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CASE REPORT

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COVID-19와 동반된 중환자 다발성 신경병의 전기진단검사 추적관찰: 증례 보고

최경열, 김민우, 이선미, 김종규
서울의료원 재활의학과

Electrodiagnostic Follow-Up of COVID-19-Associated Critical Illness Polyneuropathy: A Case Report

Kyungyeul Choi, Minwoo Kim, Son Mi Lee, Jongkyu Kim
Department of Physical Medicine and Rehabilitation, Seoul Medical Center, Seoul, Korea

Neurologic complications have been reported in patients with coronavirus disease 2019 (COVID-19). Here, we report a case of post-COVID-19 critical illness polyneuropathy and describe the longitudinal follow-up. A 73-year-old woman presented with peripheral muscle weakness following COVID-19 pneumonia and mechanical ventilation for 16 days. Despite treatment, her fever persisted, and oxygen supplementation was continued. Blood cultures revealed *Candida albicans* infection, prompting antibiotic and antifungal therapy with oxygen supplementation. Two months later, the patient responded to treatment and was extubated. However, she exhibited peripheral muscle weakness. Nerve conduction studies showed peripheral polyneuropathy with axonal involvement, consistent with critical illness polyneuropathy. After 2 months of inpatient rehabilitation, the patient's weakness and activity limitations improved. However, nerve conduction studies taken after 4.5 months showed persistent bilateral lower extremity axonal neuropathy. To the authors' best knowledge, this is the first report of longitudinal follow-up with a functional evaluation of COVID-19-associated critical illness polyneuropathy.

Keywords: COVID-19; Electrodiagnosis; Polyneuropathies

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Corresponding author:
Jongkyu Kim
Department of Physical Medicine and Rehabilitation, Seoul Medical Center, 156 Sinnae-ro, Jungnang-gu, Seoul 02053, Korea
Tel: +82-2-2276-7474
Fax: +82-2-2276-8534
E-mail: jongkyukim@seoulmc.or.kr

Introduction

Since the coronavirus disease 2019 (COVID-19) outbreak, many neurologic and neuromuscular sequelae have been reported [1]. Among these, stroke is the most notorious complication due to the thrombo-inflammatory nature of COVID-19 [1]. For cases that involve the peripheral nerves, Guillain-Barré syndrome (GBS), neuromuscular junction disorders (e.g., myasthenia gravis), and myopathies have been reported [2].

Most of these reports have focused on GBS occurring during or after COVID-19, which suggests a potential parainfectious or postinfectious process [2]. Retrospective studies found a higher frequency for GBS in COVID-19-infected patients with an odds ratio of 4.6 to 6.3 [2,3]. Furthermore, the incidence of GBS was

2.6 times higher during the COVID-19 pandemic compared with the same period last year [2,4].

Only case reports or narrative reviews regarding other peripheral neurologic complications have been reported [5,6]. A prospective study described cases of critical illness polyneuropathy (CIPN) diagnosed using nerve conduction studies (NCSs) in intensive care units (ICUs) [7]. However, most reports regarding COVID-19 associated peripheral neuropathies were diagnosed using a one-time NCS. To the best of our knowledge, longitudinal follow-up with functional evaluation of a CIPN case associated with COVID-19 has not been described previously.

Here, we report a case of CIPN following COVID-19 pneumonia and describe the longitudinal follow-up in terms of NCS findings and functional status.

Case Report

A 73-year-old woman with a history of hypertension, diabetes mellitus, and heart failure presented with fever, cough, and myalgia. She had a 3-year history of diabetes, but through lifestyle modifications, she was able to maintain a relatively well-controlled blood sugar level with a mildly elevated hemoglobin a1c (HbA1c) level (6.6%). The reverse transcription- polymerase chain reaction (nasopharyngeal swab) for severe acute respiratory syndrome coronavirus 2 was positive. Chest computed tomography revealed bilateral ground-glass opacities. These findings confirmed the diagnosis of COVID-19 pneumonia. At baseline, she did not present with limitations on ambulation or with performing activities of daily living (ADL).

On the 8th day after diagnosis, she received a 5-day course of intravenous antiviral—remdesivir. However, her dyspnea was aggravated, which prompted endotracheal intubation and mechanical ventilation for 16 days. Unfortunately, her fever persisted and the need for oxygen supplementation was continued even after successful weaning off the ventilator. During critical care, she received antibiotics, vasopressor, low molecular heparin, muscle relaxants, sedatives, and corticosteroid therapy (Supplementary Fig. 1).

On the 36th day after diagnosis, blood cultures revealed *Candida albicans* infection, which prompted caspofungin therapy. Several antibiotics were also given for the management of pneumonia. Repeated improvement and deterioration of pneumonia occurred. On the 65th day after diagnosis, the patient was off oxygen supplementation completely.

Two months later, the patient presented with weakness of the arms and legs. Neurologic examination revealed peripheral weakness with motor grades of 1 to 2. Deep tendon reflex assessment revealed hyporeflexia in both elbows and knees. She also presented with activity limitations during sit-ups, ambulation (functional ambulatory category 0), and while performing ADL (Table 1). NCS showed peripheral polyneuropathy in both the upper and lower limbs (Table 2), suggestive of axonal neuropathy. These findings were consistent with a diagnosis of CIPN.

Management with a 2-month inpatient rehabilitation program improved her muscle weakness; however, she still needed some assistance in ambulation and while performing ADL (Table 1). The patient was discharged home on the 135th day after diagnosis. A follow-up NCS conducted on the 194th disease day re-

Table 1. Improvement of Motor Strength

MRC scale	T1		T2		T3		T4	
	R	L	R	L	R	L	R	L
Shoulder flexor	2	2	3	3	3	3	3	3
Shoulder extensor	1	1	2	2	3	3	3	3
Elbow flexor	1	1	2	2	3	3	4	4
Elbow extensor	1	1	2	2	2	2	3	3
Wrist flexor	2	2	3	3	3	3	4	4
Wrist extensor	2	2	3	3	3	3	4	4
Hip flexor	1	1	2	3	3	3	3	3
Hip extensor	1	1	1	2	2	2	2	2
Knee flexor	1	1	2	2	2	2	3	3
Knee extensor	1	1	2	2	3	3	3	3
Ankle dorsiflexor	2	2	2	2	3	3	3	3
Ankle plantar flexor	1	1	2	2	2	2	3	3

MRC, Medical Research Council; T1, 2 months after disease onset, just before starting rehabilitation; T2, 3 months after disease onset; T3, 4.5 months after disease onset; T4, 7 months after disease onset; R, right; L, left.

Table 2. Nerve Conduction Studies after COVID-19 Infection: Initial and Follow-Up Tests

Nerve	Side	OL (ms)	Amp-OP (uV or mV)	Velocity (m/s)
Sensory*				
Median	Right	2.9	28.6	48
	Left	2.9	34.7	48
Ulnar	Right	2.6	27.6	54
	Left	2.4	23.8	58
Sural	Right	2.4	7.7	50
	Left	2.6	6.6	46
Superficial peroneal	Right	NE	NE	
	Left	NE	NE	
Motor*				
Median (wrist-APB)	Right	3.3	3.8	
Median (elbow-APB)		7.8	2.6	44
Median (wrist-APB)	Left	3.7	3.5	
Median (elbow-APB)		7.9	3.4	48
Ulnar (wrist-ADM)	Right	2.6	3.9	
Ulnar (elbow-ADM)		7.3	3.9	53
Ulnar (wrist-ADM)	Left	2.7	5.1	
Ulnar (elbow-ADM)		7.6	4.6	51
Deep peroneal (ankle-EDB)	Right	NE	NE	
Deep peroneal (knee-EDB)		NE	NE	
Deep peroneal (ankle-EDB)	Left	NE	NE	
Deep peroneal (knee-EDB)		NE	NE	
Tibial (ankle-AH)	Right	NE	NE	
Tibial (knee-AH)		NE	NE	
Tibial (ankle-AH)	Left	NE	NE	
Tibial (knee-AH)		NE	NE	
Sensory†				
Median	Right	2.9	17.3	48
	Left	2.9	25	48
Ulnar	Right	2.4	21.7	58
	Left	2.5	19.8	56
Sural	Right	2.3	5.6	52
	Left	2.4	6.3	50
Superficial peroneal	Right	NE	NE	
	Left	NE	NE	
Motor†				
Median (wrist-APB)	Right	3.5	7.9	
Median (elbow-APB)		7.5	7.3	50
Median (wrist-APB)	Left	3.8	6.9	
Median (elbow-APB)		7.6	6.7	53
Ulnar (wrist-ADM)	Right	2.7	9.8	
Ulnar (elbow-ADM)		6.9	8.8	55
Ulnar (wrist-ADM)	Left	2.7	9.2	
Ulnar (elbow-ADM)		6.9	8.6	55
Deep peroneal (ankle-EDB)	Right	3.6	1	
Deep peroneal (knee-EDB)		9.3	0.6	47
Deep peroneal (ankle-EDB)	Left	4.3	2.1	
Deep peroneal (knee-EDB)		10.5	1.6	44
Tibial (ankle-AH)	Right	4.4	3.1	
Tibial (knee-AH)		11.9	2.2	45
Tibial (ankle-AH)	Left	4.5	1.2	
Tibial (knee-AH)		12.3	0.7	44

Sensory nerve conduction studies were conducted with antidromic methods using skin surface (disc) electrodes. Motor nerve conduction studies were conducted using tendon-belly methods. There were no noticeable interfering factors (e.g., prominent peripheral edema, abnormal skin temperature, or other medications) in the first and follow-up nerve conduction studies. All nerve conduction studies were conducted on the same machine (Sierra Wave EMG system; Cadwell Laboratories Inc., Kennewick, WA, USA), in the same laboratory room and by the same technician.

COVID-19, coronavirus disease 2019; OL, onset latency; Amp, amplitude; OP, onset to peak; NE, not elicited; APB, abductor pollicis brevis; ADM, abductor digiti minimi; EDB, extensor digitorum brevis; AH, abductor halluces.

*Initial nerve conduction study, on the 58th day after disease onset, †follow-up nerve conduction study, on the 194th day after disease onset.

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vealed normal values for the upper extremities, but her lower extremities still showed axonal neuropathy (Table 2). A longitudinal follow-up for 7 months revealed improvements in muscle strength (grade 3 to 4) (Table 1). Her functional ambulatory category score—which indicates walking ability—improved from 0 (nonfunctional ambulation) to 4 (independent ambulator, level surfaces only).

Discussion

Since the pandemic, many sequelae of COVID-19, termed as long-COVID-19 or post-acute COVID-19 syndrome, have been reported [6]. Although COVID-19 primarily causes respiratory disease, a wide breadth of neurologic complications has also been reported [2].

Most studies regarding these neurologic complications have mainly been focused on GBS. A 6-month cohort study reported that the incidence of GBS increased during the COVID-19 pandemic, suggesting a possible association [4,8]. Another retrospective study showed that the incidence of GBS was higher in COVID-19 patients compared with non-COVID-19 patients [3]. Nowadays, GBS is considered a diagnostic umbrella, including acute inflammatory demyelinating polyradiculopathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor-sensory axonal neuropathy (AMSAN), and Miller-Fisher syndrome (MFS). Among 30 cases of GBS in patients with COVID-19, Filosto et al. [4] identified AIDP (76.6%) and AMAN (6.7%) with 5% having equivocal electrodiagnostic results. Caress et al. [9] reported AIDP (64.8%), AMSAN (13.5%), MFS (13.5%), and AMAN (2.7%) among 37 cases of COVID-19-associated GBS. In our case, NCS revealed lower extremity axonal neuropathy with equivocal upper extremity findings. This might be suggestive of GBS variant—AMSAN. However, GBS is generally considered a postinfectious or para-infectious inflammatory neuropathy [2]. Moreover, the patient's weakness presented during intensive care. Hence, these findings were more consistent with a kind of ICU acquired weakness, and NCS results supported CIPN.

There have been several reports of CIPN following COVID-19. A prospective study reported 11 cases of CIPN from 111 COVID-19 patients in ICUs [7]. However, the investigation was only at the acute stage. To the best of our knowledge, only one case has described longitudinal follow-up electrodiagnostic results for 83 days past admission [5]. It described only follow-up NCS data, and the 83-day follow-up period was too short, relatively speaking.

The exact pathogenesis of CIPN following COVID-19 is not well understood. Traditionally, CIPN has been considered a consequence of severe sepsis and prolonged mechanical ventilation. A prospective study by Frithiof et al. [7] reported a higher incidence of CIPN in ICU patients with COVID-19 compared with non-COVID-19 controls. Furthermore, they investigated the correlation between neuronal biomarkers and NCS parameters (e.g., combined motor and sensory amplitudes). However, the correlation between clinical severity and combined motor and sensory amplitudes on NCSs is still unknown. In our case, the severity of weakness and degree of recovery were similar for the upper and lower limbs. However, the NCS results for the upper and lower extremities were markedly different.

The prognosis of CIPN in patients with COVID-19 is still unclear. Studies on CIPN in COVID-19 have been focused on incidence, risk factors, and diagnostic biomarkers. Only one case described CIPN rehabilitation. COVID-19 aside, the natural history and long-term prognosis of CIPN are not well-known. Koch et al. [10] reported that 88% of critical illness myopathy patients recovered within 1 year, whereas 55% of CIPN patients recovered. Considering that peripheral nerve edema is suggested to be one of the causes of CIPN, long-term corticosteroid administration may be helpful for recovery from CIPN and may lead to an increase in compound muscle action potential amplitudes in follow-up NCSs.

Diagnostic ambiguity could be suggested in this case. We were able to rule out the possibility of diabetic polyneuropathy because the patient had a relatively short history of diabetes and relatively low HbA1c levels even without anti-diabetic medication. In the NCS results, motor nerves seemed to be more severely involved than sensory nerves. It could be analyzed as critical illness neuromyopathy—an ICU acquired weakness that involves somewhat different diagnostic criteria. The early exclusion of a GBS diagnosis and the failure to request for cerebrospinal fluid analysis and magnetic resonance imaging of the spinal cord were other weak points. Nevertheless, to the best of our knowledge, this is the first case to describe the longitudinal follow-up of CIPN following COVID-19 in terms of electrodiagnostic results and functional evaluations. An initial motor NCS showed slightly decreased amplitudes in the upper limbs with no visible compound muscle action potentials in lower limbs. Moreover, although the follow-up motor NCSs showed improvement, evidence of CIPN persisted. Unfortunately, her muscle strength and functional ambulatory category did not return to that of her pre-morbid state. This study highlights the important role of longitudinal follow-ups with NCSs and functional evaluations in the management of CIPN. Conducting regular follow-ups involving examination of functional level and electrophysiologic results until the patient acquires the pre-morbid functional level can be

helpful in understanding COVID-19 associated CIPN.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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ORCID

Kyungyeul Choi, https://orcid.org/0000-0003-4218-0102
Minwoo Kim, https://orcid.org/0000-0003-3100-9692
Son Mi Lee, https://orcid.org/0000-0001-5014-4107
Jongkyu Kim, https://orcid.org/0000-0003-1441-9227

Supplementary Materials

Further details on supplementary materials are presented online (available at https://doi.org/10.18214/jend.2021.00080).

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