrated (r=-0,26, p=0.18 and r=-0,26, p=0.176, respectively).

Finally, only heterotopic ossification was associated as an independent predictor of functional outcome (p=0.023) according to the multiple linear regression analysis, out of abovementioned variables.

Discussion

Although studies have shown that early passive mobilization of CIP patients has a significant benefit on muscle strength and functional regaining (31-33), research so far has reported that severe disability persists in 28.1% of CIP patients, with loss of ability to breathe spontaneously or walk independently. However, extended variability that occurs in the inclusion/exclusion criteria, patient heterogeneity, timing of the examination, follow-up periods and definition of the term recovery, impede the exact definition of long-term outcome after CIP (34,35). In our study, five patients (17.9%) presented Barthel scores <40 and experienced severe neuromuscular disability and total dependency at discharge. Barthel scores 40-60 were noticed in seven patients (25.0%), indicating a predictable progression in further functional development (36); however for both groups there would be no potential return to an employment status. Sixteen patients (57.1%) were above the pivotal Barthel score

Table III. *Barthel Scores among groups at admission and discharge*

		Admission Barthel score (Mean±SD)	p-value at admission	Discharge Barthel score (Mean±SD)	p-value at discharge
Gender	Male	13.9±7.9	0.242	58.6 ±23.4	0.082
	Female	18.3±11.1		73.8±12.6	
Cause of ICU treatment	Respiratory	17.5±9.4	0.179	68.7±18.3	0.186
	Sepsis	16.0±6.5		62.0±16.4	
	Cardiac	6.2±7.5		42.5±33.3	
	Neurologic	15.0±8.6		66.6±20.8	
Tracheostomy	No	15.7±9.3	0.829	67.3±21.4	0.404
	Yes	15.0±9.2		60.3±21.9	
Heterotopic ossification	No	16.4±9.6	0.290	68.8±17.7	0.023
	Yes	12.1±6.9		47.8±25.7	

ICU: Intensive Care Unit, SD: Standard Deviation

Table IV. *Impact of in-hospital neuro-rehabilitation treatment among different ICU diagnoses*

	Baseline Barthel score (Mean±SD)	Discharge Barthel score (Mean±SD)	p-value
Respiratory	17.5±9.4	68.7±18.3	<0.001
Sepsis	16.0±6.5	62.0±16.4	0.009
Cardiac	6.2±7.5	42.5±33,2	0.072
Neurologic	15.0±8.6	66.6±20.8	0.019

ICU: Intensive Care Unit, SD: Standard Deviation

60, showing a prospect in gaining gradually assisted independence and uncertain possibilities for a tailored working position in the future (36). Only three patients (10.7%) showed full recovery, achieving complete functional ability at discharge and stronger likelihood to work again.

It is difficult to evaluate whether our findings conform to other published studies due to variation of inclusion/exclusion criteria and recovery assessment. Guarneri et al. (16) and Koch et al. (18) assessed the recovery of CIP based on muscle strength and global muscle performance. The first study included four CIP patients, one of whom showed complete clinical recovery within a year after ICU discharge (16). The second study reported that 45-75% of subjects with a combination of critical illness polyneuropathy and myopathy had persistent muscle weakness, according to MRC score, one year after ICU discharge (18). However, both studies were held in ICUs, included head trauma, cerebral hemorrhage and cancer, while the authors did not define whether subjects followed any kind of rehabilitation treatment after hospital discharge. Semmler et al. studied 51 survivors of ICU-acquired weakness, 21 out of whom were subjects with CIP that followed an early rehabilitation program (19). They mentioned a favorable prognosis without severe long-term neuromuscular consequences; however, they did not report specific recovery parameters.

Recently, Intiso et al. published a prospective study in a neuro-rehabilitation center that assessed functionality based on Barthel Index (BI) scale (17). Among 42 enrolled patients, 30 suffered from CIP and showed a good recovery, as 11 of them presented 91.3 ± 5.9 Barthel scores at discharge. In our study, 3 out of 28 selected CIP patients had >85 Barthel scores. This discrepancy can be explained by several factors, including heterogeneity and severity of underlying disease, possible concomitant diseases, as well as the clinical performance of CIP, which can range from mild disabilities to tetraparesis or tetraplegia (34, 35).

As diagnosis of CIP is directly linked to extended duration of in-hospital treatment, extreme disability and poor quality of life with significant socioeconomic consequences, we assumed that a possible definition of any prognostic factors of its outcome might be beneficial for the further management of the dysfunction. Although Semmler et al. (19) have reported that age, gender and the diagnosis of sepsis do not affect the long-term neuromuscular outcome of ICU survivors after CIP, we noticed a tendency of female gender for better functional outcome. As ICU-acquired weakness has been reported to develop more likely in women (7, 10, 24), research to a greater extent on the potential better functional outcome of female gender after CIP, may contribute in identification of a specific prognostic factor of the dysfunction. We also noticed that despite all patients showed functional improvement after the rehabilitation treatment, CIP-patients who were admitted in ICUs because of in-hospital cardiac arrest presented poorer progress compared to the other groups. A

possible aggravating cause could be the overall organic disturbances in the terms of postresuscitation syndrome following cardiac arrest (37). However, the small sample size in our study impedes the extraction of robust evidence. Further research oriented towards functional recovery of cardiac patients after CIP as an independent sub-population, is required so that firmer conclusions can be drawn.

Additionally, a significant finding of this study concerned the impact of heterotopic ossification development on CIP functional outcome. Heterotopic ossification is the deposition of para-articular ectopic bone and is associated with polytrauma, burns, pancreatitis and ARDS. According to the literature, this complication during critical illness has been described in several cases (15, 38-40). We found that this parameter was an independent factor with an adverse effect on functional outcome. This awaited impact can be obviously explained by the painful restriction of range of motion, which impedes motor activity and functional progress. Early identification of heterotopic ossification could definitely be beneficial to a better prognosis.

Except for functional recovery, patients' ability to return to work is the following issue after CIP is diagnosed. According to our results, only three patients (10,7%) achieved the functional status that could provide a strong potential for return to work. However this parameter does not seem to be the unique condition. Return to work after long-term leave due to health related problems is a more complex procedure, which encompasses different dimensions of physical, cognitive and psychological reconditioning (41, 42). Protocols that assess readiness to return to work include tailored occupational preparation, as well as constant support until they reach a satisfactory level of ability to maintain the job (43). CIP patients are undoubtedly expedient candidates for occupational rehabilitation, being favored to a high degree.

Finally, it is worth mentioning that in the present study neither the tracheostomy performance - used as a measure of difficulty in weaning from the ventilator - nor the duration of in-hospital rehabilitation treatment, proved to affect the functional outcome of CIP survivors at discharge. Since, to the best of our knowledge, this is the first approach to define specific prognostic parameters of CIP outcome, further investigation on this field may prove useful.

Our study has several limitations. Firstly, our sample was small. This was due to the application of strict inclusion/exclusion criteria, aiming to obtain a coherent and representative patient sample. Nonetheless, several similar studies in literature have included a comparable patient sample size. A possible explanation for this might be the nature of the dysfunction, which impedes gaining access to large, homogeneous groups of patients. Secondly, follow-up period was brief and coincided with the time-point of discharge from the Rehabilitation Units. Due to the study design, we were unable to reach patients after discharge because of incomplete contact information. However, despite the aforementioned limitations, our study is the first study that focuses only on CIP according to specific criteria, aiming not only to evaluate the functional outcome, but also to investigate possible specific prognostic factors.

Conclusion

Although the majority of patients with CIP presented impaired functional status at the time-point of rehabilitation unit discharge, only a proportion of them experienced total dependency with a poor prospect of further development. According to the present study specific prognostic factors of CIP functional outcome can be defined. However, further research in this field is required and the present study could be used as pilot data for larger studies and future investigation.

Conflicts of interest

The authors declare the absence of any conflicts of interests.

Ethical standards

The authors declare that the present study has been approved of the common Ethical Research Committee for the three Rehabilitation Units (General Hospital of Attica 'K.A.T.' - license number: 988 & 1424). Our research complied with the ethical standards of Declaration of Helsinki in 1964.

References

1) Bolton CF, Gilbert JJ, Hahn AF, Sibbald WJ. Polyneuropathy in critically ill patients. Journal of neurology, neurosurgery, and psychiatry 1984 Nov; 47(11): 1223-31.
2) Bolton CF, Laverty DA, Brown JD, Witt NJ, Hahn AF, Sibbald WJ. Critically ill polyneuropathy: electrophysiological studies and differentiation from Guillain-Barre syndrome. Journal of neurology, neurosurgery, and psychiatry 1986; 49(5): 563-73.
3) Witt NJ, Zochodne DW, Bolton CF, Grand'Maison F, Wells G, Young GB, et al. Peripheral nerve function in sepsis and multiple organ failure. Chest 1991; 99(1): 176-84.
4) van Mook WN, Hulsewe-Evers RP. Critical illness polyneuropathy. Current opinion in critical care 2002; 8(4): 302-10.
5) Jubran A. Critical illness and mechanical ventilation: effects on the diaphragm. Respiratory care 2006; 51(9): 1054-64.
6) Berek K, Margreiter J, Willeit J. Polyneuropathy in the critically ill patient—critical illness polyneuropathy. [Die Polyneuropathie des kritisch kranken Patienten—critical illness polyneuropathy]. Wiener klinische Wochenschrift 1998; 110(7): 243-52.
7) Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G. Clinical review: Critical illness polyneuropathy and myopathy. Critical care 2008; 12(6): 238.

8) Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. Intensive care medicine 2007; 33(11): 1876-91.

9) Khan J, Harrison TB, Rich MM. Mechanisms of neuromuscular dysfunction in critical illness. Critical care clinics 2008; 24(1): 165-77.

10) Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. The New England journal of medicine 2014; 370(17): 1626-35.

11) Ydemann M, Eddelien HS, Lauritsen AO. Treatment of critical illness polyneuropathy and/or myopathy - a systematic review. Danish medical journal 2012; 59(10): A4511.

12) Mehrholz J, Pohl M, Kugler J, Burridge J, Muckel S, Elsner B. Physical rehabilitation for critical illness myopathy and neuropathy. An abridged version of Cochrane Systematic Review. European journal of physical and rehabilitation medicine 2015; 51(5): 655-61.

13) Herridge MS. Long-term outcomes after critical illness: past, present, future. Current opinion in critical care 2007 Oct; 13(5): 473-5.

14) Pati S, Goodfellow JA, Iyadurai S, Hilton-Jones D. Approach to critical illness polyneuropathy and myopathy. Postgraduate medical journal 2008; 84(993): 354-60.

15) Herridge MS. Long-term outcomes after critical illness. Current opinion in critical care 2002 Aug; 8(4): 331-6.

16) Guarneri B, Bertolini G, Latronico N. Long-term outcome in patients with critical illness myopathy or neuropathy: the Italian multicentre CRIMYNE study. Journal of neurology, neurosurgery, and psychiatry 2008; 79(7): 838-41.

17) Intiso D, Amoruso L, Zarrelli M, Pazienza L, Basciani M, Grimaldi G, et al. Long-term functional outcome and health status of patients with critical illness polyneuromyopathy. Acta neurologica Scandinavica 2011; 123(3): 211-9.

18) Koch S, Wollersheim T, Bierbrauer J, Haas K, Morgeli R, Deja M, et al. Long-term recovery In critical illness myopathy is complete, contrary to polyneuropathy. Muscle & nerve 2014; 50(3): 431-6.

19) Semmler A, Okulla T, Kaiser M, Seifert B, Heneka MT. Long-term neuromuscular sequelae of critical illness. Journal of neurology 2013; 260(1): 151-7.

20) van der Schaaf M, Beelen A, de Vos R. Functional outcome in patients with critical illness polyneuropathy. Disability and rehabilitation 2004 Oct 21; 26(20): 1189-97.

21) Oddone E, Imbriani M. [Are we underestimating occupational risks for neurodegenerative diseases?]. G Ital Med Lav Ergon 2015; 37(1): 5-7.

22) Fundarò C, Casale R. Rehabilitation and dementia in the era of elderly workers. G Ital Med Lav Ergon 2012; 34(2): 197-201.

23) Compston A. Aids to the investigation of peripheral nerve injuries. Medical Research Council: Nerve Injuries Research Committee. His Majesty's Stationery Office: 1942; pp. 48 (iii) and 74 figures and 7 diagrams; with aids to the examination of the peripheral nervous system. By Michael O'Brien for the Guarantors of Brain. Saunders Elsevier: 2010; pp. [8] 64 and 94 Figures. Brain: a journal of neurology 2010 Oct; 133(10): 2838-44.

24) De Jonghe B, Sharshar T, Lefaucheur JP, Authier FJ, Durand-Zaleski I, Boussarsar M, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. Jama 2002; 288(22): 2859-67.

25) Hough CL, Lieu BK, Caldwell ES. Manual muscle strength testing of critically ill patients: feasibility and interobserver agreement. Critical care 2011; 15(1): R43.

26) Tian-Shin Y, Chueh-Hung W, Wen-Shian C, Tyng-Guey W. Serial ultrasonography for early detection and follow-up of heterotopic ossification in stroke. Journal of Medical Ultrasound 2012; 20: 119-24.

27. Mavrogenis AF, Soucacos PN, Papagelopoulos PJ. Heterotopic ossification revisited. Orthopedics 2011; 34: 177.

28) Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. Maryland state medical journal 1965; 14: 61-5.

29) Z'Graggen WJ, Lin CS, Howard RS, Beale RJ, Bostock H. Nerve excitability changes in critical illness polyneuropathy. Brain: a journal of neurology 2006; 129(Pt 9): 2461-70.

30) Fan E. Critical illness neuromyopathy and the role of physical therapy and rehabilitation in critically ill patients. Respiratory care 2012; 57(6): 933-46.

31) Bailey P, Thomsen GE, Spuhler VJ, Blair R, Jewkes J, Bezdjian L, et al. Early activity is feasible and safe in respiratory failure patients. Crit Care Med 2007; 35(1): 139-45.

32) Burtin C, Clerckx B, Robbeets C, Ferdinande P, Langer D, Troosters T, et al. Early exercise in critically ill patients enhances short-term functional recovery. Crit Care Med 2009; 37(9): 2499-505.

33) Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Crit Care Med 2008; 36(8): 2238-43.

34) Latronico N, Guarneri B. Critical illness myopathy and neuropathy. Minerva anestesiologica 2008; 74(6): 319-23.

35) Latronico N, Shehu I, Seghelini E. Neuromuscular sequelae of critical illness. Current opinion in critical care 2005 Aug; 11(4): 381-90.

36) Granger CV, Dewis LS, Peters NC, Sherwood CC, Barrett JE. Stroke rehabilitation: analysis of repeated Barthel index measures. Archives of physical medicine and rehabilitation 1979; 60(1): 14-7.

37) El-Menyar AA. Pathophysiology and hemodynamic of postresuscitation syndrome. Saudi medical journal 2006; 27(4): 441-5.

38) Guo Y, Collaco CR, Bruera E. Heterotopic ossification in critical illness and cancer: a report of 2 cases. Archives of physical medicine and rehabilitation 2002; 83(6): 855-9.

39) Jacobs JW, De Sonnaville PB, Hulsmans HM, van Rinsum AC, Bijlsma JW. Polyarticular heterotopic ossification complicating critical illness. Rheumatology 1999; 38(11): 1145-9.

40) Clements NC, Jr., Camilli AE. Heterotopic ossification complicating critical illness. Chest 1993; 104(5): 1526-8.

41) Loisel P, Durand MJ, Berthelette D, Vezina N, Baril R, Gagnon D, et al. Disability prevention: new paradigm for the management of occupational back pain. Dis Manag Health Outcomes 2001; 9(7): 351-60.

42) Feuerstein M. A multidisciplinary approach to the prevention, evaluation, and management of work disability. J Occup Rehabil 1991; 1(1): 5-12.

43) Aasdahl L, Pape K, Jensen C, Vasseljen O, Braathen T, Johnsen R, Fimland MS. Associations Between the Readiness for Return to Work Scale and Return to Work: A Prospective Study. J Occup Rehabil. doi: 10.1007/s10926-017-9705-2.

Correspondence: *Zaira P. Symeonidou, Department of Physical Medicine and Rehabilitation, General Hospital of Attica "KAT", 14561 Athens, Greece, Mob. Numb. +306974313819, E-mail: z_sim@windowslive.com*