CASE REPORT

DOI: 10.5336/caserep.2020-76038

Critical Illness Polyneuropathy with Generalized Myoclonus

Aylin AYYILDIZ[a], Jülide ÖNCÜ[a], Roza DAĞDELEN[a], Figen YILMAZ[a], Banu KURAN[a]

[a]Department of Physical Medicine and Rehabilitation, Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, TURKEY

ABSTRACT Neuromuscular weakness is a common problem in intensive care units. In patients with muscle weakness and difficulty in separation from the ventilator, especially hospital mortality and chronic disability are increased. Critical illness myopathy (CIM), critical illness polyneuropathy (CIP) and critical illness polyneuromyopathy (CIPNM) are the most common causes of muscle weakness and difficulty in separation from the ventilator in intensive care units. In this article, we report a patient who developed CIP in only 10 days of intensive care unit stay and discuss his rehabilitation period in the follow up as a case report. A 52-year-old male patient stayed in intensive care unit (ICU) and mechanical ventilation for 10 days because of tracheal fistulisation. During ICU stay, he had myoclonus which is not common in CIP, muscle weakness of four extremities especially in proximal muscles and hypoesthesia. Clinical symptoms and electrodiagnostic studies were compatible with critical illness polyneuropathy (CIP). There is no specific treatment for CIP; just supportive treatment and rehabilitation. With rehabilitation programs, the patient was mobilized with a walker and bilateral ankle foot orthosis. During discharge, myoclonus decreased considerably. The initial and final functional independence measurement score and Barthel's daily life activities index of the patient were 47/126 and 0/100 versus 88/126 and 60/100. Rehabilitation has an important place in the early period and the diagnosis should be made as early as possible and the patient should be included in the rehabilitation program early. Accompanying CIP with myoclonus is not common; but for our patient's myoclonus is a cause of muscle weakness and cerebral hypoxia. In the presence of myoclonus, CIP diagnosis should not be ruled out. Medical treatment and rehabilitation decreased myoclonus as well. Early rehabilitation increases the functional capacity of the patient, decreases the duration of ventilator use, and the patient leaves the intensive care unit early.

Keywords: Critical illness; polyneuropathy; rehabilitation

Neuromuscular weakness is a common problem in intensive care units.[1] In patients with muscle weakness and difficulty in separation from the ventilator, especially hospital mortality and chronic disability are increased.[2] Critical illness myopathy (CIM), critical illness polyneuropathy (CIP) and critical illness polyneuromyopathy (CIPNM) are the most common causes of muscle weakness and difficulty in separation from the ventilator in intensive care units.[3] Neuromuscular muscle weakness can be seen as a result of neuromuscular diseases such as Guillain-Barré, myasthenia gravis or acquired as a result of multitrauma, serious infections and organ dysfunction.[1,4] Also neuromuscular weakness may be due to polyneuropathy, myopathy and neuromuscular blocks.[1]

The exact incidence of CIP and CIM is not known due to the width of patient population range, risk factors and diversity at the time of evaluation, and difficulties in assessing diagnostic criteria.[2] The incidence was 25-33% in clinical evaluation in patients who had mechanical ventilation for 4-7 days or who developed multiorgan failure; by electrophysiological evaluation the incidence is evidenced as 30-58%.[2,3,5,6] Incidence is 34-60% in patients with acute respiratory distress syndrome; 56-80% in patients with sepsis or systemic inflammatory response syndrome; and 100% in septic shock and severe sepsis. CIPNM, which can be seen in all age groups, is rarer in children.[1,7] Most patients are over 50 years of age.[1]

Diagnostic criteria of CIP are as follows: a critically ill patient (multiorgan dysfunction or insufficiency), weakness of the extremities and difficulty in weaning from the mechanical ventilatory with exclusion of cardiac and pulmonary causes, evidence of

Correspondence: Aylin AYYILDIZ
Department of Physical Medicine and Rehabilitation, Şişli Hamidiye Etfal Training and Research Hospital, İstanbul, TURKEY
E-mail: aylin.mrt93@gmail.com

Peer review under responsibility of Turkiye Klinikleri Journal of Case Reports.

Received: 04 May 2020 ***Received in revised form:*** 17 Jul 2020 ***Accepted:*** 25 Jul 2020 ***Available online:*** 26 Nov 2020

axonal motor and sensory polyneuropathy and the absence of decrimental response in recurrent nerve stimulation in electrophysiologic studies. In the diagnosis of CIM, the patient is not necessarily to be critically ill. Generally, patients who use neuromuscular blocking agents or corticosteroids are more likely to have predisposition. There is muscle weakness in CIM similar to CIP. In electrophysiologic evaluation, there is preserved sensory response, reduced motor response, normal repetitive nerve stimulation and short duration, low amplitude motor unit potential with early full or normal recruitment of motor unit action potentials, muscle inexcitability with direct muscle stimulation. In addition, myosin loss and myopathy findings are observed in muscle biopsy.[2,3,8,9]

There are many risk factors for CIPNM, CIP and CIM. Multiorgan failure, sepsis and severe inflamatory response syndrome (SIRS) have been shown to play a vital role in prospective and retrospective studies.[6,10] In addition, the severity of the disease, length of stay in the intensive care unit, the presence of hyperglycemia, support of vasopressor and catecholaminergic drugs, renal insufficiency and renal replacement therapy, female sex, parenteral nutrition, hyperosmolarity, low serum albumin level, neurologic failure are also risk factors for CIPNM, CIP and CIM.[2,10,11] Aminoglycoside antibiotics, neuromuscular blocking agents and steroids are contraversial risk factors.[1,11] Evaluating the patient's condition in the intensive care unit with an acute physiologic and chronic health assessment 3 score (APACHE-3) and sequential organ failure assessment score may also provide insight into the development of CIPNM.[12]

Clinical evaluation is important in the diagnosis of the disease, laboratory tests have no place in the diagnosis. In the clinical evaluation, especially proximal muscle weakness rather than distal muscle weakness, sensory deficits, limited muscle loss and generally reduced deep tendon reflexes are present. In CIM, proximal muscle weakness and atrophy are more frequent and sensory deficits are less common. CIPNM has proximal muscle weakness, distal sensory deficits and muscle atrophy as a combination of CIM and CIP. In all types, patients have normoactive reflexes in early stage of the disease which decrease progressively.[1,3,4] Cranial nerve involvement is rare and if there is cranial nerve involvement, another underlying neurological disease should be investigated.[1]

In this article, we report a patient who developed CIP in only 10 days of intensive care unit stay and discuss his rehabilitation period in the follow up. Informed consent was obtained from the patient during hospitalization.

CASE REPORT

A 52-year-old male patient without any known previous disease was admitted to the general surgery outpatient clinic of our hospital because of a swelling in his neck. He was diagnosed as multinodular goiter and he had thyroidectomy upon the diagnosis. The patient developed hematoma at the incision site postoperatively. He was admitted to the intensive care unit due to tracheal necrosis-related fistulation and deterioration in his general condition and vital signs. The patient was hospitalized in intensive care unit for 10 days and he was on mechanical ventilator for 10 days. He had hypoglycemic and hyperglycemic episodes and glycemic control was hardly achieved. During his hospitalization, he developed decubitus ulcers and loss of muscle strength and myoclonus. The patient was difficult to wean from the ventilator. Parenteral nutrition was applied. The patient's general condition and vitals improved and percutaneous endoscopic gastrostomy was removed from the patient who had oral feeding before transfer of the patient. The patient was transferred to our clinic from surgery department 5 months after the operation due to loss of muscle strength and myoclonus bilaterally in lower and upper extremities.

The patient was conscious, oriented and cooperative. He had a sitting balance and was semi-dependent for in-bed activities. The patient had a urinary catheter and percutaneous endoscopic gastrostomy. The patient had myoclonus in upper and lower extremities triggered by anxiety and exercise, and deep tendon reflexes were bilaterally normoactive. Anal and bulbocavernous reflexes were normoactive. The patient had hypoesthesia and hypoalgesia in L4-L5 and S1 dermatomes. He also had decubitus ulcers measuring 12x6 cm in the sacral region. In manuel

muscle testing, proximal muscle weakness was more prominent than distal muscle weakness. In muscle research council scale, his upper extremity proximal muscle group was 3/5 bilaterally, distal muscle group was 4/5 bilaterally. The patient had bilateral drop foot. Active and passive range of motion of both shoulders were limited (passive and active flexion is 90º, abduction is 100º) and painful.

No significant pathology was detected in the patient's brain magnetic resonance imaging (MRI) and computerized tomography (CT). The patient was evaluated with activated electroencephalography (EEG) and multiple spines spread over the entire hemisphere at intervals of 2 seconds in addition to the widespread artifact due to myoclonus, but not significant. In the electromyelographic (EMG) studies; motor response of bilateral peroneal nerve could not be obtained in m. extensor digitorum brevis and m. tibialis anterior and also sensory response could not be obtained. Conduction measurements of other motor and sensory nerve responses were found to be natural. The needle EMG showed mild fibrillation and positive spike discharges in the bilateral tibialis anterior muscle. These findings were correlated with total axonal damage affecting the motor and sensory fibers distal to the level where bilateral peroneal nerve innervated short head of m. biceps femoris. Along with detailed clinical examination and electrophysiological studies, the symptoms were found to be compatible with critical illness polyneuropathy. Inflammatory appearance and free air images extending to the mediastinum in the thyroid gland region previously seen in the thorax CT have decreased in the control. The first postoperative respiratory function tests which was done 10 days after the operation of the patient were FEV_1: 66% FVC: 63% FEV_1/FVC: 1.04; during our hospitalization, FEV_1: 77%, FVC: 77%, FEV_1/FVC: 1 were detected.

The patient was diagnosed with critical illness polyneuropathy with myoclonus secondary to hypoxia. The patient with myoclonus in trunk and 4 limbs had been using valproic acid 1000 mg before he was admitted to the ward and levatiracetam 1000mg was added to his treatment in our clinic. There was significant improvement in myoclonus after treatment. The patient was also using anticoagulant and antidiabetic drugs. Priority was given to sitting balance, and active and assistive range of motion (ROM) exercises in bed. Afterwards, mattress exercises, pelvic stabilization including abdominal and gluteal muscles, upper and lower extremity strengthening exercises were started. After strengthening of the trunk muscles of the patient, walking in the parallel bars and walker with bilateral reflex ankle-foot orthesis (AFO) were given. Neuromuscular electrical stimulation was applied to both tibialis anterior muscles. During the treatment period, decubitis ulcers regressed. Right shoulder pain was exacerbated and the patient was evaluated as adhesive capsulitis (passive and active flexion is 90º, abduction is 100º). With intraarticular steroid injection, the patient had increased range of motion of shoulder and decreased pain and increased participation in exercise. After intraarticular injection, there was no serious increase in the patient's blood glycemic level. Urinary catheter removal was attempted during the patient's hospitalization, but was repeated because the patient had recurrent urinary retention attacks. After 5 months, urinary catheter was removed and the patient was continent. Totally 51 days of hospitalization was performed in our ward. The patient was mobilized with a walker and bilateral AFO. During discharge, myoclonus decreased considerably. The initial and final functional independence measurement score and Barthel's daily life activities index patient were 47/126 and 0/100 versus 88/126 and 60/100.

DISCUSSION

CIM, CIP and CIPNM are the most common causes of neuromuscular muscle weakness in intensive care units and are also among the common causes of difficulty to wean from ventilator.[3] CIPNM is usually seen in mild form and rarely in severe forms. CIM, CIP and CIPNM is diagnosed by electrodiagnostic studies. Electrophysiological evaluation of CIPNM shows signs of motor and sensory axonal degeneration of the upper and lower extremities. In mild forms, electrodiagnostic evaluation decreases compound muscle action potential (CMAP), needle EMG evaluates several fibrillation potentials and axillary damage, more pronounced proximal muscles than distal muscles, and positive sharp waves and usually normal motor unit potentials are detected. In mild form, mus-

cle biopsy is usually normal. In severe form, foci of generalized necrosis are detected. In the electrophysiological evaluation of the heavy form, there is a significant decrease in CMAP and shows a decrease in sensory nerve action potency amplitudes (SNAP) which show axonal degeneration of sensory nerve fibers.[1-3,9] In electrophysiologic evaluation of CIP, there are reduction in CMAPs and normal SNAPs.[2] In our case, there were electrophysiological findings supporting the diagnosis of CIP.

Pathophysiology of CIPNM, patients who are critically ill have exaggerated immune response and proinflammatory cytokine production which lead to dysfunction of neuromuscular system. As a result of cytokine production, microvascular permeability, vasodilatation, extravisation of leukocyte and hypoxemia increased. And also electrical alteration of cells could happen due to Na^{+} channel dysfunction, altered Ca^{++} homeostasis and cellular inexcitability. Metabolic changes like hyperglycemia, catabolic pathway activation, mitochondrial functional dysfunction, hypoalbuminemia and reactive oxygen species production support pathogenesis of CIPNM. Ischemia caused by increased endoneural fluid pressure causes sensory and motor primary axonal damage and local muscle tissue damage.[1,3,4,6,8] Although inflammatory processes are thought to be effective in pathogenesis, there is no randomized controlled trial using intra-venous immunglobulin or plasmapheresis.[3]

Myoclonus is a sudden, brief, lightening like muscle jerk arising involuntarily from nervous system. Myoclonus can be seen due to physiological and pathological reasons. Physiological causes include sleep jerk, exercise and anxiety-induced myoclonus. For pathological reasons, there are epileptic myoclonus, myoclonus due to depot and neurological diseases, infection, metabolic and toxic causes and encephalopathy (posthypoxic, posttraumatic etc.).[13] In our case, the patient has involunteer myoclonus which is triggered by anxiety and exercises developed after hipoxia and long-term intensive care unit stay. Therefore, in the differential diagnosis of our patient, we evaluated posthypoxic myoclonic encephalopaty called Lance-Adams Syndrome (LAS). Posthypoxic myoclonus (PHM) is divided into acute and chronic types. Acute type starts 12 hours after hypoxia; chronic type starts after days or weeks from hypoxia and lasts long term. This chronic type is called Lance-Adams Syndrome. It is a very rare complication. Clinical presentation includes action myoclonus with cerebellar ataxia, postural imbalance and mild intellectual deficits accompanied by dysmethria and disarthria. Myoclonic movements are observed throughout the body, including the face. Myoclonus is aggravated by voluntary movement, sound and touch; not observed during rest and sleep. Brain MRI and CT are usually normal. Electroencephalography (EEG) shows complex polyspike waves in both frontal lobes. Our case was found to be more compatible with CIP because EEG and electromyelography (EMG) lead to diagnosis, presence of peripheral polyneuropathies and lack of cognitive deficits.[14]

In the differential diagnosis, muscle weakness due to central causes such as spinal cord injury and head trauma should be excluded first.[1,4] They can be ruled out by a good neurological examination and imaging. The patient's history is particularly important in distinguishing CIP and Guillain-Barré. A history of Campylobacter infection and diarrhea brings us closer to Guillain-Barré. It is especially difficult to distinguish the acute motor and sensory-motor axonal variants of Guillain-Barré from CIP. Electrodiagnostic studies are very effective in diagnosis. Facial muscles are not involved in CIP; there could be involvement of facial muscle in Guillain-Barré.[2] Electrolyte imbalance such as hypokalemia, hypophosphatemia and hypermagnesemia, neuromuscular blocking agents, cancer chemotherapeutics, statins, antiretroviral treatment affect neuromuscular transmission. [2] Propofol infusion syndrome is a disease with severe metabolic acidosis, cardiac and renal failure and rhabdomyolysis. Rhabdomyolysis may progress to acute necrotizing myopathy. Early discontinuation of propofol is highly effective in the healing process.[2]

There is no specific treatment for CIP. Firstly, the treatment of underlying sepsis should be done, euglycemia should be targeted, the patient should be separated from the ventilator in the early period and hospitalization should be kept short.[2,11] Prophylaxis should be performed for deep vein thrombosis during immobilization and decubitus ulcers should be pre-

vented by proper positioning.[3] Main treatment is supportive treatment. The idea that rehabilitation should be applied after the patient is clinically stable has been replaced by the earliest rehabilitation. It has been shown that early repetitive passive mobilization and passive range of motion exercises prevent disuse atrophy, prevent joint stiffness, increase the number of days without ventilator, and reduce delirium duration.[2] Pulmonary rehabilitation is also effective in rapidly recovering the patient's respiratory function. The rehabilitation program begins with passive ROM exercises, followed by active and assistive ROM exercises, bed side sitting, chair sitting and progressive ambulation. This program increases the patient's functional capacity, achieves respiratory and physical independence, and reduces bed rest complications.[10] Neuromuscular electrical stimulation (NMES) provides passive contraction of muscles, reducing disuse atrophy and reducing the time the patient has to move from bed to chair. Functional independence measure (FIM) and Barthel's daily life activities index can be used to evaluate the functional capacity of the patient; handheld dynamometer can be used for muscle strength assessment.[10]

CIP is a common complication in critically ill patients and also a reason of intensive care unit-acquired weakness. It causes muscle weakness and makes it difficult for the patient to wean from the ventilator. Accompanying CIP with myoclonus is not common. In the presence of myoclonus, CIP diagnosis should not be ruled out and it should be remembered that myoclonus may occur due to muscle weakness or other reasons mentioned above. Rehabilitation has an important place in the early period and the diagnosis should be made as early as possible and the patient should be included in the rehabilitation program early. Early rehabilitation increases the functional capacity of the patient, decreases the duration of ventilator use, and the patient leaves the intensive care unit early. Although there is no definitive evidence-based studies on the intensity, frequency and duration of rehabilitation, it is recommended to start early and be functional, individual and regular.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Banu Kuran;* ***Design:*** *Jülide Öncü;* ***Control/Supervision:*** *Jülide Öncü;* ***Data Collection and/or Processing:*** *Roza Dağdelen;* ***Analysis and/or Interpretation:*** *Aylin Ayyıldız;* ***Literature Review:*** *Figen Yılmaz;* ***Writing the Article:*** *Aylin Ayyıldız, Jülide Öncü;* ***Critical Review:*** *Banu Kuran;* ***References and Fundings:*** *Roza Dağdelen;* ***Materials:*** *Figen Yılmaz*

REFERENCES

1. Visser LH. Critical illness polyneuropathy and myopathy: clinical features, risk factors and prognosis. Eur J Neurol. 2006;13(11):1203-12. [Crossref] [PubMed]
2. Latronico N, Bolton CF. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. Lancet Neurol. 2011;10(10):931-41. [Crossref] [PubMed]
3. Shepherd S, Batra A, Lerner DP. Review of critical illness myopathy and neuropathy. Neurohospitalist. 2017;7(1):41-8. [Crossref] [PubMed] [PMC]
4. Judemann K, Lunz D, Zausig YA, Graf BM, Zink W. [Intensive care unit-acquired weakness in the critically ill: critical illness polyneuropathy and critical illness myopathy]. Anaesthesist. 2011;60(10):887-901. [Crossref] [PubMed]
5. Schefold JC, Messmer AS, Wenger S, Müller L, von Haehling S, Doehner W, et al. Nutrient pattern analysis in critically ill patients using Omics technology (NAChO) - Study protocol for a prospective observational study. Medicine (Baltimore). 2019;98(1):e13937. [Crossref] [PubMed] [PMC]
6. Diaz Ballve LP, Dargains N, Urrutia Inchaustegui JG, Bratos A, de Los Milagros Percaz M, Cesar Bueno Ardariz CB, et al. [Weakness acquired in the intensive care unit. Incidence, risk factors and their association with inspiratory weakness. Observational cohort study]. Rev Bras Ter Intensiva. 2017;29(4):466-75. [Crossref] [PubMed] [PMC]
7. Field-Ridley A, Dharmar M, Steinhorn D, McDonald C, Marcin JP. ICU-Acquired weakness is associated with differences in clinical outcomes in critically ill children. Pediatr Crit Care Med. 2016;17(1):53-7. [Crossref] [PubMed] [PMC]
8. Bolton CF. Neuromuscular manifestations of critical illness. Muscle Nerve. 2005;32(2):140-63. [Crossref] [PubMed]

9. Zhou C, Wu L, Ni F, Ji W, Wu J, Zhang H. Critical illness polyneuropathy and myopathy: a systematic review. Neural Regen Res. 2014;9(1):101-10. [Crossref] [PubMed] [PMC]
10. Doherty N, Steen CD. Critical illness polyneuromyopathy (CIPNM); rehabilitation during critical illness. Therapeutic options in nursing to promote recovery: a review of the literature. Intensive Crit Care Nurs. 2010;26(6):353-62. [Crossref] [PubMed]
11. Vanhorebeek I, Latronico N, Van den Berghe G. ICU-acquired weakness. Intensive Care Med. 2020;46(4):637-53. [Crossref] [PubMed] [PMC]
12. Bednarík J, Vondracek P, Dusek L, Moravcova E, Cundrle I. Risk factors for critical illness polyneuromyopathy. J Neurol. 2005;252(3):343-51. [Crossref] [PubMed]
13. Caviness JN. Treatment of myoclonus. Neurotherapeutics. 2014;11(1):188-200. [Crossref] [PubMed] [PMC]
14. Lee HL, Lee JK. Lance-adams syndrome. Ann Rehabil Med. 2011;35(6):939-43. [Crossref] [PubMed] [PMC]