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*Journal of Electrodiagnosis and Neuromuscular Diseases* (*J Electrodiagn Neuromuscul Dis*, JEND) is a peer-reviewed journal concerning both normal and abnormal functioning of the muscle, the neuromuscular junction, and the peripheral motor, sensory and autonomic nerves. The journal publishes clinical studies, reviews, and case reports in the fields of electrophysiology, electrodiagnosis, imaging studies including ultrasonography, and management, about neuromuscular diseases. The journal is aimed to provide an open forum for original research in basic science and clinical research that will improve our fundamental understanding and lead to effective treatments of neuromuscular diseases.
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# Contents

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## Case Reports

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JEND Journal of Electrodiagnosis and Neuromuscular Diseases

# Contents

Vol. 23, No. 3 December 2021

## Case Reports

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CASE REPORT

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# 저칼륨혈증성 주기성 마비를 동반한 진행성 근위축증: 증례 보고

배영균, 이재현, 심영주, 정호중, 김기찬

고신대학교복음병원 재활의학과

# Progressive Muscular Atrophy with Hypokalemic Periodic Paralysis: A Case Report

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Progressive muscular atrophy (PMA) is a rare disease involving lower motor neuron degeneration. Hypokalemic periodic paralysis (HypoPP) is a genetic disorder that causes temporary muscle paralysis due to decreased serum potassium levels. Mutations in the *CACNA1S* gene cause HypoPP. An altered locus closely linked near the *CACNA1S* gene suggests the possibility of motor neuron degeneration. However, PMA with HypoPP is very rare worldwide because HypoPP usually causes progressive muscle weakness involving a form of myopathy without motor neuron disease. In this report, we describe the case of a 64-year-old man who initially complained of weakness in only the left lower extremity, which subsequently progressed bilaterally. Hence, the patient was diagnosed with PMA with HypoPP based on serial electromyography and the presence of a *CACNA1S* mutation. Therefore, serial electromyography is necessary for middle-aged patients with progressive muscle weakness and a history of HypoPP.

**Keywords:** Muscular atrophy, spinal; Hypokalemic periodic paralysis; Electromyography

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## Introduction

Progressive muscular atrophy (PMA) is a rare disease that accounts for approximately 2.5% to 11% of motor neuron disease [1]. In PMA, lower motor neuron (LMN) degeneration occurs which causes isolated LMN symptoms. Patients with PMA have clinical symptoms of progressive weakness, muscle atrophy, fasciculation, and absent or reduced tendon reflexes. PMA is more common in men with a mean age of onset of 63.4 ± 11.7 years [2]. PMA has no biological marker for diagnosis. Therefore, PMA diagnosis is based on clinical symptoms and electrophysiologic features. Electrophysiologic features include LMN dysfunction in 2 or more myotomal distributions and evidence of progressive disease over time [1].

Hypokalemic periodic paralysis (HypoPP), which is an autosomal dominantly inherited channelopathy, represents temporary paralysis with decreased serum potassium level [3]. Symptoms usually begin in puberty and rarely after 25 years of age [3]. A paralytic episode can be precipitated by rest or sleep and the symptoms may be limited to certain muscles or may affect all ex-

tremities. HypoPP diagnosis is based on low serum potassium level during a paralysis event and exclusion of secondary hypokalemia. Frequency of paralytic event is reduced during the third to fifth decades of life; however, some permanent weakness may remain [4]. In a previous study, proximal muscle weakness occurred without paralytic attacks in patients over 50 years old [5]. Similarly, a case of spinal muscular atrophy with HypoPP was shown through clinical and biopsy evidence [6]. However, PMA with HypoPP is not well known, and only few cases had been reported. Here, we report a case which was identified as PMA with HypoPP.

## Case Report

A 64-year-old man visited the outpatient clinic due to weakness of the left ankle 3 years ago. The patient had a history of paralysis attacks that improved after potassium injection during puberty. Two of his brothers also had a history of paralytic attacks after sleeping. Manual muscle test (MMT) was performed using a medical research council scale. Motor grade of the left first toe and ankle dorsiflexor muscles were grade 1 with tingling sensation in the entire left lower extremity. Deep tendon reflex (DTR) of the left knee and ankle were considered normal. Upper motor neuron (UMN) signs, including Babinski reflex and ankle clonus, were not observed. Muscle atrophy was observed in the left vastus medialis, tibialis anterior, and extensor digitorum brevis muscles. In a nerve conduction study (NCS), compound muscle action potential (CMAP) amplitudes on tibial and peroneal motor nerves were lower in the left extremity (Table 1). Sensory nerve action potential amplitude and H-reflex on both sides were normal. Upon needle electromyography (EMG), high amplitude and polyphasic motor unit potential with reduced recruitment pattern were observed in the left adductor magnus, vastus medialis, tibialis anterior, and peroneus longus muscles (Table 2). There was no abnormal spontaneous activity in paraspinal muscles. Based on the results, he was diagnosed with left lumbosacral plexopathy. After 2 years, the patient visited the outpatient clinic again due to progressive weakness of both lower extremities. In MMT, motor grade of both ankle and 1st toe dorsiflexor muscles were grade 1. Motor grade of both toe and ankle plantarflexor muscles, and the left knee and hip were grade 2. Other muscles on both lower extremities were grade 3. DTR of both knee and ankle was decreased. In NCS, CMAP amplitudes of both lower extremites were reduced (Table 3). High amplitude and polyphasic motor unit potentials with reduced recruitment pattern were observed in most muscles on both lower extremities and in the right biceps brachii muscle. These suggest dysfunction in cervical distribution as well as lumbosarcral distribution. Abnormal spontaneous activity was observed in some muscles on both lower extremities (Table 4). The patient was admitted with a suspicion of motor neuron disease. Fasciculations over the tongue and both thigh muscles, and hypesthesia on both lower extremities were noted. There were no definite abnormalities causing progressive weakness in the brain or spinal magnetic resonance imaging. There were also no specific findings on abdomen and chest computed tomography. Serum creatinine phosphokinase and thyroid hormone were normal. Antiganglioside antibody and antinuclear antibody were not detected. Pulmonary function was normal, and there was no swallowing difficulty. The patient had no UMN symptoms. Genetic testing identified mutations in the *CACNA1S* gene as the only genetic abnormality. Unlike amyotrophic lateral sclerosis, the patient could be diagnosed with

**Table 1.** Initial Nerve Conduction Study in both Lower Extremities

| Nerve stimulation (record) | Latencies (ms) | Amplitude (μV) | Conduction velocity (ms) |
|---|---|---|---|
| | Distal/proximal | Distal/proximal | |
| Motor | | | |
| Right tibial (AH) | 4.3/13.5 | 7,600/4,100 | 42 |
| Right peroneal (EDB) | 4.7/13.2 | 1,400/1,200 | 44 |
| Right peroneal (TA) | 4.4/5.7 | 5,000/3,700 | 54 |
| Right femoral (VM) | 3.6 | 4,400 | - |
| Left tibial (AH) | 4.5/14.1 | 4,600/3,100 | 41 |
| Left peroneal (EDB) | - | No response | - |
| Left peroneal (TA) | 3.9/5.5 | 700/400 | 50 |
| Left femoral (VM) | 3.6 | 3,200 | - |
| Sensory | | | |
| Right sural (ankle) | 2.4/3.2 | 10 | 47 |
| Left sural (ankle) | 2.2/3.0 | 11 | 50 |

AH, abductor hallucis; EDB, extensor digitorum brevis; TA, tibialis anterior; VM, vastus medialis; -, not applicable.


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**Table 2.** Initial Needle Electromyography in both Lower Extremities

| Muscle | Insertion activity | Spontaneous activity | | | Motor unit potential | | |
|---|---|---|---|---|---|---|---|
| | | Fibrillation | PSW | Fasciculation | Duration/amplitude | Phases | Recruitment |
| Right | | | | | | | |
| L4/5 paraspinal muscle | Normal | 0 | 0 | 0 | - | - | - |
| L5/S1 paraspinal muscle | Normal | 0 | 0 | 0 | - | - | - |
| Left | | | | | | | |
| Gluteus maximus | Normal | 0 | 0 | 0 | Normal | Normal | Complete |
| Adductor magnus | Normal | 0 | 0 | 0 | Long/high | Increased | Reduced |
| Biceps femoris (short head) | Normal | 0 | 0 | 0 | Normal | Normal | Reduced |
| Tensor fasciae latae | Normal | 0 | 0 | 0 | Normal | Normal | Complete |
| Iliopsoas | Normal | 0 | 0 | 0 | Normal | Normal | Complete |
| Vastus medialis | Normal | 0 | 0 | 0 | Long/high | Increased | Reduced |
| Peroneus longus | Normal | 0 | 0 | 0 | Long/high | Increased | Reduced |
| Tibialis anterior | Normal | 0 | 0 | 0 | Long/high | Increased | Reduced |
| Gastrocnemius | Normal | 0 | 0 | 0 | Normal | Normal | Reduced |
| Extensor digitorum brevis | Normal | 0 | 0 | 0 | - | - | Not detectable |
| L4/5 paraspinal muscle | Normal | 0 | 0 | 0 | - | - | - |
| L5/S1 paraspinal muscle | Normal | 0 | 0 | 0 | - | - | - |

PSW, positive sharp wave; -, not applicable.

**Table 3.** Follow-Up Nerve Conduction Study in both Lower Extremities

| Nerve stimulation (record) | Latencies (ms) | Amplitude (μV) | Conduction velocity (ms) |
|---|---|---|---|
| | Distal/proximal | Distal/proximal | |
| Motor | | | |
| Right median | 3.7/8.2 | 6,400/5,700 | 56 |
| Right ulnar | 2.67.2 | 12,000/10,100 | 59 |
| Left median | 4.4/9.4 | 4,700/4,500 | 52 |
| Left ulnar | 2.6/7.0 | 8,700/6,100 | 57 |
| Right tibial (AH) | 5.8/17.2 | 2,000/300 | 36 |
| Right peroneal (EDB) | 9.5/18.3 | 300/300 | 40 |
| Right peroneal (TA) | 5.9/6.9 | 600/600 | 60 |
| Right femoral (VM) | - | No response | - |
| Left tibial (AH) | 5.8/15.3 | 1,000/900 | 40 |
| Left peroneal (EDB) | - | No response | - |
| Left peroneal (TA) | - | No response | - |
| Left femoral (VM) | - | No response | - |
| Sensory | | | |
| Right median | 2.8/4.1 | 20 | 51 |
| Right ulnar | 2.3/3.1 | 18 | 52 |
| Left median | 2.8/4.1 | 31 | 50 |
| Left ulnar | 2.3/2.9 | 19 | 52 |
| Right sural (ankle) | 2.2/3.1 | 14 | 41 |
| Left sural (ankle) | 2.2/3.1 | 11 | 41 |

AH, abductor hallucis; EDB, extensor digitorum brevis; TA, tibialis anterior; VM, vastus medialis; -, not applicable.

PMA due to slow-progressing muscle weakness with LMN dysfunction of 2 myotomal distributions (i.e., cervical and lumbosacral) in NCS/needle EMG and tongue fasciculation which is the bulbar symptom (Table 4). Finally, we diagnosed the patient as PMA with HypoPP and treated him with riluzole. The patient was transferred to another hospital after 1 month.

**Table 4.** Follow-Up Needle Electromyography in both Lower Extremities

| Muscle | Insertion activity | Spontaneous activity | | | Motor unit potential | | |
|---|---|---|---|---|---|---|---|
| | | Fibrillation | PSW | Fasciculation | Duration/amplitude | Phases | Recruitment |
| Right | | | | | | | |
| Biceps brachii | Normal | 0 | 0 | 0 | Long/high | Increased | Reduced |
| Flexor carpi radialis | Normal | 0 | 0 | 0 | Normal | Normal | Complete |
| Abductor pollicis brevis | Normal | 0 | 0 | 0 | Normal | Normal | Complete |
| 1st dorsal interosseous | Normal | 0 | 0 | 0 | Normal | Normal | Complete |
| Gluteus maximus | Normal | 0 | 0 | 0 | Normal | Normal | Complete |
| Gluteus medius | Normal | 0 | 0 | 0 | Long/high | Increased | Reduced |
| Adductor magnus | Increased | 0 | 0 | 0 | Long/high | Increased | Reduced |
| Iliopsoas | Normal | + | + | + | Normal | Normal | Complete |
| Tensor fasciae latae | Normal | + | + | + | Long/high | Increased | Reduced |
| Vastus medialis | Normal | 0 | 0 | 0 | Long/high | Increased | Reduced |
| Gastrocnemius | Normal | 0 | 0 | 0 | Long/high | Increased | Reduced |
| Tibialis anterior | Normal | 0 | 0 | 0 | - | - | Poor volition |
| Biceps femoris (short head) | Normal | 0 | 0 | 0 | Long/high | Increased | Reduced |
| Semimembranosus | Normal | ++ | ++ | ++ | Long/high | Increased | Reduced |
| L4/5 paraspinal muscle | Normal | 0 | 0 | 0 | - | - | - |
| L5/S1 paraspinal muscle | Normal | 0 | 0 | 0 | - | - | - |
| Left | | | | | | | |
| Gluteus maximus | Normal | 0 | 0 | 0 | Normal | Normal | Complete |
| Gluteus medius | Normal | 0 | 0 | 0 | Long/high | Increased | Reduced |
| Adductor magnus | Normal | + | + | + | Long/high | Increased | Discrete |
| Iliopsoas | Normal | + | + | + | Normal | Normal | Reduced |
| Tensor fasciae latae | Normal | 0 | 0 | 0 | - | - | Single MUAP |
| Vastus medialis | Normal | 0 | 0 | 0 | Normal | Normal | Markedly Reduced |
| Gastrocnemius | Normal | 0 | 0 | 0 | Long/high | Increased | Reduced |
| Tibialis anterior | Normal | 0 | 0 | 0 | | | No volition |
| Biceps femoris (short head) | Normal | 0 | 0 | 0 | Long/high | Increased | Reduced |
| Semimembranosus | Normal | ++ | ++ | ++ | Long/high | Increased | Reduced |
| L4/5 paraspinal muscle | Normal | 0 | 0 | 0 | - | - | - |
| L5/S1 paraspinal muscle | Normal | 0 | 0 | 0 | - | - | - |

PSW, positive sharp wave; MUAP, motor unit action potential; -, not applicable.

## Discussion

We report a patient with a history of HypoPP and progressive weakness after middle age. The patient initially complained of weakness on the left ankle. After 2 years, he complained with weakness on both lower extremities. He had characteristic symptoms of isolated LMN lesion and electrophysiologic findings of LMN dysfunction. He also had a characteristic history of paralytic attacks and family history of HypoPP. In genetic testing, *CACNA1S* gene mutation was identified. Finally, we diagnosed the patient as PMA with HypoPP.

When a patient complains of a tongue fasciculation, bulbar symptom and weakness of asymmetrical progressive lower extremity, Kennedy's disease (KD) should be suspected. The disease is a X-linked bulbospinal neuronopathy and characterized by slowly progressive proximal and bulbar weakness, muscular atrophy, muscle pain and gynecomastia [7]. Also the age at onset of KD is in adolescence and ultimately, the diagnosis is confirmed through genetic testing that shows an expansion of polymorphic tandem CAG repeat in the first exon of the androgen receptor gene [7]. The middle-aged patient in our case showed no gynecomastia and the only *CACNA1S* gene mutation was identified in genetic testing. Therefore, we could rule out the KD.

HypoPP is mostly caused by gene mutation of the calcium channel *CACNA1S*, R528H, and R1239H. Approximately 80% of these gene mutations result in late onset myopathy [8]. In this case, the patient had the *CACNA1S* mutation leading to a diag-



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nosis of HypoPP. The *CACNA1S* mutation involves the membrane of the transverse tubular system and causes abnormalities in muscle contraction and relaxation [8]. According to a previous molecular research on PMA, TAR DNA-binding protein 43 (TDP-43)-positive inclusions were associated with isolated LMN degeneration without UMN symptoms [9]. However, only few PMA cases had TDP-43 mutations. The pathogenesis of PMA is not well known which makes diagnosis more difficult. Therefore, other LMN syndromes should be excluded for PMA diagnosis, which is delayed for an average of 23 months after symptom onset.

A previous case report described PMA with HypoPP caused by *CACNA1S* gene mutation [8]. They suggested that an altered locus, which is closely linked near CACNA1S, has the capability to produce motor neuron degeneration. No further cases on PMA with HypoPP have been reported worldwide. Our study supports the possibility that the *CACNA1S* gene may be involved in development of PMA. Hence, further molecular research is needed on how this gene is involved in development of PMA.

The relationship between PMA and HypoPP is not well known. When a patient with a past history of HypoPP complains of muscle weakness, myopathy is suspected. Myopathy after HypoPP is relatively well known, and diagnosis is based on characteristic findings of myopathy in EMG [10]. Myopathy in HypoPP can occur independent of paralytic attacks, and progressive weakness may occur, especially in proximal muscles of the lower extremities. However, the patient initially complained of distal weakness without characteristic findings of myopathy on EMG. During initial EMG, he was misdiagnosed with a left lumbosacral plexopathy. It was difficult to diagnose PMA because the patient's initial symptom was weakness on unilateral lower extremity, and there was no abnormal spontaneous activity on paraspinal muscles. After 2 years, the weakness progressed to both lower extremities, and we diagnosed him with PMA and characteristic findings of LMN degeneration based on EMG. Therefore, if a patient with history of HypoPP develops progressive muscle weakness after middle age, serial EMG should be performed. Follow-up of the weakness symptoms should be performed to determine if a new abnormality occurred.

## Conflict of Interest

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

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CASE REPORT

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# 울혈반모양 혈관병증 환자에서 발생한 다발성 단신경병증: 증례 보고

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# Multiple Mononeuropathy Associated with Livedoid Vasculopathy: A Case Report and Review

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This report describes a rare case of livedoid vasculopathy (LV) with sensory and motor neurologic deficits. A 46-year-old woman who had been diagnosed with LV developed acute left-foot drop. An electrodiagnostic study showed multiple mononeuropathy involving both the common peroneal and sural nerves, primarily on the left side. Nerve biopsy findings showed intravascular thrombosis in the perineurium and extensive infarct of the peripheral nerve. The patient was prescribed continuous anticoagulants, which resulted in a good clinical outcome. LV associated with multiple mononeuropathy is a rare condition, and the exact pathophysiologic mechanism of nerve involvement and treatment for neurologic deficits remain unclear. The histologic findings in the present case support the possibility that the peripheral neuropathy related to LV was primarily derived from an ischemic injury rather than inflammation. Continuous anticoagulant use could be helpful in the neurologic recovery of LV patients with multiple mononeuropathy.

**Keywords:** Livedoid vasculopathy; Mononeuropathies; Case reports

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## Introduction

Livedoid vasculopathy (LV) is a chronic, painful, thrombo-occlusive cutaneous vasculopathy. It affects the lower extremities, and clinical symptoms are primarily confined to the skin [1]. In rare cases, there is involvement of the peripheral nervous system, which the most common form is multiple mononeuropathy [2].

The exact pathophysiologic mechanism of the nerve involvement in LV and treatment for neurologic deficits remain unclear. Case reports have suggested that multiple mononeuropathy in LV can result from ischemic injury [3,4]; however, perivascular lymphocytes have been observed in microscopic findings of nerve biopsies, suggesting that inflammation could also be the cause [2,4-8]. A systematic review of LV suggests that patients' ulcerations, pain, or purpura can be treated with anticoagulants, anabolic steroids, antiplatelets, intravenous immunoglobulins, thrombolytics [9]; a fully successful treatment for peripheral nerve involvement, however, has not yet been established, and

only a few reports have suggested specific therapies [3-7].

We report on an LV patient presenting with multiple mononeuropathy, which helps identify the mechanism and has been successfully treated. In addition, we review 6 previous LV cases with multiple mononeuropathy in which nerve biopsies were performed. Written informed consent was obtained from the patient for publication of this case report.

## Case Report

The patient was a 46-year-old woman who came to the neuromuscular disease clinic of our institution mainly complaining of a left-foot drop. Although the patient had no history of trauma, she had suffered from radiating pain in the left lower extremity 3 months previously; 4 days before visiting our clinic, she suddenly had trouble moving her left foot.

The patient had been diagnosed with LV in 1996 and suffered painful ulcerations during the summer on all extremities. She denied other medical histories except surgery for an ectopic pregnant in 2008. There was no familial history. She took pentoxifylline and rivaroxaban prescribed by another clinic only in the summer but did not take them in the autumn voluntarily when she visited the clinic.

A clinical examination revealed skin lesions with livedo reticularis and multiple hyperpigmented patches on all extremities, and lower extremities had fibrosclerotic white scars. Muscle strength in her left leg was graded using the Medical Research Council (MRC) scale: ankle dorsiflexion, grade 1; great toe extension, grade 3; ankle plantarflexion, grade 4; and ankle eversion and inversion, grade 4 for each. No muscle weakness was observed in other muscles. There was a decrease in light touch and pin-prick sensation in the left lateral, posterior calf, foot dorsum, and sole. Both knees and ankles had decreased deep muscle reflexes, and there was no Babinski's sign or ankle clonus on either side. A steppage gait pattern was observed in the left leg during gait.

Laboratory tests were within normal limits for complete blood count, liver function test, electrolytes, prothrombin time, activated partial thromboplastin time. Her rheumatoid factor was elevated (36 IU/mL [normal < 14 IU/mL]). However, she was negative for antinuclear antibody Ab, direct and indirect Coombs test, anti-cyclic citrullinated peptide Ab, anti-Sjögren's-syndrome-related antigen A, B Ab, anticardiolipin immunoglobulin (Ig) G, M, anti-double-stranded DNA Ig G, and antineutrophil cytoplasmic Abs. She had negative serologic tests for syphilis, human immunodeficiency virus, and hepatitis B and C.

Lumbar spine magnetic resonance imaging showed no definite

**Table 1.** Nerve Conduction Study Findings 4 Days after the Patient First Experienced Foot Drop

| Nerve | Record site | Segment | Latency (ms) | Amplitude | NCV (m/s) |
|---|---|---|---|---|---|
| Motor | | | | | |
| Median (R/L) | APB | DL | 2.86/3.07 | 12.8/12.5 | |
| | | W-E | | 12.7/11.9 | 58.4/60.2 |
| | | F-wave | 24.01/24.22 | | |
| Ulnar (R/L) | ADM | DL | 3.07/2.70 | 10.7/10.3 | |
| | | W-E | | 9.8/10.1 | 65.1/61.9 |
| Peroneal (R/L) | EDB | DL | 3.02/2.45 | 3.3/3.6 | |
| | | A-BK | | 2.5/1.8 | 48.3/43.9 |
| | TA | DL | 3.02/2.45 | 3/2.5 | |
| | | BK-AK | | 2.7/2 | 49.2/46.8 |
| Tibial (R/L) | AH | DL | 3.39/3.44 | 11.5/10.4 | |
| | | A-PF | | 7.9/7.7 | 45.3/48 |
| | | F-wave | 46.35/46.25 | | |
| | | H-reflex | 28.44/28.39 | | |
| Sensory | | | | | |
| Median (R/L) | Digit III | F-W | | 50.1/53.4 | 42.0/41.3 |
| Ulnar (R/L) | Digit V | F-W | | 30.6/44 | 42.0/40.1 |
| Superficial peroneal (R/L) | Ankle | A-C | | NE/NE | |
| Sural (R/L) | Ankle | A-C | | NE/NE | |

Amplitudes are measured in millivolt (mV, motor) and microvolt (μV, sensory).
NCV, nerve conduction velocity; R, right; L, left; APB, abductor pollicis brevis; DL, distal latency; W, wrist; E, elbow; F, finger; ADM, abductor digiti minimi; EDB, extensor digitorum brevis; A, ankle; BK, below knee; TA, tibialis anterior; AK, above knee; AH, abductor hallucis; PF, popliteal fossa; C, calf; NE, not evoked.

abnormal findings. Computed tomography angiography in lower extremities was normal.

A nerve conduction study (NCS) was performed 4 days after the patient first complained of left-foot drop. She did not exhibit evoked sensory nerve action potentials (SNAPs) in either superficial peroneal or sural nerves. There were decreased amplitudes of the compound motor nerve action potentials (CMAPs) of both peroneal nerves recorded from the tibialis anterior muscles (Table 1). Needle electromyography showed no motor unit action potential (MUAP) in the left tibialis anterior muscle, but other sampled muscles had no abnormal findings (Table 2). The electrodiagnostic study showed multiple mononeuropathy involving both the common peroneal and sural nerves.

Follow-up NCS and needle electromyography were conducted 20 days after complaining foot drop. The SNAPs were not evoked in both superficial peroneal nerves; however, a SNAP in

**Table 2.** Needle Electromyography Findings 4 Days after the Patient First Experienced Foot Drop

| Muscle | IA | ASA | MUAP | Recruitment pattern | Interferential pattern |
|---|---|---|---|---|---|
| B. L2–L5 PSP | N | None | | | |
| B. BB | N | None | N | N | N |
| B. FCR | N | None | N | N | N |
| B. FDI | N | None | N | N | N |
| B. Gmax | N | None | N | N | N |
| B. Gmed | N | None | N | N | N |
| L. BF (short) | N | None | N | N | N |
| L. BF (long) | N | None | N | N | N |
| L. ST | N | None | N | N | N |
| B. VM | N | None | N | N | N |
| R. TA | N | None | N | N | N |
| L. TA | N | None | No MUAP | | |
| L. PL | N | None | N | N | N |
| L. TP | N | None | N | N | N |
| B. GCM (medial) | N | None | N | N | N |

IA, insertional activity; ASA, abnormal spontaneous activity; MUAP, motor unit action potential; B, both; PSP, paraspinalis; N, normal; BB, biceps brachii; FCR, flexor carpi radialis; FDI, first dorsal interosseous; Gmax, gluteus maximus; Gmed, gluteus medius; L, left; BF, biceps femoris; ST, semitendinosus; VM, vastus medialis; R, right; TA, tibialis anterior; PL, peroneus longus; TP, tibialis posterior; GCM, gastrocnemius.

**Table 3.** Nerve Conduction Study and Needle Electromyography Findings 20 Days after the Patient First Experienced Foot Drop

| | Record site | Segment | Latency (ms) | Amplitude | NCV (m/s) | IA | ASA | MUAP | Recruitment pattern | Interferential pattern |
|---|---|---|---|---|---|---|---|---|---|---|
| Motor nerve | | | | | | | | | | |
| Peroneal (R/L) | EDB | DL | 3.23/5.83 | 3.7/0.4 | | | | | | |
| | | A-BK | | 3.2/0.3 | 47.2/28.8 | | | | | |
| | TA | DL | 2.03/2.50 | 3.6/0.8 | | | | | | |
| | | BK-AK | | 3.6/0.7 | 50.1/34.9 | | | | | |
| Tibial (R/L) | AH | DL | 3.85/5.10 | 10.1/9.9 | | | | | | |
| | | A-PF | | 9.7/8.7 | 48.7/60.4 | | | | | |
| | | F-wave | 41.30/46.15 | | | | | | | |
| Sensory nerve | | | | | | | | | | |
| Superficial peroneal (R/L) | Ankle | A-C | | NE/NE | | | | | | |
| Sural (R) | Ankle | A-C | | 5.6 | 33.4 | | | | | |
| Muscle | | | | | | | | | | |
| L. TA | | | | | | Decreased | Fib/PSW | N | Reduced | Discrete |

Amplitudes are measured in millivolt (mV, motor) and microvolt (μV, sensory).
NCV, nerve conduction velocity; IA, insertional activity; ASA, abnormal spontaneous activity; MUAP, motor unit action potential; R, right; L, left; EDB, extensor digitorum brevis; DL, distal latency; A, ankle; BK, below knee; TA, tibialis anterior; AK, above knee; AH, abductor hallucis; PF, popliteal fossa; C, calf; NE, not evoked; N, normal.


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the right sural nerve was newly evoked with low amplitude. Amplitudes of the CMAPs in both peroneal nerves recorded on tibialis anterior muscles were decreased, more on the left side. In needle electromyography, fibrillation and positive sharp wave were observed in the left tibialis anterior muscle and MUAPs were newly observed with reduced recruitment patterns (Table 3).

A nerve biopsy was performed on the left sural nerve, and microscopic pathological examination showed asymmetric loss of myelinated fibers within and between the fascicles. There were hyalinized dermal blood vessels with intravascular thrombosis in the perineurium and extensive infarct of the peripheral nerve and Schwann cells. Only a few perivascular mononuclear cells infiltrates were observed (Fig. 1).

A day before the nerve biopsy, we prescribed her oral prednisolone 50 mg per day and enoxaparin 50 mg via subcutaneous injection twice per day first. Prednisolone had been given due to the possibility of secondary neuropathy derived from systemic inflammation of the LV. Five days after the start of treatment, oral rivaroxaban 10mg per day was substituted for enoxaparin. After confirming that the pathologic finding showed little inflammation, oral prednisolone was gradually stopped.

After 2 weeks, her left ankle dorsiflexion muscle strength improved to MRC grades 2. The patient continued to take oral rivaroxaban for 1 year. After a follow-up period of 1 year, her left ankle dorsiflexion gradually rose to MRC grade 5. The patient's gait pattern was normal, but numbness on the dorsum area of the left-foot persisted.

## Discussion

LV pathogenesis is related to occlusion of the cutaneous capillary circulation leading to thrombosis, ischemia, and infarction [1]. However, LV can be secondary to rheumatoid arthritis, scleroderma, systemic lupus erythematosus, connective tissue disease, polyarteritis nodosa, Sjögren's syndrome, and solid organ or hematologic malignancies [1].

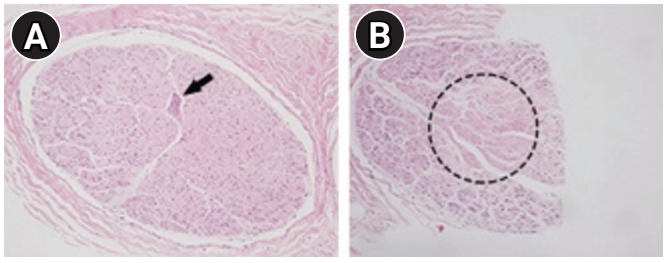


**Fig. 1.** Sural nerve biopsy, lateral malleolus, left. (A) Hyalinized dermal blood vessels with an intravascular thrombosis (arrow) (paraffin section; H&E, ×100). (B) Severe loss of myelinated fibers and some axonal degeneration due to ischemic necrosis (circle with dotted line) (paraffin section; H&E, ×100).

There have been 6 previously reported LV cases with multiple mononeuropathy in which nerve biopsies were performed (Table 4) [2-4,6-8]. Nerve biopsies in 3 cases (Pai and Pai [6], Toth et al. [7], and Tubone et al. [8]) showed chronic histologic findings; a nerve biopsy performed by Malaguti et al. [4] showed pleomorphic mononuclear cell infiltration in the endoneurium, perineurium, and epineurium. Four histologic findings from nerve biopsies could not distinguish whether multiple mononeuropathy in LV was derived from inflammation or infarction.

The peripheral nerve involvement in our patient was derived from ischemic injury rather than inflammation. In our case, the laboratory results showed no evidence of connective tissue disease or vasculitis. The sural nerve biopsy showed intravascular thrombosis in the perineurium and extensive infarct of the peripheral nerve and Schwann cells but few perivascular mononuclear cells infiltrates. Prednisolone, which was administered before the biopsy, had the potential to suppress inflammation; however, the biopsy was conducted the day after the treatment, which was unlikely to have a significant effect on the pathology result.

Similarly, the report by Kim et al. [3] described a patient who had occasional perivascular lymphocytes infiltrating the arterioles in the epineurium; moreover, the patient's nerve biopsy showed endoneurial capillary congestion with hemorrhage and infarct in the peripheral nerve and Schwann cells. The histologic findings from both our case and Kim et al. [3]'s case demonstrate that the neuropathy of LV was primarily caused by capillary occlusion leading to ischemic injury rather than inflammation.

LV cases with peripheral nerve involvement are much rarer, and treatment for a neurologic deficit remains unknown. Our patient was initially treated with both anabolic steroids and anticoagulants before her histologic findings. After confirming the nerve biopsy findings, anabolic steroids were gradually discontinued. The patient had taken an anticoagulant, rivaroxaban, for over a year as maintenance therapy. After we added oral rivaroxaban to her drug regimen, the patient showed improved motor capability in her left ankle dorsiflexion with no complications.

Among the 6 previously reported cases of LV with multiple mononeuropathy, 4 were initially treated with anticoagulants, antiplatelets, anabolic steroids, or immunosuppressants (Table 4) [2-4,6-8].

In the case reported by Toth et al. [7], the patient had an improvement in skin lesions after treatment with anabolic steroids, but numbness appeared in a new location after steroid administration was discontinued. The sensory deficit improved after

**Table 4.** Nerve Biopsies in Previous Cases of Patients with Livedoid Vasculopathy and Multiple Mononeuropathy

| Study (year) | Type of study | Biopsy site (n) | Histologic findings | Motor symptom | Initial treatment | Maintenance treatment | Outcome |
|---|---|---|---|---|---|---|---|
| Toth et al. [7], 2003 | Case report | Peroneal nerve (2) | Decreased large myelinated fibers with chronic axonal loss. Occasional lymphocytes near vessels. | None | Methylprednisolone, prednisone | Warfarin | Subjective improved sensation and skin lesion |
| Kim et al. [3], 2011 | Case report | Sural nerve (1) | Endoneurial capillary ectasia and hemorrhagic congestion. Extensive infarct in the peripheral nerve. Occasional perivascular lymphocytes infiltrating the arterioles in the epineurium. Intravascular thrombosis with mild lymphocytic infiltration in the epineurium. | None | Pentoxifylline, clopidogrel | | Not aggravated |
| Pai and Pai [6], 2013 | Case report | Sural nerve (1) | Chronic vasculitis with marked sectorial fiber loss and chronic axonopathy | Both distal upper limbs weakness | Prednisolone, azathioprine, pentoxifylline | Prednisolone, azathioprine | Complete healing in skin lesions |
| Tubone et al. [8], 2013 | Case report | Sural nerve (1) | Chronic neuropathy, degenerative alterations, and predominantly perivascular inflammatory infiltrate | None | Not mentioned | | |
| Malaguti et al. [4], 2015 | Case report | Sural nerve (1) | Symmetric loss of myelinated fibers. High proportion of fibers at different stages of Wallerian degeneration with regenerating small myelinated fibers. Some pleomorphic mononuclear cell infiltrates in the endoneurium, perineurium, and epineurium. | Left ulnar innervated hand muscles weakness | Acetylsalicylate | | Improved neurological symptoms |
| Gardette et al. [2], 2018 | Observational study | Undescribed (1) | Severe loss of myelinated axons associated with vasculopathy. Alterations of the endoneurium with endothelial cell damage and necrosis of capillaries. | None | Not mentioned | | |
| Current case | Case report | Sural nerve (1) | Asymmetric loss of myelinated fibers. Hyalinized dermal blood vessels with intravascular thrombosis in the perineurium. Extensive infarct of the peripheral nerve. Few perivascular mononuclear cell infiltrates. | Left foot drop | Enoxaparin, prednisolone | Rivaroxaban | Complete motor recovery |

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treatment with an appropriate dose of warfarin. In the case described by Kim et al. [3], the patient received antithrombotic and antifibrinolytic agents and had no further attacks, but improvement in neurological symptoms was not described.

Two cases of LV with multiple mononeuropathy showed motor impairment. In the case reported by Pai and Pai [6], there was no motor improvement after treatment with antiplatelets, an anabolic steroid, and an immunosuppressant agent. Malaguti et al. [4] described neurological improvement after treatment with acetylsalicylate, but the motor improvement was not communicated.

Rarely, multiple mononeuropathy can occur in LV. According to histologic findings of our case, multiple mononeuropathy in LV was induced by ischemic injury rather than inflammation. In this case, multiple mononeuropathy in LV with motor deficits showed good clinical outcomes after anticoagulant treatment; therefore, it is thought that early anticoagulation treatment may be helpful in LV with peripheral nerve involvement.

## Conflict of Interest

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

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CASE REPORT

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# 전이성 뇌종양에서 확인된 말초운동신경의 연접횡단 변성: 2예에서 관찰된 전기생리학적 소견

원준희, 채현준, 김기원, 현성은
서울대학교 의과대학 서울대학교병원 재활의학과

# Trans-Synaptic Degeneration of Peripheral Motor Axons from Metastatic Brain Tumors: Electrophysiological Findings in Two Cases

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Denervation potentials obtained during electromyography (EMG) are usually considered as evidence of axonal degeneration in the peripheral nervous system (PNS). However, they may also appear when only central nervous system (CNS) lesions exist. Here, we present trans-synaptic degeneration from CNS lesions in 2 cases with electrophysiologic findings of motor axon degeneration caused not by PNS lesions, but by metastatic tumors involving the corresponding primary motor cortexes. When cancer patients show denervation potentials in needle EMG results, physicians usually consider PNS-related etiologies first, such as drug-induced generalized peripheral polyneuropathy or metastatic lesions (e.g., Pancoast tumor). However, metastatic brain tumors in the motor cortex could cause the same denervation potentials as PNS lesions, such as cervical polyradiculopathies or plexopathies. When PNS-type abnormalities are revealed on EMG in cancer patients, further screening to evaluate CNS lesions involving the corresponding corticospinal tracts should be included to ensure a timely and proper intervention.

**Keywords:** Brain neoplasms; Nervous system; Trans-synaptic degeneration

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## Introduction

Cancer patients suffer from various neuromuscular complications during their clinical courses. If cancer patients mainly complain of lower motor neuron (LMN) symptoms, electrodiagnostic study (EDX) is usually recommended to localize any abnor-

malities in the peripheral nervous system (PNS).

Although abnormal spontaneous activities such as fibrillation and positive sharp waves are diagnostic characteristics of PNS pathologies, lesions of the central nervous system (CNS) generate such abnormalities in the needle electromyography (EMG) results through motor neuronal axonal degeneration [1,2]. This can cause confusion in interpreting electrophysiologic studies and diagnostic errors while planning appropriate therapy for cancer patients. Herein, we report 2 cases of motor weakness of LMN type with a huge amount of denervation potentials, actually caused by axonal degeneration from metastatic brain tumors.

## Case Reports

### Case 1

A 62-year-old female visited the outpatient clinic complaining of pain in her right shoulder and right upper extremity which lasted for 3 months. She underwent exploratory laparotomy and resection for ovarian cancer 2 years ago, followed by adjuvant chemotherapy with paclitaxel and carboplatin. Thereafter, approximately 1 year ago, a computed tomography (CT) scan further revealed newly appeared lymph node metastasis. During conservative care for recurred ovarian cancer, she suddenly experienced upper extremity pain and difficulty in moving her arm. On physical examination using the Medical Research Council (MRC) scale, the right shoulder abduction and elbow flexion were grade 3, while elbow extension, wrist dorsiflexion, wrist volar flexion, and finger flexion were grade 2. Muscle strength in the patient's left arm was normal. Light touch sensation was diminished on her entire right arm and hand. The muscle stretch reflexes were increased in right biceps, brachioradialis, and bilateral quadriceps.

EDX was first performed to differentiate brachial plexopathy from a metastatic lesion versus cervical spinal metastasis, due to asymmetric, focal-distributed weakness. The nerve conduction study (NCS) results were normal. The needle EMG demonstrated profound fibrillation potentials and positive sharp waves in the right biceps, pronator teres, flexor carpi ulnaris muscles (Fig. 1A). The interference pattern was also reduced in the entire sampled muscles in her right upper extremity, and her left first dorsal interosseous and pronator teres muscle (Table 1).

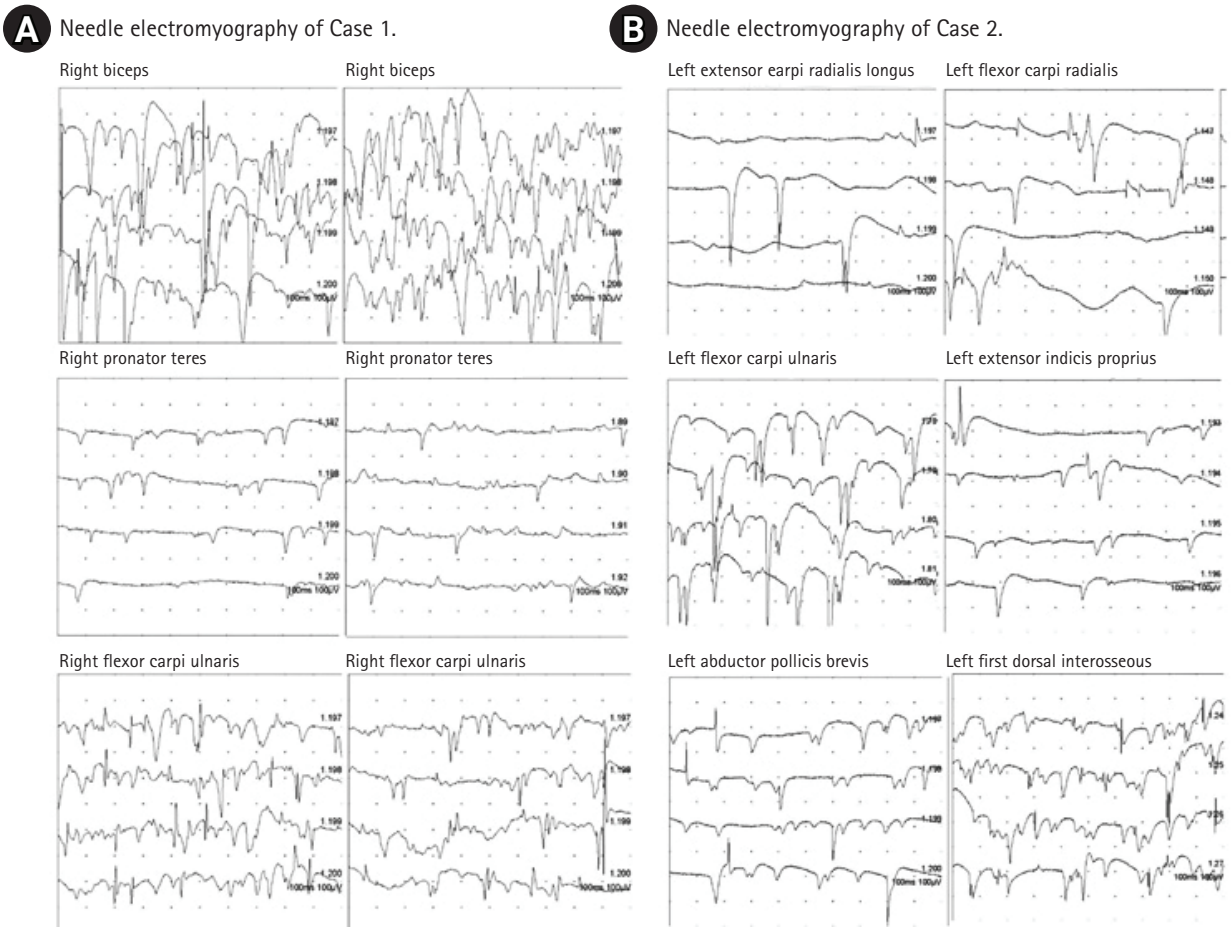


Fig. 1. Electromyography shows abundant positive sharp waves and fibrillation potentials in the muscles of case 1 (A) and case 2 (B).

**Table 1.** Nerve Conduction Study and Needle Electromyography Results of Case 1

| | Nerve conduction study (right/left) | | | | | | Needle electromyography | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Spontaneous activity | | | MUAP | | | |
| | Stimulation site | Recording site | Latency (ms) | Amplitude | NCV (m/s) | F wave (ms) | IA | Fibrillation | PSW | Amplitude | Duration | Phase | Interference pattern |
| Motor nerve | | | | | | | | | | | | | |
| Median | Wrist | APB | 3.18*/3.13 | 6.6/12.5 | 62/55.7 | 24.0/22.9 | | | | | | | |
| | Elbow | APB | 6.56/6.35 | 6.4/12 | | | | | | | | | |
| Ulnar | Wrist | ADM | 2.45/2.34 | 9.5/10.7 | 60/61.4 | 23.4/23.3 | | | | | | | |
| | Elbow | ADM | 5.36/5.52 | 8.8/9.9 | | | | | | | | | |
| Radial | Forearm | EIP | 2.29/2.14 | 5.5/4.8 | 67.9/63.4 | | | | | | | | |
| | Elbow | EIP | 4.43/4.74 | 4.7/4.7 | | | | | | | | | |
| Axillary | Erb's point | Deltoid | 1.88/2.34 | 11.1/10.2 | | | | | | | | | |
| MC | Erb's point | BB | 1.88/2.19 | 7.2/6.6 | | | | | | | | | |
| SS | Erb's point | SST | 1.98/2.03 | 10.1/9 | | | | | | | | | |
| | Erb's point | IST | 2.45/1.93 | 8.5/9.8 | | | | | | | | | |
| Sensory nerve | | | | | | | | | | | | | |
| Median | Wrist | Digit II | 2.71/2.6 | 39.7/38.8 | | | | | | | | | |
| Ulnar | Wrist | Digit V | 2.29/2.14 | 24.9/35.1 | | | | | | | | | |
| Radial | Forearm | Snuff box | 1.98/1.98 | 64.2/64.2 | | | | | | | | | |
| MAC | Elbow crease | Forearm | 1.2/1.35 | 18.1/20.5 | | | | | | | | | |
| LAC | Elbow crease | Forearm | 1.67/1.82 | 16.3/18.3 | | | | | | | | | |
| Muscle | | | | | | | | | | | | | |
| Rt. BB | | | | | | | NL | 3+ | 3+ | NL | NL | NL | Discrete |
| Rt. PT | | | | | | | NL | 2+ | 2+ | Large | NL | NL | Reduced |
| Rt. FCU | | | | | | | NL | 3+ | 3+ | NL | NL | NL | Discrete |
| Rt. EDC | | | | | | | NL | NL | NL | NL | NL | NL | Discrete |
| Rt. FDI | | | | | | | NL | NL | NL | Large | NL | NL | Reduced |
| Rt. C5 PSP | | | | | | | IIA | NL | NL | | | | |
| Rt. C6 PSP | | | | | | | NL | NL | NL | | | | |
| Rt. C7 PSP | | | | | | | NL | NL | NL | | | | |
| Lt. BB | | | | | | | NL | NL | NL | NL | NL | NL | Complete |
| Lt. PT | | | | | | | NL | NL | NL | Large | NL | NL | Reduced |
| Lt. FDI | | | | | | | NL | NL | NL | NL | NL | Polys | Reduced |

Amplitudes are measured in millivolt (mV, motor) and microvolt (μV, sensory).
NCV, nerve conduction velocity; IA, insertional activity; PSW, positive sharp wave; MUAP, motor unit action potential; APB, abductor pollicis brevis; ADM, abductor digiti minimi; EIP, extensor indicis proprius; MC, musculocutaneous; BB, biceps brachii; SS, suprascapular; SST, supraspinatus; IST, infraspinatus; MAC, medial antebrachial cutaneous; LAC, lateral antebrachial cutaneous; Rt., right; NL, normal; PT, pronator teres; FCU, flexor carpi ulnaris; EDC, extensor digitorum communis; FDI, first dorsal interossei; PSP, paraspinalis; IIA, increased insertional activity; Lt., left.
*Indicating abnormal findings of nerve conduction study result.

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Based on the initial EDX indicating right cervical polyradiculopathies, we first suspected spinal metastasis as the primary cause for her pain and weakness. However, neither bone scan nor cervical spine magnetic resonance image (MRI) showed any evidence of bone or spinal cord metastasis. Subsequently, we conducted brain MRI which finally demonstrated multiple brain metastasis with perilesional edema in the left parietal lobe around the primary motor cortex, combined with lesions at the right temporal and the occipital lobes without involving the motor cortex (Fig. 2). She, therefore, underwent gamma knife surgery and chemotherapy for further management of brain metastasis.

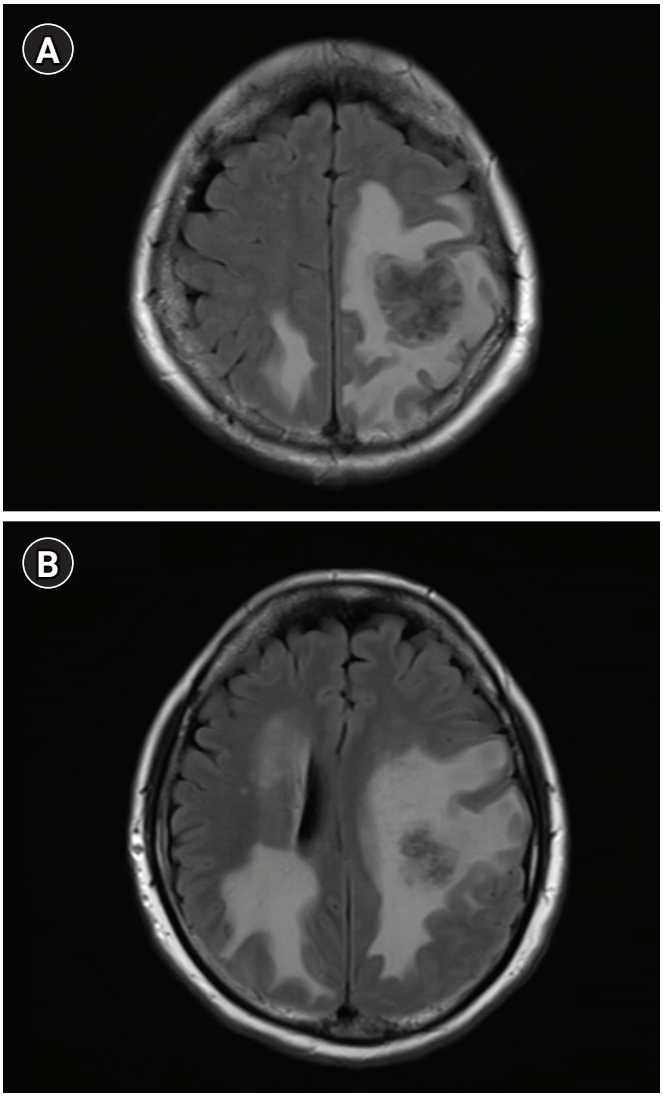


**Fig. 2.** Magnetic resonance imaging of the brain in case 1 (axial view). Fluid-attenuated inversion recovery images show (A) brain metastasis in the left parietal lobe, involving the primary motor cortex, and (B) peritumoral edema involving the white matter.

**Case 2**

A 61-year-old male presented with left-side upper extremity weakness that had aggravated since the past month. He explained that initial weakness started from only hand but spread to his proximal arm. He had a history of lung cancer with lymph node metastasis (adenocarcinoma, stage IIIA) and underwent concurrent chemoradiotherapy a year ago. Previous CT and 18F-fluorodeoxyglucose positron emission tomography (PET) scans 6 months ago showed a reduced size of lung cancer and no more lymph node metastasis, suggesting a stable disease state. The C-spine MRI at the time of this newly aggravating weakness and pain showed no definite pathologies to cause any neurologic symptoms of his left arm.

On the physical examination, his left shoulder abduction, elbow flexion, and elbow extension were grade 3, and his left finger extension and finger abduction were grade 0 according to the MRC scale. He felt pain and tingling sensation on the medial side of his left forearm and hand. Muscle stretch reflexes were all normal. Atrophy was definite in the intrinsic muscles of his left hand. To differentiate left brachial plexopathy or chemotherapy-induced peripheral polyneuropathy, EDX was conducted 1 month after the onset of weakness. The NCS showed decreased medial antecubital cutaneous sensory nerve action potential on the left side, undetectable compound motor action potential on the left radial nerve, and prolonged latencies in bilateral median sensory and motor nerves. The NCS results in right upper limb were normal except median nerve (Table 2). We observed abundant abnormal spontaneous activities in the left abductor pollicis brevis, first dorsal interosseous, extensor indicis proprius, flexor carpi radialis, flexor carpi ulnaris, and extensor carpi radialis longus muscles (Fig. 1B). No motor unit action potential (MUAP) was noted in the left first dorsal interosseous, extensor indicis proprius, flexor carpi radialis, flexor carpi ulnaris muscles, and MUAP recruitment decreased in the left deltoid, supraspinatus, and latissimus dorsi muscles. Otherwise, cervical paraspinal muscles and muscles in the right upper limb were normal. The EDX result suggested possibilities of left brachial plexopathy mainly involving lower trunk level or post-ganglionic cervical polyradiculopathies.

An immediate brain MRI followed when he visited the emergency room 15 days after the EDX due to abrupt progression of symptoms, weakness even in the lower limbs and gait disturbance. A cystic mass in the right frontoparietal lobe was diagnosed (Fig. 3). A PET scan showed the progression of lung cancer and hematogenous spread of multiple metastasis in the lung and brain, but without metastasis in the vertebrae, spinal cord, or brachial plexus. The patient was admitted and underwent gam-

**Table 2.** Nerve Conduction Study and Needle Electromyography Results of Case 2

| | Nerve conduction study (right/left) | | | | | | Needle electromyography | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Spontaneous activity | | | MUAP | | | |
| | Stimulation site | Recording site | Latency (ms) | Amplitude | NCV (m/s) | F wave (ms) | IA | Fibrillation | PSW | Amplitude | Duration | Phase | Interference pattern |
| Motor nerve | | | | | | | | | | | | | |
| Median | Wrist | APB | 4.95*/4.58* | 5.2/5.2 | 48.0*/51.3 | 29.8/30.9 | | | | | | | |
| | Elbow | APB | 9.74/9.06 | 4.7/4.8 | | | | | | | | | |
| Ulnar | Wrist | ADM | 2.66/2.92 | 7.9/6.6 | 60.5/52.6 | 27.2/33.2 | | | | | | | |
| | Elbow | ADM | 6.46/7.29 | 7.5/5.7 | | | | | | | | | |
| Radial | Forearm | EIP | 2.6/NR* | 7.3/NR* | 64/NR* | | | | | | | | |
| | Elbow | EIP | 3.54/NR* | 7/NR* | | | | | | | | | |
| Axillary | Erb's point | Deltoid | 4.32/4.06 | 14.8/14.1 | | | | | | | | | |
| MC | Erb's point | BB | 4.64/4.48 | 18.2/16 | | | | | | | | | |
| SS | Erb's point | SST | 2.6/3.54 | 9.3/7.2 | | | | | | | | | |
| | Erb's point | IST | 3.75/3.44 | 7.3/7.7 | | | | | | | | | |
| Sensory nerve | | | | | | | | | | | | | |
| Median | Wrist | Digit II | 3.23*/3.13 | 14.6/13.9 | | | | | | | | | |
| Ulnar | Wrist | Digit V | 2.14/2.08 | 15/15.9 | | | | | | | | | |
| Radial | Forearm | Snuff box | 2.19/2.19 | 15.8/13.1 | | | | | | | | | |
| MAC | Elbow crease | Forearm | 1.3/2.03 | 6.6/1.2* | | | | | | | | | |
| LAC | Elbow crease | Forearm | 1.88/1.15 | 21.4/12.4 | | | | | | | | | |
| Muscle | | | | | | | | | | | | | |
| Lt. APB | | | | | | | NL | 3+ | 3+ | NL | NL | Polys | Single |
| Lt. FDI | | | | | | | NL | 4+ | 4+ | | | | No MUAP |
| Lt. EIP | | | | | | | NL | 3+ | 3+ | | | | No MUAP |
| Lt. FCR | | | | | | | NL | 2+ | 2+ | | | | No MUAP |
| Lt. FCU | | | | | | | NL | 4+ | 4+ | | | | No MUAP |
| Lt. triceps | | | | | | | NL | NL | NL | NL | NL | NL | Complete |
| Lt. ECRL | | | | | | | NL | 3+ | 3+ | NL | NL | Polys | Single |
| Lt. BB | | | | | | | NL | NL | NL | NL | NL | NL | Complete |
| Lt. deltoid | | | | | | | NL | NL | NL | NL | NL | Polys | Reduced |
| Lt. SST | | | | | | | NL | NL | NL | NL | NL | Polys | Reduced |
| Lt. LD | | | | | | | NL | NL | NL | NL | NL | Polys | R/C |
| Lt. PM | | | | | | | NL | NL | NL | NL | NL | NL | Complete |
| Lt. SA | | | | | | | NL | NL | NL | NL | NL | NL | Complete |
| Lt. cervical PSP | | | | | | | NL | NL | NL | | | | |
| Rt. APB | | | | | | | NL | NL | NL | NL | NL | NL | Complete |
| Rt. FDI | | | | | | | NL | NL | NL | NL | NL | NL | Complete |

Amplitudes are measured in millivolt (mV, motor) and microvolt (μV, sensory).
NCV, nerve conduction velocity; IA, insertional activity; PSW, positive sharp wave; MUAP, motor unit action potential; APB, abductor pollicis brevis; ADM, abductor digiti minimi; EIP, extensor indicis proprius; MC, musculocutaneous; BB, biceps brachii; SS, suprascapular; SST, supraspinatus; IST, infraspinatus; MAC, medial antebrachial cutaneous; LAC, lateral antebrachial cutaneous; Lt., left; NL, normal; FDI, first dorsal interossei; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; ECRL, extensor carpi radialis longus; LD, latissimus dorsi; PM, pectoralis major; SA, serratus anterior; PSP, paraspinalis; Rt., right.
*Indicates abnormal NCS results; left brachial plexopathy mainly involving lower trunk level or post-ganglionic cervical polyradiculopathies, combined with carpal tunnel syndrome on the right side.

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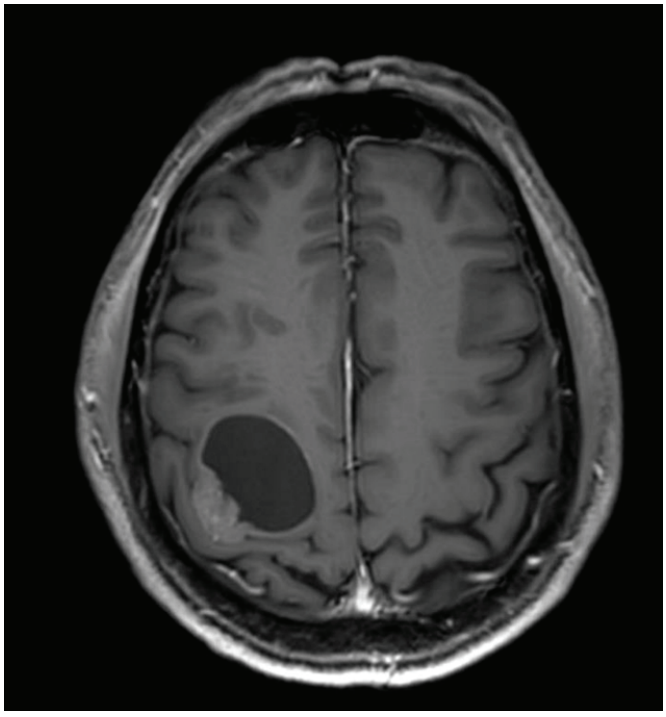

Fig. 3. Magnetic resonance imaging of the brain in case 2. Axial T1-weighted contrast-enhanced images demonstrate cystic metastasis of lung cancer in the right frontoparietal lobe.

ma knife surgery for brain metastasis of lung cancer.

## Discussion

Both patients developed LMN-type weakness and initially were misdiagnosed as radiculopathy or plexopathy according to the EDX. If cancer patient complains of neurologic symptoms, the following diagnoses should all be considered; direct effect of the primary tumor or metastasis involving the nervous system and the indirect effect of paraneoplastic syndrome, neural damage due to cancer treatment [3] or other idiopathic pathology such as neuralgic amyotrophy. In these cases, generalized peripheral polyneuropathy owing to paraneoplastic syndrome or chemotherapy was excluded based on the EDX abnormalities limited in unilateral arm. As the patient in case 1 complained prolonged weakness and pain more than 3 months and the patient in case 2 presented weakness without pain, the clinical course of two cases is different from that of neuralgic amyotrophy, typically presenting new-onset pain which develops suddenly and disappears and subsequent weakness [4]. Therefore, neuralgic amyotrophy could be ruled out. The possibility of lesions in anterior horn cell, spinal nerve root, or plexus, initially suggested following the EDX in our cases, was further excluded by additional spine MRIs or PETs. The brain metastasis damaging the corresponding motor cortex of symptomatic limbs, was only lesion that can explain patients' weakness.

The EDX abnormalities in both patients, originated from the CNS lesions, can be explained by antegrade transneuronal degradation of α-motor neurons, also known as trans-synaptic degeneration (TSD) from motor cortex/corticospinal tracts. TSD is the spread of neuronal degradation into adjacent neurons caused by the loss of trophic signals of nearby neurons. Likewise, the deprivation of upper motor neuron control of α-motor neurons could further influence of axonal flow and result in axonal degeneration in the secondary motor neurons as well [2]. Alternatively, neurotoxic molecules or signals from metastatic lesions may transport from the upper motor neuron to the LMN to induce LMN degeneration.

This phenomenon was also previously described in patients with several other types of CNS lesions. Zhang et al. [5] demonstrated secondary neurodegeneration at the substantia nigra or ipsilateral thalamus after middle cerebral artery territory infarctions. Nonetheless, the existence of TSD through the corticospinal tracts outside the brain is still controversial. A postmortem study suggested that peripheral α-motor neurons were not likely to exhibit similar Wallerian degeneration of corticospinal tracts because other inputs from various afferent systems via interneurons continued [6]. However, an animal study discovered neuronal loss in the ventral horns in rats with infarction at the contralateral side [7], and severe secondary degeneration was also reported in peripheral motor axons below the level of injury in patients with spinal cord injury [8]. In stroke patients, denervation-potentials were found at affected limbs after 2 to 3 weeks since onset, continued until 1 year, and usually diminished when volitional activity and spasticity developed. The abnormal spontaneous activities were more predominant in upper extremities than lower extremities, and in distal muscles than proximal ones, suggested as distal hand muscles receive more cortical innervations [2].

In addition to stroke, primary brain tumors also reported Wallerian degeneration in the corticospinal tracts [9,10]. However, the involvement pattern of TSD in cancer patients was not reported in previous studies. Although serial EDX were not followed, these two cases illustrated abundant denervation potentials 1 to 3 months after symptom, but no definite discrepancy between proximal and distal muscles. Further studies are required to evaluate the pattern, progression, and clinical impact of this TSD superimposed on already paretic limbs from CNS metastases. Since any CNS insult could cause an accompanying PNS dysfunction through this TSD, the functional disability of

patients would be aggravated if this additional pathologies are ignored and only spontaneous recovery after CNS lesions are appreciated.

In conclusion, any metastatic CNS lesions involving corticospinal tracts responsible for weakened muscles should also be included in the list for differential diagnosis, even when cancer patients complained of focal, LMN-type neurologic symptoms. Although denervation potentials are usually considered as common evidence of PNS lesions, such fibrillations and positive sharp waves can appear from brain metastatic lesions if motor cortex fail to generate normal trans-synaptic signals to motor axons and peripheral muscles.

## Conflict of Interest

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

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# 가슴 무딘 외상에 따른 편측 횡격막 신경 마비: 증례 보고

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# Unilateral Phrenic Nerve Palsy Following Blunt Chest Trauma: A Case Report

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Phrenic nerve (PN) injury without a direct injury is unusual and difficult to diagnose. This case report is the first to describe the diagnosis of unilateral PN palsy following blunt chest trauma by fluoroscopic diaphragmatic movement testing (FDT) and electrodiagnostic testing. A 68-year-old man was admitted to the emergency department after a motorcycle accident. Chest radiography showed an elevated right hemidiaphragm. More than 7 months later, he experienced dyspnea on exertion and orthopnea, prompting him to visit the Department of Physical Medicine and Rehabilitation. FDT showed no movement in the right diaphragm during maximum inspiration and expiration, but the left diaphragm was intact. Electrodiagnostic testing showed absent compound motor action potential (CMAP) in the right diaphragm, but normal CMAP in the left diaphragm. We hypothesize that in patients with orthopnea symptoms after blunt chest trauma, electrodiagnostic testing paired with FDT may be useful for diagnosing diaphragm palsy.

**Keywords:** Phrenic nerve; Blunt trauma; Fluoroscopy

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## Introduction

The phrenic nerve, the only nerve supply to the diaphragm, is both a sensory and motor nerve. Weakness in the primary respiratory muscle causes respiratory dysfunctions. The diaphragm functions as 2 separate units, a left and a right hemidiaphragm. The paresis of one hemidiaphragm can be completely asymptomatic as its counterpart and external intercostal muscles compensate for the weakened hemidiaphragm [1]. The causes of diaphragmatic palsy are divided into the following categories: traumatic, compression, neurological, infectious, and idiopathic. Cardiovascular surgery is the most common source of traumatic phrenic nerve palsy. Penetrating trauma is also another trigger of diaphragmatic muscle rupture or phrenic nerve damage [2]. As opposed to penetrating trauma, blunt trauma is caused by physical trauma of impactful force to a body part [3]. Phrenic nerve

injury after penetrating trauma is identifiable, but phrenic nerve injury after chest blunt trauma is unusual, and it is often misdiagnosed as a diaphragmatic rupture.

The cause of the diaphragm elevation was difficult to identify through chest radiography and a CT scan, so we conducted an electrodiagnostic test and fluoroscopic diaphragmatic movement test (FDT). On the basis of these results, we diagnosed phrenic nerve palsy following chest blunt trauma. Many studies have shown that FDT and electrodiagnostic tests can be helpful in diagnosing phrenic nerve palsy [2]. This case report is the first to diagnose unilateral phrenic nerve palsy following chest blunt trauma by employing fluoroscopic diaphragmatic movement test and an electrodiagnostic test.

## Case Report

A 68-year-old man was admitted to the emergency department due to a motorcycle accident. During the accident, he struck his right chest against the motorcycle's handlebar and fell on his right side. He experienced loss of consciousness for approximately 10 minutes, but no shortness of breath or nausea. His chest radiograph showed fractures of the right 4th and 5th ribs. The trachea was deviated to the right of the midline and showed an elevated right hemidiaphragm (Fig. 1A). The patient's chest CT scan showed multifocal subsegmental atelectasis in the left lingular segment, right middle lobe, and right lower lobe. He left emergency department under his own strength. The day after the accident, he experienced dyspnea when lifting objects, but no shortness of breath when walking or doing other daily activities. He was also unable to lay supine because of shortness of breath. To address these symptoms, 130 days after their onset, he visited the Department of Respiratory Medicine. To relieve the patient's respiratory distress, 221 days after the onset of his symptoms, he was transferred to the Department of Physical Medicine and Rehabilitation for pulmonary rehabilitation.

The patient was a farmer with a smoking history (30 years). His medical history was unremarkable aside from hypertension of 10 years' duration and alcoholic liver cirrhosis of 1 year duration. The patient's chest radiograph taken during our evaluation process prior to pulmonary rehabilitation continued to show an elevated right diaphragm and the trachea was deviated to the right of the midline (Fig. 1B). The previously observed rib fractures were no longer present, and the patient presented with no complaints of chest wall tenderness. Pulmonary function tests revealed forced vital capacity (FVC) in a sitting position of 3.01 L (90% of what was predicted), and FVC in a supine position of 2.89 L (87% of what was predicted). Maximum inspiratory pressure (MIP) was 71 $cmH_2O$ (98.7% of what was predicted) and maximum expiratory pressure was 115 $cmH_2O$ (118.1% of what was predicted). These test results did not suggest diaphragm palsy, as the decrease in FVC in the supine position was not significant and MIP was almost within the normal range. Despite these results, the elevated diaphragm observed in the chest radiograph and the orthopnea symptoms prompted us to further evaluate the patient. We used fluoroscopy to observe inspiration and expiration of the diaphragm as well as an electrodiagnostic test to dif-

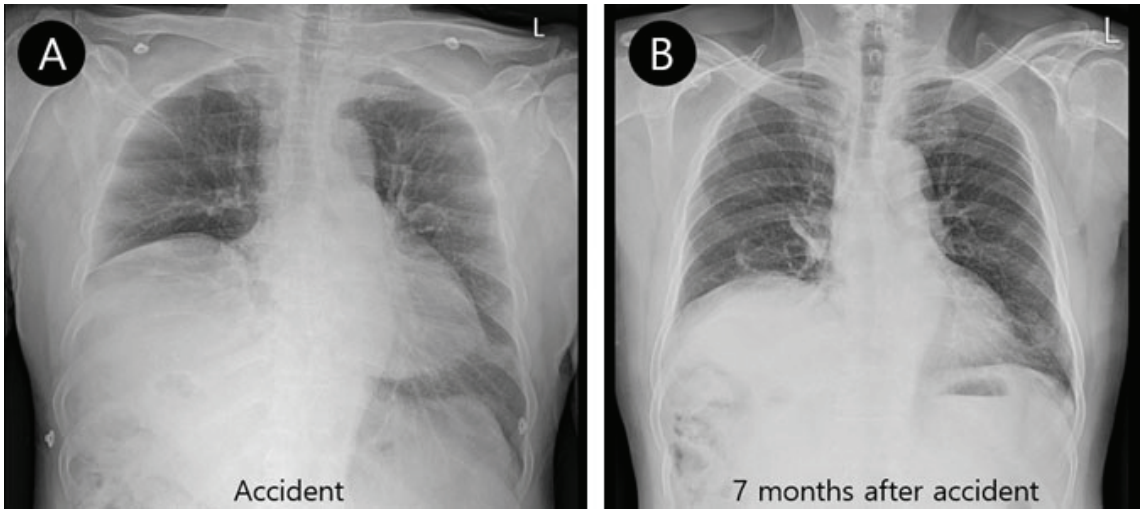


**Fig. 1.** (A) Chest radiograph at admission shows that the trachea was deviated to the right of the midline and an elevated right hemidiaphragm. (B) Chest radiograph taken 228 days after onset continued to show an elevated right diaphragm, although the new radiograph reflected mild improvement since the previous chest radiograph was taken. The new radiograph also showed that the trachea was deviated to the right of the midline.


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ferentiate right hemidiaphragm palsy. Anteroposterior fluoroscopic images were acquired with a C-arm image intensifier (BV Pulsera mobile C-arm; Philips Healthcare Co., Ltd., The Netherlands) with the patient in a seated position. In the examination process, the patient was instructed to inhale deeply and exhale as much as possible. Each sequence was recorded for each hemidiaphragm. The FDT showed no movement in the right diaphragm during maximum inspiration and expiration, but normal movement in the left diaphragm (Fig. 2).

The electrodiagnostic test for the phrenic nerve was performed on day 221 after the patient's accident. Surface stimulation was performed above the clavicle, just lateral to the sternal portion of the sternocleidomastoid muscle. During surface stimulation, a ground electrode was placed on the sternum, an active electrode was fixed on the eighth intercostal space at the anterior axillary line, and a reference electrode was placed caudal to this on the ninth intercostal space. The results revealed that the right diaphragm had an absence of compound motor action potential (CMAP). In contrast, the left phrenic nerve's CMAP amplitude was decreased (0.1 mV) and the CMAP latency was within a normal range (7.85 ms) (Fig. 3).

## Discussion

The present case demonstrates that an electrodiagnostic test and FDT are useful in the diagnosis of phrenic nerve palsy following chest blunt trauma.

Electrodiagnostic tests of the phrenic nerve have been used to evaluate patients with respiratory failure and suspected neuromuscular disorders [4]. There was a study on the stimulation location of the phrenic nerve and this study reported that the ideal stimulation location is the supraclavicular fossa just above the clavicle [5]. Based on their study's findings, we performed supramaximal stimulation in the supraclavicular fossa just above the clavicle. In our case, the absence of CMAPs in the right diaphragm indicated that the right phrenic nerve was severely injured.

Previous study reported that the amplitude lower limit of the left phrenic nerve was 0.25 mV and the upper limit of latency was 8.56 ms in healthy subjects [6]. CMAP onset latency is a useful parameter for detecting phrenic nerve demyelination and CMAP amplitude can be used to detect neuronal or axonal lesions [7]. The CMAP amplitude of our patient's phrenic nerve was decreased (0.1 mV) and his CMAP latency was within a normal range (7.85 ms). This indicated that the left phrenic nerve was also damaged, but no abnormal findings were observed in the dynamic imaging test. Phrenic nerve conduction studies (NCSs), in contrast with other motor NCSs, are technically challenging as the examiner is unable to visualize the twitching of the target muscle. As a consequence, phrenic NCSs performed in isolation are associated with false negative results [8]. This aspect of the NCSs prompted us to hypothesize that dynamic imaging study might enhance diagnostic accuracy of phrenic nerve palsy.

Previous study reported that in patients with complete hemidiaphragm palsy, FVC in a supine position decreased by 15% to 20% and MIP reduced to approximately 60% [2]. These results showed that the pulmonary function test conducted in supine position was helpful in diagnosing diaphragm palsy. In our case, diaphragm palsy was difficult to detect by pulmonary function testing as the values mentioned above were near normal range. This could be due to the other respiratory muscles sufficiently compensating for the weakened diaphragm. In a previous study, although it was an animal experiment, there was a report that compensatory change in inspiratory related muscle activation occurred 14 days after onset in the presence of unilateral diaphragm paralysis [9]. In our case, we thought that the onset was long enough for compensation to occur and the symptoms in

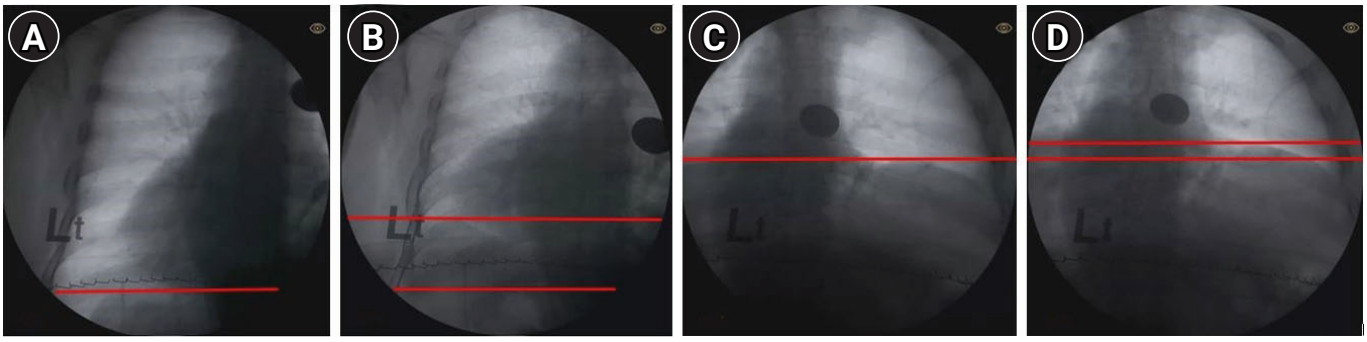


Fig. 2. Anteroposterior fluoroscopic images with the patient in a seated position. Left diaphragm during maximum inspiration (A) and expiration (B). Right diaphragm during maximum inspiration (C) and expiration (D). The patient's fluoroscopic sniff test showed no movement in the right diaphragm during maximum inspiration and exhalation, but normal movement in the left diaphragm.

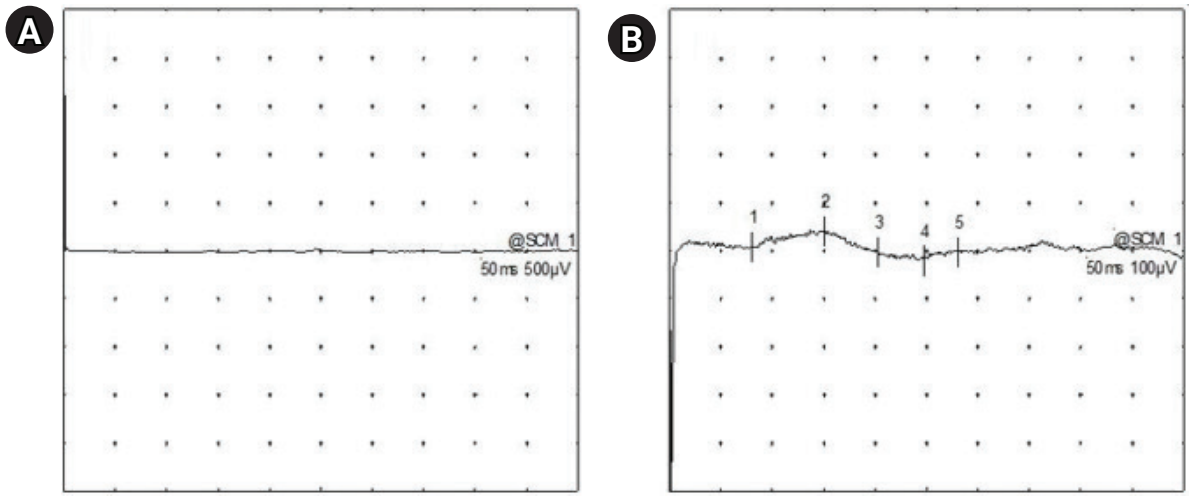


**Fig. 3.** An electrodiagnostic test for the phrenic nerve was performed on day 221 after the patient's accident. (A) The right diaphragm showed an absence of compound motor action potential (CMAP). (B) In contrast, the CMAP amplitude of the left phrenic nerve was decreased (0.1 mV) and CMAP latency of the left phrenic nerve was within the normal range (7.85 ms).

daily life were not prominent, so the decrease in pulmonary function test was not observed. It was more important to see the diaphragm's movement through imaging tests and check the phrenic nerve's condition.

In normal individuals, both hemidiaphragms descend caudally during tidal breathing by at least one intercostal space [2]. In our patient's case, the left hemidiaphragm showed more than one intercostal space movement, but almost no movement in the right hemidiaphragm.

There have been rare case of a patient with phrenic nerve palsy following chest blunt trauma [10]. They observed that the patient could maintain his airway and that self-ventilation was possible; this was similar to our patient's case. The patient mentioned in this report underwent a chest radiography and a chest CT scan. He was misdiagnosed with diaphragmatic rupture and was given surgical treatment [10]. If an electrodiagnostic test and FDT had been performed, then he would not have needed the laparotomy. Considering that phrenic nerve travels downward into the chest to pass between the heart and lungs towards the diaphragm, a nerve injury due to chest blunt trauma cannot be fully explained unless it is a direct injury. An accurate diagnosis is still important, even if chest radiographs and chest CT scans showed no evidence of a phrenic nerve injury.

To prevent early pulmonary complications, diaphragm palsy needs to be diagnosed accurately and as early as possible. Early detection of unilateral diaphragmatic paralysis also predicts a patient's prognosis. This will help to establish proper treatment strategies.

In conclusion, finding the cause of diaphragm elevation using only chest radiographs and CT scans are insufficient. If patients complain of unexplained shortness of breath in a supine position, experience orthopnea, and show an elevated diaphragm on chest radiographs, a thorough diagnosis is needed. An electrodiagnostic test paired with FDT are useful in the diagnosis of phrenic nerve palsy following chest blunt trauma.

## Conflict of Interest

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

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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

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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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## 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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## Supplementary Materials

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

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CASE REPORT

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# 탈수초신경병으로 최초 진단 후 유전성 Transthyretin 아밀로이드증으로 최종 진단된 증례 모음

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# Hereditary Transthyretin Amyloidosis Misdiagnosed as Demyelinating Neuropathy: A Report of Three Cases

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Transthyretin amyloidosis (aTTR) is a life-threatening type of systemic amyloidosis that has been associated with autosomal dominant mutations in the transthyretin gene. In this case series, we reviewed 3 patients initially treated for acquired demyelinating neuropathy that was later confirmed by pathologic testing and genetic analysis as aTTR. These patients had systemic symptoms and family records of sudden deaths that could not be explained by acquired demyelinating neuropathy. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a treatable neuropathy; however, 20% to 33% of CIDP patients remain refractory to conventional immunotherapy, and incorrect diagnoses might be the cause of this therapeutic failure. This case series revealed that the electrophysiological findings of aTTR could resemble the findings of demyelinating neuropathy.

**Keywords:** Amyloidosis; Polyneuropathies; Polyradiculoneuropathy, chronic inflammatory demyelinating

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## Introduction

Transthyretin amyloidosis (aTTR) is a rare life-threatening systemic amyloidosis resulting from autosomal dominant mutations in the transthyretin (*TTR*) gene. Amyloid deposition in the peripheral nerves causes a form of polyneuropathy known as familial amyloidotic polyneuropathy [1].

Identification of demyelination features in the diagnosis of polyneuropathy is clinically important because of their treatable characteristics. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a typical example of treatable acquired polyneuropathies. Patients with CIDP usually receive immunotherapy including intravenous immunoglobulin, plasmapheresis, or corticosteroids. However, 20% to 33% of CIDP patients remain refractory [2]. The refractory CIDP is not completely understood; however, incorrect diagnosis is considered to be among the causes of this therapeutic failure [3,4]. The most commonly used electrophysiological criteria for CIDP showed 80% of accu-

racy and this limitation can sometimes lead to misdiagnoses resulting to prescription of ineffective treatment [5,6].

We performed a retrospective review of 3 patients initially treated as acquired demyelinating polyneuropathy such as CIDP but finally confirmed as aTTR. This report was approved by the Institutional Review Board (IRB) and the Pharmacy and Therapeutic Committees at Konkuk University Medical Center, Seoul, South Korea (No. KUH1170167). In consideration of the characteristics of medical record analysis, informed consent was waived by the IRB.

## Case Reports

The clinical characteristics and the *TTR* gene mutations of the 3 aTTR patients are summarized in Table 1.

### Case 1

This male patient initially exhibited paresthesia of both lower limbs at the age of 38. After 3 years of progression of the sensory symptoms, he developed weakness of his distal limbs in a length-dependent pattern. His mother had died of heart disease but there was no information on whether she had any form of neuropathy. On the initial nerve conduction study (NCS), a severe sensorimotor polyneuropathy was noted. Conduction block and increased duration of compound muscle action potential (CMAP) were presented on 3 nerves in both upper limbs (Table 2, Fig. 1). The laboratory tests excluded all other potential causes of demyelinating polyneuropathy. The patient was treated with oral prednisolone (1 mg/kg for a month) and intravenous immunoglobulin (over a course of 2 g/kg, divided within 5 days) without improvement. He further developed new symptoms, including orthostatic hypotension and diarrhea. Dilated cardiomyopathy was confirmed by echocardiography. After the presentation of autonomic symptoms, he was diagnosed with amyloidosis by colon tissue biopsy and was genetically confirmed to have a Lys35Asn mutation in the *TTR* gene.

### Case 2

This female patient initially presented urinary incontinence at the age of 45, 2 years before the onset of the neuropathic symptoms. The patient had already been aware of her high arched foot in her 40s. She referred to the neurology department with progressive generalized weakness and anorexia. Her father had died in his 60s of an unknown cause. On neurological examination, amyotrophy of her feet and distal dominant weakness with sensory loss were noted. Upon electrophysiological examination, severe sensorimotor polyneuropathy was identified (Table 2). Late responses and motor nerve conduction of the lower limbs were not evoked, whereas significantly delayed terminal latencies, slow nerve conduction velocities and extended duration of CMAP were indicative of demyelinating neuropathy. Despite of the administration of steroids, her symptoms kept worsening and she complained of decreased visual acuity. Considering that cataract caused by steroids, she was subjected to ophthalmological examination. Nevertheless, the vitreous opacity was associated to amyloid deposit. Holter monitoring confirmed arrhythmia with right bundle branch block of suggesting systemic dispersion of amyloidosis. Genetic analysis demonstrated that the patient was heterozygous for the Lys35Asn mutation in the *TTR* gene.

### Case 3

The third patient was a 46-year-old man who complained of weakness of distal lower limbs and paresthesia of all 4 limbs. He had lost 11 kg in 1 year, due to chronic diarrhea. On neurological examination, sensory loss and distal dominant weakness with a length-dependent pattern were noted. Upon electrophysiological examination, severe sensorimotor polyneuropathy was confirmed. On motor NCS, conduction block and increased duration of CMAP were presented on 2 nerves of both upper limbs (Table 2). Despite steroid treatment, he exhibited no clinical im-

**Table 1.** Summary of Patients' Clinical Features

| Patient | Sex | Age at onset (y) | Age at diagnosis (y, genetic analysis) | Main neurologic signs of neuropathy | Combined systemic symptoms | Mutation |
|---|---|---|---|---|---|---|
| 1 | Male | 38 | 42 | Distal dominant weakness and paresthesia of all limbs<br>Generalized areflexia | Diarrhea<br>Arrhythmia<br>Orthostatic hypotension | Lys35Asn |
| 2 | Female | 45 | 47 | Distal dominant weakness of lower limbs<br>Generalized areflexia<br>Carpal tunnel syndrome | Urinary incontinence<br>Arrhythmia<br>Cataracts | Lys35Asn |
| 3 | Male | 45 | 46 | Distal dominant weakness of lower limbs<br>Generalized areflexia | Diarrhea<br>Orthostatic hypotension | Ala36Pro |


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**Table 2.** Patients' Initial Nerve Conduction Studies

| Nerve/site | Latency (ms)* | | | Amplitude | | | NCV (m/s) | | | Peak duration (ms) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patient 1 | Patient 2 | Patient 3 | Patient 1 | Patient 2 | Patient 3 | Patient 1 | Patient 2 | Patient 3 | Patient 1 | Patient 2 | Patient 3 |
| Motor NCS | | | | | | | | | | | | |
| Right median nerve | | | | | | | | | | | | |
| Wrist | 4.45 | 9.05 | 5.15 | 7.7 | 0.7 | 5.2 | | | | 7.0 | 7.20 | 7.05 |
| Elbow | | | | 3.1 | 0.5 | 2.4 | 45.7 | 22.3 | 38.4 | 8.65 | 7.05 | 4.75 |
| Axilla | | | | 2.8 | 0.5 | 2.1 | 53.3 | 25.5 | 57.1 | 8.65 | 6.50 | 4.85 |
| F-wave | 27.6 | 65.6 | 36.0 | | | | | | | | | |
| Left median nerve | | | | | | | | | | | | |
| Wrist | 4.95 | 9.85 | 4.10 | 6.5 | 2.6 | 5.4 | | | | 5.5 | 8.60 | 6.60 |
| Elbow | | | | 3.5 | 2.2 | 4.4 | 51.9 | 20.8 | 43.5 | 5.4 | 10.0 | 6.90 |
| Axilla | | | | 2.7 | 2.0 | 4.4 | 60.0 | 27.7 | 57.1 | 10.0 | 10.0 | 6.90 |
| F-wave | 27.20 | 66.5 | 28.4 | | | | | | | | | |
| Right ulnar nerve | | | | | | | | | | | | |
| Wrist | 3.60 | 7.05 | 6.40 | 6.8 | 2.7 | 0.9 | | | | 6.50 | 7.55 | 5.95 |
| Below the elbow | | | | 3.0 | 1.5 | 0.7 | 54.1 | 15.7 | 20.2 | 5.85 | 8.05 | 8.80 |
| Above the elbow | | | | 3.0 | 1.5 | 0.6 | 62.1 | 19.4 | 34 | 9.10 | 9.60 | 9.40 |
| Axilla | | | | 2.9 | 1.4 | 0.6 | 66.7 | 18.6 | 60 | 9.60 | 10.6 | 8.65 |
| F-wave | 25.9 | NP | 30.0 | | | | | | | | | |
| Left ulnar nerve | | | | | | | | | | | | |
| Wrist | 4.60 | 6.6 | 3.80 | 7.1 | 3.0 | 5.6 | | | | 6.50 | 8.25 | 7.60 |
| Below the elbow | | | | 3.7 | 1.6 | 2.6 | 41.2 | 15.8 | 45.5 | 8.70 | 11.0 | 7.75 |
| Above the elbow | | | | 3.4 | 1.6 | 2.6 | 48.6 | 16.6 | 48.6 | 11.0 | 11.5 | 7.20 |
| Axilla | | | | 2.9 | 1.6 | 2.6 | 52.6 | 26.2 | 60 | 10.2 | 11.5 | 7.05 |
| F-wave | 29.7 | NP | 32.7 | | | | | | | | | |
| Right common peroneal nerve | | | | NP | NP | NP | | | | | | |
| Left common peroneal nerve | | | | NP | NP | NP | | | | | | |
| Right tibial nerve | | | | NP | NP | NP | | | | | | |
| Right H-wave | | | | NP | NP | NP | | | | | | |
| Left tibial nerve | | | | NP | NP | NP | | | | | | |
| Left H-wave | | | | NP | NP | NP | | | | | | |
| Sensory NCS | | | | | | | | | | | | |
| Right median nerve | | | | | | | | | | | | |
| Finger-wrist | 2.95 | | | 2.3 | NP | NP | 37.3 | | | | | |
| Palm-wrist | 2.55 | | | 3.6 | NP | NP | 39.2 | | | | | |
| Wrist-elbow | 4.50 | | 4.85 | 7.8 | NP | 10.0 | 46.7 | | 41.2 | | | |
| Elbow-axilla | 2.35 | 2.05 | 2.20 | 33.5 | 5.7 | 22.2 | 51.1 | 53.7 | 54.5 | | | |
| Left median nerve | | | | | | | | | | | | |
| Finger-wrist | | | 3.15 | NP | NP | 4 | | | 41.3 | | | |
| Palm-wrist | | | 2.75 | NP | NP | 4.1 | | | 43.6 | | | |
| Wrist-elbow | 4.70 | | 4.70 | 9.6 | NP | 11.2 | 44.7 | | 44.7 | | | |
| Elbow-axilla | 2.40 | 2.75 | 2.15 | 39.8 | 9.6 | 54.3 | 50.0 | 43.6 | 55.8 | | | |
| Right ulnar nerve | | | | | | | | | | | | |
| Finger-wrist | | | | NP | NP | NP | | | | | | |
| Palm-wrist | | | | NP | NP | NP | | | | | | |
| Wrist-elbow | 4.40 | | 5.20 | 7.4 | NP | 5.4 | 45.5 | | 36.5 | | | |
| Elbow-axilla | 2.45 | 2.85 | 2.45 | 26.2 | 2.7 | 7.4 | 49.0 | 42.1 | 49.0 | | | |
| Left ulnar nerve | | | | | | | | | | | | |
| Finger-wrist | | | 3.15 | NP | NP | 1.1 | | | 38.1 | | | |
| Palm-wrist | | | 2.50 | NP | NP | 2.7 | | | 44.0 | | | |
| Wrist-elbow | | | 5.00 | NP | NP | 6.2 | | | 44.0 | | | |
| Elbow-axilla | 2.72 | 2.40 | 2.35 | 33.5 | 4.6 | 11.3 | 43.6 | 45.8 | 51.1 | | | |

(Continued to the next page)

**Table 2.** Continued

| Nerve/site | Latency (ms)* | | | Amplitude | | | NCV (m/s) | | | Peak duration (ms) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patient 1 | Patient 2 | Patient 3 | Patient 1 | Patient 2 | Patient 3 | Patient 1 | Patient 2 | Patient 3 | Patient 1 | Patient 2 | Patient 3 |
| Right sural nerve | | | | NP | NP | NP | | | | | | |
| Left sural nerve | | | | NP | NP | NP | | | | | | |
| Right superficial peroneal nerve | | | | NP | NP | NP | | | | | | |
| Left superficial peroneal nerve | | | | NP | NP | NP | | | | | | |

Amplitudes are measured in millivolt (mV, motor NCS) and microvolt (μV, sensory NCS).
NCV, nerve conduction velocity; NCS, nerve conduction study; NP, no potential.
*Motor NCS: terminal latency, sensory NCS: latency.

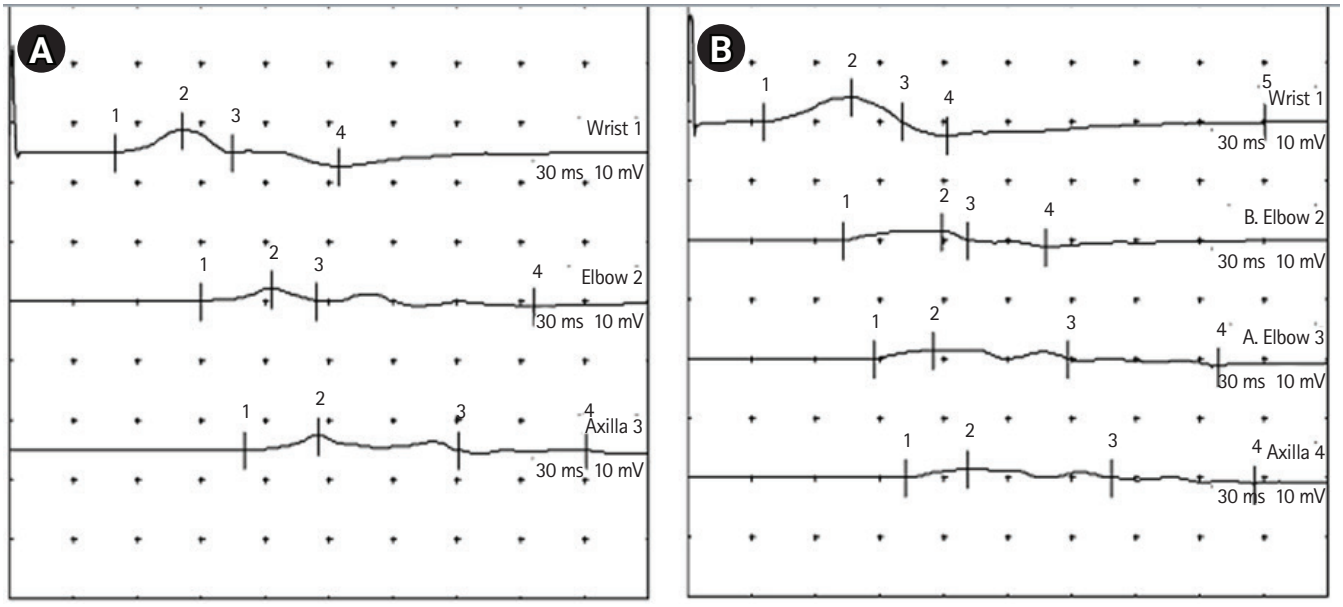


**Fig. 1.** Motor nerve conduction studies of case 1. A demyelinating pattern with conduction block and temporal dispersion was observed in the left median nerve (A) and the right ulnar nerve (B).

provement. In addition to weakness progression, orthostatic hypotension occurred, and diarrhea got aggravated. However, he had no family members with similar symptoms. The possibility that the patient had amyloidosis was considered after the autonomic abnormalities significantly worsened. Gastrointestinal amyloidosis was confirmed by following colon tissue biopsy and the heterozygous mutation as Ala36Pro was detected in *TTR* gene.

## Discussion

NCS has been considered the gold standard for detecting segmental demyelination of peripheral nerves. Although electrophysiologic confirmation is key factor in diagnosis of acquired demyelinating polyneuropathies, they do not always accurately reflect the pathology of the disease [3]. A recent study showed 15% of demyelinating aTTR patients in French cohort (13 of 84 patients) and demonstrated misleading features of aTTR fulfilling electrodiagnostic criteria of CIDP are not uncommon in clinical practice [7]. In previous studies, the most notable features of NCS in aTTR fulfilling electrodiagnostic criteria of CIDP were pronged distal latency of the median nerve and the other is co-existence of severe motor axonal loss not only demyelinating features [7,8]. These features are also shown in all patients in this report (Table 2).

These 3 patients had significant clinical symptoms that could have also been considered as clues for correct diagnosis, such as gastrointestinal, urinary, or cardiac dysfunction. Moreover, the unevaluated causes for the sudden death of the patients' parents were clue for the existence of a hereditary disease. All 3 patients initially received immunomodulatory treatment considering CIDP, but it might be also noticeable that all 3 patients presented distal dominant weakness. Although distal acquired demyelinat-

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ing symmetric polyneuropathy and others (e.g., Lewis-Sumner syndrome, pure motor or pure sensory) are classified as subtypes of CIDP, they are still considered atypical and uncommon.

CIDP still has no typical biomarker diagnosed by the identification of characteristic electrophysiological findings. Because of their treatable characteristic, many clinicians might tend to try an early application of therapy considering the CIDP in the case of an incomplete diagnosis. In addition, the diagnostic criteria for refractory CIDP also have not yet been established. Steroids or immunoglobulins are usually applied as the first-line treatment, and if there is no effect, additional immunomodulatory treatment is performed. If there is no effect leading to remission in this series of treatments, it is considered refractory [9]. Yet, recent studies on CIDP reported that almost half of the patients referred for second opinion due to insufficient outcome of immunotherapy and were finally diagnosed with alternative diseases, with aTTR being the case for 5% of them [3,4]. Other diseases to consider when the final alternative diagnosis was made in patients with presumed refractory CIDP were diverse including diabetic polyneuropathy, amyotrophic lateral sclerosis, multifocal motor neuropathy, idiopathic small fiber neuropathy, fibromyalgia and etc. Therefore, in the case of clinically refractory CIDP, the differential diagnosis may need to be re-examined [3,4].

Since current medical or surgical intervention can halt the progression of aTTR, early and correct diagnosis becomes an important issue. In conclusion, clinicians should be aware that the electrophysiological outcome of aTTR patients can sometimes mimic the findings of patients with a demyelinating disease.

## Conflict of Interest

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

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# Instructions for Authors

JEND
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*Journal of Electrodiagnosis and Neuromuscular Diseases* (*J Electrodiagn Neuromuscul Dis*, JEND), an official journal of the Korean Association of EMG Electrodiagnostic Medicine, is published Three times a year. It regards all aspects of EMG, electrodiagnostic medicine, and neuromuscular diseases, including clinical practice, experimental and applied research, and education, and its formal abbreviated journal name is J Electrodiagn Neuromuscul Dis.

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