pISSN: 2733-6581
eISSN: 2733-659X

# JEND

## Journal of Electrodiagnosis and Neuromuscular Diseases

VOL. 24
NO. 3
DECEMBER
2022

JEND
Journal of Electrodiagnosis and Neuromuscular Diseases

VOL. 24, NO. 3 DECEMBER 2022
Pages 57-120

JEND
Journal of Electrodiagnosis and Neuromuscular Diseases

KOREAN ASSOCIATION OF EMG
ELECTRODIAGNOSTIC MEDICINE

KOREAN ASSOCIATION OF EMG
ELECTRODIAGNOSTIC MEDICINE

e-jend.org

JEND
Journal of Electrodiagnosis and Neuromuscular Diseases

e-jend.org

pISSN 2733-6581
eISSN 2733-659X

Vol. 24, No. 3 December 2022

## Aims and Scope

*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.
JEND is the official journal of the Korean Association of EMG Electrodiagnostic Medicine.

## Subscription

Korean Association of EMG Electrodiagnostic Medicine will send JEND for free to some relevant individuals and institutions. Full text PDF files are also available at the official website (http://www.e-jend.org). To order a subscription to JEND, please contact our editorial office.

## Open Access



### Publisher
Korean Association of EMG Electrodiagnostic Medicine

### Editor-in-Chief
Dong Hwee Kim, Korea University, Korea

### Editorial Office
Department of Physical Medicine and Rehabilitation, Korea University Ansan Hospital,
123 Jeokgeum-ro, Danwon-gu, Ansan 15355, Korea
Tel: +82-31-412-5330 Fax: +82-31-412-4215 E-mail: editjend@gmail.com

### Printing Office
M2PI
8th FL, DreamTower, 66 Seongsui-ro, Seongdong-gu, Seoul 04784, Korea
Tel: +82-2-6966-4930 Fax: +82-2-6966-4945 E-mail: support@m2-pi.com

Published on December 31, 2022

JEND Journal of Electrodiagnosis and Neuromuscular Diseases

# Editorial Board

pISSN: 2733-6581 · eISSN: 2733-659X

JEND Journal of Electrodiagnosis and Neuromuscular Diseases

# Contents

Vol. 24, No. 3 December 2022

## Review Articles



## Original Articles



## Case Reports

pISSN: 2733-6581 · eISSN: 2733-659X

JEND Journal of Electrodiagnosis and Neuromuscular Diseases

# Contents

Vol. 24, No. 3 December 2022

JEND Journal of Electrodiagnosis and Neuromuscular Diseases

REVIEW ARTICLE

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2022;24(3):57-61
https://doi.org/10.18214/jend.2022.00087

# Immune-Mediated Necrotizing Myopathy: A Review for Clinicians

Jong-Mok Lee

Department of Neurology, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Korea

Immune-mediated necrotizing myopathy (IMNM) is a group of inflammatory myopathies showing necrotic and regenerating fibers without noteworthy inflammatory cell infiltration on pathology. The pathologic findings are different from those of dermatomyositis or sporadic inclusion body myositis. Furthermore, the discovery of myositis-specific antibodies in patients with IMNM, such as anti-signal recognition particle or anti-3-hydroxy-3-methylglutaryl-CoA reductase antibodies, has enabled us to expand our knowledge of IMNM. However, the phenotype and pathological findings of IMNM are unremarkable; therefore, it is difficult to diagnose, and IMNM has been relatively unrecognized. In this review, we introduce the clinical features, diagnosis, pathomechanism, and treatment of IMNM for clinicians.

**Keywords:** Myositis; Dermatomyositis; Myositis, inclusion body

**Received:** June 28, 2022
**Revised:** August 5, 2022
**Accepted:** August 18, 2022

**Corresponding author:**
Jong-Mok Lee
Department of Neurology, School of Medicine, Kyungpook National University, 680 Gukchaebosang-ro, Jung-gu, Daegu 41944, Korea
Tel: +82-53-200-5765
Fax: +82-53-422-4265
E-mail: azulmar@gmail.com

## Introduction

Idiopathic inflammatory myopathy (IIM) is a heterogeneous disease group characterized by muscle weakness, elevated serum levels of creatine kinase (CK), and inflammatory features of muscle pathology. Dermatomyositis (DM) and polymyositis (PM) were introduced by Bohan and Peter [1], and this classification was then widely recognized until sporadic inclusion body myositis (sIBM) was proposed in the 1990s. Starting in the 2000s, debate ensued regarding the existence of PM, because many patients diagnosed with PM were later considered to have sIBM, DM, overlap syndrome with connective tissue disease, or immune-mediated necrotizing myopathy (IMNM) [2,3]. DM, sIBM, and anti-synthetase syndrome have been well recognized as subtypes of IIM showing prominent lymphocytic infiltration on muscle biopsy [4]. However, in the last two decades, muscle pathologic findings showing many necrotic fibers without significant lymphocyte infiltration have been reported; this presentation is now widely recognized as IMNM [5].

To date, two different myositis-specific antibodies (MSAs) have been associated with IMNM: anti-signal recognition particle (SRP) and hydroxy-3-methylglutaryl-CoA reductase (HMGCR) antibodies. The SRP complex comprises a 7S RNA and six protein subunits with molecular weights of 9, 14, 19, 54, 68, and 72 kDa [4]. SRP is essential for the translocation of nascent polypeptides into the endoplasmic reticulum and was first identified in the 1980s by RNA immunoprecipitation (RNA-IP) [6]. The anti-HMGCR antibody was first recognized in 2010 from necrotizing myositis as anti-200 kD/100 kD [7]. The 100 kDa protein was later identified as a monomer of HMGCR [8]. Furthermore, IMNM patients with anti-HMGCR antibodies were reported to show a homogeneous phenotype, and 63% of patients had been exposed to statins [7].

Distinct muscle pathology findings and the involvement of MSAs separated IMNM as a subtype of IIM. Here, we review how IMNM differs from other subtypes of IIM from a clinical standpoint.

## Epidemiology

The incidence of IMNM has not been analyzed. The global incidence of IIM ranges from 1.16 to 19 per 1 million person-years [9]. In Korea, the incidence of IIM was estimated at 2.9 to 5.2 per 1 million person-years [10].

Anti-SRP IMNM accounts for 5% to 15% of patients with IIM [11]. Anti-SRP IMNM is common in patients in the fifth or sixth decades of life and is more frequent in women than in men [11]. Anti-HMGCR IMNM is present in 6%-10% of IIM cases, and it occurs more frequently in women older than 40 years [11]. The target of the anti-HMGCR antibody is also the target of statins, and exposure to a statin may be a trigger of the disease. However, anti-HMGCR IMNM in childhood has also been reported [12], and statin exposure is not frequent in Asia [13]. Therefore, other factors may be able to provoke anti-HMGCR IMNM besides statin exposure.

## Clinical Features

### 1) Muscular phenotype

The main feature of IMNM is limb weakness. Most patients with IMNM exhibit limb weakness of subacute onset from several weeks to months. A few cases have been reported with a slowly progressive onset for several years [14]. The distribution of muscle weakness in IMNM is similar to that in other idiopathic inflammatory myopathies, except for sIBM. Bilateral proximal limb weakness is notable, in which lower limb weakness precedes upper limb weakness [15]. Patients with anti-SRP antibody tend to have concomitant dysphagia (30%-70%), unlike those with anti-HMGCR antibody (Table 1) [11,15–17]. Patients with anti-SRP IMNM also show more severe muscle weakness and atrophy than those with anti-HMGCR IMNM [15,16]. The level of serum CK is high in both types of IMNM, ranging from 1,000 to 10,000 IU/L, which is higher than in other IIM groups [11]. The serum level of lactate dehydrogenase is also elevated, ranging from 350 to 840 IU/L (normal range, 100-250 IU/L), but it is not as high as in patients with metabolic myopathy [18].

Table 1. Comparison Between Anti-SRP and Anti-HMGCR IMNM

| | Anti-SRP | Anti-HMGCR |
|---|---|---|
| Statin exposure | ± | + to ++ |
| Severe muscle weakness | +++ | ++ |
| Dysphagia | +++ | ++ |
| Muscle atrophy | ++ | + |
| Interstitial lung disease | + | ± |
| Cancer association | - | + |
| Treatment response | ± | + |
| MAC deposition on sarcolemma on histology | + | ++ |

SRP, signal recognition particle; HMGCR, anti-3-hydroxy-3-methylglutaryl-coA reductase; IMNM, immune-mediated necrotizing myopathy; +, ++, +++, less common to more common; -, none; MAC, membrane attack complex.
Modified from [15-17].

### 2) Extramuscular phenotype

Interstitial lung disease has been reported to be present in 23% to 38% of patients with anti-SRP IMNM [11]. However, these patients did not complain of dyspnea. Myocarditis can also be seen in 2%-40% of these patients, presenting as chest pain, palpitations, congestive heart failure, and electrocardiographic abnormalities [11]. The risk of malignancy is unclear, but was reported to be slightly increased in anti-HMGCR IMNM (Table 1) [19,20]. In seronegative IMNM, a high incidence of associated cancer was observed, with an incidence ratio of 8.35 (95% confidence interval, 1.68-24.41; $p < 0.01$) [19]. Anti-SRP IMNM is not associated with cancer [15].

## Diagnosis

### 1) Myositis-specific antibody

The identification of MSA is necessary to classify the subtype of IMNM. However, a uniform method to test MSA for IMNM has not been established. For anti-SRP IMNM, an anti-SRP antibody is screened by an enzyme-linked immunosorbent assay (ELISA) or the line blot technique, which detects only the 54-kDa SRP subunit in the commercial kit [4]. Many patients with anti-SRP IMNM do not have reactivity against this protein. Thus, false negatives can result [14]. The presence of anti-SRP antibody can be confirmed by RNA-IP, the immunoprecipitation of radioactively labeled whole-cell extracts, or the *in vitro* transcription and translation protein products, which enable the detection of other subunits. However, RNA-IP is laborious, limiting its clinical applications. The anti-HMGCR antibody is screened by ELISA, the false positivity rate of which is only 0.7% [21]. Thus, ELISA is recommended to be performed when the probability of anti-HMGCR IMNM is high. In a research setting, immunoprecipitation of purified HMGCR protein is required for confirmation [4].

### 2) Muscle magnetic resonance imaging

Muscle magnetic resonance imaging (MRI) is an excellent non-invasive tool for measuring the extension of muscle damage. However, the MRI findings in patients with IMNM are not specific enough for diagnosis compared with the detection of MSA



https://doi.org/10.18214/jend.2022.00087

or the findings of muscle biopsy [11]. Despite the limitation of muscle MRI in diagnosing IMNM, several studies have shown distinctive findings in IMNM compared to other types of IIM [22,23]. Muscle damage showed a tendency to affect the gluteus minimus, gluteus maximus, lumbar extensor, and subscapularis in patients with IMNM compared to those with sIBM [22]. In thigh muscle MRI, atrophy and fatty replacement were identified in the lateral rotators, glutei, and medial and lateral compartments of IMNM patients [23]. Among IMNM patients, patients with anti-SRP IMNM showed more extensive edema, atrophy, and fatty replacement than those with anti-HMGCR IMNM [23].

### 3) Pathology

On light microscopy, one of the features distinguishing IMNM from other types of IIM is the presence of necrotic and regenerating fibers without definite endomysial inflammatory cell infiltration on hematoxylin and eosin (H&E) staining (Fig. 1A). Those fibers are randomly scattered. Necrotic and regenerating fibers can exhibit different phases of necrosis, with paleness, coarseness, and phagocytosis [11]. The presence of perifascicular atrophy or lymphocytes surrounding non-necrotic fibers is uncommon [4]. On modified Gomori-trichrome (mGT) staining, necrotic and regenerating fibers can be seen in accordance with the findings of H&E staining [11]. However, rods or ragged-red fibers are not evident on mGT staining.

On immunohistochemistry, major histocompatibility complex (MHC) class I positivity is noted on the sarcolemma of scattered fibers in IMNM, but MHC class II is absent from the sarcolemma [11]. Deposits of C5b-9 (membrane attack complex) on the sarcolemma can be observed, which is not unique for IMNM [11]. An autophagy marker, p62, can be highlighted in several fibers showing fine granular or homogeneous staining (Fig. 1B) [11]. These findings are different from those of sIBM, which harbors fibers stained as plaque-like by p62 [11].

## Pathomechanism

The precise pathogenesis of IMNM is not fully understood [4]. However, several roles of anti-SRP and HMGCR antibodies have been clarified [4]. Clinically, the serum anti-SRP or HMGCR antibody titer correlates with disease activity. A previous study showed that the anti-SRP antibody level was reduced after plasma exchange [24]. Furthermore, the serum level of CK correlates with anti-SRP and HMGCR autoantibody titers [20,24]. *In vitro*, both anti-SRP and HMGCR antibodies have been proven to induce muscle fiber atrophy [25]. This study demonstrated that the transcription of genes encoding atrophic factors (muscle atrophy F-box protein and E3 ubiquitin-protein ligase TRIM63) increased [25]. Furthermore, the co-culture of muscle fibers with purified anti-SRP and HMGCR antibodies was associated with high levels of tumor necrosis factors and interleukin-6, resulting in muscle atrophy. Simultaneously, reduced levels of the anti-inflammatory cytokines interleukin-4 and interleukin-13 induced impaired muscle regeneration by myoblast fusion defects [25]. In a mouse model, $Rag2^{-/-}$ mice were injected with purified

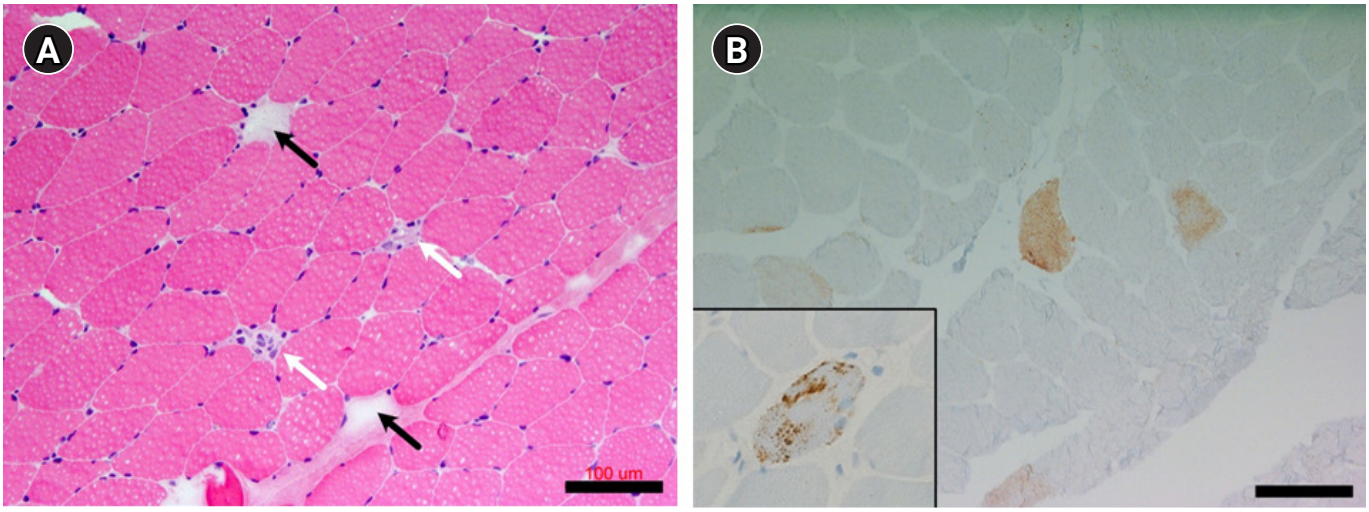


Fig. 1. Light microscopic findings from a patient with anti-SRP antibody. (A) A few scattered necrotic (black arrows) and regenerating (white arrows) fibers are seen on hematoxylin and eosin staining. (B) A fiber showing fine granular staining is noted using antibody targeting p62 (sc-28359, 1:200 dilutions; Santa Cruz Biotechnology, Dallas, TX, USA). For the purpose of comparison, a plaque-like stain can be seen in sporadic inclusion body myositis (small box). Scale bar, 100 μm.

immunoglobulin G (IgG) from patients with anti-SRP and HMGCR IMNM for 21 days. Grip strength was evaluated on days 8, 14, and 21. The strength significantly decreased in both anti-SRP and HMGCR IgG-injected mice [26]. The pathology of mice receiving purified IgG from anti-SRP IMNM showed multiple necrotic fibers and complement C5b-9 deposits [26].

## Treatment

No randomized, blinded, controlled trials of IMNM have been published. Most treatments rely on case reports or expert consensus. However, corticosteroids remain the first line. Intravenous methylprednisolone (1 g for 5 days) is followed by oral high-dose prednisone (1 mg/kg daily) [5]. Of note, oral corticosteroids must be tapered to the lowest dose as soon as possible [5,11]. Within 1 month after corticosteroid administration, oral methotrexate (0.3 mg/kg weekly, maximum dose 25 mg/week) or azathioprine (3 mg/kg daily) is highly recommended [5]. It is also necessary to monitor hepatic function and the blood count [5]. Many studies have warned against treatment with steroids alone. In pediatric patients with anti-HMGCR IMNM, no patients achieved clinical remission with only corticosteroid treatment [12]. In a literature review, a mean number of 1.5 different additional immunosuppressants were needed in patients with anti-HMGCR IMNM [27]. The European Neuromuscular Center guidelines recommend using rituximab as a second or third agent in patients with anti-SRP IMNM, which was also supported in other reports [5,17]. However, rituximab did not show notable efficacy in patients with anti-HMGCR IMNM [28]. Intravenous immunoglobulin was reported to be efficacious both in patients with anti-HMGCR IMNM and in those with anti-SRP IMNM [5,11,29]. The prognosis of patients with IMNM is poor. Despite 4 years of immunotherapy, one-third and half of anti-HMGCR and anti-SRP IMNM patients showed no recovery, respectively [11].

## Conclusion

We summarized the clinical features, phenotype, pathomechanism, and treatment of IMNM. The phenotype and pathological findings of IMNM are not straightforward to diagnose, but some findings in the differential diagnosis for IMNM are evident, such as MSA specific to IMNM. Clinicians need to remain alert and should not overlook the diagnosis of IMNM.

## Conflict of Interest

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

## ORCID

Jong-Mok Lee, https://orcid.org/0000-0002-2918-6166

## References

1. Bohan A, Peter JB: Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975;292:344–347.
2. Lundberg IE, de Visser M, Werth VP: Classification of myositis. Nat Rev Rheumatol 2018;14:269–278.
3. Amato AA, Griggs RC: Unicorns, dragons, polymyositis, and other mythological beasts. Neurology 2003;61:288–289.
4. Pinal-Fernandez I, Casal-Dominguez M, Mammen AL: Immune-mediated necrotizing myopathy. Curr Rheumatol Rep 2018;20:21.
5. Allenbach Y, Mammen AL, Benveniste O, Stenzel W; Immune-Mediated Necrotizing Myopathies Working Group: 224th ENMC International Workshop: clinico-sero-pathological classification of immune-mediated necrotizing myopathies Zandvoort, The Netherlands, 14-16 October 2016. Neuromuscul Disord 2018;28:87–99.
6. Okada N, Mimori T, Mukai R, Kashiwagi H, Hardin JA: Characterization of human autoantibodies that selectively precipitate the 7SL RNA component of the signal recognition particle. J Immunol 1987;138:3219–3223.
7. Christopher-Stine L, Casciola-Rosen LA, Hong G, Chung T, Corse AM, Mammen AL: A novel autoantibody recognizing 200-kd and 100-kd proteins is associated with an immune-mediated necrotizing myopathy. Arthritis Rheum 2010;62:2757–2766.
8. Mammen AL, Chung T, Christopher-Stine L, Rosen P, Rosen A, Doering KR, et al: Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. Arthritis Rheum 2011;63:713–721.
9. Meyer A, Meyer N, Schaeffer M, Gottenberg JE, Geny B, Sibilia J: Incidence and prevalence of inflammatory myopathies: a systematic review. Rheumatology (Oxford) 2015;54:50–63.
10. Cho SK, Kim H, Myung J, Nam E, Jung SY, Jang EJ, et al: Incidence and Prevalence of Idiopathic Inflammatory Myopathies in Korea: a Nationwide Population-based Study. J Korean Med Sci 2019;34:e55.



https://doi.org/10.18214/jend.2022.00087

11. Allenbach Y, Benveniste O, Stenzel W, Boyer O: Immune-mediated necrotizing myopathy: clinical features and pathogenesis. Nat Rev Rheumatol 2020;16:689–701.
12. Liang WC, Uruha A, Suzuki S, Murakami N, Takeshita E, Chen WZ, et al: Pediatric necrotizing myopathy associated with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies. Rheumatology (Oxford) 2017;56:287–293.
13. Ge Y, Lu X, Peng Q, Shu X, Wang G: Clinical characteristics of anti-3-hydroxy-3-methylglutaryl coenzyme A reductase antibodies in Chinese patients with idiopathic inflammatory myopathies. PLoS One 2015;10:e0141616.
14. Suzuki S, Nishikawa A, Kuwana M, Nishimura H, Watanabe Y, Nakahara J, et al: Inflammatory myopathy with anti-signal recognition particle antibodies: case series of 100 patients. Orphanet J Rare Dis 2015;10:61.
15. Watanabe Y, Uruha A, Suzuki S, Nakahara J, Hamanaka K, Takayama K, et al: Clinical features and prognosis in anti-SRP and anti-HMGCR necrotising myopathy. J Neurol Neurosurg Psychiatry 2016;87:1038–1044.
16. Kurashige T: Anti-HMGCR myopathy: clinical and histopathological features, and prognosis. Curr Opin Rheumatol 2021;33:554–562.
17. Pinal-Fernandez I, Parks C, Werner JL, Albayda J, Paik J, Danoff SK, et al: Longitudinal course of disease in a large cohort of myositis patients with autoantibodies recognizing the signal recognition particle. Arthritis Care Res (Hoboken) 2017;69:263–270.
18. Yang H, Tian X, Zhang L, Li W, Liu Q, Jiang W, et al: Clinical and pathological features of immune-mediated necrotising myopathies in a single-centre muscle biopsy cohort. BMC Musculoskelet Disord 2022;23:425.
19. Allenbach Y, Keraen J, Bouvier AM, Jooste V, Champtiaux N, Hervier B, et al: High risk of cancer in autoimmune necrotizing myopathies: usefulness of myositis specific antibody. Brain 2016;139(Pt 8):2131–2135.
20. Tiniakou E, Pinal-Fernandez I, Lloyd TE, Albayda J, Paik J, Werner JL, et al: More severe disease and slower recovery in younger patients with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase-associated autoimmune myopathy. Rheumatology (Oxford) 2017;56:787–794.
21. Mammen AL: Statin-associated autoimmune myopathy. N Engl J Med 2016;374:664–669.
22. Landon-Cardinal O, Koumako C, Hardouin G, Granger B, Reyngoudt H, Boisserie JM, et al: Severe axial and pelvifemoral muscle damage in immune-mediated necrotizing myopathy evaluated by whole-body MRI. Semin Arthritis Rheum 2020;50:1437–1440.
23. Pinal-Fernandez I, Casal-Dominguez M, Carrino JA, Lahouti AH, Basharat P, Albayda J, et al: Thigh muscle MRI in immune-mediated necrotising myopathy: extensive oedema, early muscle damage and role of anti-SRP autoantibodies as a marker of severity. Ann Rheum Dis 2017;76:681–687.
24. Benveniste O, Drouot L, Jouen F, Charuel JL, Bloch-Queyrat C, Behin A, et al: Correlation of anti-signal recognition particle autoantibody levels with creatine kinase activity in patients with necrotizing myopathy. Arthritis Rheum 2011;63:1961–1971.
25. Arouche-Delaperche L, Allenbach Y, Amelin D, Preusse C, Mouly V, Mauhin W, et al: Pathogenic role of anti-signal recognition protein and anti-3-Hydroxy-3-methylglutaryl-CoA reductase antibodies in necrotizing myopathies: myofiber atrophy and impairment of muscle regeneration in necrotizing autoimmune myopathies. Ann Neurol 2017;81:538–548.
26. Bergua C, Chiavelli H, Allenbach Y, Arouche-Delaperche L, Arnoult C, Bourdenet G, et al: In vivo pathogenicity of IgG from patients with anti-SRP or anti-HMGCR autoantibodies in immune-mediated necrotising myopathy. Ann Rheum Dis 2019;78:131–139.
27. Rademacher JG, Glaubitz S, Zechel S, Oettler M, Tampe B, Schmidt J, et al: Treatment and outcomes in anti-HMG-CoA reductase-associated immune-mediated necrotising myopathy: comparative analysis of a single-centre cohort and published data. Clin Exp Rheumatol 2022;40:320–328.
28. Landon-Cardinal O, Allenbach Y, Soulages A, Rigolet A, Hervier B, Champtiaux N, et al: Rituximab in the treatment of refractory anti-HMGCR immune-mediated necrotizing myopathy. J Rheumatol 2019;46:623–627.
29. Binns EL, Moraitis E, Maillard S, Tansley S, McHugh N, Jacques TS, et al: Effective induction therapy for anti-SRP associated myositis in childhood: a small case series and review of the literature. Pediatr Rheumatol Online J 2017;15:77.

JEND Journal of Electrodiagnosis and Neuromuscular Diseases

REVIEW ARTICLE

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2022;24(3):62-69
https://doi.org/10.18214/jend.2022.00143

# *MPZ*-, *GDAP1*-, and *NEFL*-Related Charcot-Marie-Tooth Disease with Diverse Clinical and Electrophysiological Phenotypes

Hye Jin Kim[1], Hye Mi Kwon[1], Sang Beom Kim[2], Ki Wha Chung[3], Byung-Ok Choi[1,4]

[1]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[2]Department of Neurology, Kyung Hee University Hospital at Gangdong, Kyung Hee University School of Medicine, Seoul, Korea
[3]Department of Biological Sciences, Kongju National University, Gongju, Korea
[4]Stem Cell & Regenerative Medicine Institute, Samsung Medical Center, Seoul, Korea

Charcot-Marie-Tooth disease (CMT) is a spectrum of clinically and genetically heterogeneous peripheral neuropathies. CMT can be classified into demyelinating, intermediate, or axonal neuropathy based on clinical, histopathological, and electrophysiological findings. Approximately 140 genes have been reported to be associated with CMT. Mutations in the myelin protein zero (*MPZ*), ganglioside-induced differentiation related protein 1 (*GDAP1*), and neurofilament light-chain polypeptide (*NEFL*) genes have been reported to cause all three types of CMT, which is noteworthy because most CMT-related genes cause a single type of neuropathy (either demyelinating or axonal). In contrast, it remains unclear why these genes cause several types of CMT. CMT is presently incurable; however, ongoing attempts to treat CMT with various drugs, dietary supplements have increased the importance of an exact genetic diagnosis for precision medicine. Therefore, it is important to identify the causative mutations and compare the associated clinical characteristics. Taken together, a comparison of causative mutations and clinical features of patients with *MPZ*, *GDAP1*, and *NEFL* mutations will be the first step in understanding how different types of CMT are caused, and will enable a molecular genetic diagnosis. In this review, we describe the clinical, electrophysiological, and genetic characteristics of *MPZ*-, *GDAP1*-, and *NEFL*-related CMT.

**Keywords:** Charcot-Marie-Tooth disease; *MPZ*; *GDAP1*; *NEFL*; Phenotype

**Received:** August 8, 2022
**Revised:** October 4, 2022
**Accepted:** October 6, 2022

**Corresponding author:**
Byung-Ok Choi
Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: +82-2-3410-1296
Fax: +82-2-3410-0052
E-mail: bochoi77@hanmail.net

## Introduction

Charcot-Marie-Tooth disease (CMT) is an inherited peripheral neuropathy that is genetically highly heterogeneous, with more than 140 different genes involved [1–3]. Classically, CMT can be divided according to clinical, histopathological, and electrophysiological findings into three types: the demyelinating type (CMT1), with a median motor nerve conduction velocity (MMNCV) below 38 m/s; axonal neuropathy (CMT2), with an MMNCV above 38 m/s; and the intermediate type (CMTDID), with an MMNCV lying between 25 and 45 m/s and nerve pathology showing axonal and/or demyelinating features [4]. Mutations in the myelin protein zero (*MPZ*), ganglioside-induced differentiation related protein 1 (*GDAP1*) and neurofilament light-chain polypeptide (*NEFL*) genes have been reported to cause all three CMT types (demyelinating, axonal, and intermediate) (Fig. 1).

Strictly expressed in myelinated Schwann cells, MPZ is a transmembrane protein that is a major component of peripheral myelin [5]. Mutations in *MPZ* have been reported to cause demye-

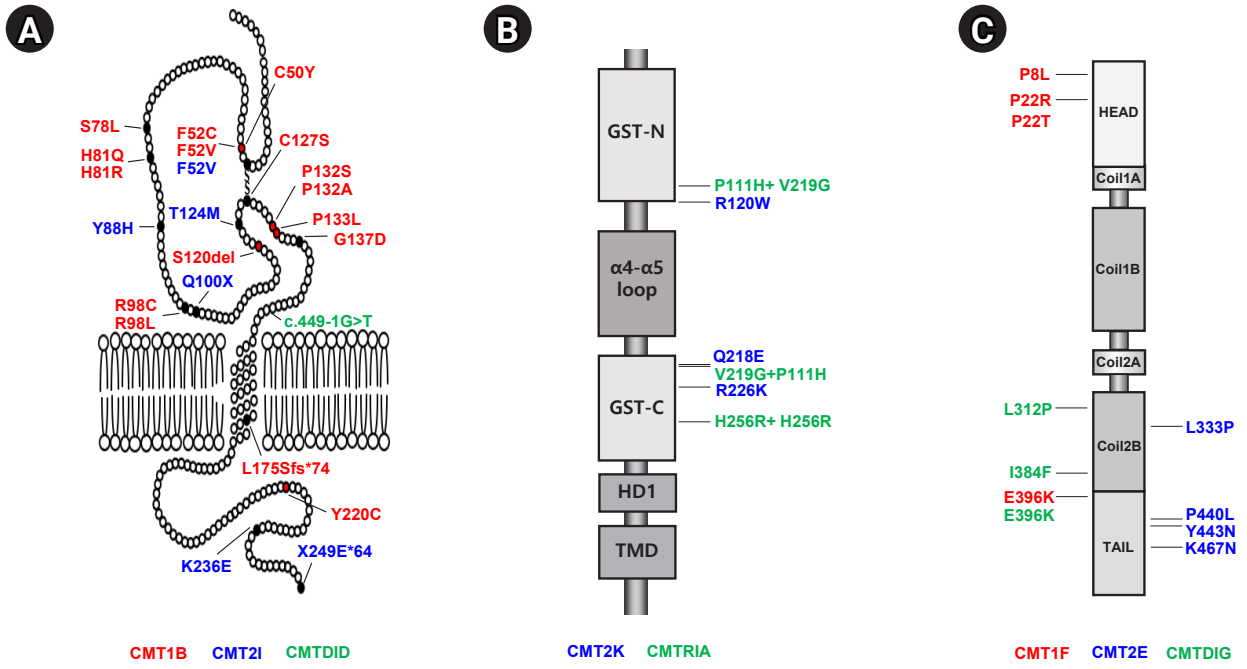


Fig. 1. Structure and distribution of mutations in *MPZ* (A), *GDAP1* (B), and *NEFL* (C) found in Korean CMT families. Vertical arrows indicate the mutation sites. Amino acid changes are indicated in red (demyelinating), blue (axonal), and green (intermediate).

linating CMT1B (MIM 118200), axonal CMT2I (MIM 607677), and intermediate CMTDID (MIM 607791) (Table 1) [6–11]. CMT1B patients generally exhibit an early onset, while CMT2I patients are characterized by a late onset [12,13]. *MPZ*-related CMT patients display a spectrum of diverse phenotypes, with phenotypic variations even in the same mutation. [8,14,15].

GDAP1 is mainly expressed in neurons, is located in the outer membrane of the mitochondria, and belongs to the glutathione S-transferase family [16]. Mutations in the *GDAP1* gene were reported for the first time in 2002 to cause autosomal recessive (AR) CMT4A (MIM 214400) in Tunisian families [17]. Since then, *GDAP1* mutations have been reported to cause axonal forms (CMT2K; MIM 607831) [18,19], axonal forms with vocal cord paresis (MIM 607706) [18] and intermediate forms (CMTRIA; MIM 608340) of disease (Table 1) [20]. *GDAP1*-related patients harboring AR inheritance exhibit severe clinical features with early onset, but autosomal dominant *GDAP1* mutations show mild clinical symptoms with an adult onset [17,18].

NEFL is the most abundant of the three neurofilament proteins, which are major components of the axoskeleton that provide structural support for axons and regulate axon diameter. Patients with *NEFL* mutations exhibit a diverse phenotypic spectrum [21]. A mutation in *NEFL* was first reported to cause CMT2E (MIM 607684) in 2000, and several mutations were subsequently revealed to be associated with CMT1F (MIM 607734), CMTDIG (MIM 617882) (Table 1) [21–25].

Table 1. Diseases Caused by Mutations in the *MPZ*, *GDAP1*, and *NEFL* Genes

| Gene | Locus | Phenotype | MIM number | Heredity |
|---|---|---|---|---|
| *MPZ* | 1q23.3 | CMT1B | 118200 | AD |
| | | CMT2I | 607677 | AD |
| | | CMTDID | 607791 | AD |
| *GDAP1* | 8q21.11 | CMT4A | 214400 | AR |
| | | CMT2K | 607831 | AD, AR |
| | | CMTRIA | 608340 | AR |
| *NEFL* | 8p21.2 | CMT1F | 607734 | AD, AR |
| | | CMT2E | 607684 | AD |
| | | CMTDIG | 617882 | AD |

AD, autosomal dominant; AR, autosomal recessive.

Most CMT-related genes cause one CMT neuropathy subtype—demyelinating, axonal, or intermediate neuropathy. Thus, it is noteworthy when a single gene causes multiple subtypes of CMT. In this review, we introduce the various types of CMT in a Korean cohort, caused by mutations in *MPZ*, *GDAP1*, and *NEFL*, and describe their clinical, electrophysiological, and genetic characteristics.

## Myelin Protein Zero (*MPZ*)

### 1) Clinical diversity of *MPZ*-related patients

The frequency of Korean CMT families with the *MPZ* mutation was found to be 3.2% in all independent patients and 4.7% in CMT families without *PMP22* duplicates (Table 2) [21,23,26–43]. These mutation frequencies were similar to those reported in China (3.3% and 6.4%, respectively) and Britain (3.1% and 5.1%, respectively) but lower than those reported for most other investigated ethnic groups [26,27].

Table 2. *MPZ*, *GDAP1*, and *NEFL* Mutation Detection Rates in Various Populations

| Gene | Population | Frequency | | Reference |
|---|---|---|---|---|
| | | Total CMT patients (%) | CMT patients excluding CMT1A (%) | |
| *MPZ* | Korean | 3.2 | 4.7 | [34] |
| | Chinese | 3.3 | 6.4 | [26] |
| | Japanese | 5.1 | NA | [29] |
| | German | 4.2 | 6.4 | [31] |
| | British | 3.1 | 5.1 | [27] |
| | American | 4.1 | 6.5 | [35] |
| | Spanish | 4.3 | 7.5 | [32] |
| | Italian | 4.3 | 12.3 | [33] |
| | Hungarian | 4.5 | 7.5 | [36] |
| | Norwegian | 6.0 | NA | [37] |
| | Russian | 3.5 | 5.2 | [21] |
| | Finnish | 5.2 | NA | [38] |
| | Austrian | 4.0 | NA | [39] |
| *GDAP1* | Korean | 0.7 | 1.0 | [40] |
| | Chinese | NA | 1.6 | [30] |
| | Japanese | NA | 0.9 | [29] |
| | British | 0.5 | 0.8 | [27] |
| | American | 0.7 | 1.6 | [28] |
| | Spanish | 11.1 | 20.7 | [32] |
| | Italian | 5.4 | 11.0 | [33] |
| *NEFL* | Korean | 1.5 | 2.1 | [41] |
| | Chinese | 1.9 | 3.7 | [26] |
| | Japanese | 0.9 | NA | [29] |
| | | 2.3 | 2.7 | [23] |
| | German | 0.0 | 0.0 | [31] |
| | | 0.1 | 0.1 | [42] |
| | British | 0.2 | 0.2 | [27] |
| | American | 0.7 | 1.6 | [28] |
| | | 0.7 | 1.1 | [35] |
| | | 0.5 | 0.8 | [43] |
| | Spanish | 0.9 | 1.6 | [32] |
| | Italian | 0.6 | 1.8 | [33] |
| | Norwegian | 0.7 | NA | [37] |

CMT, Charcot-Marie-Tooth disease; NA, not available.

The mean age at onset was 9.3 ± 10.7 years for CMT1B patients, 21.2 ± 13.7 years for CMTDID patients, and 38.7 ± 13.6 years for CMT2I patients (Table 3). The age at onset was significantly different between CMT1B and CMTDID patients ($p = 0.025$) or CMT2I patients ($p < 0.001$). However, the age at onset was not significantly different between CMTDID and CMT2I patients. Functional disability was significantly more severe in CMT1B patients than in CMT2I patients (CMT neuropathy score version 2 [CMTNS], $p = 0.004$, and functional disability scale [FDS], $p = 0.022$). The CMTNS and FDS values of the CMT1B patients were higher than those of the CMTDID patients, but the difference was not significant. When comparing the degree of disability based on CMTNS, most patients had moderate disease (53%), followed by those with severe disease (31%) and mild disease (17%) in CMT1B families. In CMTDID and CMT2I families, most patients had mild disease (75% and 80%, respectively).

### 2) Electrophysiological findings in *MPZ*-related patients

The mean MNCV of CMT1B patients was 12.2 ± 11.0 m/s, which was significantly lower than that of CMT2I patients (46.0 ± 6.6 m/s, $p < 0.001$) and CMTDID patients (41.3 ± 3.1 m/s, $p < 0.001$) (Table 3). The mean sensory nerve conduction velocity (SNCV) (7.4 ± 11.7 m/s) of CMT1B patients was significantly lower than that of CMTDID patients (18.0 ± 25.5 m/s, $p = 0.021$) and CMT2I patients (34.4 ± 4.3 m/s, $p < 0.001$). In addition, the peroneal MNCV and sural SNCV were significantly reduced in CMT1B patients compared to CMTDID or CMT2I patients. The median motor nerve compound muscle action potential (CMAP) amplitudes (6.0 ± 5.6 mV) in the CMT1B patients were significantly lower in CMTDID (12.8 ± 1.9 mV, $p = 0.033$) and CMT2I patients (13.0 ± 4.3 mV, $p = 0.011$). The peroneal nerve CMAP and median and sural sensory nerve action potential (SNAP) amplitudes were also significantly lower in CMT1B patients than in CMTDID and CMT2I patients.

## Ganglioside-Induced Differentiation Related Protein 1 (*GDAP1*)

### 1) Clinical diversity of *GDAP1* mutations

The *GDAP1* mutation frequency rate was found to be 0.7% in all patients and 1.0% in patients negative for *PMP22* duplication (Table 2). Similar frequencies have been reported in most Asian and Western countries, including Japan, China, Germany, the United States, and the United Kingdom [27–31]. However, higher frequencies of *GDAP1* mutations have been reported in cer-


https://doi.org/10.18214/jend.2022.00143

Table 3. Clinical and Electrophysiological Features of Korean CMT Patients with *MPZ* Mutations

| Item | CMT1B | CMT2I | CMTDID | p-value | | | |
|---|---|---|---|---|---|---|---|
| | | | | 1B vs. 2I | 1B vs. DID | 2I vs. DID | ANOVA |
| Patient number | 48 | 7 | 5 | | | | |
| Female ratio (%) | 54 | 14 | 20 | | | | |
| Examined age (y) | 26.4 ± 19.6 | 51.1 ± 11.7 | 40.8 ± 23.3 | 0.002 | 0.129 | 0.332 | 0.005 |
| Onset age (y) | 9.3 ± 10.7 | 38.7 ± 13.6 | 21.2 ± 13.7 | < 0.001 | 0.025 | 0.053 | < 0.001 |
| Disability score | | | | | | | |
| CMTNS | 16.0 ± 7.4 | 8.0 ± 3.2 | 9.8 ± 1.0 | 0.004 | 0.102 | 0.326 | 0.023 |
| FDS | 2.8 ± 1.3 | 1.3 ± 0.5 | 1.8 ± 0.4 | 0.022 | 0.092 | 0.092 | 0.004 |
| Nerve conduction studies | | | | | | | |
| Patient number | 38 | 5 | 4 | | | | |
| Median motor nerve | | | | | | | |
| CMAP (mV) | 6.0 ± 5.6 | 13.0 ± 4.3 | 12.8 ± 1.9 | 0.011 | 0.033 | 0.915 | 0.006 |
| MNCV (m/s) | 12.2 ± 11.0 | 46.0 ± 6.6 | 41.3 ± 3.1 | < 0.001 | < 0.001 | 0.431 | < 0.001 |
| Peroneal nerve | | | | | | | |
| CMAP (mV) | 0.9 ± 2.0 | 2.1 ± 2.8 | 4.0 ± 3.1 | 0.231 | 0.001 | 0.132 | 0.002 |
| MNCV (m/s) | 5.1 ± 9.0 | 20.4 ± 19.4 | 25.7 ± 17.2 | 0.004 | < 0.001 | 0.278 | < 0.001 |
| Median sensory nerve | | | | | | | |
| SNAP (μV) | 2.3 ± 4.7 | 15.6 ± 12.5 | 10.8 ± 15.3 | < 0.001 | < 0.001 | 0.718 | < 0.001 |
| SNCV (m/s) | 7.4 ± 11.7 | 34.4 ± 4.3 | 18.0 ± 25.5 | < 0.001 | 0.021 | 0.78 | < 0.001 |
| Sural nerve | | | | | | | |
| SNAP (μV) | 1.1 ± 3.5 | 5.4 ± 5.9 | 6.9 ± 9.7 | 0.059 | 0.001 | 0.346 | 0.002 |
| SNCV (m/s) | 3.4 ± 9.0 | 17.2 ± 14.9 | 13.3 ± 18.7 | 0.02 | 0.016 | 0.643 | 0.007 |

All data are expressed as the mean ± standard deviation. Normal nerve conduction velocity values: motor median nerve ≥ 50.5 m/s; sensory median nerve ≥ 39.3 m/s; sural nerve ≥ 32.1 m/s. Normal amplitude values: motor median nerve ≥ 6 mV; sensory median nerve ≥ 8.8 μV; sural nerve ≥ 6.0 μV. CMT, Charcot-Marie-Tooth disease; ANOVA, analysis of variance; CMTNS, CMT neuropathy score; FDS, functional disability scale; CMAP, compound muscle action potential; MNCV, motor nerve conduction velocity; SNAP, sensory nerve action potential; SNCV, sensory nerve conduction velocity.

tain regions in Italy and Spain [32,33].

The functional disabilities and clinical characteristics were different between CMT2K and CMTRIA patients. CMT2K patients exhibited mild to moderate disabilities, with a late age at onset (19.7 ± 7.7 years), but CMTRIA patients showed severe disabilities with an early age at onset (1.7 ± 0.6 years) (Table 4). Functional disability was significantly more severe in CMTRIA patients than in CMT2K patients. The mean value of the FDS [44] was 2.3 ± 1.4 in CMT2K patients and 5.3 ± 1.2 in CMTRIA patients ($p = 0.010$). The mean CMTNS score [45] was 11.1 ± 6.6 in CMT2K patients and 24.7 ± 3.2 in CMTRIA patients ($p = 0.011$). High values of the FDS (scores of 6-7) were observed only in CMTRIA patients. In contrast, low values of the FDS (scores < 5) were observed in CMT2K patients. All three CMTRIA patients were classified in the severe category (CMTNS ≥ 21). Foot deformities were frequent, and four patients had scoliosis. However, no wheelchair dependence, diaphragmatic weakness, vocal cord paresis, or hoarseness was observed.

**2) Electrophysiological findings in *GDAP1*-related patients**

Electrophysiological findings verified that CMTRIA patients were more severely affected than CMT2K patients. In CMT2K patients, the conduction velocity mostly did not decrease, excluding nerves with a very low amplitude. In CMTRIA patients, the decreases in CMAP and SNAP amplitudes were even more pronounced, and these parameters were not measured when nerves were explored. These results were worse in the lower extremities than in the upper extremities.

## Neurofilament Light-Chain Polypeptide (*NEFL*)

**1) Clinical diversity of *NEFL* mutations**

The frequency of *NEFL* mutations was reported to range from 0.9% to 2.3% in Japanese and Chinese cohorts and in Korea (Table 2). Data on the frequency of *NEFL* mutations are extremely limited, though the proportion of the *NEFL* mutation in CMT has rarely been reported to be below 1%. Therefore, the frequency of *NEFL* mutations observed in East Asian countries

Table 4. Clinical and Electrophysiological Features of Korean CMT Patients with *GDAP1* Mutations

| Item | CMT2K | CMTRIA | p-value |
|---|---|---|---|
| Patient number | 7 | 3 | |
| Female ratio (%) | 29 | 67 | |
| Examined age (y) | 42.6 ± 15.7 | 9.7 ± 4.2 | 0.009 |
| Onset age (y) | 19.7 ± 7.7 | 1.7 ± 0.6 | 0.004 |
| Disability score | | | |
| CMTNS | 11.1 ± 6.6 | 24.7 ± 3.2 | 0.011 |
| FDS | 2.3 ± 1.4 | 5.3 ± 1.2 | 0.010 |
| Nerve conduction studies | | | |
| Patient number | 7 | 3 | |
| Median motor nerve | | | |
| CMAP (mV) | 11.2 ± 5.8 | 1.4 ± 1.2 | 0.024 |
| MNCV (m/s) | 52.0 ± 5.8 | 32.3 ± 28.0 | 0.092 |
| Peroneal nerve | | | |
| CMAP (mV) | 1.8 ± 1.8 | 0.0 ± 0.1 | 0.127 |
| MNCV (m/s) | 21.7 ± 20.4 | 0.0 ± 0.0 | 0.113 |
| Median sensory nerve | | | |
| SNAP (μV) | 6.3 ± 3.0 | 0.9 ± 1.3 | 0.051 |
| SNCV (m/s) | 38.2 ± 1.2 | 12.5 ± 17.7 | 0.005 |
| Sural nerve | | | |
| SNAP (μV) | 0.2 ± 0.6 | 0.0 ± 0.0 | 0.604 |
| SNCV (m/s) | 4.8 ± 11.8 | 0.0 ± 0.0 | 0.604 |

All data are expressed as the mean ± standard deviation. Normal nerve conduction velocity values: motor median nerve ≥ 50.5 m/s; sensory median nerve ≥ 39.3 m/s; sural nerve ≥ 32.1 m/s. Normal amplitude values: motor median nerve ≥ 6 mV; sensory median nerve ≥ 8.8 μV; sural nerve ≥ 6.0 μV.
CMT, Charcot-Marie-Tooth disease; ANOVA, analysis of variance; CMTNS, CMT neuropathy score; FDS, functional disability scale; CMAP, compound muscle action potential; MNCV, motor nerve conduction velocity; SNAP, sensory nerve action potential; SNCV, sensory nerve conduction velocity.

is higher than that reported in other countries.

The prevalence of *NEFL* mutations was 0.44% in CMT1F patients (5/1,137), 0.35% in CMT2E patients (4/1,137), and 0.70% in CMTDIG patients (8/1,137). The age of onset was thus significantly earlier in CMT1F patients (10.2 ± 7.3 years, p = 0.013) and CMTDIG patients (12.7 ± 7.9, p = 0.007) than in CMT2E patients (24.2 ± 9.4 years) (Table 5). However, the CMTNS and FDS, as measures of disease-related disability, showed no differences among the *NEFL*-related CMT subtypes. Gait ataxia was identified as the most frequent symptom of *NEFL*-related CMT patients (78% of CMT1F patients, 50% of CMT2E patients, and 79% of CMTDIG patients). Patients were genetically tested for spinocerebellar ataxia, but no associated mutations were found. In CMT1F and CMTDIG patients, early-onset dementia was observed. Interestingly, ptosis was predominantly observed in CMT2E patients (50%).

**2) Electrophysiological findings in *NEFL*-related patients**

In CMT1F patients, the amplitudes of evoked peroneal motor responses were often markedly decreased, and the amplitudes were predominantly unrecordable in 6 of 8 patients (75%) (Table 5). However, peroneal CMAP amplitudes in CMT2E patients could not be recorded in only 1 of 4 patients (25%). Interestingly, peroneal CMAP amplitudes in CMTDIG patients (36%) occupied an intermediate position between the CMT1F and CMT2E patients. The mean MNCV of the median nerve was 16.1 ± 10.5 m/s in CMT1F patients and 47.7 ± 8.1 m/s in CMT2E patients. The mean MNCV of the median nerve was 39.6 ± 4.4 m/s in CMTDIG patients . No SNAP amplitudes of the median nerve were observed in 63% of CMT1F patients, 32% of CMTDIG patients, and 25% of CMT2E patients. Furthermore, sural SNAP amplitudes were not evoked in any of the CMT1F patients, nor were they observed in 36% of CMTDIG patients and 25% of CMT2E patients.

## Conclusion

In this review, we described the clinical, electrophysiological, and genetic characteristics of various types of CMT caused by mutations in *MPZ*, *GDAP1*, and *NEFL*. CMT is a peripheral neuropathy with extreme clinical and genetic heterogeneity. Of the 140 causative genes for CMT and other related diseases, *MPZ*, *GDAP1*, and *NEFL* are the only genes that cause all three subtypes of CMT (demyelinating, axonal, and intermediate). CMT is presently incurable; however, the ongoing attempts to treat it with various drugs, dietary supplements, and increase the importance of an exact genetic diagnosis for precision medicine. Therefore, it is important to compare the genetic and clinical features of patients with *MPZ*, *GDAP1*, and *NEFL* mutations. Taken together, a comparison of the causative mutations and clinical features of patients with *MPZ*-, *GDAP1*-, and *NEFL*-related CMT will be the first step in understanding how the different types of CMT are caused, and will enable molecular genetic diagnosis.

## Conflict of Interest

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

## ORCID

Hye Jin Kim, https://orcid.org/0000-0002-7636-3639
Hye Mi Kwon, https://orcid.org/0000-0003-3978-1855


https://doi.org/10.18214/jend.2022.00143

Table 5. Clinical and Electrophysiological Features of Korean CMT Patients with *NEFL* Mutations

| Item | CMT1F | CMT2E | CMTDIG | p-value | | | |
|---|---|---|---|---|---|---|---|
| | | | | 1B vs. 2I | 1B vs. DIG | 2I vs. DIG | ANOVA |
| Patient number | 9 | 4 | 24 | | | | |
| Female ratio (%) | 44 | 25 | 50 | | | | |
| Examined age (y) | 32.4 ± 16.8 | 42.7 ± 6.9 | 37.3 ± 16.3 | 0.271 | 0.453 | 0.524 | 0.536 |
| Onset age (y) | 10.2 ± 7.3 | 24.2 ± 9.4 | 12.1 ± 7.4 | 0.013 | 0.523 | 0.007 | 0.011 |
| Disability score | | | | | | | |
| CMTNS | 24.1 ± 5.1 | 16.2 ± 12.3 | 18.4 ± 7.9 | 0.136 | 0.071 | 0.641 | 0.169 |
| FDS | 4.9 ± 1.9 | 3.2 ± 3.0 | 3.4 ± 2.0 | 0.243 | 0.055 | 0.914 | 0.165 |
| Nerve conduction studies | | | | | | | |
| Patient number | 8 | 4 | 22 | | | | |
| Median motor nerve | | | | | | | |
| CMAP (mV) | 3.1 ± 4.3 | 8.7 ± 5.2 | 9.6 ± 3.5 | 0.075 | < 0.001 | 0.666 | 0.001 |
| MNCV (m/s) | 16.1 ± 10.5 | 47.7 ± 8.1 | 39.6 ± 4.4 | < 0.001 | < 0.001 | 0.007 | < 0.001 |
| Peroneal nerve | | | | | | | |
| CMAP (mV) | 0.5 ± 1.0 | 3.1 ± 4.0 | 1.7 ± 2.0 | 0.104 | 0.122 | 0.298 | 0.148 |
| MNCV (m/s) | 6.4 ± 12.2 | 26.3 ± 18.9 | 21.2 ± 17.1 | 0.049 | 0.033 | 0.591 | 0.066 |
| Median sensory nerve | | | | | | | |
| SNAP (μV) | 4.6 ± 7.8 | 9.7 ± 15.4 | 5.0 ± 6.0 | 0.449 | 0.877 | 0.275 | 0.509 |
| SNCV (m/s) | 13.0 ± 18.5 | 29.0 ± 19.4 | 23.7 ± 17 | 0.194 | 0.146 | 0.581 | 0.246 |
| Sural nerve | | | | | | | |
| SNAP (μV) | 0.0 ± 0.0 | 6.0 ± 9.0 | 2.5 ± 2.6 | 0.073 | 0.011 | 0.119 | 0.028 |
| SNCV (m/s) | 0.0 ± 0.0 | 23.4 ± 16.4 | 18.2 ± 14.6 | 0.002 | 0.002 | 0.522 | 0.004 |

All data are expressed as the mean ± standard deviation. Normal nerve conduction velocity values: motor median nerve ≥ 50.5 m/s; sensory median nerve ≥ 39.3 m/s; sural nerve ≥ 32.1 m/s. Normal amplitude values: motor median nerve ≥ 6 mV; sensory median nerve ≥ 8.8 μV; sural nerve ≥ 6.0 μV. CMT, Charcot-Marie-Tooth disease; ANOVA, analysis of variance; CMTNS, CMT neuropathy score; FDS, functional disability scale; CMAP, compound muscle action potential; MNCV, motor nerve conduction velocity; SNAP, sensory nerve action potential; SNCV, sensory nerve conduction velocity.

Sang Beom Kim, https://orcid.org/0000-0001-8225-3922
Ki Wha Chung, https://orcid.org/0000-0003-0363-8432
Byung-Ok Choi, https://orcid.org/0000-0001-5459-1772

## References

1. Madrid R, Bradley WG, Davis CJ: The peroneal muscular atrophy syndrome: clinical, genetic, electrophysiological and nerve biopsy studies. Part 2. Observations on pathological changes in sural nerve biopsies. J Neurol Sci 1977;32:91–122.
2. Cortese A, Wilcox JE, Polke JM, Poh R, Skorupinska M, Rossor AM, et al: Targeted next-generation sequencing panels in the diagnosis of Charcot-Marie-Tooth disease. Neurology 2020;94:e51–e61.
3. Gonzaga-Jauregui C, Harel T, Gambin T, Kousi M, Griffin LB, Francescatto L, et al: Exome sequence analysis suggests that genetic burden contributes to phenotypic variability and complex neuropathy. Cell Rep 2015;12:1169–1183.
4. Rossor AM, Polke JM, Houlden H, Reilly MM: Clinical implications of genetic advances in Charcot-Marie-Tooth disease. Nat Rev Neurol 2013;9:562–571.
5. Lemke G, Axel R: Isolation and sequence of a cDNA encoding the major structural protein of peripheral myelin. Cell 1985;40:501–508.
6. De Jonghe P, Timmerman V, Ceuterick C, Nelis E, De Vriendt E, Löfgren A, et al: The Thr124Met mutation in the peripheral myelin protein zero (MPZ) gene is associated with a clinically distinct Charcot-Marie-Tooth phenotype. Brain 1999;122(Pt 2):281–290.
7. Hayasaka K, Himoro M, Sato W, Takada G, Uyemura K, Shimizu N, et al: Charcot-Marie-Tooth neuropathy type 1B is associated with mutations of the myelin P0 gene. Nat Genet 1993;5:31–34.
8. Kochański A: Mutations in the Myelin Protein Zero result in a spectrum of Charcot-Marie-Tooth phenotypes. Acta Myol 2004;23:6–9.
9. Mastaglia FL, Nowak KJ, Stell R, Phillips BA, Edmondston JE, Dorosz SM, et al: Novel mutation in the myelin protein zero gene in a family with intermediate hereditary motor and sensory neuropathy. J Neurol Neurosurg Psychiatry 1999;67:174–179.
10. Sanmaneechai O, Feely S, Scherer SS, Herrmann DN, Burns J, Muntoni F, et al: Genotype-phenotype characteristics and baseline

natural history of heritable neuropathies caused by mutations in the MPZ gene. Brain 2015;138(Pt 11):3180–3192.
11. Senderek J, Hermanns B, Lehmann U, Bergmann C, Marx G, Kabus C, et al: Charcot-Marie-Tooth neuropathy type 2 and P0 point mutations: two novel amino acid substitutions (Asp61Gly; Tyr119Cys) and a possible "hotspot" on Thr124Met. Brain Pathol 2000;10:235–248.
12. Hattori N, Yamamoto M, Yoshihara T, Koike H, Nakagawa M, Yoshikawa H, et al: Demyelinating and axonal features of Charcot-Marie-Tooth disease with mutations of myelin-related proteins (PMP22, MPZ and Cx32): a clinicopathological study of 205 Japanese patients. Brain 2003;126(Pt 1):134–151.
13. Shy ME, Jáni A, Krajewski K, Grandis M, Lewis RA, Li J, et al: Phenotypic clustering in MPZ mutations. Brain 2004;127(Pt 2):371–384.
14. Mazzeo A, Muglia M, Rodolico C, Toscano A, Patitucci A, Quattrone A, et al: Charcot-Marie-Tooth disease type 1B: marked phenotypic variation of the Ser78Leu mutation in five Italian families. Acta Neurol Scand 2008;118:328–332.
15. Senderek J, Ramaekers VT, Zerres K, Rudnik-Schöneborn S, Schröder JM, Bergmann C: Phenotypic variation of a novel nonsense mutation in the P0 intracellular domain. J Neurol Sci 2001;192:49–51.
16. Estela A, Pla-Martín D, Sánchez-Piris M, Sesaki H, Palau F: Charcot-Marie-Tooth-related gene GDAP1 complements cell cycle delay at G2/M phase in Saccharomyces cerevisiae fis1 gene-defective cells. J Biol Chem 2011;286:36777–36786.
17. Baxter RV, Ben Othmane K, Rochelle JM, Stajich JE, Hulette C, Dew-Knight S, et al: Ganglioside-induced differentiation-associated protein-1 is mutant in Charcot-Marie-Tooth disease type 4A/8q21. Nat Genet 2002;30:21–22.
18. Cuesta A, Pedrola L, Sevilla T, García-Planells J, Chumillas MJ, Mayordomo F, et al: The gene encoding ganglioside-induced differentiation-associated protein 1 is mutated in axonal Charcot-Marie-Tooth type 4A disease. Nat Genet 2002;30:22–25.
19. Claramunt R, Pedrola L, Sevilla T, López de Munain A, Berciano J, Cuesta A, et al: Genetics of Charcot-Marie-Tooth disease type 4A: mutations, inheritance, phenotypic variability, and founder effect. J Med Genet 2005;42:358–365.
20. Senderek J, Bergmann C, Ramaekers VT, Nelis E, Bernert G, Makowski A, et al: Mutations in the ganglioside-induced differentiation-associated protein-1 (GDAP1) gene in intermediate type autosomal recessive Charcot-Marie-Tooth neuropathy. Brain 2003;126(Pt 3):642–649.
21. Mersiyanova IV, Perepelov AV, Polyakov AV, Sitnikov VF, Dadali EL, Oparin RB, et al: A new variant of Charcot-Marie-Tooth disease type 2 is probably the result of a mutation in the neurofilament-light gene. Am J Hum Genet 2000;67:37–46.
22. Jordanova A, De Jonghe P, Boerkoel CF, Takashima H, De Vriendt E, Ceuterick C, et al: Mutations in the neurofilament light chain gene (NEFL) cause early onset severe Charcot-Marie-Tooth disease. Brain 2003;126(Pt 3):590–597.
23. Abe A, Numakura C, Saito K, Koide H, Oka N, Honma A, et al: Neurofilament light chain polypeptide gene mutations in Charcot-Marie-Tooth disease: nonsense mutation probably causes a recessive phenotype. J Hum Genet 2009;54:94–97.
24. Yum SW, Zhang J, Mo K, Li J, Scherer SS: A novel recessive Nefl mutation causes a severe, early-onset axonal neuropathy. Ann Neurol 2009;66:759–770.
25. Berciano J, García A, Peeters K, Gallardo E, De Vriendt E, Pelayo-Negro AL, et al: NEFL E396K mutation is associated with a novel dominant intermediate Charcot-Marie-Tooth disease phenotype. J Neurol 2015;262:1289–1300.
26. Hsu YH, Lin KP, Guo YC, Tsai YS, Liao YC, Lee YC: Mutation spectrum of Charcot-Marie-Tooth disease among the Han Chinese in Taiwan. Ann Clin Transl Neurol 2019;6:1090–1101.
27. Murphy SM, Laura M, Fawcett K, Pandraud A, Liu YT, Davidson GL, et al: Charcot-Marie-Tooth disease: frequency of genetic subtypes and guidelines for genetic testing. J Neurol Neurosurg Psychiatry 2012;83:706–710.
28. DiVincenzo C, Elzinga CD, Medeiros AC, Karbassi I, Jones JR, Evans MC, et al: The allelic spectrum of Charcot-Marie-Tooth disease in over 17,000 individuals with neuropathy. Mol Genet Genomic Med 2014;2:522–529.
29. Yoshimura A, Yuan JH, Hashiguchi A, Ando M, Higuchi Y, Nakamura T, et al: Genetic profile and onset features of 1005 patients with Charcot-Marie-Tooth disease in Japan. J Neurol Neurosurg Psychiatry 2019;90:195–202.
30. Pakhrin PS, Xie Y, Hu Z, Li X, Liu L, Huang S, et al: Genotype-phenotype correlation and frequency of distribution in a cohort of Chinese Charcot-Marie-Tooth patients associated with GDAP1 mutations. J Neurol 2018;265:637–646.
31. Gess B, Schirmacher A, Boentert M, Young P: Charcot-Marie-Tooth disease: frequency of genetic subtypes in a German neuromuscular center population. Neuromuscul Disord 2013;23:647–651.
32. Sivera R, Sevilla T, Vílchez JJ, Martínez-Rubio D, Chumillas MJ, Vázquez JF, et al: Charcot-Marie-Tooth disease: genetic and clinical spectrum in a Spanish clinical series. Neurology 2013;81:1617–1625.
33. Sadjadi R, Reilly MM, Shy ME, Pareyson D, Laura M, Murphy S, et al: Psychometrics evaluation of Charcot-Marie-Tooth Neuropathy Score (CMTNSv2) second version, using Rasch analysis. J Peripher Nerv Syst 2014;19:192–196.

 https://doi.org/10.18214/jend.2022.00143

34. Kim HJ, Nam SH, Kwon HM, Lim SO, Park JH, Kim HS, et al: Genetic and clinical spectrums in Korean Charcot-Marie-Tooth disease patients with myelin protein zero mutations. Mol Genet Genomic Med 2021;9:e1678.
35. Fridman V, Bundy B, Reilly MM, Pareyson D, Bacon C, Burns J, et al: CMT subtypes and disease burden in patients enrolled in the Inherited Neuropathies Consortium natural history study: a cross-sectional analysis. J Neurol Neurosurg Psychiatry 2015;86:873–878.
36. Milley GM, Varga ET, Grosz Z, Nemes C, Arányi Z, Boczán J, et al: Genotypic and phenotypic spectrum of the most common causative genes of Charcot-Marie-Tooth disease in Hungarian patients. Neuromuscul Disord 2018;28:38–43.
37. Østern R, Fagerheim T, Hjellnes H, Nygård B, Mellgren SI, Nilssen Ø: Diagnostic laboratory testing for Charcot Marie Tooth disease (CMT): the spectrum of gene defects in Norwegian patients with CMT and its implications for future genetic test strategies. BMC Med Genet 2013;14:94.
38. Silander K, Meretoja P, Juvonen V, Ignatius J, Pihko H, Saarinen A, et al: Spectrum of mutations in Finnish patients with Charcot-Marie-Tooth disease and related neuropathies. Hum Mutat 1998;12:59–68.
39. Miltenberger-Miltenyi G, Schwarzbraun T, Löscher WN, Wanschitz J, Windpassinger C, Duba HC, et al: Identification and in silico analysis of 14 novel GJB1, MPZ and PMP22 gene mutations. Eur J Hum Genet 2009;17:1154–1159.
40. Kim HS, Kim HJ, Nam SH, Kim SB, Choi YJ, Lee KS, et al: Clinical and neuroimaging features in Charcot-Marie-Tooth patients with GDAP1 mutations. J Clin Neurol 2021;17:52–62.
41. Kim HJ, Kim SB, Kim HS, Kwon HM, Park JH, Lee AJ, et al: Phenotypic heterogeneity in patients with NEFL-related Charcot-Marie-Tooth disease. Mol Genet Genomic Med 2022;10:e1870.
42. Rudnik-Schöneborn S, Tölle D, Senderek J, Eggermann K, Elbracht M, Kornak U, et al: Diagnostic algorithms in Charcot-Marie-Tooth neuropathies: experiences from a German genetic laboratory on the basis of 1206 index patients. Clin Genet 2016;89:34–43.
43. Saporta AS, Sottile SL, Miller LJ, Feely SM, Siskind CE, Shy ME: Charcot-Marie-Tooth disease subtypes and genetic testing strategies. Ann Neurol 2011;69:22–33.
44. Manganelli F, Tozza S, Pisciotta C, Bellone E, Iodice R, Nolano M, et al: Charcot-Marie-Tooth disease: frequency of genetic subtypes in a Southern Italy population. J Peripher Nerv Syst 2014;19:292–298.
45. Birouk N, LeGuern E, Maisonobe T, Rouger H, Gouider R, Tardieu S, et al: X-linked Charcot-Marie-Tooth disease with connexin 32 mutations: clinical and electrophysiologic study. Neurology 1998;50:1074–1082.

JEND Journal of Electrodiagnosis and Neuromuscular Diseases

ORIGINAL ARTICLE

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2022;24(3):70-78
https://doi.org/10.18214/jend.2022.00080

# Analysis of Electrodiagnostic Recovery after Carpal Tunnel Release: A Retrospective Study

Hyungsun Peo, Jun Gyu Lee, Yoonhee Kim, Don-Kyu Kim, Hyun Iee Shin, Du Hwan Kim

Department of Physical Medicine and Rehabilitation, Chung-Ang University College of Medicine, Seoul, Korea

**Objective:** We investigated the factors affecting electrodiagnostic (EDX) parameters after carpal tunnel release (CTR).

**Methods:** Thirty-nine cases with clinically diagnosed carpal tunnel syndrome who received CTR and EDX studies before and after CTR were enrolled in this study. We analyzed EDX parameters such as distal onset latency and the amplitude of median compound motor action potentials (CMAPs) and sensory nerve action potentials (SNAPs).

**Results:** Among 39 cases, 24 (61.5%) showed improvement of at least 1 grade, based on Bland's scale, after CTR. Follow-up EDX studies were performed 6 to 36 months after CTR. Improvement on Bland's scale was shown in 50% of patients who received follow-up EDX studies at 6 and 12 months after CTR and in all patients who received follow-up at 24 and 36 months. The EDX parameters showed significant recovery. Younger patients showed greater recovery of SNAP amplitude ($p = 0.021$, $r = -0.369$) after CTR. The preoperative severe group showed greater recovery of CMAP (both amplitude and latency) than the non-severe group ($p = 0.011$ and $p = 0.038$, respectively).

**Conclusion:** We confirmed the effectiveness of CTR through EDX studies. Age and preoperative EDX severity can affect the recovery of EDX parameters after CTR.

**Keywords:** Carpal tunnel syndrome; Carpal tunnel release; Electrodiagnosis

**Received:** June 23, 2022
**Revised:** August 2, 2022
**Accepted:** August 9, 2022

**Corresponding author:**
Du Hwan Kim
Department of Physical Medicine and Rehabilitation, Chung Ang University Hospital, Chung-Ang University College of Medicine, 102 Heukseok-ro, Dongjak-gu, Seoul 06973, Korea
Tel: +82-2-6299-1866
Fax: +82-2-6298-1866
E mail: ri-pheonix@hanmail.net

## Introduction

Carpal tunnel syndrome (CTS) is the most common focal entrapment mononeuropathy, affecting 1% of the population [1,2]. When patients do not improve with conservative treatment, carpal tunnel release (CTR) surgery is frequently performed. Approximately 70% to 90% of patients have good to excellent long-term outcomes with CTR [3]. The remaining patients have poor outcomes, which can be classified into one of 3 categories: persistent, recurrent, or new symptoms [4]. An understanding of the factors that predict a poor outcome after CTR would be beneficial during preoperative counseling and provide more accurate expectations for postoperative outcomes.

Many existing studies on CTS have reported its risk factors, along with methods for its diagnosis and treatment; however, few have investigated the factors affecting the postoperative improvement of CTS. Even in studies that identified predictors of postoperative outcomes, the results were inconsistent. Previous studies have found that worse outcomes of CTR have been associated with preoperative variables such as preoperative muscle weakness or atrophy [5–7], predisposing medical conditions [6], including diabetes and thyroid disease [8], heavy or repetitive manual work [9,10], and exposure to vibration [11]. However, other studies have found that predisposing medical comorbidi-

ties [12–18], patient factors (age, sex) [19,20], duration of symptoms before surgery [19], neurophysiologic testing [19,21], physical examination findings [22], and body mass index [23] did not affect the postoperative outcomes. The severity of nerve conduction or electromyographic abnormalities is generally not associated with surgical outcomes [6,7,9,10].

Most previous studies have evaluated postoperative improvements in CTS through patient-reported symptom relief and satisfaction [24–30]. There have been few comparative studies on electrodiagnostic (EDX) studies before and after CTR in the same patients. Our study intended to analyze changes in EDX parameters after CTR instead of patient-reported symptom relief. The aim of this study was to describe the quantitative changes in EDX parameters after CTR and to clarify the factors affecting the recovery of the EDX parameters. Our hypothesis was that older age, longer durations of symptoms, and greater preoperative severity might negatively affect EDX recovery. An understanding of the factors that predict postoperative outcomes would be beneficial during preoperative counseling and provide more accurate expectations for the prognosis.

## Materials and Methods

This retrospective study was approved by the ethics committee of Chung Ang University Hospital (approval number: 2109-029-19386) and was performed in accordance with the Declaration of Helsinki.

### 1) Participants

We retrospectively screened patients who visited an EDX laboratory affiliated with the Department of Physical Medicine and Rehabilitation of a single tertiary hospital from January 2012 to January 2022 and who presented with hand tingling. Patients were eligible if they met all of the following criteria: (1) they were diagnosed with CTS based on an EDX study, (2) they received CTR by a single orthopedic surgeon at the same hospital, and (3) they received a follow-up EDX study after CTR.

Patients were excluded if (1) they had diabetes before CTR; (2) they had no medical records concerning their medical comorbidities, including diabetes and duration of symptoms at the time of CTR; (3) their EDX results suggested combined cervical myeloradiculopathy or ulnar neuropathy, generalized demyelinating polyneuropathies, generalized axonal neuropathy related to end-stage renal disease, or trauma-related median neuropathy; or (4) they were on hemodialysis. A total of 39 cases in 35 patients were enrolled in this study.

We expected that age, sex, duration of symptoms, and the severity of findings on the preoperative EDX study might affect the results of the follow-up EDX studies. We surveyed these factors through a review of medical records.

The performance of CTR was dependent on the surgeon's decision and based on each patient's preoperative severity, duration of symptoms, previous history of treatments, comorbidities, and other factors.

### 2) Electrodiagnostic studies and outcome measurements

The EDX studies were performed using a Nicolet EDX EMG system (Natus, Pleasanton, CA, USA). In our EDX laboratory, the patient's skin temperature was routinely maintained between 31°C and 34°C. In nerve conduction studies (NCSs), the conventional surface electrode technique was used. The active recording electrode was placed on the belly of the abductor pollicis brevis muscle, and the reference electrode was attached distally to the insertion of the muscle during the motor NCSs. Wrist stimulation was performed 8 cm proximal to the active recording electrode. The onset latency ($CMAP_{latency}$) and baseline to peak amplitude ($CMAP_{amplitude}$) values of the compound motor action potential (CMAP) were measured.

Antidromic sensory nerve conduction was recorded from the index finger and stimulated in the wrist. The distance between the recording electrode and stimulator was 14 cm. Of the sensory nerve action potentials (SNAPs), the onset latencies ($SNAP_{latency}$) and baseline to peak amplitudes ($SNAP_{amplitude}$) were measured.

In EDX studies, CTS was diagnosed when one or more of the following criteria were satisfied: (1) When the median $CMAP_{latency}$ was 4.2 ms or more, (2) When the median $SNAP_{latency}$ was 3.2 ms or more [31,32].

Additive NCS of other nerves and needle electromyography ruled out CTS-mimicking diseases such as cervical radiculopathy, motor neuron disease, and brachial plexopathy.

The degree of the patient's median nerve damage was classified into grades 1 to 6 according to Bland's neurophysiologic grading scale (Table 1) [33]. The patient's preoperative severity was classified as severe (Bland's scale 4-6) or non-severe (Bland's scale 1-3). Improvement was defined as at least a 1-grade positive change on Bland's scale after CTR. We also evaluated the recovery of EDX parameters by measuring the differences ($\Delta CMAP_{amplitude}$, $\Delta CMAP_{latency}$, $\Delta SNAP_{amplitude}$, and $\Delta SNAP_{latency}$) between the preoperative and postoperative $CMAP_{amplitude}$, $CMAP_{latency}$, $SNAP_{amplitude}$, and $SNAP_{latency}$ values.

### 3) Statistical analysis

Statistical analyses were performed using IBM SPSS ver. 21.0

**Table 1.** Bland's Neurophysiologic Grading Scale for Carpal Tunnel Syndrome

| Grade | EDX abnormality |
|---|---|
| 1. Very mild | CTS detected by only PWDSLD |
| 2. Mild | Median DML < 4.5 ms and sensory NCV < 40 |
| 3. Moderately severe | Median DML > 4.5 ms and < 6.5 ms with preserved SNAP |
| 4. Severe | Median DML > 4.5 ms and < 6.5 ms with absent SNAP |
| 5. Very severe | Median DML > 6.5 ms with CMAP > 0.2 mV |
| 6. Extremely severe | Median CMAP from APB < 0.2 mV |

EDX, electrodiagnostic; CTS, carpal tunnel syndrome; PWDSLD, palm wrist distal sensory latency difference; DML, distal motor latency; NCV, nerve conduction velocity; SNAP, sensory nerve action potential; CMAP, compound motor action potential; APB, abductor pollicis brevis muscle.
Based on [33].

**Table 2.** Clinical Characteristics of the Study Population

| Clinical characteristic | Value |
|---|---|
| No. of patients | 34 |
| No. of CTS cases | 39 |
| Sex (male:female) | 4:35 |
| Age (y) | 56.3 ± 8.7 (30–70) |
| Duration of symptoms (mo) | 27.8 ± 38.7 (1–120) |
| Affected side of the CTS (no. of patients) | |
| Right | 15 |
| Left | 16 |
| Bilateral | 4 |
| Preoperative severity (Bland's scale) (no. of cases) | |
| Grade 2: mild | 5 (12.8) |
| Grade 3: moderately severe | 20 (51.3) |
| Grade 4: severe | 2 (5.1) |
| Grade 5: very severe | 7 (17.9) |
| Grade 6: extremely severe | 5 (12.8) |
| Period of follow-up EDX study (no. of cases) | |
| 6 mo after surgery | 20 (51.3) |
| 12 mo after surgery | 10 (25.6) |
| 24 mo after surgery | 6 (15.4) |
| 36 mo after surgery | 3 (7.7) |

Values are presented as mean ± standard deviation (range) or number (%).
CTS, carpal tunnel syndrome; EDX, electrodiagnostic.

(IBM Corp., Armonk, NY, USA). The paired t-test was used to compare the differences between the preoperative and postoperative $\Delta CMAP_{amplitude}$, $\Delta CMAP_{latency}$, $\Delta SNAP_{amplitude}$, and $\Delta SNAP_{latency}$ values. The Mann-Whitney U-test and chi-square tests were used to identify significant variables in the univariate analysis of improvement according to Bland's scale. Spearman's correlation analysis was performed to examine the correlation between changes in EDX parameters ($\Delta CMAP_{amplitude}$, $\Delta CMAP_{latency}$, $\Delta SNAP_{amplitude}$, and $\Delta SNAP_{latency}$) and continuous variables (age and duration of symptoms). Point-biserial correlation analysis was conducted to assess the correlation between changes in EDX parameters and categorical variables (sex and preoperative severity).

All statistical tests were conducted at a two-sided 5% significance level, and all reported p-values were two-sided. Statistical significance was set at $p < 0.05$.

## Results

### 1) Clinical characteristics of the study populations

In total, 39 CTS cases from 35 patients were included in this study. Four patients had bilateral CTS and received bilateral CTR. The clinical characteristics of patients are summarized in Table 2. The mean age of the patients was 56.3 ± 8.7 years, and the mean duration of symptoms at the first visit was 27.8 ± 38.7 months. Four cases (10.3%) were in men and 35 cases (89.7%) were in men. Fifteen cases (38.5%) were on the right, 16 cases (41.0%) were on the left, and 4 cases were on both sides (Table 2).

Based on Bland's scale, 5 cases (12.8%) were classified as grade 2 (mild), 20 cases (51.3%) were grade 3 (moderately severe), 2 cases (5.1%) were grade 4 (severe), 7 cases (17.9%) were grade 5 (very severe), and 5 cases (12.8%) were grade 6 (extremely severe). Patients were classified into 2 subgroups according to their preoperative severity: severe (Bland's scale 4-6) and non-severe group (Bland's scale 1-3). The severe group accounted for 14 cases (35.9%) and the non-severe group accounted for 25 cases (64.1%). The subgroups did not show significant differences in terms of the sex ratio ($p = 0.123$). However, there were significant differences in age and duration of symptoms between the 2 groups (age, $p = 0.006$; duration of symptoms, $p = 0.028$) (Table 3).

Postoperative follow-up EDX studies were performed in 20 cases (51.3%) at 6 months, 10 cases (25.6%) at 12 months, 6 cases (15.4%) at 24 months, and 3 cases (7.7%) at 36 months.

### 2) The changes in EDX parameters after CTR

There was significant recovery of EDX parameters, such as $\Delta CMAP_{amplitude}$, $\Delta CMAP_{latency}$, $\Delta SNAP_{amplitude}$, and $\Delta SNAP_{latency}$ ($\Delta CMAP_{amplitude}$, $p = 0.024$; $\Delta CMAP_{latency}$, $p < 0.001$; $\Delta SNAP_{amplitude}$, $p < 0.001$; and $\Delta SNAP_{latency}$, $p < 0.001$) after CTR (Table 4).

Even in the cases with "no response" on the preoperative EDX studies, the recovery of obtainable EDX responses after CTR was reported in 25.0% of cases (1 of 4) for CMAP and 50.0% of cases (6 of 12) for SNAP, respectively.


https://doi.org/10.18214/jend.2022.00080

Table 3. Baseline Characteristics of the Subgroups according to Preoperative Severity

| Variable | Severe group* | Non-severe group | p-value |
|---|---|---|---|
| Number | 14 | 25 | |
| Sex (male:female) | 3:11 | 1:24 | 0.123 |
| Age (y) | 61.6 ± 6.9 (52–70) | 53.3 ± 8.3 (30–69) | 0.006† |
| Duration of symptoms (mo) | 46.0 ± 50.4 (4–120) | 17.7 ± 26.4 (1–120) | 0.028† |

Values are presented as mean ± standard deviation, except for the number of patients and sex ratio.
*Preoperative severity classifications were based on Bland's scale (severe [Bland's scale 4–6] and non-severe [Bland's scale 1-3]).
†$p < 0.05$, Mann-Whitney U-test.

Table 4. Changes in Electrodiagnostic Parameters after Carpal Tunnel Release

| Parameter | Preoperative | Postoperative | Difference (Δ) | p-value |
|---|---|---|---|---|
| CMAP amplitude (mV) | 7.5 ± 4.4 | 8.3 ± 4.5 | 0.8 ± 2.1 | 0.024* |
| SNAP amplitude (μV) | 10.4 ± 11.8 | 17.2 ± 13.4 | 6.8 ± 9.1 | < 0.001* |
| CMAP latency (ms) | 6.1 ± 3.0 | 4.8 ± 2.6 | 1.2 ± 1.9 | < 0.001* |
| SNAP latency (ms) | 4.9 ± 1.5 | 3.8 ± 1.4 | 1.1 ± 1.2 | < 0.001* |

Values are presented as mean ± standard deviation.
CMAP, compound motor action potential; SNAP, sensory nerve action potential.
*$p < 0.05$ by the paired t-test.

### 3) Changes in Bland's scale after CTR

We analyzed improvement patterns according to cases' preoperative severity based on Bland's scale. Of the 39 cases, 24 cases (61.5%) showed improvements (at least a 1-grade positive change on Bland's scale) after CTR, and 15 cases (38.5%) showed non-improvement.

The final change in each case's Bland's scale after CTR is presented in Fig. 1A. The line with a slope of 1 presents cases with the same Bland's scale before and after CTR. The cases below the line are those in which improvement occurred, while those above and at the line comprise non-improvement cases. Improvement was observed in (60%) out of 5 cases with preoperative Bland's scale 2, 12 (60%) out of 20 cases with preoperative Bland's scale 3, one (50.0%) out of 2 cases with preoperative Bland's scale 4, 6 (85.7%) out of 7 cases with preoperative Bland's scale 5, 2 (40%) out of 5 cases with preoperative Bland's scale 6 (Fig. 1A). The overall patients were classified according to the timing of the follow-up EDX study. Follow-up EDX studies were performed 6 months to 36 months after CTR. Ten (50.0%) of 20 patients who received a follow-up EDX study at 6 months after CTR showed improvement on Bland's scale (Fig. 1B). Five (50.0%) of 10 patients who received follow-up at 12 months after CTR revealed improvement on Bland's scale (Fig. 1C). All patients who received follow-up EDX at 24 (n = 6) and 36 months (n = 3) after CTR demonstrated improvement on Bland's scale (Fig. 1D, E).

### 4) Analysis of the clinical factors affecting improvement based on Bland's scale after CTR

Univariate analysis revealed that improvements in Bland's scale were not associated with any clinical factors (sex, $p = 0.631$; age, $p = 0.875$; duration, $p = 0.598$; preoperative severity, $p = 1.000$; and period of follow-up EDX study, $p = 0.051$). The improvement group received follow-up EDX studies on average 15.5 ± 10.8 months after CTR, and the non-improvement group had follow-up examinations at an average of 8.0 ± 2.9 months after CTR. Even though no statistically significant difference in the timing of follow-up EDX studies was found between the improvement group and the non-improvement group ($p = 0.051$), the follow-up period of the improvement group tended to be longer than that of the non-improvement group (Table 5).

### 5) Analysis of clinical factors affecting the recovery of EDX parameters after CTR

The quantitative analysis of changes in EDX parameters after CTR showed a significant inverse correlation between age and $\Delta SNAP_{amplitude}$, suggesting that younger age was associated with greater recovery of $\Delta SNAP_{amplitude}$ after CTR ($p = 0.021$, $r = -0.369$). A significant correlation was found between preoperative severity and recovery of both $\Delta CMAP_{amplitude}$ and $\Delta CMAP_{latency}$ values after CTR, in which the preoperative severe group showed more recovery of $\Delta CMAP_{amplitude}$ and $\Delta CMAP_{latency}$ values after CTR ($\Delta CMAP_{amplitude}$, $p = 0.011$, $r = 0.403$; $\Delta CMAP_{latency}$, $p = 0.038$, $r = 0.334$) (Table 6).

## Discussion

Among 39 cases, 24 (61.5%) showed improvement in CTS (at least a 1-grade positive change on Bland's scale) in the follow-up EDX study after CTR. This was similar to the 70% to 90% improvement rates reported in other studies [3,34]. There was a significant recovery of EDX parameters such as $\Delta CMAP_{amplitude}$, $\Delta CMAP_{latency}$, $\Delta SNAP_{amplitude}$, and $\Delta SNAP_{latency}$ after CTR. No statistically significant associations were found between improvements on Bland's scale and clinical factors (sex, age, duration of symptoms, and preoperative severity), whereas the quantitative analysis of EDX parameters suggested that age and preoperative severity can affect the recovery of EDX parameters after CTR.

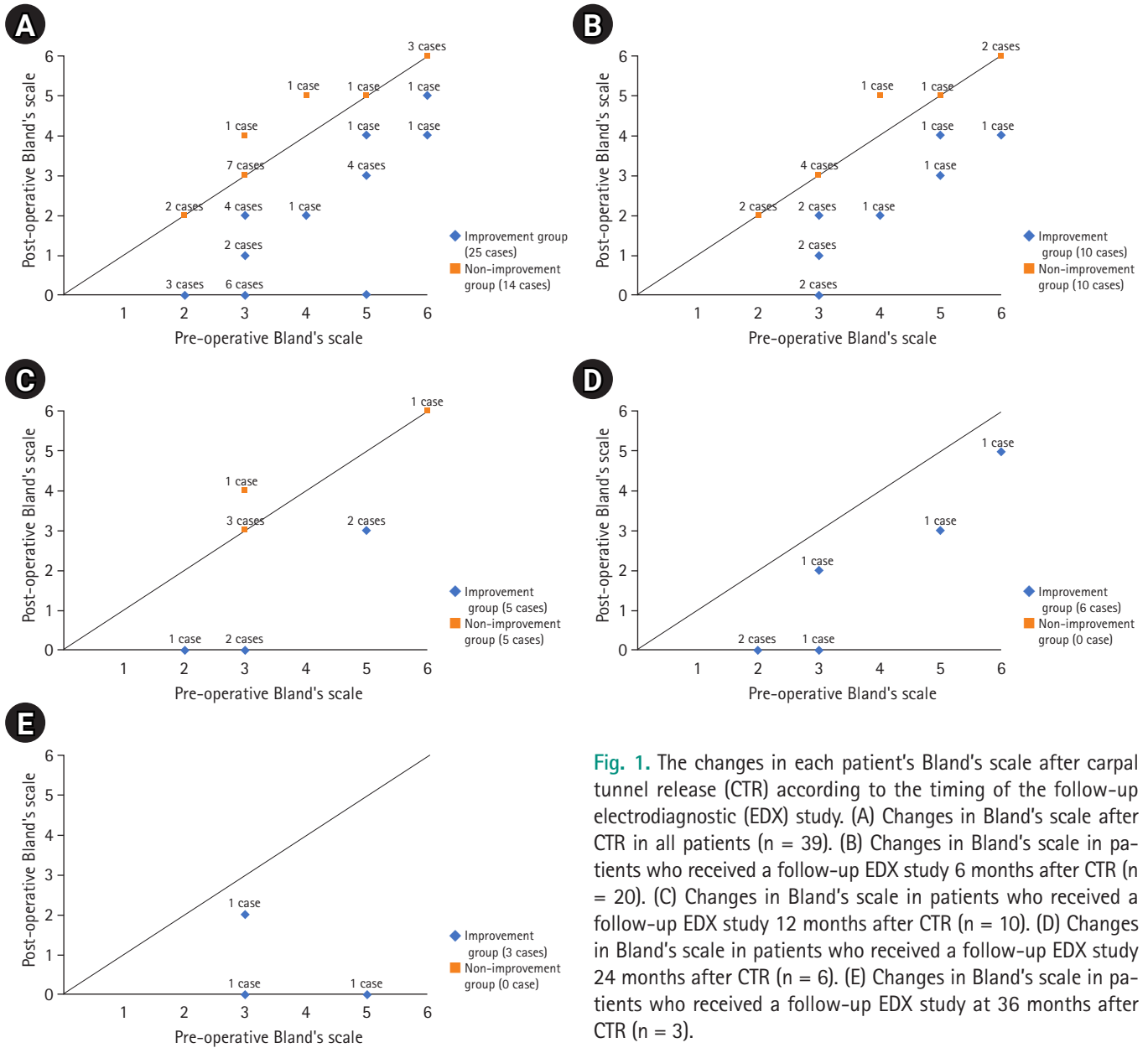


Fig. 1. The changes in each patient's Bland's scale after carpal tunnel release (CTR) according to the timing of the follow-up electrodiagnostic (EDX) study. (A) Changes in Bland's scale after CTR in all patients (n = 39). (B) Changes in Bland's scale in patients who received a follow-up EDX study 6 months after CTR (n = 20). (C) Changes in Bland's scale in patients who received a follow-up EDX study 12 months after CTR (n = 10). (D) Changes in Bland's scale in patients who received a follow-up EDX study 24 months after CTR (n = 6). (E) Changes in Bland's scale in patients who received a follow-up EDX study at 36 months after CTR (n = 3).

Table 5. Analysis of Clinical Factors Affecting Improvement Based on Bland's Scale after Carpal Tunnel Release

| Variable | Improvement group* | Non-improvement group | p-value |
|---|---|---|---|
| Number | 24 (61.5) | 15 (38.5) | |
| Sex | | | |
| Female | 22 | 13 | 0.631 |
| Male | 2 | 2 | |
| Age (y) | 56.4 ± 8.4 | 56.0 ± 9.4 | 0.875 |
| Duration of symptoms (mo) | 30.0 ± 42.8 | 24.3 ± 32.1 | 0.598 |
| Preoperative severity | | | |
| Severe group | 9 | 5 | 1.000 |
| Non-severe group | 15 | 10 | |
| Timing of follow-up EDX study (mo) | 15.5 ± 10.8 | 8.0 ± 2.9 | 0.051 |

Values are presented as number (%) or mean ± standard deviation.
EDX, electrodiagnostic.
*Improvement was defined as at least a 1-grade positive change on Bland's scale after carpal tunnel release.


https://doi.org/10.18214/jend.2022.00080

**Table 6.** Analysis of Clinical Factors Affecting the Recovery of Electrodiagnostic Parameters After Carpal Tunnel Release

| Variable | $\Delta CMAP_{amplitude}$ | | $\Delta SNAP_{amplitude}$ | | $\Delta CMAP_{latency}$ | | $\Delta SNAP_{latency}$ | |
|---|---|---|---|---|---|---|---|---|
| | r | p-value | r | p-value | r | p-value | r | p-value |
| Age | -0.023 | 0.890 | -0.369 | 0.021* | 0.055 | 0.741 | -0.128 | 0.437 |
| Sex | 0.016 | 0.922 | 0.045 | 0.784 | 0.053 | 0.750 | 0.026 | 0.873 |
| Duration | 0.048 | 0.773 | -0.169 | 0.303 | 0.127 | 0.443 | 0.122 | 0.458 |
| Preoperative severity | 0.403 | 0.011† | -0.218 | 0.183 | 0.334 | 0.038† | 0.029 | 0.862 |
| Period of follow-up EDX study | -0.007 | 0.966 | 0.233 | 0.153 | 0.185 | 0.261 | 0.183 | 0.265 |

Δ indicates the difference in each parameter between the preoperative and postoperative values.
CMAP, compound motor action potential; SNAP, sensory nerve action potential; EDX, electrodiagnostic.
*$p < 0.05$, Spearman correlation analysis.
†$p < 0.05$, point-biserial correlation analysis.

This study aimed to describe quantitative changes in EDX parameters after CTR and to clarify the factors affecting the recovery of EDX parameters. We analyzed the association between improvement based on Bland's scale and each clinical factor (sex, age, duration of symptoms, and preoperative severity), as well as correlations between the recovery of quantitative EDX parameters and clinical factors. A unique feature of our study was that surgical outcomes were quantified objectively by analyzing changes in EDX parameters instead of using patient-reported subjective symptoms and satisfaction. No statistically significant associations were found between improvements on Bland's scale and clinical factors, whereas preoperative severity and age affected changes in quantitative EDX parameters. Younger patients showed greater recovery of $\Delta SNAP_{amplitude}$ values after CTR. The degree of CMAP recovery was greater (for both $\Delta CMAP_{amplitude}$ and $\Delta CMAP_{latency}$) in the preoperative severe group. These results may be related to the relatively low granularity of Bland's scale. For example, an improvement in $\Delta CMAP_{latency}$ values may not be reflected by a change on Bland's scale.

Our results showed significant differences in age and duration of symptoms between the preoperative severe (Bland's scale 4-6) and non-severe (Bland's scale 1-3) groups. The mean age and duration of symptoms in the severe group were greater and longer than those in the non-severe group, respectively. Chronic entrapment may cause severe nerve damage, such as irreversible axonal damage during a long disease period, which can affect severity.

Our quantitative analysis of EDX parameters was consistent with our hypothesis that age can affect the recovery of EDX parameters after CTR, suggesting that younger patients showed greater recovery of $\Delta SNAP_{amplitude}$ values after CTR. It is widely known that motor and sensory nerve conduction responses gradually decline with aging in the general population. Several studies also have reported a significant correlation between age and the course of entrapment neuropathy. Schwartz and Chan reported a progressive increase in distal motor latency and a progressive decrease in the CMAP amplitudes of older patients with CTS compared to younger patients; therefore, these older patients may require different therapeutic approaches [35]. Kim et al. [36] also compared NCS findings between younger and older groups and reported that CTS often has a progressive, non-remitting course in elderly patients aged over 60 years, possibly due to different mechanisms according to age. Based on the current evidence, elderly patients have less predictable symptomatic and functional improvements after CTR than younger patients [37]. These results are in line with our finding that EDX recovery after CTR was related to age.

Regarding the effect of preoperative severity on surgical outcomes, the recovery of CMAP after CTR was contrary to our hypothesis that patients with severe CTS would have worse outcomes. This result is probably due to the difference in the preoperative $CMAP_{amplitude}$ values between the severe and non-severe groups based on Bland's scale. In our criteria for preoperative severity, the severe group (Bland's scale 4-6) had relatively low $CMAP_{amplitude}$ values in the preoperative EDX studies, and there was substantial potential for recovery after CTR. In contrast, in the non-severe group (Bland's scale 1-3), the preoperative $CMAP_{amplitude}$ values were nearly normal in most cases, suggesting a limited possibility for recovery after CTR. Although our results may have been influenced by the relatively low granularity of Bland's scale, obtainable CMAP responses after CTR were reported in 25.0% (1 of 4 cases) of the "no response" cases in preoperative EDX studies. Reversible demyelination and nerve regeneration may be possible, even in extremely severe cases.

We expected that a longer duration of symptoms would be related to poorer EDX recovery. Debate continues regarding how symptom duration affects surgical outcomes. Some studies have suggested that a longer duration is associated with worse outcomes (i.e., less improvement in symptoms after surgery) [5,7,8,34]. Long-term exposure to entrapment can cause severe nerve damage, including irreversible axonal damage, leading to a

poor prognosis. However, Porter et al. [19] reported that the preoperative durations of symptoms did not affect postoperative outcomes. Our study likewise revealed that symptom duration was not significantly associated with improvements in CTS based on both Bland's scale and the quantitative analysis of EDX parameters after CTR, which was contrary to our hypotheses. We expected that chronicity might result in irreversible axonal loss, which therefore might lead to poor recovery, even with CTR. However, the pathological process of entrapment neuropathy can involve both axonal loss and reversible demyelination and remyelination [37]. Surgical decompression can be effective even in some cases of chronic advanced compressive neuropathy by enhancing the reversibility of the demyelination and axonal regeneration [37–42]. Therefore, surgery can be beneficial, regardless of the duration of symptoms.

Our results suggest that various clinical factors should be considered when making surgical decisions. Our quantitative analysis of the recovery of EDX parameters revealed that younger patients showed more recovery of $\Delta SNAP_{amplitude}$ values. This finding suggests that age can affect EDX recovery after CTR and serve as a factor helping to determine whether surgery is indicated. Several studies have suggested that different therapeutic approaches are needed for older and younger patients, as these ages undergo different clinical courses via different mechanisms [35,36]. Elderly patients with CTS may develop severe motor impairment within a short period, so they should be promptly referred for surgical decompression [35]. However, our study also suggested that improvement after CTR occurred regardless of factors such as preoperative severity and duration of symptoms, although the severe group was relatively older. Patients with severe CTS also showed some improvement after CTR. Clinicians should decide on surgery with consideration of not only age, but also several other clinical factors.

Postoperative follow-up EDX studies were performed 6 to 36 months after CTR in previous several studies [43,44]. Interestingly, our study showed that 9 (37.5%) out of 24 cases that showed improvement received follow-up EDX studies 24 to 36 months after CTR. This result suggests that sustained EDX recovery is possible even more than 1 year after CTR. Although this trend was statistically marginal ($p = 0.051$), the interval of recovery after CTR tended to be longer in cases of improvement. A previous study reported that advanced CTS patients with severe axonal damage took considerably longer to recover after CTR, and several months of follow-up did not suffice to evaluate postoperative EDX recovery in these patients [42]. Our results also suggest that the EDX parameters might gradually recover after CTR over a long period of time, and serial follow-up studies for sufficient periods are recommended to determine the effects of CTR [42,44].

However, this study has some limitations. First, the sample size was relatively small. Second, this was a retrospective study. This study only analyzed the EDX recovery after CTR, and could not investigate the correlation between EDX recovery and clinical symptoms. Third, the period of the postoperative follow-up EDX studies was not standardized. Fourth, there may have been selection bias because not all patients underwent a follow-up EDX study after CTR. Fifth, the composition of the patients was quite heterogeneous, as the patients had many different reasons for receiving follow-up EDX studies after CTR. Further prospective studies are required to obtain more accurate outcome measures.

## Conclusion

We confirmed the effectiveness of CTR through EDX studies regardless of preoperative EDX severity, the duration of symptoms, and sex. Our results suggest that the EDX parameters might gradually recover after CTR over a long period of time. Significant recovery of EDX parameters, including $\Delta CMAP_{amplitude}$, $\Delta CMAP_{latency}$, $\Delta SNAP_{amplitude}$, and $\Delta SNAP_{latency}$, was noted after CTR. No statistically significant associations were found between improvements in Bland's scale and clinical factors, whereas the quantitative analysis of EDX parameters suggested that age and preoperative severity can affect the recovery of EDX parameters after CTR.

## Conflict of Interest

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

## ORCID

Hyungsun Peo, https://orcid.org/0000-0001-6537-4781
Jun Gyu Lee, https://orcid.org/0000-0001-8302-2827
Yoonhee Kim, https://orcid.org/0000-0002-6839-8049
Don-Kyu Kim, https://orcid.org/0000-0001-8619-830X
Hyun Iee Shin, https://orcid.org/0000-0002-9748-7585
Du Hwan Kim, https://orcid.org/0000-0002-9980-8549

## References

1. Wang L: Guiding treatment for carpal tunnel syndrome. Phys Med Rehabil Clin N Am 2018;29:751–760.
2. Levine DW, Simmons BP, Koris MJ, Daltroy LH, Hohl GG, Fossel

AH, et al: A self-administered questionnaire for the assessment of severity of symptoms and functional status in carpal tunnel syndrome. J Bone Joint Surg Am 1993;75:1585–1592.
3. Brown RA, Gelberman RH, Seiler JG, Abrahamsson SO, Weiland AJ, Urbaniak JR, et al: Carpal tunnel release: a prospective, randomized assessment of open and endoscopic methods. J Bone Joint Surg Am 1993;75:1265–1275.
4. Patrick DL, Deyo RA: Generic and disease-specific measures in assessing health status and quality of life. Med Care 1989;27(3 Suppl):S217–S232.
5. Nau HE, Lange B, Lange S: Prediction of outcome of decompression for carpal tunnel syndrome. J Hand Surg Br 1988;13:391–394.
6. Kulick MI, Gordillo G, Javidi T, Kilgore ES, Newmayer WL: Long-term analysis of patients having surgical treatment for carpal tunnel syndrome. J Hand Surg Am 1986;11:59–66.
7. Mühlau G, Both R, Kunath H: Carpal tunnel syndrome: course and prognosis. J Neurol 1984;231:83–86.
8. DeStefano F, Nordstrom DL, Vierkant RA: Long-term symptom outcomes of carpal tunnel syndrome and its treatment. J Hand Surg Am 1997;22:200–210.
9. Yu GZ, Firrell JC, Tsai TM: Pre-operative factors and treatment outcome following carpal tunnel release. J Hand Surg Br 1992;17:646–650.
10. Al-Qattan MM, Bowen V, Manktelow RT: Factors associated with poor outcome following primary carpal tunnel release in non-diabetic patients. J Hand Surg Br 1994;19:622–625.
11. Hagberg M, Nyström A, Zetterlund B: Recovery from symptoms after carpal tunnel syndrome surgery in males in relation to vibration exposure. J Hand Surg Am 1991;16:66–71.
12. Cagle PJ, Reams M, Agel J, Bohn D: An outcomes protocol for carpal tunnel release: a comparison of outcomes in patients with and without medical comorbidities. J Hand Surg Am 2014;39:2175–2180.
13. Mondelli M, Padua L, Reale F, Signorini AM, Romano C: Outcome of surgical release among diabetics with carpal tunnel syndrome. Arch Phys Med Rehabil 2004;85:7–13.
14. Jenkins PJ, Duckworth AD, Watts AC, McEachan JE: The outcome of carpal tunnel decompression in patients with diabetes mellitus. J Bone Joint Surg Br 2012;94:811–814.
15. Roh YH, Lee BK, Noh JH, Oh JH, Gong HS, Baek GH: Effects of metabolic syndrome on the outcome of carpal tunnel release: a matched case-control study. J Hand Surg Am 2015;40:1303–1309.
16. Zyluk A, Puchalski P: A comparison of outcomes of carpal tunnel release in diabetic and non-diabetic patients. J Hand Surg Eur Vol 2013;38:485–488.
17. Thomsen NO, Cederlund R, Rosén I, Björk J, Dahlin LB: Clinical outcomes of surgical release among diabetic patients with carpal tunnel syndrome: prospective follow-up with matched controls. J Hand Surg Am 2009;34:1177–1787.
18. Thomsen NO, Cederlund RI, Andersson GS, Rosén I, Björk J, Dahlin LB: Carpal tunnel release in patients with diabetes: a 5-year follow-up with matched controls. J Hand Surg Am 2014;39:713–720.
19. Porter P, Venkateswaran B, Stephenson H, Wray CC: The influence of age on outcome after operation for the carpal tunnel syndrome: a prospective study. J Bone Joint Surg Br 2002;84:688–691.
20. Lee J, Kwon YW, Choi JC, Choi JH, Lim HS, Kim SK: Prevalence of and risk factors for carpal tunnel syndrome in a rural population. J Korean Acad Rehab Med 2001;25:818–826.
21. Choi SJ, Ahn DS: Correlation of clinical history and electrodiagnostic abnormalities with outcome after surgery for carpal tunnel syndrome. Plast Reconstr Surg 1998;102:2374–2380.
22. Stone OD, Clement ND, Duckworth AD, Jenkins PJ, Annan JD, McEachan JE: Carpal tunnel decompression in the super-elderly: functional outcome and patient satisfaction are equal to those of their younger counterparts. Bone Joint J 2014;96-B:1234–1238.
23. Bodavula VK, Burke FD, Dubin NH, Bradley MJ, Wilgis EF: A prospective, longitudinal outcome study of patients with carpal tunnel surgery and the relationship of body mass index. Hand (N Y) 2007;2:27–33.
24. Higgs PE, Edwards DF, Martin DS, Weeks PM: Relation of preoperative nerve-conduction values to outcome in workers with surgically treated carpal tunnel syndrome. J Hand Surg Am 1997;22:216–221.
25. Nathan PA, Meadows KD, Keniston RC: Rehabilitation of carpal tunnel surgery patients using a short surgical incision and an early program of physical therapy. J Hand Surg Am 1993;18:1044–1050.
26. Kronlage SC, Menendez ME: The benefit of carpal tunnel release in patients with electrophysiologically moderate and severe disease. J Hand Surg Am 2015;40:438–444.
27. Jansen MC, Evers S, Slijper HP, de Haas KP, Smit X, Hovius SE, et al: Predicting clinical outcome after surgical treatment in patients with carpal tunnel syndrome. J Hand Surg Am 2018;43:1098–1106.
28. Katz JN, Losina E, Amick BC, Fossel AH, Bessette L, Keller RB: Predictors of outcomes of carpal tunnel release. Arthritis Rheum 2001;44:1184–1193.
29. Watchmaker JD, Watchmaker GP: Independent variables affecting outcome of carpal tunnel release surgery. Hand (N Y) 2017;13:285–291.
30. Ebrahimzadeh MH, Mashhadinejad H, Moradi A, Kachooei AR: Carpal tunnel release in diabetic and non-diabetic patients. Arch

Bone Jt Surg 2013;1:23–27.
31. Fowler JR, Cipolli W, Hanson T: A comparison of three diagnostic tests for carpal tunnel syndrome using latent class analysis. J Bone Joint Surg Am 2015;97:1958–1961.
32. Deryani E, Aki S, Muslumanoglu L, Rozanes I: MR imaging and electrophysiological evaluation in carpal tunnel syndrome. Yonsei Med J 2003;44:27–32.
33. Bland JD: A neurophysiological grading scale for carpal tunnel syndrome. Muscle Nerve 2000;23:1280–1283.
34. Yang SN, Yoon JS, Kim SJ, Kim GS: A long-term follow up study of prognostic factors after carpal tunnel release. J Korean Acad Rehab Med 2006;30:580–583.
35. Schwartz MS, Chan TP: Carpal tunnel syndrome: age as an important factor. Muscle Nerve 1998;21:829–830.
36. Kim JY, Park HY, Kang SS: The importance of age as a factor of carpal tunnel syndrome management. Ann Clin Neurophysiol 2001;3:15–20.
37. Pham K, Gupta R: Understanding the mechanisms of entrapment neuropathies. Neurosurg Focus 2009;26:E7.
38. Miller RG: Acute vs. chronic compressive neuropathy. Muscle Nerve 1984;7:427–430.
39. Dy CJ, Mackinnon SE: Ulnar neuropathy: evaluation and management. Curr Rev Musculoskelet Med 2016;9:178–184.
40. Fung BW, Tang CY, Fung BK: Does aging matter? The efficacy of carpal tunnel release in the elderly. Arch Plast Surg 2015;42:278–281.
41. Daniel D, Anthony AA, Machiel Z: Electrodiagnostic Medicine. 2nd ed. Philadelphia: Hanley & Belfus; 2002, p1068.
42. Kanatani T, Fujioka H, Kurosaka M, Nagura I, Sumi M: Delayed electrophysiological recovery after carpal tunnel release for advanced carpal tunnel syndrome: a two-year follow-up study. J Clin Neurophysiol 2013;30:95–97.
43. Yang JW, Sung YH, Park KH, Lee YB, Shin DJ, Park HM: Clinical and electrophysiological changes after open carpal tunnel release: preliminary study of 25 hands. Korean J Clin Neurophysiol 2014;16:21–26.
44. Louie D, Earp B, Blazar P: Long-term outcomes of carpal tunnel release: a critical review of the literature. Hand (N Y) 2012;7:242–246.


https://doi.org/10.18214/jend.2022.00080

JEND Journal of Electrodiagnosis and Neuromuscular Diseases

ORIGINAL ARTICLE

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2022;24(3):79-83
https://doi.org/10.18214/jend.2022.00122

# Electrophysiological Changes in Patients with Carpal Tunnel Syndrome after Open Carpal Tunnel Release

Chaehyun Song[1], Seung Jun Lee[1], Seong Woo Kim[1], Sung Hoon Kim[2], Ha Ra Jeon[1]

[1]Department of Physical Medicine and Rehabilitation, National Health Insurance Service Ilsan Hospital, Goyang, Korea
[2]Department of Orthopedic Surgery, National Health Insurance Service Ilsan Hospital, Goyang, Korea

**Objective:** Carpal tunnel syndrome (CTS) is the most common peripheral neuropathy affecting the upper limbs. Various treatment methods exist for this disease, but only a few reports have compared the effects of various treatments using objective indicators. This study analyzed the changes in electrophysiological parameters after carpal tunnel release.

**Methods:** In patients planning to undergo surgical treatment for CTS, electrophysiological studies, including nerve conduction studies and electromyography (EMG), of both upper extremities were performed before and 6 to 8 weeks after mini-open transverse carpal ligament release and median nerve neurolysis.

**Results:** After surgical intervention, the onset latency and amplitude of the sensory nerve action potential (SNAP) and the onset latency of the compound muscle action potential (CMAP) of the median nerve improved. Additionally, the grade of abnormal spontaneous activity in needle EMG of the abductor pollicis brevis (APB) and the severity of the electrodiagnostic study results significantly decreased after the intervention compared to the initial evaluation.

**Conclusion:** This study shows that the onset latency of SNAP and CMAP, the amplitude of SNAP of the median nerve, and EMG findings in the APB can be useful electrodiagnostic parameters for postoperative monitoring in CTS patients.

**Keywords:** Carpal tunnel syndrome; Electrophysiology; Surgical procedure

**Received:** July 25, 2022
**Revised:** September 27, 2022
**Accepted:** September 30, 2022

**Corresponding author:**
Ha Ra Jeon
Department of Physical Medicine and Rehabilitation, National Health Insurance Service Ilsan Hospital, 100 Ilsan-ro, Ilsandong-gu, Goyang 10444, Korea
Tel: +82-31-900-0970
Fax: +82-31-900-0028
E-mail: jeon1021@nhimc.or.kr

## Introduction

Carpal tunnel syndrome (CTS) is the most common peripheral neuropathy affecting the upper extremities. This syndrome is characterized by median nerve entrapment at or around the wrist level, resulting in dysfunction of the median nerve [1,2]. CTS can be diagnosed based on clinical symptoms and physical examination findings. Patients often report pain and paresthesia in the distribution of the median nerve and show positive physical examination findings, such as the Tinel sign or Phalen maneuver [1,2]. Ultrasonography and electrodiagnosis (EDx) are useful for confirming the diagnosis of CTS and ruling out other causes. Ultrasonography analyzes anatomical structures and nerves to assess the cross-sectional area of the median nerve, which is altered by the disease. However, in general, EDx is the gold-standard test for the diagnosis of CTS. Among various EDx methods, nerve conduction studies (NCS) can confirm CTS by detecting impaired median nerve conduction across the carpal tunnel, and electromyography (EMG) expresses pathological changes in the abductor pollicis brevis (APB) muscle innervated by the median nerve. EDx has the advantage of being able to classify the severity of the disease to determine the treatment strategy and predict the prognosis after surgery. The severity is classi-

fied into 4 categories: normal, mild, moderate, and severe. Patients with prolonged latency in median nerve sensory conduction, but normal motor conduction, are classified as mild. Moderate disease is defined as prolonged latency in median motor nerve conduction. In patients with severe CTS, EDx shows (1) decreased sensory nerve action potential (SNAP) amplitude, (2) decreased compound muscle action potential (CMAP) amplitude, or (3) the appearance of fibrillation potential or motor unit potential changes on needle EMG [2–5].

Several treatment options exist for CTS, including surgical and nonsurgical methods. In patients with moderate to severe CTS, surgical treatment is performed by dividing the transverse carpal ligament to increase the space of the carpal tunnel and reduce the pressure on the median nerve. Nonsurgical methods for patients with mild to moderate CTS include hand bracing, wrist splinting, oral medications, and local corticosteroid injections [1,6].

Multiple treatment options can be considered for CTS, but only a few reports have compared treatment effectiveness using objective indicators [7–11]. Commonly used outcome assessment tools include the visual analog scale (VAS) rating system, self-reported symptom questionnaires, follow-up NCS, and EMG. Previous studies mainly used self-reported function and symptom improvement questionnaires to investigate the preoperative and postoperative status of patients with CTS in terms of symptom improvement. Few reports have investigated the main neurophysiological changes after surgical interventions in patients with CTS [12,13]. In this study, we analyzed and compared electrophysiological parameters and pain scale scores before and after carpal tunnel release (CTR) to determine whether any significant changes took place.

## Materials and Methods

Among the patients with suspected CTS, those who met the following inclusion criteria and did not meet the exclusion criteria were included in this study. The inclusion criteria were as follows: (1) electrophysiologically diagnosed CTS, (2) unilateral or bilateral involvement, and (3) no history of surgical intervention. The following cutoff values were applied for the diagnosis of CTS: 3.5 ms for SNAP onset latency, 20 μV for SNAP amplitude, 4 ms for CMAP onset latency, and 5 mV for CMAP amplitude [14]. The exclusion criteria were as follows: (1) no abnormal EDx findings or other neurological problems such as cervical radiculopathy, polyneuropathy, or myelopathy; (2) discontinuation of postsurgical follow-up; and (3) a requested to withdraw from the study.

This study was conducted prospectively and approved by the Institutional Review Board (IRB) of National Health Insurance Service Ilsan Hospital (IRB no. 2015-06-019-008). Informed consent was obtained from all participants who agreed to participate in this study, and an initial clinical evaluation was performed by a specialist in physical medicine and rehabilitation.

After the initial NCS and EMG were performed, the patients were referred to the Department of Orthopedic Surgery and underwent surgical treatment by the same surgeon. After confirming the results of EDx and patient-reported symptoms, CTR was performed when the clinician determined that surgery was necessary. The patients were followed up 6-8 weeks after surgery.

Electrophysiological studies, including NCS and EMG, of both upper extremities were performed before and 6 to 8 weeks after the mini-open transverse carpal ligament release and neurolysis of the median nerve. The objective of the NCS was to examine the onset latency and amplitude of the median SNAP and the onset latency and amplitude of CMAP. The objective of EMG was to assess the grade of abnormal spontaneous activity (ASA), which is reported as a gradation of either positive sharp waves (PSWs) or fibrillation potentials in the APB muscle. ASA was rated on a scale of 1 (transient but reproducible discharges) to 4 (abundant spontaneous potentials). All EDx cases were graded as electrophysiologically normal, mild, moderate, or severe according to the criteria presented by Werner and Andary [5].

The pain scales reflecting patients' subjective discomfort were also compared before and after surgery. In this study, the short-form McGill Pain Questionnaire (SF-MPQ) and VAS were used to identify the quality of pain associated with CTS. The SF-MPQ is a shorter version of the original MPQ, which has 2 subscales (sensory and affective). The sensory subscale contains 11 items, and the affective subscale contains 4 items. Each item is rated on an intensity scale ranging from 0 (no pain) to 3 (severe pain). The VAS and present pain intensity (PPI) were also used to provide overall intensity scores [15].

Statistical analysis was performed using IBM SPSS ver. 26.0 (IBM Corp., Armonk, NY, USA). Comparisons between groups were performed using the paired t-test for paired continuous and ordinal variables, and comparisons between categorical data were performed using the McNemar test. Any p-value $< 0.05$ was considered significant.

## Results

After screening, 49 wrists in 33 patients were included in this study. Twenty-nine female patients (87.9%) and 4 male patients (12.1%) were evaluated, and all completed the follow-up studies.


https://doi.org/10.18214/jend.2022.00122

The mean age was 63.7 years, and the average disease duration was 21.6 months. Eleven (33.3%) patients underwent surgical intervention on the right hand, 6 (18.2%) on the left hand, and 16 (48.5%) on both hands (Table 1).

In the initial EDx, the onset latencies of the median SNAP and CMAP were prolonged, and the amplitudes of the median SNAP and CMAP were low. After surgical intervention, the onset latencies and amplitudes of the median SNAP and the onset latencies of CMAP significantly improved (Table 2).

In addition, the ASA grade on needle EMG observed in the APB was significantly better after the surgical intervention than on the initial needle EMG. The proportion of ASA grade 0 increased, while those of ASA grades 1, 2, and 3 decreased after the surgical intervention (Table 3).

The severity of EDx significantly improved after the surgical intervention. The proportion of patients with normal EDx increased, and that of patients with severe EDx decreased after the surgical intervention (Table 4).

The degree of pain significantly reduced after surgery. The scores of the sensory and affective subscales of the SF-MPQ significantly improved after the surgical intervention. The VAS and PPI scores also significantly improved after the surgical intervention (Table 5).

**Table 1.** Demographic and Clinical Characteristics of Patients (n = 33)

| Characteristic | Value |
|---|---|
| Sex | |
| Male | 4 (12.1) |
| Female | 29 (87.9) |
| Age (y) | 63.7 ± 10.9 |
| Affected side | |
| Right | 11 (33.3) |
| Left | 6 (18.2) |
| Both | 16 (48.5) |
| Diabetes mellitus | |
| No | 7 (21.2) |
| Yes | 26 (78.8) |

Values are presented as number (%) or mean ± standard deviation.

**Table 2.** NCS of the Median Nerve before and after Surgical Intervention

| Median nerve | Before | After | p-value |
|---|---|---|---|
| SNAP | | | |
| Onset latency (ms) | 5.6 ± 2.9 | 3.7 ± 2.0 | < 0.001* |
| Amplitude (μV) | 9.3 ± 9.1 | 15.6 ± 9.8 | < 0.001* |
| CMAP | | | |
| Onset latency (ms) | 5.3 ± 2.3 | 4.2 ± 1.2 | 0.002* |
| Amplitude (mV) | 6.9 ± 4.1 | 7.2 ± 3.6 | 0.508 |

Values are mean ± standard deviation. The cutoff values are 3.5 ms for SNAP onset latency, 20 μV for SNAP amplitude, 4 ms for CMAP onset latency, and 5 mV for CMAP amplitude.
NCS, nerve conduction study; SNAP, sensory nerve action potential; CMAP, compound muscle action potential.
*p < 0.05.

## Discussion

Patients who undergo surgical intervention for CTS have been reported to show symptom improvement within 1 to 2 weeks after surgery [1]. The patients in our study also showed improvements in the degree of VAS and PPI and severity of EDx 6 to 8

**Table 3.** The Grade of ASA on Needle EMG Observed in the APB before and after Surgical Intervention (n = 49)

| The grade of ASA | Before | After | p-value |
|---|---|---|---|
| 0 | 5 (10.2) | 28 (57.1) | |
| 1 | 18 (36.7) | 12 (24.5) | |
| 2 | 12 (24.5) | 2 (4.1) | < 0.001* |
| 3 | 13 (26.5) | 6 (12.2) | |
| 4 | 1 (2.0) | 1 (2.0) | |

Values are presented as number (%).
ASA, abnormal spontaneous activity; EMG, electromyography; APB, abductor pollicis brevis.
*p < 0.05.

**Table 4.** The Severity of Electrodiagnostic Study Findings after Surgical Intervention (n = 49)

| | Initial | Follow-up | p-value |
|---|---|---|---|
| Normal | 0 (0) | 13 (26.5) | |
| Mild | 1 (2.0) | 1 (2.0) | < 0.001* |
| Moderate | 20 (40.8) | 28 (57.1) | |
| Severe | 28 (57.1) | 7 (14.3) | |

Values are presented as number (%).
*p < 0.05.

**Table 5.** The Degree of Pain before and after Surgical Intervention

| Pain scale | Before | After | p-value |
|---|---|---|---|
| MPQ | | | |
| MPQ-sensory | 19.1 ± 7.3 | 9.6 ± 5.6 | < 0.001* |
| MPQ-affective | 2.7 ± 3.2 | 1.5 ± 2.2 | 0.017* |
| MPQ-total | 21.8 ± 9.8 | 11.1 ± 7.4 | < 0.001* |
| VAS | 6.9 ± 0.8 | 4.0 ± 2.1 | < 0.001* |
| PPI | 2.9 ± 1.0 | 1.6 ± 0.8 | < 0.001* |

Values are mean ± standard deviation.
MPQ, McGill Pain Questionnaire; VAS, visual analog scale; PPI, present pain intensity.
* p < 0.05.

weeks after surgery.

CTR is the treatment for patients with severe sensory or motor impairments in the hand, worsening axonal loss, or findings indicating denervation of the median nerve. Most patients who received surgical intervention for CTS showed moderate or severe abnormal findings on EDx, and the severity of EDx after surgery improved. Previous studies categorized severity into 3 grades (1, normal to mild; 2, moderate; 3, severe), whereas our study considered 4 grades for a more detailed comparison. Earlier studies showed improvements in the Michigan Hand Outcomes Questionnaire score or subjective symptoms after surgery within each grade, but changes in the grade itself were not compared [16,17]. Other studies analyzed EDx before and after surgery, confirming that CMAP latency, amplitude, and sensory conduction velocity improved postoperatively; however, a comparative analysis of disease severity was not performed [18].

This study presented the electrophysiological changes after surgical intervention in patients with CTS. All NCS and EMG parameters improved after the surgical intervention, and none of the participants showed any worsening findings on electrophysiological studies or clinical symptoms at follow-up. In particular, the onset latency and amplitude of SNAP, onset latency of CMAP, and ASA grade on needle EMG of the APB significantly improved after the surgical intervention. In severe CTS, the APB and first and second lumbricals innervated by the median nerve may show abnormal findings, such as fibrillations or PSWs, on needle EMG. The ASA grade in the APB improved after surgery. The severity of CTS (i.e., the grade according to the criteria presented by Werner and Andary [5]) also showed a significant improvement after the surgical intervention.

As pointed out in the Introduction section, various treatment methods exist for CTS, but only a few reports have compared the effects and predicted the outcomes of various treatments using objective indicators. Some studies have investigated neurological changes after surgery [12,13,18]. These studies mainly monitored the SNAP latency, amplitude, and sensory conduction velocity of the median or ulnar nerves and reported improvements in SNAP amplitude and conduction velocity of the median and ulnar nerves after intervention. In our study, we compared motor conduction study findings, EMG changes, and EDx severity before and after the surgical intervention. The results of our study suggest that the improvements in EDx severity can be attributed to improvements in SNAP onset latency, amplitude, and ASA grade. Based on the results of this study, the onset latency of SNAP and CMAP, amplitude of SNAP, and EMG findings can be useful parameters for monitoring patients with CTS after surgery.

Owing to the limited follow-up time and sample size, further studies with larger sample sizes and long-term follow-up are required to achieve more accurate and comprehensive results. In addition, as we evaluated the outcomes using electrophysiological indicators before and after open CTR, the indicators can be used to compare the efficacy between different types of surgical approaches or between surgical and nonsurgical treatments for CTS.

## Conclusion

Various EDx parameters and the patients' symptoms improved after open CTR. In particular, the onset latency of SNAP and CMAP of the median nerve, amplitude of SNAP of the median nerve, and EMG findings of the APB can be used to assess outcomes after surgical interventions in patients with CTS.

## Conflict of Interest

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

## ORCID

Chaehyun Song, https://orcid.org/0000-0002-0689-1524
Seung Jun Lee, https://orcid.org/0000-0002-7152-2880
Seong Woo Kim, https://orcid.org/0000-0002-1548-8147
Sung Hoon Kim, https://orcid.org/0000-0003-1831-7930
Ha Ra Jeon, https://orcid.org/0000-0001-9446-9552

## References

1. Wipperman J, Goerl K: Carpal tunnel syndrome: diagnosis and management. Am Fam Physician 2016;94:993–999.
2. Aroori S, Spence RA: Carpal tunnel syndrome. Ulster Med J 2008;77:6–17.
3. Chen YT, Williams L, Zak MJ, Fredericson M: Review of ultrasonography in the diagnosis of carpal tunnel syndrome and a proposed scanning protocol. J Ultrasound Med 2016;35:2311–2324.
4. Pimentel BF, Faloppa F, Tamaoki MJ, Belloti JC: Effectiveness of ultrasonography and nerve conduction studies in the diagnosing of carpal tunnel syndrome: clinical trial on accuracy. BMC Musculoskelet Disord 2018;19:115.
5. Werner RA, Andary M: Electrodiagnostic evaluation of carpal tunnel syndrome. Muscle Nerve 2011;44:597–607.
6. Petrover D, Richette P: Treatment of carpal tunnel syndrome: from ultrasonography to ultrasound guided carpal tunnel release. Joint

 https://doi.org/10.18214/jend.2022.00122

Bone Spine 2018;85:545–552.
7. Shi Q, Bobos P, Lalone EA, Warren L, MacDermid JC: Comparison of the short-term and long-term effects of surgery and nonsurgical intervention in treating carpal tunnel syndrome: a systematic review and meta-analysis. Hand (N Y) 2020;15:13–22.
8. Celik G, Ilik MK: Effects of two different treatment techniques on the recovery parameters of moderate carpal tunnel syndrome: a six-month follow-up study. J Clin Neurophysiol 2016;33:166–170.
9. Jørgsholm P, Flondell M, Björkman A, Thomsen NO: Outcome of carpal tunnel release in patients with normal nerve conduction studies. J Orthop Sci 2021;26:798–803.
10. Zhang S, Wang F, Ke S, Lin C, Liu C, Xin W, et al: The effectiveness of ultrasound-guided steroid injection combined with minniscalpel-needle release in the treatment of carpal tunnel syndrome vs. steroid injection alone: a randomized controlled study. Biomed Res Int 2019;2019:9498656.
11. Osiak K, Mazurek A, Pękala P, Koziej M, Walocha JA, Pasternak A: Electrodiagnostic studies in the surgical treatment of carpal tunnel syndrome-A systematic review. J Clin Med 2021;10:2691.
12. El-Hajj T, Tohme R, Sawaya R: Changes in electrophysiological parameters after surgery for the carpal tunnel syndrome. J Clin Neurophysiol 2010;27:224–226.
13. Ginanneschi F, Milani P, Reale F, Rossi A: Short-term electrophysiological conduction change in median nerve fibres after carpal tunnel release. Clin Neurol Neurosurg 2008;110:1025–1030.
14. Park D, Kim BH, Lee SE, Kim DY, Eom YS, Cho JM, et al: Electrodiagnostic, sonographic, and clinical features of carpal tunnel syndrome with bifid median nerve. J Pain Res 2021;14:1259–1269.
15. Hawker GA, Mian S, Kendzerska T, French M: Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S240–S252.
16. Lama M: Carpal tunnel release in patients with negative neurophysiological examinations: clinical and surgical findings. Neurosurgery 2009;65(4 Suppl):A171–A173.
17. Dagtas MZ, Unal OK: Long-term outcome of electrodiagnostic values and symptom improvement after carpal tunnel release: a retrospective cohort study. J Hand Surg Am 2022;47:727–735.
18. Meyers A, Annunziata MJ, Rampazzo A, Bassiri Gharb B: A systematic review of the outcomes of carpal ligament release in severe carpal tunnel syndrome. J Hand Surg Am 2022 Jan 18 [Epub]. https://doi.org/10.1016/j.jhsa.2021.11.015.

JEND Journal of Electrodiagnosis and Neuromuscular Diseases

ORIGINAL ARTICLE

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2022;24(3):84-88
https://doi.org/10.18214/jend.2022.00164

# Comparison of the Vestibular Evoked Myogenic Potential and the Blink Reflex in Cerebellar and Brainstem Infarction Patients

Min Woo Kim[1], Jeong Mee Park[1], Ji Seon Hong[1], Ji Yoon Jang[1], Seo Hyun Kim[2]

[1]Department of Rehabilitation Medicine, Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine, Wonju, Korea
[2]Department of Neurology, Yonsei University Wonju College of Medicine, Wonju, Korea

**Objective:** This study investigated whether the blink reflex could be substituted for the vestibular evoked myogenic potential (VEMP), which has some limitations for use in stroke patients.
**Methods:** Thirty-four patients with cerebellar or brainstem ischemic stroke underwent VEMP and blink reflex testing. We compared the P13 latency of VEMP and the R1, R2, R2' latency of the blink reflex in stroke patients. Statistical analysis was conducted using the Fisher exact test and independent t-test, with a p-value < 0.05 indicating statistical significance.
**Results:** In 29 stroke patients, excluding those with bilateral lesions, the VEMP and the blink test did not show a statistically significant relationship ($p = 0.27$). In all 34 stroke patients participating in the study, including those with bilateral lesions, R2' mean showed a statistically significant difference ($p = 0.008$) according to the presence of normal or abnormal VEMP.
**Conclusion:** R2' of the blink reflex passes through more neural pathways and polysynaptic pathways than R1 and R2; therefore, it showed a more prominent difference between the normal and abnormal VEMP groups.

**Keywords:** Vestibular evoked myogenic potentials; Blink reflex; Brain Stem; Stroke; Poly-synaptic pathways

**Received:** August 20, 2022
**Revised:** October 21, 2022
**Accepted:** October 24, 2022

**Corresponding author:**
Ji Seon Hong
Department of Rehabilitation Medicine, Wonju Severance Christian Hospital, Yonsei University Wonju College of Medicine, 20 Ilsan-ro, Wonju 26426, Korea
Tel: +82-33-741-1455
Fax: +82-33-741-1455
E-mail: g7284@naver.com

## Introduction

Patients with cerebellar and brainstem stroke often complain of dizziness, nausea, or loss of balance. These symptoms are known to result from the involvement of the vestibular pathway, which affects the sense of balance. The vestibular evoked myogenic potential (VEMP) is a test that can evaluate the vestibular system in these patients. VEMP is used to determine whether the vestibular nerve pathway is abnormal by examining the inhibitory electromyography (EMG) response in the neck muscle or the excitatory EMG response in the extraocular muscle caused by auditory stimulation [1].

The blink reflex test is an electrodiagnostic test that can be used to precisely localize lesions in brainstem stroke patients. The blink reflex is a brainstem reflex triggered by electrical stimulation of the trigeminal supraorbital nerve, eliciting contraction of the orbicular muscles by the facial nerve. The waves of the blink reflex consist of the ipsilateral R1 response recorded initially and the ipsilateral R2 and contralateral R2' responses, which are recorded later [2,3].

To the best of our knowledge, the VEMP and blink reflex tests have not shown any relationship, since they test the vestibular nerve and trigeminofacial nerve pathways, respectively. However, the pathways of VEMP and the blink reflex share a common feature—namely, they pass through the brainstem.

Therefore, we hypothesized that the VEMP and the blink re-

flex tests might have a correlation with each other. Moreover, because there are more neural pathways and synapses along R2' than R2 and along R2 than R1, we hypothesized that the difference between normal and abnormal findings would be most prominent in R2', followed in descending order by R2 and R1.

Because the VEMP test requires active cervical rotation or cervical flexion, it is difficult to use in unconscious or hemiplegic patients, whereas the blink reflex does not have those limitations. Therefore, if a significant correlation between the blink reflex and VEMP is confirmed according to our hypothesis, then we could substitute the blink reflex for VEMP in patients who are unable to cooperate with VEMP testing.

## Materials and Methods

Thirty-four patients with cerebellar or brainstem ischemic stroke were prospectively enrolled in this study. The Institutional Review Board (IRB) of Wonju Severance Christian Hospital approved the study (IRB no. CR317055). Written informed consent was obtained. The patients were confirmed to have cerebellar or brainstem infarction, using magnetic resonance imaging and computed tomography imaging. Patients were excluded from the study if they had hearing problems, abnormalities in the visual or somatosensory system, or difficulty in performing an appropriate test due to other conditions such as poor cooperation or medications.

The parameters used to determine whether the VEMP was normal or abnormal were the presence of a response, latency to P13, amplitude of the P13 wave, and lowering of the threshold. The measurements may be affected by several variables, such as the subject's posture, age, muscle contraction degree, the position of electrodes, and equipment [4].

The VEMP study was performed using a Nicolet Viking IV D device (Nicolet. Biomedical Inc., Madison, WI, USA). The patients were placed in a supine position, and then the active electrode was attached to the center of the sternocleidomastoid muscle, the reference electrode was attached to the sternum, and the ground electrode was attached to the center of the forehead. In order to reduce the false-positive rate due to muscle fatigue, the vestibular trigger potential on the contralateral side was measured in the same way following a 5-minute rest after testing the ipsilateral side. No response was defined as the inability to visually confirm a biphasic P13 to N23 waveform. A delay of latency was defined as an ipsilateral P13 latency longer than the normal control group by more than 2 standard deviations. No response or delayed latency was considered abnormal.

The blink reflex study was performed using a Dantec Keypoint Medtronics device (Alpine BioMed, Skovlunde, Denmark). The patients were placed in a supine position, and then the cathode ray of the positive electric stimulator attached to the supraorbital notch stimulated the supraspinatus nerve. An absent waveform, a difference in R1, R2, or R2' latency of more than 2 ms relative to the contralateral side, or a difference in the ipsilateral R1, R2, or R2' latency of more than 2 ms from the reference data was defined as abnormal. The reference data were obtained from previous studies [5,6].

In the statistical analysis, the P13 latency of VEMP and the R1, R2, R2' latency of the blink reflex were compared with the Fisher exact test and the independent t-test using SPSS for Windows ver. 11.0 (SPSS Inc., Chicago, IL, USA). A p-value of 0.05 or less was considered to indicate statistical significance.

## Results

Pontine, cerebellar, medullar, and midbrain infarctions were diagnosed in 23 (67.6%), 6 (17.6%), 4 (11.8%), and 1 (2.9%) patients, respectively. Twenty-two patients were men (64.7%) and 12 (35.3%) were women. The patients ranged in age from 33 to 100 years (mean age, 69.2 years).

The VEMP and blink reflex tests were compared in 29 of the 34 patients, with the exclusion of 5 patients with bilateral lesions. In the group with normal VEMP, 4 patients (25%) had normal blink reflexes, and 12 patients (75%) had abnormal blink reflexes. In the group with abnormal VEMP, 6 patients (46.2%) had normal blink reflexes and 7 patients (53.8%) had abnormal blink reflexes. These distributions did not show a statistically significant difference ($p = 0.27$ by the Fisher exact test). Therefore, the VEMP and the blink reflex tests were independent, and there was no statistically significant relationship between the 2 tests (Table 1).

Furthermore, as shown in Tables 2-4, the VEMP and blink tests showed no statistically significant relationships in subgroups defined according to the location of the infarction lesion

**Table 1.** Comparison of Abnormalities in Stroke Patients Excluding Those with Bilateral Lesions (n = 29)

| VEMP | Blink reflex test | | |
|---|---|---|---|
| | Normal | Abnormal | Total |
| Normal | 4 (13.8) | 12 (41.4) | 16 (55.2) |
| Abnormal | 6 (20.7) | 7 (24.1) | 13 (44.8) |
| Total | 10 (34.5) | 19 (65.5) | 29 (100) |

Values are presented as the number (%). The comparison between the VEMP and the blink test in 29 patients did not show a statistically significant relationship by Fisher exact test, p = 0.27.
VEMP, vestibular evoked myogenic potential.

Table 2. Comparison of Abnormalities in Cerebellar Infarction Patients (n = 5)

| VEMP | Blink reflex test | | |
|---|---|---|---|
| | Normal | Abnormal | Total |
| Normal | 2 (40.0) | 1 (20.0) | 3 (60.0) |
| Abnormal | 0 (0) | 2 (40.0) | 2 (40.0) |
| Total | 2 (40.0) | 3 (60.0) | 5 (100) |

Values are presented as the number (%). The comparison between the VEMP and the blink test in these 5 patients did not show a statistically significant relationship by Fisher exact test, p = 0.40.
VEMP, vestibular evoked myogenic potential.

Table 3. Comparison of Abnormalities in Medullar Infarction Patients (n = 4)

| VEMP | Blink reflex test | | |
|---|---|---|---|
| | Normal | Abnormal | Total |
| Normal | 0 (0) | 3 (75.0) | 3 (75.0) |
| Abnormal | 1 (25.0) | 0 (0) | 1 (25.0) |
| Total | 1 (25.0) | 3 (75.0) | 4 (100) |

Values are presented as the number (%). The comparison between the VEMP and the blink test in these 4 patients did not show a statistically significant relationship (p = 0.25*).
VEMP, vestibular evoked myogenic potential.
*Tested by the Fisher exact test, p = 0.25.

Table 4. Comparison of Abnormalities in Pons Infarction Patients (n = 19)

| VEMP | Blink reflex test | | |
|---|---|---|---|
| | Normal | Abnormal | Total |
| Normal | 2 (10.5) | 8 (42.1) | 10 (52.6) |
| Abnormal | 5 (26.3) | 4 (21.1) | 9 (47.4) |
| Total | 7 (36.8) | 12 (63.2) | 19 (100) |

Values are presented as the number (%). The comparison between the VEMP and the blink test in these 19 patients did not show a statistically significant relationship by Fishder exact test, p = 0.17.
VEMP, vestibular evoked myogenic potential.

(pons, medulla, or cerebellum) based on an analysis of 2 × 2 contingency tables using the Fisher exact test.

All cerebral infarction patients (34 patients) were divided into normal and abnormal groups by VEMP results, and we compared the blink reflex latency between these 2 groups. Patients with abnormal VEMP findings (19 patients) showed no statistically significant difference in R1 latency compared with the normal VEMP group. (8.21 ± 2.10 ms vs. 7.32 ± 2.82 ms, p = 0.30). R2 latency also showed no statistically significant difference between the 2 groups. (36.85 ± 4.48 ms vs. 34.28 ± 4.46 ms, p = 0.12). However, patients with abnormal VEMP findings showed significantly longer R2' latency than those with normal VEMP findings (38.90 ± 3.22 ms vs. 34.90 ± 4.61 ms, p = 0.008) (Table 5).

Table 5. Comparison between VEMP and R1 mean, R2 mean, and R2' mean of the blink reflex

| | Normal VEMP (n = 15) | Abnormal VEMP (n = 19) | p-value |
|---|---|---|---|
| R1 | 7.32 ± 2.82 | 8.21 ± 2.10 | 0.30 |
| R2 | 34.28 ± 4.46 | 36.85 ± 4.48 | 0.12 |
| R2' | 34.90 ± 4.61 | 38.90 ± 3.22 | 0.008* |

Values are presented as mean ± standard deviation. In all cerebral infarction patients (34 patients) participating in the study, including those with bilateral lesions, a statistically significant result was found for the relationship of R2' mean with abnormal or normal VEMP (p = 0.008).
VEMP, vestibular evoked myogenic potential.
*Tested by the independent t-test, p < 0.05.

## Discussion

VEMP was first described by Colebatch and Halmagyi in 1992 [7]. VEMP testing can be performed in 2 ways: cervical VEMP and ocular VEMP. Cervical VEMP is an inhibitory electromyographic response in the sternocleidomastoid muscle following auditory stimulation, and ocular VEMP is an excitatory electromyographic response in the extraocular muscle caused by auditory stimulation [8].

Some previous studies have analyzed VEMP in patients with cerebral infarction or hemorrhage. One study identified abnormal VEMP results in 12 of 29 patients with cerebral infarction [9]. In another study of 21 patients with lateral medullary infarction, abnormal VEMP results were confirmed in 9 patients [10]. However, a study investigating the correlation of VEMP with cerebellar lesions found that VEMP showed normal results in those patients [11].

A study investigated the association of the n10 component of ocular VEMP with R1 of the blink reflex, based on the fact that both the blink reflex and ocular VEMP are rested by applying electrical stimulation to the forehead and recording the response from the muscles of the infraorbital surface. That study did not find a statistically significant relationship between the 2 responses [12].

The present study found a statistically significant difference in R2' of the blink reflex between the normal and abnormal VEMP groups. We suggest that pathological electrical conductivity would be more distinct in R2' than in R1 or R2 due to the complex polysynaptic neurophysiologic pathway.

R1 of the blink reflex emerges as it passes through the pons. R2 and R2' pass through the lateral aspect of the medulla, as well as the pons, and come out through complex synaptic reflexes [2,3].


https://doi.org/10.18214/jend.2022.00164

Therefore, R2 and R2' pass through more neural pathways and synapses than R1, and patients with abnormal VEMP may show a more prominent difference from the normal VEMP group in R2 and R2' than in R1 and in R2' than in R2. Although the anatomical structure of the VEMP neurotransmission process has not been fully elucidated, the most up-to-date knowledge on the neurotransmission pathway is that an electrical signal originating from the saccule is transmitted to the sternocleidomastoid muscle via the vestibular nerve, the vestibular nerve nucleus, and the medial vestibulospinal tract [1]. The vestibular nucleus is divided into the superior vestibular nucleus, the inferior vestibular nucleus, the lateral vestibular nucleus, and the medial vestibular nucleus. Anatomically, the superior vestibular nucleus is located in the pons, and the rest of the inferior vestibular nucleus, the lateral vestibular nucleus, and the medial vestibular nucleus are located in the medulla oblongata [13]. Therefore, when the blink reflex test is performed in patients with abnormal VEMP, R2 and R2', which pass through the medulla as well as the pons, would show a more prominent difference from the normal group than R1, which only passes through the pons. Furthermore, R2' of the blink reflex passes through more neural pathways and polysynaptic pathways than R1 and R2; thus, the difference is more prominent in patients with abnormal VEMP than in patients with normal VEMP.

In this study, although the VEMP and blink tests were independent in brainstem and cerebellar infarction patients, R2' of the blink reflex showed a statistically significant difference according to whether the VEMP was normal or abnormal. Additionally, R1 and R2 of the blink reflex showed prolonged latency in the abnormal VEMP group compared to the normal VEMP group, although the relationship was not statistically significant. Since this study was conducted in only 34 patients, more cases from multiple centers would be needed in further studies, and it is reasonable to predict that R1 and R2 of the blink reflex may show statistically significant relationships with the VEMP in a larger study. This research suggests that the blink reflex may be a complementary test for VEMP, rather than a replacement. Further research should also compare the latency of VEMP and the blink reflex to show numerical correlations between these tests.

The limitations of this study include the fact that it was conducted at a single medical institution using a single machine among only 34 patients. In addition, the neurotransmission pathways of VEMP and the blink reflex have not been clearly identified. Finally, since this study was conducted with only cervical VEMP, it also seems necessary to conduct ocular VEMP in future studies.

## Conclusion

R2' of the blink reflex passes through more neural pathways and polysynaptic pathways than R1 and R2; therefore, it shows a more prominent difference in patients with abnormal VEMP than in those with normal VEMP. The blink reflex can complement VEMP, but larger studies should be performed to clarify whether the blink reflex could substitute for VEMP.

## Conflict of Interest

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

## ORCID

Min Woo Kim, https://orcid.org/0000-0001-7610-9772
Jeong Mee Park, https://orcid.org/0000-0001-6341-6167
Ji Seon Hong, https://orcid.org/0000-0002-7412-2145
Ji Yoon Jang, https://orcid.org/0000-0002-7635-8901
Seo Hyun Kim, https://orcid.org/0000-0001-5937-5729

## References

1. Suh MW, Jeong SH, Kim JS: Vestibular evoked myogenic potential: recording methods and clinical application. J Korean Neurol Assoc 2010;28:1–12.
2. Gonzalez EG, Myers SJ, Edelstein JE, Lieberman JS, Downey JA: Downey and Darling's physiological basis of rehabilitation medicine. 3rd ed. Woburn: Butterworth-Heinemann; 2001, pp347–358.
3. Kimura J: Electrodiagnosis in diseases of nerve and muscle: principle and practice: 3rd ed. New York: Oxford; 2001, pp409–438.
4. Suh MW, Kim JS, Koo JW: Influence of blood pressure manometer feedback on the parameters of the vestibular evoked myogenic potential test. Ann Otol Rhinol Laryngol 2009;118:281–286.
5. Brooks JB, Jardim MR, Papais-Alvarenga RM, Fragoso YD: Time parameters of the blink reflex in normal subjects. Neurophysiology 2014;46:221–224.
6. Gao Z, Ni D, Li F: The normal value and clinical applications of the blink reflex. Zhonghua Er Bi Yan Hou Ke Za Zhi 1998;33:347–349.
7. Colebatch JG, Halmagyi GM: Vestibular evoked potentials in human neck muscles before and after unilateral vestibular deafferentation. Neurology 1992;42:1635–1636.
8. Lee MY, Suh MW: The principle and methodology of vestibular evoked myogenic potential. Res Vestib Sci 2015;14:9–14.

9. Heide G, Luft B, Franke J, Schmidt P, Witte OW, Axer H: Brainstem representation of vestibular evoked myogenic potentials. Clin Neurophysiol 2010;121:1102–1108.
10. Kim S, Kim HJ, Kim JS: Impaired sacculocollic reflex in lateral medullary infarction. Front Neurol 2011;2:8.
11. Pollak L, Kushnir M, Stryjer R: Diagnostic value of vestibular evoked myogenic potentials in cerebellar and lower-brainstem strokes. Neurophysiol Clin 2006;36:227–233.
12. Smulders YE, Welgampola MS, Burgess AM, McGarvie LA, Halmagyi GM, Curthoys IS: The n10 component of the ocular vestibular-evoked myogenic potential (oVEMP) is distinct from the R1 component of the blink reflex. Clin Neurophysiol 2009;120:1567–1576.
13. Kim BK: Anatophysiology of central vestibular system. Res Vestib Sci 2002;1:176–183.


https://doi.org/10.18214/jend.2022.00164

JEND Journal of Electrodiagnosis and Neuromuscular Diseases

CASE REPORT

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2022;24(3):89-95
https://doi.org/10.18214/jend.2022.00031

# Extensive Neuromusculoskeletal Complications—Including Multi-Level Vertebral Osteomyelitis, Myelopathy, Polyradiculopathy, and Multiple Muscle Abscesses—after Lumbar Transforaminal Epidural Block: A Case Report

Ji Woong Park, Jeong Se Noh

Department of Physical Medicine and Rehabilitation, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, Korea

Vertebral osteomyelitis (VO) is a rare, slowly progressing disease that often causes neuromuscular complications. Epidural block is a non-surgical treatment used in patients with radicular pain to deliver drugs to the epidural space; it is generally known to be a safe method, but it can occasionally cause infection. Herein, we present a rare case of VO with severe neuromuscular complications that developed in a patient who underwent lumbar transforaminal epidural block for back pain. Imaging studies showed VO, multiple pyogenic abscesses, and compressive cervical myelopathy. Electrodiagnostic studies showed clear evidence of cervical myelopathy and polyradiculopathy. With early treatment using a multidisciplinary approach, including medical treatment, surgery, and comprehensive rehabilitation, recovery of motor weakness and functional improvement were achieved after 2 months of treatment. Electrodiagnostic studies are advantageous for localizing and determining the degree of neuromuscular damage following VO. A multidisciplinary approach to the diagnosis and treatment of VO could improve patients' prognosis, functional ability, and quality of life.

**Keywords:** Osteomyelitis; Electrodiagnosis; Rehabiliation

**Received:** March 30, 2022
**Revised:** August 24, 2022
**Accepted:** August 25, 2022

**Corresponding author:**
Jeong Se Noh
Department of Physical Medicine and Rehabilitation, Soonchunhyang University Seoul Hospital, 59 Daesagwan-ro, Yongsan-gu, Seoul 04401, Korea
Tel: +82-2-709-9260
Fax: +82-2-709-9265
E-mail: nohderek2@gmail.com

## Introduction

Vertebral osteomyelitis (VO) is a rare disease that is characterized by infection of the vertebral body and adjacent intervertebral discs [1–3]. VO may cause neurological complications, such as motor weakness or sensory abnormalities [1,3,4].

Epidural block, which is commonly used in patients with radicular pain, allows the effective delivery of drugs to the epiradicular space. Although epidural block is generally known to be a safe method, complications including infection occasionally occur [5–7].

Herein, we present a rare case of VO with serious neuromuscular complications, including cervical and lumbar radiculopathy, myelopathy, and multiple pyogenic abscesses, which developed in a patient who underwent lumbar transforaminal epidural block for back pain.

It is difficult for a physician to determine the exact cause of weakness when multiple etiologies are suspected. Electrodiagnostic studies such as nerve conduction studies (NCS) and needle electromyography (EMG) could enhance the differential di-

agnosis of the etiology. The use of electrodiagnostic studies in addition to imaging studies, such as computed tomography (CT) and magnetic resonance imaging (MRI), helped to determine the degree and locations of nerve and muscle damage and decide on a treatment strategy.

Furthermore, the early application of a multidisciplinary approach, including medical treatment, surgery, and comprehensive rehabilitation enhanced the patient's prognosis and functional recovery.

## Case Report

A 64-year-old man visited an outpatient clinic due to low back pain radiating to the left lower extremity that started 1 month ago. A neurological examination revealed no sensory deficit or motor weakness. MRI revealed herniation of the left L4-5 intervertebral disc, and the patient underwent transforaminal epidural block on the left side at the L5 level. However, 2 days after the procedure, he developed general weakness. Since the symptoms worsened, he was admitted to the emergency department 5 days after the procedure.

The patient had been diagnosed with diabetes mellitus (DM) 10 years ago. He had been taking medication intermittently in the last year and stopped taking it entirely in the last 2 weeks.

He complained of generalized weakness in the bilateral upper and lower extremities. In a manual muscle strength evaluation, the bilateral upper limb strength was measured as Medical Research Council (MRC) grade 4-5/5 and bilateral lower limb strength as MRC grade 2-3/5.

In a sensory evaluation, both light touch and pinprick tests showed no abnormalities. The deep tendon reflex was normal, and there were no pathological reflexes. The sensation of deep anal pressure was decreased and voluntary anal contraction was slightly weak, but the bulbocavernous reflex was preserved.

His white blood cell count was 8,100 cells/μL with a neutrophil predominance, the serum C- reactive protein level was 43.05 mg/L (normal range, < 0.5 mg/L), and the erythrocyte sedimentation rate was 120 mm/h (normal range, 0-20 mm/h). The procalcitonin level was 5.71 ng/mL (normal range, 0-0.5 ng/mL). The hemoglobin A1C level was 8.4% (normal range, < 6.1%), which was consistent with an elevated estimated average glucose level of 391 mg/dL.

Lumbar spine MRI showed degenerative changes and VO with fluid collection at the L4-5 and L5-S1 levels, as well as abscesses in the bilateral paraspinalis and left psoas muscles. Cervical spine MRI showed degenerative changes at the C4-5 level without any evidence of infection (Fig. 1). Decompressive laminectomy and spinal abscess removal were performed the next day, and methicillin-susceptible *Staphylococcus aureus* was simultaneously identified in the tissue culture and blood culture.

Intensive antibiotic therapy was started for 2 weeks, but the patient's weakness progressed. A repeat neurological examina-

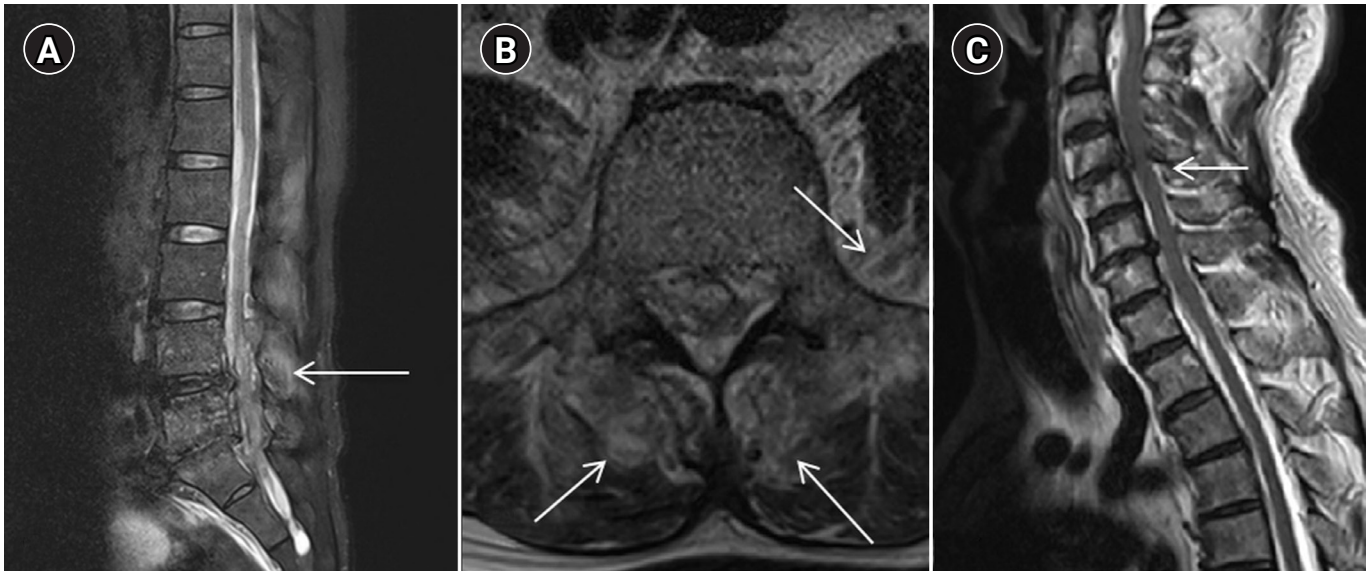


Fig. 1. Initial lumbar spine magnetic resonance imaging (MRI) showing degenerative changes and fluid collection at the L4-5 and L5-S1 levels with high signal intensity on T2-weighted images, suggestive of vertebral osteomyelitis (A, arrow), and abscess formation in the bilateral paraspinalis and left psoas muscles (B, arrows). Cervical spine MRI showing degenerative changes at the C4-5 level, without infectious signs (C, arrow).


https://doi.org/10.18214/jend.2022.00031

tion was performed. In the sensory evaluation, both light touch and pinprick tests showed sensory deficits below the C3 level. The upper limb weakness worsened to MRC grade 3/5 on the right side and MRC grade 2-3/5 on the left side; therefore, we performed cervical spine MRI and abdominopelvic CT. Cervical spine MRI showed discitis at C4/5 and epidural abscesses at C1-C4 with spinal cord compression (Fig. 2). Abdominopelvic CT showed bilateral abscesses in the iliopsoas, paraspinalis at L4-5, and the right gluteus maximus muscle (Fig. 3). Surgical decompression of the cervical spine and CT-guided aspiration of the abscess in the right gluteus maximus muscle were performed.

Electrodiagnostic studies were conducted to determine the cause of weakness.

A sensory NCS showed delayed-onset latency of sensory nerve action potential in the bilateral median and sural nerves, and a motor NCS showed delayed distal latency of compound muscle action potentials in the bilateral median and tibial nerves, as well as the right ulnar and peroneal nerves.

Somatosensory evoked potentials in both the median and tibial nerves showed delayed response in all extremities. Motor evoked potentials showed more delayed responses in the left upper extremity compared to the right side.

Needle EMG showed increased insertional activity and abnormal spontaneous activity at rest (grades 2 to 3+) in the bilateral biceps, pronator teres, flexor carpi ulnaris, extensor digitorum communis, abductor digiti minimi, abductor pollicis brevis, triceps, deltoid, tibialis anterior, extensor hallucis longus, gastroc-

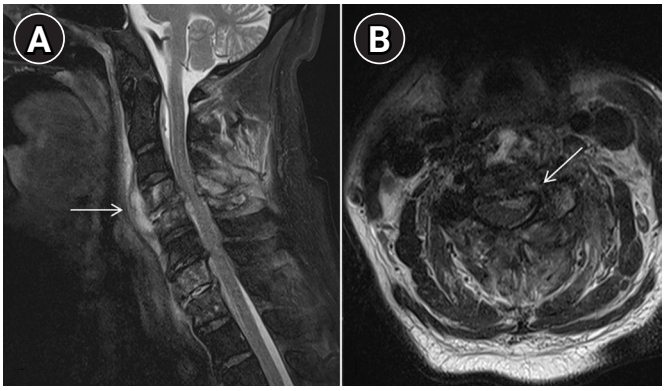


Fig. 2. Cervical spine magnetic resonance imaging, with sagittal (A) and axial (B) views at the C4 level showing discitis at the C4/5 level and multiple abscesses in the retropharyngeal space at C3-T1 (A, arrow) and epidural space at the C1-4 levels with spinal cord compression (B, arrow).

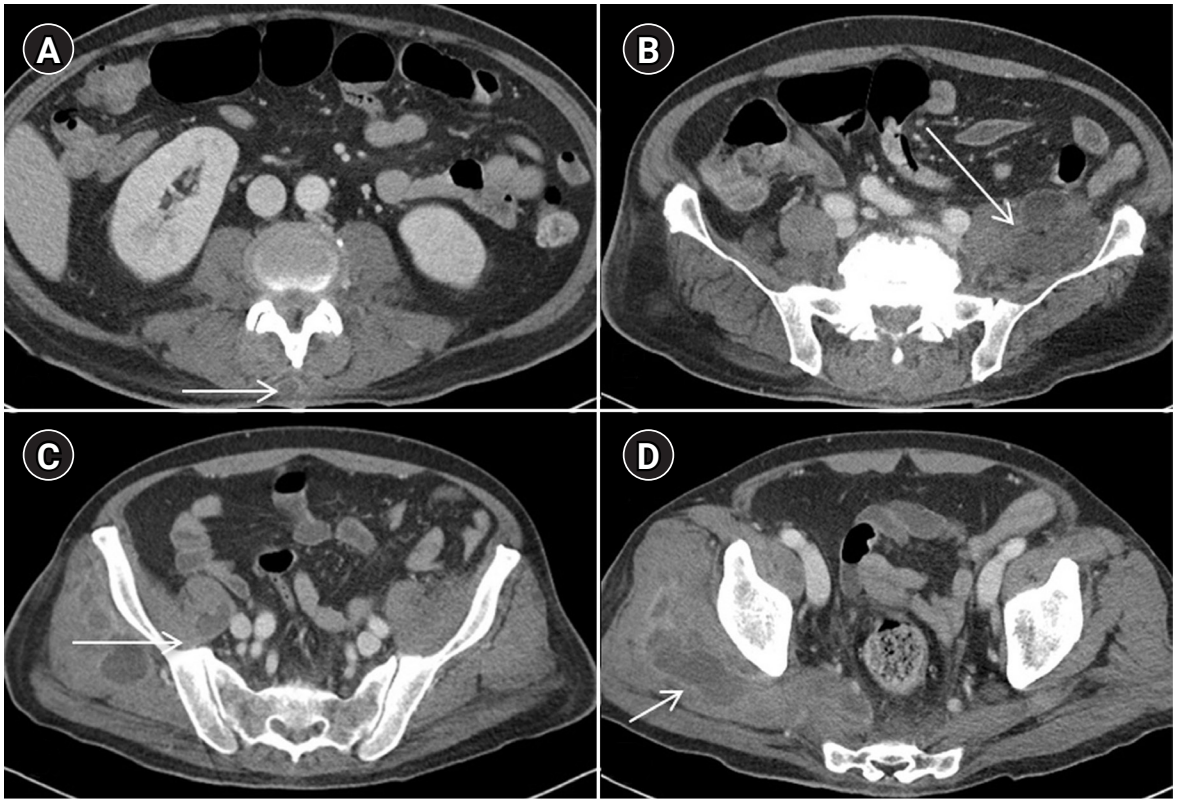


Fig. 3. Abdominopelvic computed tomography images obtained 2 weeks after admission showing abscess formation in the paraspinal muscle (A, arrow), left psoas muscle (B, arrow), right psoas muscle (C, arrow) and right gluteus maximus muscle (D, arrow).

nemius, peroneus longus, iliacus, iliopsoas, and paraspinalis (C5-T1, L2-S1) muscles. During minimal muscle contraction, polyphasic motor unit action potentials of large amplitude and long duration were observed, and the recruitment pattern generally decreased during maximum muscle contraction in the above-mentioned muscles (Tables 1, 2). It revealed multiple etiologies of weakness, including cervical and lumbar polyradiculopathy, polyneuropathy, and cervical myelopathy.

Treatment was started with an early multidisciplinary approach. Intravenous antibiotic therapy was applied for 6 addi-

**Table 1.** Nerve Conduction Studies at 2 Weeks after Admission

| Side | Nerve | Stimulation site | Recording site | Latency (ms) | Amplitude (μV) | Distance (cm) | Velocity (m/s) |
|---|---|---|---|---|---|---|---|
| Nerve conduction studies | | | | | | | |
| Sensory | | | | | | | |
| Rt. | Median | Wrist | III digit | 3.23 | 39.2 | 14 | 43.4* |
| | Ulnar | Wrist | V digit | 2.6 | 34.0 | 14 | 53.8 |
| | Sural | Calf | Ankle | 3.39 | 34.1 | 10 | 29.5* |
| | Superficial peroneal | Leg | Ankle | 2.19 | 17.9 | 10 | 45.7 |
| Lt. | Median | Wrist | III digit | 3.39 | 29.2 | 14 | 41.4* |
| | Ulnar | Wrist | V digit | 2.34 | 25.3 | 14 | 59.7 |
| | Sural | Calf | Ankle | 3.23 | 18.4 | 10 | 31.0* |
| | Superficial peroneal | Leg | Ankle | 2.03 | 19.2 | 10 | 49.2 |
| Motor | | | | | | | |
| Rt. | Median | Wrist | APB | 4.27* | 7.0 | NA | NA |
| | | Elbow | | 9.43* | 6.6 | 26 | 50.4 |
| | Ulnar | Wrist | ADM | 4.11* | 8.2 | NA | NA |
| | | Below elbow | | 8.18* | 8.0 | 21 | 51.7 |
| | | Above elbow | | 10.05* | 7.4 | 10 | 53.3 |
| | Deep peroneal | Ankle | EDB | 6.25* | 2.5 | NA | NA |
| | | Fibular head | | 13.44* | 2.0 | 30 | 41.7 |
| | Tibial | Ankle | AH | 6.93* | 12.4 | NA | NA |
| | | Knee | | 15.10* | 11.6 | 33 | 40.4 |
| Lt. | Median | Wrist | APB | 5.26* | 3.2* | NA | NA |
| | | Elbow | | 9.38* | 2.8* | 26 | 63.2 |
| | Ulnar | Wrist | ADM | 3.65 | 7.1 | NA | NA |
| | | Below elbow | | 7.81 | 5.9 | 21 | 50.4 |
| | | Above elbow | | 9.79 | 5.5 | 10 | 50.5 |
| | Deep peroneal | Ankle | EDB | 5.52 | 2.5 | NA | NA |
| | | Fibular head | | 13.02 | 2.3 | 30 | 40.0 |
| | Tibial | Ankle | AH | 7.71* | 11.5 | NA | NA |
| | | Knee | | 15.89* | 6.4 | 33 | 40.4 |
| Somatosensory evoked potential† | | | | | | | |
| Rt. | Median | Wrist | Scalp | 25.16* | 32.71* | NA | NA |
| Lt. | | | | 24.74* | 31.15* | NA | NA |
| Rt. | Tibial | Ankle | Scalp | NA | NA | 50.31* | 73.65* |
| Lt. | | | | NA | NA | 56.25* | 73.54* |
| Motor evoked potential | | | | | | | |
| Rt. | Median | Scalp | APB | 24.58 | 0.9 | NA | NA |
| Lt. | | | | 29.69* | 0.3* | NA | NA |
| Rt. | Tibial | Scalp | AH | 49.48 | 2.3 | NA | NA |
| Lt. | | | | 49.11 | 2.0 | NA | NA |

Rt., right; Lt., left; APB, abductor pollicis brevis; ADM, abductor digiti minimi; EDB, extensor digitorum brevis; AH, abductor halluces; NA, not available.
*Abnormal values.
†Somatosensory evoked potentials are measured in N20 (ms), P25 (ms), P40 (ms), and P60 (ms).


https://doi.org/10.18214/jend.2022.00031

**Table 2.** Needle Electromyography at 2 Weeks after Admission

| Side | Muscle | Spontaneous activity | | | MUAP | | | Recruitment |
|---|---|---|---|---|---|---|---|---|
| | | IA | Fib. | PSW | Amplitude | Duration | Poly. | |
| Needle electromyography | | | | | | | | |
| Rt. | TA | Inc. | +++ | +++ | Large | Long | + | Reduced |
| | PL | Inc. | +++ | +++ | Large | Long | + | Discrete |
| | GCM | Inc. | +++ | +++ | Large | Long | + | Discrete |
| | EHL | Inc. | +++ | +++ | Large | Long | + | Discrete |
| | VM | Normal | None | None | Normal | Long | + | Reduced |
| | GM | Inc. | +++ | +++ | Large | Long | + | Discrete |
| | Gm | Inc. | ++ | ++ | Large | Long | + | Discrete |
| | IC | Inc. | ++ | ++ | Normal | Long | + | Discrete |
| | IP | Inc. | +++ | +++ | Normal | Long | + | Discrete |
| | LPS | Inc. | +++ | +++ | NA | NA | NA | NA |
| | APB | Inc. | +++ | +++ | Large | Long | + | Reduced |
| | PT | Inc. | +++ | +++ | Large | Long | + | Discrete |
| | ADM | Inc. | ++ | ++ | Large | Long | + | Reduced |
| | FCU | Inc. | ++ | ++ | Normal | Long | + | Discrete |
| | EDC | Inc. | +++ | +++ | Large | Long | + | Discrete |
| | TB | Inc. | ++ | ++ | Large | Long | + | Discrete |
| | BB | Inc. | +++ | +++ | Large | Long | + | Reduced |
| | CPS | Inc. | ++ | ++ | NA | NA | NA | NA |
| Lt. | TA | Inc. | +++ | +++ | Large | Long | + | Reduced |
| | PL | Inc. | +++ | +++ | Large | Long | + | Discrete |
| | GCM | Inc. | +++ | +++ | Large | Long | + | Discrete |
| | EHL | Inc. | ++ | ++ | Large | Long | + | Discrete |
| | VM | Normal | None | None | Normal | Long | + | Reduced |
| | GM | Inc. | +++ | +++ | Large | Long | + | Discrete |
| | Gm | Inc. | ++ | ++ | Large | Long | + | Discrete |
| | IC | Inc. | ++ | ++ | Normal | Long | + | Discrete |
| | IP | Inc. | +++ | +++ | Normal | Long | + | Discrete |
| | LPS | Inc. | +++ | +++ | NA | NA | NA | NA |
| | APB | Inc. | +++ | +++ | Large | Long | + | Reduced |
| | PT | Inc. | +++ | +++ | Large | Long | + | Discrete |
| | ADM | Inc. | +++ | +++ | Large | Long | + | Discrete |
| | FCU | Inc. | +++ | +++ | Large | Long | + | Discrete |
| | EDC | Inc. | +++ | +++ | Large | Long | + | Discrete |
| | TB | Inc. | ++ | ++ | Large | Long | + | Discrete |
| | BB | Inc. | +++ | +++ | Large | Long | + | Discrete |
| | CPS | Inc. | ++ | ++ | NA | NA | NA | NA |

IA, insertional activity; Fib., fibrillation potential; PSW, positive sharp wave; MUAP, motor unit action potential; Poly., polyphasic motor unit action potentials; Rt., right; TA, tibialis anterior; Inc., increased; PL, peroneus longus; GCM, gastrocnemius (medial head); EHL, extensor hallucis longus; VM, vastus medialis; GM, gluteus maximus; Gm, gluteus medius; IC, iliacus; IP, iliopsoas; LPS, lumbar paraspinalis; APB, abductor pollicis brevis; PT, pronator teres; ADM, abductor digiti minimi; FCU, flexor carpi ulnaris; EDC, extensor digitorum communis; TB, triceps brachii; BB, biceps brachii; CPS, cervical paraspinalis; Lt., left; NA, not available.

tional weeks. Strengthening exercises for both upper and lower extremities with progressive gait training were performed in sessions.

After 2 months of hospitalization, the patient's functional state improved to achieve independent walker-assisted gait.

## Discussion

VO is a rare disease that accounts for approximately 1% of all skeletal infections [2,8]. It mainly involves 2 vertebral bodies and the adjacent intervertebral discs [4]. Most cases involve a single

region (94%), and the most common location was reported to be the lumbar spine (58%) [3,8]. However, the involvement of multiple levels has rarely been reported in previous studies, accounting for 4% of all VO cases, and only 3% of cases were skip lesions [2].

VO has an insidious onset, and its progression is slow [4]. Neurological deficits, including motor or sensory deficits and bladder or bowel dysfunction, were reported in one-third of cases [3]. *S. aureus* is the most commonly isolated causative agent (32%-67%) [2]. VO is mostly caused by hematogenous seeding (50%), Direct inoculation after iatrogenic procedures (15%-40%), or contiguous spread from an adjacent area (3%) [1,4]. VO often causes myositis or abscess in surrounding structures, such as the paravertebral, epidural, or psoas abscesses [3,8]. In addition, cervical involvement significantly increases the risk of spinal cord compression, according to Doutchi et al. [8]. The evaluation of VO should include a history, physical examination, laboratory results, and MRI [4]. MRI can diagnose VO with high accuracy (90%).

Epidural injections are a widely used non-surgical treatment for patients with radicular pain by disc herniation. Transforaminal injection is a method that effectively delivers corticosteroids to the epiradicular space [6]. It is generally known to be a safe method, but epidural space infections, discitis, and osteomyelitis can occasionally occur [5–7]. Absolute contraindications include local infection around the injection site, anticoagulant use, uncontrolled DM, and congestive heart failure [6]. In this case, based on the patient's medical history, his DM was uncontrolled for the last 2-3 months. The patient was in an immunosuppressed state, which caused the disseminated infection.

It is important to implement an intensive and early multidisciplinary approach, including medical treatment, surgery, and rehabilitative treatment, to achieve favorable outcomes in VO. In the case presented herein, a rapid diagnosis and a multidisciplinary approach were applied to determine the focus of infection and causative organism, and early surgical and rehabilitative treatment was performed in parallel.

Of particular note, a detailed rehabilitative approach and the identification of multiple causes of paralysis are essential for patients with VO. Since neurologic complications can cause functional loss and low quality of life, the early application of comprehensive rehabilitation could be the key to a good prognosis, the recovery of functional ability, and improvement of the quality of life for patients with VO.

Physicians often experience difficulty in the field when a precise differential diagnosis of weakness is necessary. Electrodiagnostic studies are advantageous for determining the degree of damage and for follow-up of improvement in patients with VO. Electrodiagnostic studies could be a good diagnostic tool for physicians in determining the etiology of weakness in patients with VO.

There is a potential risk of iatrogenic complications when performing needle EMG, including bleeding, infection, nerve injury, pneumothorax, and other local trauma [9]. In particular, the risk of seeding infection should be considered in patients with a suspected infection [10]. There is no quantitative evidence on the theoretical risk of seeding infection according to previous studies [10]. To reduce this risk, sterilized, disposable concentric needles were used. The examiner washed hands before and after the procedure, ad patient's skin was cleaned with alcohol. It was clear in our case that a precise diagnosis was more important than the theoretical risk [9,10].

## Conflict of Interest

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

## Acknowledgements

This research was supported by the Soonchunhyang University Research Fund.

## ORCID

Ji Woong Park, https://orcid.org/0000-0001-7987-3581
Jeong Se Noh, https://orcid.org/0000-0003-4529-3225

## References

1. McHenry MC, Easley KA, Locker GA: Vertebral osteomyelitis: long-term outcome for 253 patients from 7 Cleveland-area hospitals. Clin Infect Dis 2002;34:1342–1350.
2. Mylona E, Samarkos M, Kakalou E, Fanourgiakis P, Skoutelis A: Pyogenic vertebral osteomyelitis: a systematic review of clinical characteristics. Semin Arthritis Rheum 2009;39:10–17.
3. Zimmerli W: Clinical practice. Vertebral osteomyelitis. N Engl J Med 2010;362:1022–1029.
4. Boody BS, Jenkins TJ, Maslak J, Hsu WK, Patel AA: Vertebral osteomyelitis and spinal epidural abscess: an evidence- based review. J Spinal Disord Tech 2015;28:E316–E327.
5. Knight JW, Cordingley JJ, Palazzo MG: Epidural abscess following epidural steroid and local anaesthetic injection. Anaesthesia 1997;52:576–578.

 https://doi.org/10.18214/jend.2022.00031

6. Weinstein SM, Herring SA; NASS: Lumbar epidural steroid injections. Spine J 2003;3(3 Suppl):37S–44S.
7. Yue WM, Tan SB: Distant skip level discitis and vertebral osteomyelitis after caudal epidural injection: a case report of a rare complication of epidural injections. Spine (Phila Pa 1976) 2003;28:E209–E211.
8. Doutchi M, Seng P, Menard A, Meddeb L, Adetchessi T, Fuentes S, et al: Changing trends in the epidemiology of vertebral osteomyelitis in Marseille, France. New Microbes New Infect 2015;7:1–7.
9. Al-Shekhlee A, Shapiro BE, Preston DC: Iatrogenic complications and risks of nerve conduction studies and needle electromyography. Muscle Nerve 2003;27:517–526.
10. Spolter YS, Katirji B, Preston DC: Electromyographic diagnosis of multifocal pyomyositis. Muscle Nerve 2015;51:293–296.

JEND Journal of Electrodiagnosis and Neuromuscular Diseases

CASE REPORT

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2022;24(3):96-99
https://doi.org/10.18214/jend.2022.00052

# Chronic Musculocutaneous Nerve Injury: An Important Differential in Progressive Arm Atrophy

Umer Younas, Muhammad Tawab Khalil, Rehana Yasmeen, Omar Shafiq, Imran Irshad

Department of Electrodiagnostics, Armed Forces Institute of Rehabilitation Medicine, Rawalpindi, Pakistan

An isolated musculocutaneous nerve (MCN) injury is a rare condition that can be easily missed if it presents late. A 28-year-old man reported painless and progressive wasting of the right arm for 6 months. On examination, there was visible wasting of the right biceps brachii muscle along with its slight weakness, depressed biceps jerk, and an impaired pinprick sensation in the lateral antebrachial cutaneous nerve distribution. He described a history of a road traffic accident 14 months beforehand. Based on the history and clinical examination, the differential diagnosis included an isolated MCN injury, upper trunk plexopathy, lateral cord plexopathy, C5/6 radiculopathy, and monomelic amyotrophy involving the C5/6 myotomes on the right side. The results of nerve conduction studies and electromyography were consistent with chronic proximal MCN neuropathy (right). In cases of arm wasting without pain or numbness, MCN injury should be included in the differential diagnosis, even in the presence of good power of the elbow flexors. The importance of detailed history-taking and clinical correlation cannot be over-emphasized in such cases.

**Keywords:** Brachial plexus injuries; Electrodiagnosis; Peripheral nerve injuries; Proximal neuropathies; Nerve conduction studies/electromyography

**Received:** May 2, 2022
**Revised:** September 18, 2022
**Accepted:** November 5, 2022

**Corresponding author:**
Umer Younas
Department of Electrodiagnostics, Armed Forces Institute of Rehabilitation Medicine, Convoy Rd, Rawalpindi, Punjab 46000, Pakistan
Tel: +92-3338421194
E-mail: umeryounassp@gmail.com

## Introduction

Traumatic injuries to the nerves in the upper limbs most frequently involve the ulnar nerve [1]. In contrast, isolated musculocutaneous nerve (MCN) injuries are rare [2]. The reported causes include direct stab injury, crush injury, strenuous activity, repetitive sports injury, and prolonged awkward positioning of the arm while asleep [2,3]. The MCN receives its nerve supply from the C5, C6, and C7 nerve roots. It arises from the lateral cord of the brachial plexus and supplies the muscles of the anterior compartment of the arm. It also gives off a cutaneous supply to the lateral aspect of the forearm [4].

In addition to being rare, such injuries may remain unnoticed, as elbow flexors such as the brachioradialis muscle and pronator teres muscle, which are innervated by the radial and median nerves, respectively, compensate for the weakness of the biceps brachii and brachialis muscles. We present a rare case of an isolated MCN injury in a young man that remained undetected for a long period.

The aim of reporting this case is to highlight the critical importance of taking a detailed medical history, performing a thorough clinical examination, and then ordering appropriate investigations to reach a correct diagnosis.

## Case Report

A 28-year-old man presented to an electrodiagnostic clinic with the complaint of painless and progressive wasting of the

right arm for last 6 months. The referring physician had a query of cervical radiculopathy or monomelic amyotrophy. On initial history-taking, the patient stated that he had no significant past medical history or neck pain. An examination revealed visible wasting of the right biceps brachii muscle (Fig. 1), with an arm girth 1.5 cm less compared to the left side (10 cm proximal to lateral epicondyle). The active range of motion at the elbow was full, and the right biceps brachii muscle strength was grade 4 on the Medical Research Council (MRC) scale, with only mild elbow flexion and forearm supination weakness compared to the left side. A sensory examination revealed impaired dull and sharp pinprick sensations on the anterolateral aspect of the right forearm. The deep tendon reflexes were intact (grade 2+), except right biceps jerk, which was grade 1+. The Hoffman, Lhermitte, Spurling, and Gower signs were negative, with a flexor plantar response. The power in the other muscles of the upper limbs was graded 5 on the MRC scale. A neurological examination of the cervical spine, cranial nerves, and cerebellum (finger nose test, dysdiadochokinesia test, and heel-to-shin test) was unremarkable. The patient was re-enquired to recall any significant events preceding his current complaints. As a result, the patient recalled that he was in a motorbike accident 14 months previously and sustained a right shoulder contusion due to an impact on the cement track. Immediately after the injury, patient experienced severe pain, weakness, and numbness in the right upper limb. The patient stated that he had no history of an open or penetrating wound or head injury at the time of injury. He was evacuated to a local medical facility where plain X-rays of the cervical spine, right shoulder, and arm did not reveal any bony injury. The patient was discharged on oral painkiller medications and topical analgesics. Over the next month, his right arm pain decreased significantly. However, he had weakness of elbow flexion with an inability to lift objects and persistent numbness in the right forearm. He visited a local medical facility, where he was advised on a home-based physiotherapy plan (hot pack and range of motion exercises) in addition to analgesics. He privately received magnetic resonance imaging of the cervical spine and right shoulder, which were reported as normal. Over the next few months, the patient had significant symptomatic relief and came up with trick movements to compensate for his elbow flexion weakness, relying basically on the brachioradialis muscle. However, mild numbness was present but now localized to the lateral aspect of the right forearm. Initially, he had a slight suspicion of arm asymmetry in front of the mirror, which he ignored as he engaged in routine activities of daily living without any activity limitations or participation restrictions. Later, the right arm wasting gradually progressed without any associated pain, when he finally visited a tertiary care hospital.

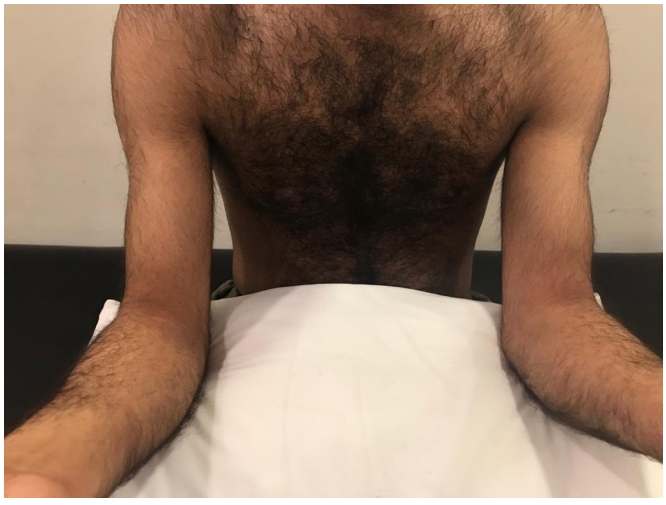

Fig. 1. Relative muscle wasting of the biceps brachii (right).

Following a correlation between the clinical history and physical examination, the differential diagnosis included isolated MCN injury, upper trunk plexopathy, lateral cord plexopathy, C5/6 radiculopathy, and monomelic amyotrophy involving the C5/6 myotomes on the right side. To confirm a definitive diagnosis, nerve conduction studies (NCS) and electromyography (EMG) were carried out. For motor NCS of the MCN, recording and reference surface electrodes were placed on the belly of the biceps brachii muscle and biceps brachii tendon, respectively [5]. A side-to-side comparison showed a reduced compound muscle action potential amplitude and prolonged distal motor latency of the right MCN nerve (Table 1). For sensory NCS of the lateral antebrachial cutaneous nerve (LACN), a recording surface electrode was placed on the lateral forearm 12 cm distal to the cubital fossa and a reference surface electrode was placed 4 cm distal to the recording electrode.5 A side-to-side comparison showed a reduced sensory nerve action potential amplitude of the right LACN. Needle EMG of the right biceps brachii muscle showed no abnormal involuntary activity, but large polyphasic motor unit action potentials with decreased recruitment resulting in incomplete interference, an EMG finding that is consistent with reinnervation. EMG of the cervical paraspinal muscles (to rule out cervical radiculopathy), deltoid, brachioradialis muscles (to rule out upper trunk plexopathy), pronator teres muscle (to rule out lateral cord plexopathy), triceps brachii, extensor digitorum and first dorsal interosseous muscles showed no abnormal involuntary activities, with normal motor unit action potentials and interference patterns. The clinico-electrophysiological correlation was consistent with chronic, proximal MCN neuropathy

Table 1. Motor and Sensory Nerve Conduction Studies

| Nerve sites | Latency (ms) | | Amplitude (mV) | | CV (m/s) | |
|---|---|---|---|---|---|---|
| | Right | Left | Right | Left | Right | Left |
| Motor NCS | | | | | | |
| Median | 3.4 | 3.7 | 11.9 | 11.3 | 52 | 55 |
| Ulnar | 2.5 | 2.7 | 10.2 | 11.8 | 51 | 53 |
| Radial | 2.8 | 2.9 | 5.8 | 5.9 | 52 | 54 |
| Musculocutaneous | 5.8 | 4.6 | 6.8 | 12.4 | - | - |
| Sensory NCS | | | | | | |
| Median | 2.9 | 2.8 | 40* | 38* | 52 | 55 |
| Ulnar | 2.3 | 2.2 | 38* | 37* | 51 | 50 |
| Radial | 1.8 | 2 | 40* | 38* | 52 | 51 |
| Lateral antebrachial cutaneous | 1.8 | 1.5 | 7* | 12* | 50 | 58 |

NCS, nerve conduction studies; CV, conduction velocity; -, not applicable.
*Amplitudes are measured in microvolt (μV).

(right) with good recovery (right biceps brachii muscle strength of grade 4 on the MRC scale and the presence of recovery potentials on needle EMG).

The patient was advised to take a mecobalamin tablet (500 μg) once daily. He was further advised to engage in a resistive exercise plan to strengthen the right biceps brachii muscle and scheduled for follow-up at 12 weeks. However, he was lost to follow up.

## Discussion

NCS/EMG is an extension of the clinical examination and it always starts with a brief history-taking and clinical examination [6]. It is the most important diagnostic test to confirm the diagnosis of peripheral neuropathy and to comment on whether peripheral neuropathy is acute or chronic, hereditary or acquired, and axonal or demyelinating [6]. In cases of peripheral mono-neuropathies, NCS/EMG helps to localize the location of nerve damage [6].

MCN neuropathy commonly occurs due to trauma, iatrogenic causes (shoulder arthroplasty, rotator cuff repair, humeral shaft reconstruction, and shoulder arthroscopy) and idiopathic causes. It may be of mixed type, isolated motor neuropathy of the MCN, or isolated sensory neuropathy of the MCN [7]. Following an acute MCN injury, the patient might not present for medical care at all, as intact pronator teres and brachioradialis muscles also assist in elbow flexion. If it remains undiagnosed, an atypical presentation of chronic MCN injury in later life might become a diagnostic challenge.

Our patient had a motorbike accident during the peak of the second wave of coronavirus disease 2019 and could not access a tertiary care facility due to lockdown conditions. He was able to perform elbow flexion by contraction of the brachioradialis muscle, which was also reported by Tinel [8]. Fortunately, the patient showed spontaneous, clinically significant motor recovery. However, based on an isolated complaint of painless progressive arm wasting, his primary physician referred him for NCS/EMG with differentials of cervical radiculopathy and monomelic amyotrophy. Visible atrophy of the arm warrants a detailed clinical history and examination to search for the possible causes, including (but not limited to) central pathology, anterior horn cell disorder, radiculopathy, plexopathy, peripheral nerve injury, or atypical myopathy. This case report also highlights the need to keep unusually delayed presentations of such peripheral nerve injuries in mind while examining a patient with muscle wasting without any other marked neurological symptoms

The management of MCN neuropathy includes conservative and surgical treatment. A comprehensive multidisciplinary rehabilitation plan formulated by a physiatrist facilitates recovery and prevents dependence in activities of daily living by avoiding or reducing possible complications secondary to immobility (such as muscle wasting, contracture, joint stiffness), neuropathic or musculoskeletal pain, and adhesive capsulitis. However, some cases, like our patient, recover on their own over time and use self-learned trick movements to assist in activities of daily living. Surgical options include conventional nerve transfer or double fascicular nerve transfer [9].

In conclusions, chronic isolated MCN injury is a rare presentation. Such cases may become a diagnostic challenge and warrant a meticulous clinical history and thorough physical examination, especially when an electrodiagnostic facility is not available. In most cases, conservative management is successful and is consid-


https://doi.org/10.18214/jend.2022.00052

ered the first line of treatment. If unsuccessful, a surgical intervention is needed. An accurate and timely diagnosis with an appropriate intervention ensures the best possible outcome.

## Conflict of Interest

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

## Acknowledgements

We used the CARE guidelines (www.care-statement.org) for this case report. We acknowledge the efforts of Dr Farooq Ahmad Rathore, who voluntarily helped in proofreading the manuscript. Informed consent was obtained from the patient.

## ORCID

Umer Younas, https://orcid.org/0000-0001-5402-2983
Muhammad Tawab Khalil, https://orcid.org/0000-0002-2119-4575
Rehana Yasmeen, https://orcid.org/0000-0001-8409-972X
Omar Shafiq, https://orcid.org/0000-0002-7223-1487
Imran Irshad, https://orcid.org/0000-0003-4019-2556

## References

1. Tapp M, Wenzinger E, Tarabishy S, Ricci J, Herrera FA: The epidemiology of upper extremity nerve injuries and associated cost in the US emergency departments. Ann Plast Surg 2019;83:676–680.
2. Kwon S, Han EY, Min K, Im SH: Isolated musculocutaneous nerve injury following a pedestrian-automobile collision: a case report. Neurol Asia 2019;24:267–270.
3. Kissel JA, Leonardelli C: Isolated musculocutaneous neuropathy: a case report. J Can Chiropr Assoc 2019;63:162–170.
4. Demircay E, Musluman AM, Cansever T, Yuce I, Civelek E, Yilmaz A, et al: Spinal nerve root compositions of musculocutaneous nerve: an anatomical study. Turk Neurosurg 2014;24:880–884.
5. Preston DC, Shapiro BE: Electromyography and neuromuscular disorders: clinical-electrophysiologic-ultrasound correlations. 4th ed. Philadelphia: Elsevier; 2021, pp117–123.
6. Siao P, Kaku M: A clinician's approach to peripheral neuropathy. Semin Neurol 2019;39:519–530.
7. Sirico F, Castaldo C, Baioccato V, Marino N, Zappia M, Montagnani S, et al: Prevalence of musculocutaneous nerve variations: Systematic review and meta-analysis. Clin Anat 2019;32:183–195.
8. Nerve wounds symptomatology of peripheral nerve lesions caused by war wounds. By J. Tinel, late Chef de Clinique at La Salpêtrière, with preface by professor Dejerine, translated by Fred. Rothwell, revised and edited by Cecil A. Joll. pp. xii + 317, with 323 illustrations. London Baillière, Tindal & Cox. 15s. net. Br J Surg 2017;5:517.
9. Bhandari PS, Deb P: Management of isolated musculocutaneous injury: comparing double fascicular nerve transfer with conventional nerve grafting. J Hand Surg Am 2015;40:2003–2006.

JEND Journal of Electrodiagnosis and Neuromuscular Diseases

CASE REPORT

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2022;24(3):100-103
https://doi.org/10.18214/jend.2022.00066

# Ischemic Stroke with Antiphospholipid Syndrome in a Myotonic Dystrophy Type 1 Patient: A Rare Case Report

Eun Ji Lee, Dong Jae Shin, Young Jin Ko, So Yeon Jun

Department of Rehabilitation Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Myotonic dystrophy type 1 (DM1) is a rare autosomal dominant disorder with various phenotypes involving multiple systems. Stroke co-occurrence in DM1 is rare, but can cause severe dysfunction in a patient's quality of life. However, the mechanism of stroke in patients with DM1 is poorly understood. In this case report, we present a patient who was diagnosed with DM1 while suffering from a brain embolic infarction due to antiphospholipid syndrome (APS). This is the first known case of DM1 with APS. The coexistence of these two multisystem diseases may make the diagnosis difficult, and there is the possibility of symptoms involving multiple organs. We should pay attention to the possibility of the coexistence of autoimmune disease and stroke in DM1 patients based on this rare case of a DM1 patient with stroke and an autoimmune disease.

**Keywords:** Myotonic dystrophy; Brain infarction; Antiphospholipid syndrome

**Received:** May 23, 2022
**Revised:** July 26, 2022
**Accepted:** August 12, 2022

**Corresponding author:**
So Yeon Jun
Department of Rehabilitation Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea. 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea
Tel: +82-2-2258-1730
Fax: +82-2-2258-5518
E-mail: iamsj17@naver.com

## Introduction

Myotonic dystrophy type 1 (DM1) is considered the most common type of adult-onset muscular dystrophy and is known to be related to cytosine-thymine-guanine (CTG) repeat expansion in the myotonic dystrophy protein kinase (*DMPK*) gene [1]. DM1 is a multisystem disease that presents with motor weakness, including the distal limb muscles and facial muscles, with manifestations including ptosis, myotonia, cataracts, dyslipidemia, and cardiac involvement [2,3].

Due to the multisystem involvement of DM1, studies have reported stroke occurrence in DM1 patients, including reports of cardioembolism [4,5] and stroke-like episodes [2]. However, the exact pathomechanism of stroke in DM1 patients has not been well established [2,5]. Additionally, antiphospholipid syndrome (APS) is a disease that can cause an embolic infarction, but there have been no reported cases of APS in DM1 patients [6]. Here, we introduce the rare case of a DM1 patient who suffered from a stroke co-occurring with APS.

## Case Report

A 46-year-old woman visited the emergency department due to aphasia, urinary difficulty, and gait disturbance in June 2019, which occurred on the same day. Brain magnetic resonance imaging showed multiple embolic infarctions in the bilateral posterior watershed zones (Fig. 1). The blood test results showed a fasting glucose level of 87 mg/dL, a total cholesterol level of 199 mg/dL, a low-density lipoprotein level of 89 mg/dL, and a hemoglobin A1c level of 5.4%, indicating that the patient did not have diabetes or hyperlipidemia. Furthermore, the laboratory results related to coagulation, including prothrombin time, activated partial thromboplastin time, and D-dimer level, which is known to be related to oral contraceptive medication, were normal. Electrocardiography also showed a normal sinus rhythm. She had previously taken oral contraceptives for several years af-

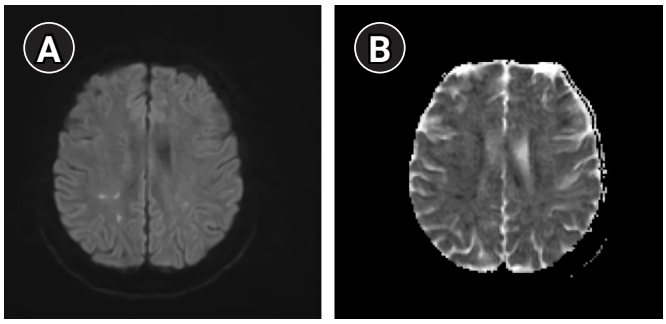


Fig. 1. Brain magnetic resonance imaging shows high signal intensities on both posterior watershed zones in a diffusion-weighted image (A) with low signals on an apparent diffusion coefficient map (B).

ter two miscarriages and menopausal transition symptoms. She was diagnosed with APS through three consecutive tests confirming antinuclear antibody, anti-β2-glycoprotein I antibody, and anticardiolipin antibody. After the diagnosis of cerebral embolic infarction, she stopped using oral contraceptives, and started warfarin to prevent recurrence.

She visited the Department of Rehabilitation Medicine for post-stroke rehabilitation. Physical examinations showed bilateral weakness of the upper and lower extremities, with generally good grades in the upper and lower extremities, except for both finger flexion, which had a fair-plus grade. According to the patient, the weakness in both hands started several decades ago, which did not match the patient's symptoms of cerebral infarction. Therefore additional history-taking and another examination were needed. Notably, in her family history, one of her five siblings (the first sister) had been diagnosed with DM1, with symptoms including difficulty walking up the stairs and weakness in both upper and lower extremities. Therefore, we recommended genetic testing and an electrodiagnostic (EDX) study for her. As a result of genetic testing, our patient, as well as her first and fourth older sisters, was newly diagnosed with DM1 with the expansion of more than 150 repetitions of unstable CTG repeats in the *DMPK* gene.

In EDX, a nerve conduction study showed decreased amplitudes of compound muscle action potentials in the right common peroneal nerve recording at the tibialis anterior (TA) and the left common peroneal nerve recording at the extensor digitorum brevis and TA muscles (Table 1). On needle electromyography, we found abnormal spontaneous activities, including prominent myotonic discharges at rest, in the right biceps brachii, flexor carpi radialis (FCR), extensor digitorum communis (EDC), first dorsal interosseous (FDI), vastus medialis, TA, and medial head of gastrocnemius (GCM) muscles. Small, short, or polyphasic motor unit action potentials were observed in the right FCR, EDC, TA, and medial head of GCM muscles. Furthermore, the examination showed early recruitment patterns in the right biceps brachii, FCR, EDC, FDI, and the medial head of GCM muscles (Table 2). Based on the EDX, we concluded that the patient had myotonic dystrophy, mainly involving the upper and distal lower extremities (more involving the upper extremities), clinically corresponding to DM1.

Currently, the patient is receiving neurorehabilitation at our outpatient clinic for the sequelae of cerebral infarction and DM1, including gait training and occupational therapy for weakness in both hands. Comprehensive physical and occupational rehabilitation therapy has ameliorated her balance and activities of daily living, with her Berg balance score improving from 49 to 53, and her Korean version of modified Barthel index improving from 68 to 93.

## Discussion

To the best of our knowledge, this is the first reported case of a DM1 patient with a stroke accompanied by APS. Sugie et al. [5] stated that cardiogenic embolism is a major cause of stroke in DM1 patients and emphasized that the CTG repetition numbers were generally higher (1,000-1,500) in DM1 patients with stroke. However, our patient showed a notably different risk factor, APS, which contributed to stroke through a thrombogenic mechanism [7].

According to Tieleman et al. [6], DM2 has a stronger association with autoimmune disease than DM1. A few case reports have described stroke in DM1 patients [2,5], but no cases of APS-induced stroke have been reported to date in DM1 patients. Although there were previous reports of co-existing autoimmune diseases, these reports only involved Sjögren's syndrome or Crohn's disease in DM1 patients [6,8].

In a few cases of stroke occurrence in DM1, other risk factors such as dyslipidemia and arrhythmia were additionally identified [5], but it has yet to be elucidated how the DM1 disease entity affects the pathomechanism of stroke has not yet been elucidated [4,5]. Additionally, unlike DM2, it had not been confirmed whether DM1 co-existed with autoimmune diseases such as APS [6]. Finally, the rarity of this case is underscored by the fact that APS has not been reported among the causes of embolic stroke in DM1.

In addition, when the patient visited the hospital, the bilateral distal dominant weakness was not related to the actual location of the infarction. Therefore, when these symptoms are present, a further study should be conducted to rule out the possibility of

**Table 1.** Nerve Conduction Study

| | Stimulation | Latency (ms)* | Amplitude | CV (m/s) |
|---|---|---|---|---|
| Sensory nerve | | | | |
| Rt. median (digit III) | Wrist | 3.45 | 37.3 | 52.8 |
| | Palm | 1.80 | 43.6 | 50.0 |
| Rt. ulnar (digit V) | Wrist | 3.30 | 40.8 | 57.1 |
| Rt. radial (Snuffbox) | Forearm | 2.15 | 30.9 | 62.5 |
| Rt. sural | Calf | 3.60 | 19.9 | 48.3 |
| Lt. sural | Calf | 3.40 | 23.5 | 51.9 |
| Rt. superficial peroneal | Lateral leg | 3.25 | 23.7 | 56.0 |
| Rt. superficial peroneal | Lateral leg | 3.15 | 21.5 | 60.9 |
| Motor nerve | | | | |
| Rt. median (APB) | Wrist | 300 | 8.2 | |
| | Elbow | 6.40 | 7.9 | 52.9 |
| Rt. ulnar (ADM) | Wrist | 2.75 | 13.2 | |
| Rt. peroneal (EDB) | Ankle | 3.65 | 3.5 | |
| | Fibular head | 9.45 | 2.8 | 50.0 |
| Lt. peroneal (EDB) | Ankle | 3.55 | 2.2 | |
| | Fibular head | 9.80 | 1.7 | 46.4 |
| Rt. peroneal (TA) | Fibular head | 2.40 | 2.6 | |
| Lt. peroneal (TA) | Fibular head | 2.40 | 3.0 | |
| Rt. tibial (AH) | Ankle | 3.05 | 19.0 | |
| | Popliteal | 10.55 | 13.5 | 49.3 |
| Lt. tibial (AH) | Ankle | 3.10 | 17.3 | |
| | Popliteal | 10.45 | 13.3 | 49.0 |

Amplitudes are measured in microvolt (μV, sensory) and millivolt (mV, motor).
CV, conduction velocity; Rt., right; Lt., left; APB, abductor pollicis brevis; ADM, abductor digiti minimi; EDB, extensor digitorum brevis; TA, tibialis anterior; AH, abductor; ms, millisecond; m/s, meter/second.
*Sensory nerve: peak latency, motor nerve: onset latency.

**Table 2.** Needle Electromyography

| Muscle | IA | Fib | PSW | Myotonic discharge | MUAP | Recruitment pattern | Interferential pattern |
|---|---|---|---|---|---|---|---|
| Rt. biceps | NL | 2+ | 2+ | + | NL | Early | Full |
| Rt. flexor carpi radialis | NL | 1+ | 2+ | + | Poly | Early | Full |
| Rt. extensor digitorum communis | NL | 2+ | 2+ | + | Poly | Early | Full |
| Rt. first dorsal interosseous | NL | 4+ | 4+ | + | NL | Early | Full |
| Rt. gluteus maximus | NL | None | None | None | NL | NL | Full |
| Rt. vastus medialis | NL | None | 1+ | None | NL | NL | Full |
| Rt. tibialis anterior | Dec | 2+ | 2+ | + | Short, poly | Early | Full |
| Rt. gastrocnemius (medial head) | Dec | 2+ | 2+ | + | Small, poly | Early | Reduced |

IA, insertional activity; Fib, fibrillation; PSW, positive sharp wave; MUAP, motor unit action potential; Rt., right, NL, normal; dec, decreased; poly, polyphasic.

other concurrent diseases. In this case, the patient was additionally diagnosed with DM1 and the etiology was identified; thus, surveillance education for possible complications and genetic counseling were possible [9].

As mentioned above, APS and DM1 are both multisystem diseases and may be accompanied by various systemic symptoms. In particular, stroke can severely deteriorate function in daily life in APS or DM1 patients. Therefore, to predict and prevent stroke in DM1 patients, it is very important to pay attention to the relationship between APS and DM1. Based on this case, we can consider the need for more early and active evaluation starting at the initial stage by considering the co-occurrence of autoimmune

 https://doi.org/10.18214/jend.2022.00066

diseases such as APS as a risk factor for stroke in DM1 patients. Furthermore, it is necessary to consider whether autoantibody-positive findings in APS are related to the genetic abnormalities seen in DM1. This case provides new insight into the clinical mechanisms underlying the association between DM1 and APS from the standpoint of stroke occurrence.

## Conflict of Interest

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

## ORCID

Eun Ji Lee, https://orcid.org/0000-0002-3352-2417
Dong Jae Shin, https://orcid.org/0000-0001-9152-4712
Young Jin Ko, https://orcid.org/0000-0001-5123-5369
So Yeon Jun, https://orcid.org/0000-0003-3217-1990

## References

1. Park JS, Park D, Park JM: Cancer frequency among the patients with myotonic dystrophy in the South Korean population using the national health insurance database. J Neurol Sci 2021;420:117212.
2. Rollnik JD, Heinz U, Lenz O: Myotonic dystrophy type 1 presenting with stroke-like episodes: a case report. BMC Res Notes 2013;6:243.
3. Turner C, Hilton-Jones D: The myotonic dystrophies: diagnosis and management. J Neurol Neurosurg Psychiatry 2010;81:358–367.
4. Finsterer J: Stroke and stroke-like episodes in muscle disease. Open Neurol J 2012;6:26–36.
5. Sugie M, Sugie K, Eura N, Iwasa N, Shiota T: Characteristics of risk-factor profiles associated with stroke in patients with myotonic dystrophy type 1. J Rare Disord Diagn Ther 2016;2:article no.19.
6. Tieleman AA, den Broeder AA, van de Logt AE, van Engelen BG: Strong association between myotonic dystrophy type 2 and autoimmune diseases. J Neurol Neurosurg Psychiatry 2009;80:1293–1295.
7. Gašperšič N, Zaletel M, Kobal J, Žigon P, Čučnik S, Šemrl SS, et al: Stroke and antiphospholipid syndrome-antiphospholipid antibodies are a risk factor for an ischemic cerebrovascular event. Clin Rheumatol 2019;38:379-384.
8. Kitsis EA, Napier F, Juthani V, Geyer HL: Association of Sjögren's syndrome with myotonic dystrophy type 1. BMJ Case Rep 2019;12:e229611.
9. Gutiérrez Gutiérrez G, Díaz-Manera J, Almendrote M, Azriel S, Eulalio Bárcena J, Cabezudo García P, et al: Clinical guide for the diagnosis and follow-up of myotonic dystrophy type 1, MD1 or Steinert's disease. Neurologia (Engl Ed) 2020;35:185-206.

JEND Journal of Electrodiagnosis and Neuromuscular Diseases

CASE REPORT

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2022;24(3):104-108
https://doi.org/10.18214/jend.2022.00094

# True Neurogenic Thoracic Outlet Syndrome with Elongated C7 Transverse Processes in a Hemiplegic Patient: A Case Report

Yeon Gyu Jeong, Jin Hee Jung, Joo Sup Kim, Hyo Jeong Lee

Department of Rehabilitation Medicine, Bundang Jesaeng Hospital, Seongnam, Korea

Thoracic outlet syndrome (TOS) is caused by the compression of neurovascular structures in the thoracic cage. TOS can be classified into neurogenic TOS (NTOS) and vascular TOS. Congenital anomalies, such as cervical ribs and elongated C7 transverse processes, may be the cause of NTOS. NTOS can be subcategorized as either disputed NTOS or true NTOS. True NTOS, a very rare disease with a prevalence of about one in a million, is diagnosed by the weakness and atrophy of T1-innervated intrinsic muscles of the hand and corresponding electrodiagnostic abnormalities. We report a case of a 42-year-old patient, who presented with a 5-year history of clumsiness and 1-year history of weakness and atrophy in her right hand. The patient was diagnosed with true NTOS during comprehensive rehabilitation, which she received for left hemiplegia due to intracranial hemorrhage. Elongated bilateral C7 transverse processes were found on a radiological evaluation. True NTOS is often overlooked or mistaken for carpal tunnel syndrome, thus delaying the diagnosis and inevitably worsening outcomes. Therefore, an electrodiagnostic study is crucial for detecting true NTOS, rather than typical physical examinations such as the Roos stress test and Adson's test.

**Keywords:** Brachial plexus neuropathies; Thoracic outlet syndrome; Hemiplegia

**Received:** July 1, 2022
**Revised:** August 2, 2022
**Accepted:** August 9, 2022

**Corresponding author:**
Hyo Jeong Lee
Department of Rehabilitation Medicine, Bundang Jesaeng Hospital, 20 Seohyeon-ro 180beon-gil, Bundang-gu, Seongnam 13590, Korea
Tel: +82-31-779-0063
Fax: +82-31-779-0635
E-mail: anaell730@gmail.com

## Introduction

Thoracic outlet syndrome (TOS) is a complex of symptoms caused by the compression or irritation of neurovascular structures in the thoracic cage [1]. TOS can be classified into neurogenic TOS (NTOS) and vascular TOS. NTOS is a compressive peripheral neuropathy—specifically, a type of entrapment neuropathy caused by the compression of the brachial plexus. NTOS accounts for 95% of all TOS [1]. Congenital anomalies found in the cervical ribs and elongated C7 transverse processes may be the cause of NTOS [2]. NTOS can be subcategorized as either disputed NTOS or true NTOS [3]. Disputed NTOS occurs in a large group of patients with unexplained pain in the brachial, scapular, and cervical regions, with a rate that has been widely quoted as 3 to 80 per 1,000 people [3,4]. Disputed NTOS requires a clinical diagnosis without standard diagnostic criteria that depends on symptoms and provocative maneuvers, such as the Roos stress test and Adson's test, because nerve conduction studies and electromyography are commonly negative for disputed NTOS [1,3]. In contrast, true NTOS, a very rare disease with a prevalence of about one in a million, resulting from the compression of C8 and T1 roots (T1 dominant) or proximal lower trunk of the brachial plexus, is diagnosed on the basis of objective weakness and atrophy of T1-innervated intrinsic muscles of the hand and corresponding electrodiagnostic abnormalities [5–7]. We report the case of a 42-year-old patient with progressive weakness and atrophic changes in the intrinsic muscles of the right hand, diagnosed with true NTOS during comprehensive

rehabilitation after intracranial hemorrhage (ICH).

## Case Report

A 42-year-old woman was referred to our hospital with sudden-onset left-side weakness and an acute ICH of approximately 3.8 cm in the right basal ganglia. She was transferred to the Department of Rehabilitation Medicine after a month to start early comprehensive rehabilitation treatment. She demonstrated a full range of motion in all bilateral joints, with Medical Research Council (MRC) grade of 2 in her left upper and lower extremities. Meanwhile, atrophy and weakness of her right hand's intrinsic muscles were remarkable (Fig. 1A, B), despite the lack of any lesion in the left brain on computed tomography (CT) scans. A physical examination revealed MRC grades of 0 in her right abductor pollicis brevis (APB) muscle and 2 in her abductor digiti minimi (ADM) and first dorsal interosseous (FDI) muscles. According to the patient, discomfort that disabled her from any fine movements in her right hand had gradually progressed for 5 years. She visited an orthopedic center at the first onset of symptoms and was informed of the possibility of carpal tunnel syndrome (CTS). An electromyographic (EMG) study revealed that a differential diagnosis for brachial plexopathy was necessary.

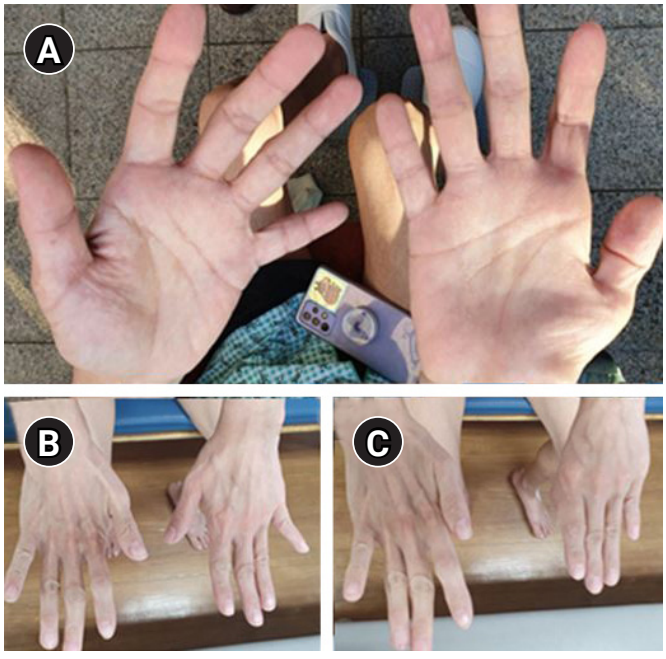


Fig. 1. Atrophic changes in (A) right abductor pollicis brevis, abductor digiti minimi, and (B) right first dorsal interosseous muscles. (C) Positive Wartenberg's sign in the right hand. We received the patient's consent form about publishing all photographic materials.

However, based on her clinical symptoms, she was given an explanation of CTS and recommended to receive conservative treatment. The weakness and atrophy gradually progressed over the past years, making her daily activities, such as using a spoon, increasingly difficult, but were not aggravated within the last 3 months. No changes in the sensation of light touch and temperature were observed on her right side. She also did not complain of any pain in the upper arm or cervical regions. Special physical examinations for median nerve lesions including Phalen's test, Tinel's sign, and the hand of benediction were all negative. During the ulnar nerve examination, Wartenberg's sign was positive in her right hand (Fig. 1C), whereas Froment's sign and Tinel's sign were negative. Additional examinations also revealed negative findings for the Roos stress test and Adson's test. To determine the cause of the weakness and atrophy, electrodiagnostic studies were conducted using the Viking Select EMG NCS Machine (NICOLET EDX; Natus, Pleasanton, CA, USA). No compound motor action potential (CMAP) response in the right median nerve and a low amplitude of sensory nerve action potentials in the right ulnar and median antebrachial cutaneous (MABC) nerves were observed. The right median sensory nerve action potential was normal, and although the right ulnar CMAP amplitude was slightly decreased compared to that of the left side, it was still within the normal range (Table 1). In needle EMG, despite the lack of abnormal spontaneous activity, there was increased insertional activity, large motor unit action potentials (MUAPs), and reduced recruitment in the right C8 and T1-innervated muscles, including the extensor indicis proprius, abductor pollicis longus, flexor carpi ulnaris, FDI, and ADM. No MUAP was observed in the right APB muscle (Table 2). The EMG findings suggested right brachial plexopathy involving the lower trunk level, clinically consistent with NTOS. We consulted a thoracic surgeon and performed plain radiography and chest CT, which revealed elongated bilateral C7 transverse processes, which were thought to be the cause of TOS (Fig. 2). She was diagnosed with true NTOS and the thoracic surgeon did not recommend surgical treatment due to the long period of onset, severe atrophy, and the lack of recent exacerbation of symptoms. A month later, the symptoms of true NTOS did not show any further deterioration.

## Discussion

Congenital anomalies of bony, fibrous, or muscular structures are often reported as etiologies of NTOS and can be associated with traumatic or functional causes. Bony anomalies, including cervical ribs and elongated C7 transverse processes, are reported

**Table 1.** Results of Nerve Conduction Studies

| Nerve | Stimulation site | Recording site | Latency (ms) | Amplitude | Conduction velocity (m/s) |
|---|---|---|---|---|---|
| Motor nerve conduction | | | | | |
| Rt. median | Wrist | APB | NR* | NR* | NR* |
| | Elbow | APB | NR* | NR* | NR* |
| Lt. median | Wrist | APB | 3.1 | 9.8 | 60 |
| | Elbow | APB | 7.1 | 7.5 | |
| Rt. ulnar | Wrist | ADM | 3.0 | 5.9 | 56 |
| | Below elbow | ADM | 7.1 | 5.6 | 77 |
| | Above elbow | ADM | 8.4 | | |
| Lt. ulnar | Wrist | ADM | 2.0 | 8.7 | 68 |
| | Below elbow | ADM | 5.4 | 8.4 | 71 |
| | Above elbow | ADM | 6.8 | 7.8 | |
| Rt. radial | Forearm | EIP | 2.5 | 3.4 | NA |
| Lt. radial | Forearm | EIP | 2.0 | 2.8 | NA |
| Sensory nerve conduction | | | | | |
| Rt. median | Wrist | Third digit | 3.1 | 25 | NA |
| Lt. median | Wrist | Third digit | 2.8 | 26 | NA |
| Rt. ulnar | Wrist | Fifth digit | 2.9 | 8* | NA |
| Lt. ulnar | Wrist | Fifth digit | 3.0 | 38 | NA |
| Rt. radial | Forearm | Snuffbox | 2.7 | 31 | NA |
| Lt. radial | Forearm | Snuffbox | 1.9 | 25 | NA |
| Rt. MABC | Elbow | Forearm | 2.3 | 12 | NA |
| Lt. MABC | Elbow | Forearm | 2.1 | 18 | NA |
| Rt. LABC | Elbow | Forearm | 2.5 | 32 | NA |
| Lt. LABC | Elbow | Forearm | 1.9 | 32 | NA |

Amplitudes are measured in millivolts (mV, motor) and microvolts (μV, sensory).
Rt., right; APB, abductor pollicis brevis; NR, no response; Lt., left; ADM, abductor digiti minimi; EIP, extensor indicis proprius; NA, not applicable; MABC, medial antebrachial cutaneous; LABC, lateral antebrachial cutaneous.
*Abnormal findings are represented with asterisks; an abnormal finding was defined by a greater than 50% reduction of amplitude or 30% delay of latency compared to the unaffected side, or no response of sensory nerve action potential and compound motor action potential.

to account for 30% of NTOS cases [8]. Cervical ribs are known to have a prevalence of 0.5% to 2%, but they are rarely the cause of NTOS. Their prevalence in true NTOS, which requires a thorough documentation of objective findings of nerve compression for diagnosis, is even rarer, with only 1 in 20,000 to 80,000 cervical ribs leading to true NTOS [8]. To our knowledge, the prevalence of elongation of the C7 transverse process has not yet been clearly reported. However, when clinical and electrodiagnostic findings suggest brachial plexopathy at the lower trunk level, the possibility of true NTOS caused by bony abnormalities increases [8]. In our case, the elongation of the bilateral C7 transverse processes was confirmed by radiologic evaluations, in which the right transverse process was slightly longer than the left, corresponding to the symptoms and signs of true NTOS found only on the patient's right side. Because true NTOS, an extremely rare disease, exhibits clinical symptoms similar to those of CTS, ulnar neuropathy, and cervical radiculopathies, it is often misdiagnosed, as in our case. If a patient exhibits problems only in the hand, as reflected in our case, NTOS is often mistaken for CTS [6]. A physical examination of the median and ulnar nerves and special examinations for NTOS, such as the Roos stress test and Adson's test, are helpful for establishing a clinical suspicion of NTOS. In the Roos stress test, the patient sits with full external rotation and 90° abduction of the shoulder joint and 90° flexion of the elbow joint, and repeatedly opens and closes the hand for 3 minutes. The provocation of pain or paresthesia is defined as a positive test finding (sensitivity, 52%-84%; specificity, 30%-100%). In Adson's test, after the patient fully extends the elbow joint on the symptomatic side, the examiner palpates the radial pulse, as the patient turns the neck toward the symptomatic side while holding a deep breath. A change in the radial pulse indicates a positive test (sensitivity, 79%; specificity, 74%-100%) [1,3]. In order to exclude other possibilities from the differential diagnosis and confirm true NTOS, an electrodiagnostic study is

 https://doi.org/10.18214/jend.2022.00094

**Table 2.** Results of Needle Electromyography

| Muscle | Insertional activity | Spontaneous activity | MUAP | | | Recruitment pattern | Volitional effort |
|---|---|---|---|---|---|---|---|
| | | | Polyphasic | Duration | Amplitude (mV) | | |
| C6–7 paraspinal, R | N | - | | | | | |
| C7–T1 paraspinal, R | N | - | | | | | |
| C6–7 paraspinal, L | N | - | | | | | |
| C7–T1 paraspinal, L | N | - | | | | | |
| Sternal head of pectoralis major, R | N | - | - | N | N | Full | Max |
| Deltoid, R | Increased | - | - | Slightly long | N | Slightly reduced | Max |
| Triceps brachii, R | Increased | - | - | Slightly long | N | Slightly reduced | Max |
| Pronator teres, R | Increased | - | - | Slightly long | N | Slightly reduced | Max |
| Brachioradialis, R | Increased | - | - | Slightly long | N | Slightly reduced | Max |
| Flexor carpi ulnaris, R | Increased | - | - | Slightly long | Large (5–6) | Slightly reduced | Max |
| Extensor carpi ulnaris, R | Increased | - | - | N | N | Slightly reduced | Max |
| Extensor digitorum communis, R | Increased | - | - | N | N | Slightly reduced | Max |
| Extensor indicis proprius, R | Increased | - | - | Long | Large (6–7) | Reduced | Max |
| Abductor pollicis longus, R | Increased | - | - | Long | Large (7–8) | Reduced | Max |
| First dorsal interosseous, R | Increased | - | - | Long | N | Markedly reduced | Max |
| Abductor digiti minimi, R | Increased | - | - | Long | N | Markedly reduced | Max |
| Abductor pollicis brevis, R | Increased | - | No MUAP | | | | |

MUAP, motor unit action potential; R, right; N, normal; -, negative; L, left; Max, maximal.

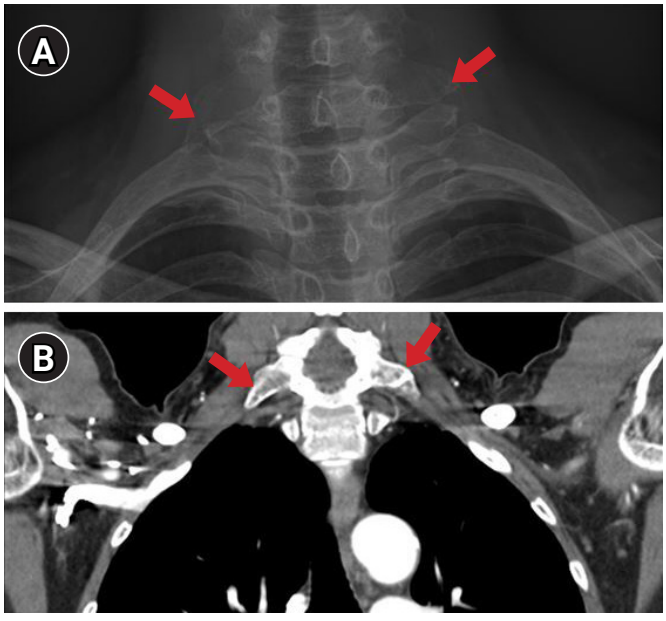


**Fig. 2.** Elongation of bilateral C7 transverse processes confirmed by plain radiography (A) and chest computed tomography (B).

essential [3]. In nerve conduction studies, reduced median CMAP, ulnar and MABC SNAP amplitudes, and normal median SNAP and ulnar CMAP amplitudes indicate chronic axonal loss at the lower trunk level of the brachial plexus [6,9]. On needle electromyography, denervation potentials in C8- and T1-innervated muscles (dominant T1), including the APB, ADM, FDI, and other hand intrinsic muscles, are typical findings of true NTOS [6,9]. Abnormal MABC SNAP (sensitivity, 95%) and abnormalities in the APB (sensitivity, 97%) on needle EMG are highly sensitive for true NTOS [7,10]. In our case, the electrodiagnostic findings were compatible with those of true NTOS. In addition, this case is noteworthy due to the mild decrease in the right ulnar CMAP amplitude, abnormalities in the C8-innervated muscles in needle electromyography, and evidence of chronic denervation, such as high MUAP amplitudes instead of abnormal spontaneous activities, reflecting the patient's long period of onset and severe atrophy. Based on the electrodiagnostic results and clinical findings that revealed no deterioration of symptoms in the past 3 months, it could be inferred that the denervation was not an ongoing process; thus, conservative treatment was recommended.

This is a rare case in which true NTOS was diagnosed 5 years after the onset of symptoms, during comprehensive rehabilitation that the patient received for left hemiplegia due to an unrelated cause. True NTOS is often overlooked or mistaken for CTS, thus delaying the diagnosis and inevitably worsening the outcomes. In addition to detailed history-taking and a physical examination, an electrodiagnostic study is crucial to detect brachial plexopathy and rule out other possibilities in the differential diagnosis, and radiologic evaluations may also be helpful.

## Conflict of Interest

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

## ORCID

Yeon Gyu Jeong, https://orcid.org/0000-0003-0456-245X
Jin Hee Jung, https://orcid.org/0000-0002-6513-497X
Joo Sup Kim, https://orcid.org/0000-0001-7541-1603
Hyo Jeong Lee, https://orcid.org/0000-0001-8300-3407

## References

1. Laulan J, Fouquet B, Rodaix C, Jauffret P, Roquelaure Y, Descatha A: Thoracic outlet syndrome: definition, aetiological factors, diagnosis, management and occupational impact. J Occup Rehabil 2011;21:366–373.
2. Povlsen S, Povlsen B: Diagnosing thoracic outlet syndrome: current approaches and future directions. Diagnostics (Basel) 2018;8:21.
3. Hooper TL, Denton J, McGalliard MK, Brismée JM, Sizer PS: Thoracic outlet syndrome: a controversial clinical condition. Part 1: anatomy, and clinical examination/diagnosis. J Man Manip Ther 2010;18:74–83.
4. Illig KA, Rodriguez-Zoppi E: How common is thoracic outlet syndrome? Thorac Surg Clin 2021;31:11–17.
5. Gilliatt RW: Thoracic outlet syndrome. Br Med J (Clin Res Ed) 1983;287:764.
6. Le Forestier N, Moulonguet A, Maisonobe T, Léger JM, Bouche P: True neurogenic thoracic outlet syndrome: electrophysiological diagnosis in six cases. Muscle Nerve 1998;21:1129–1134.
7. Tsao BE, Ferrante MA, Wilbourn AJ, Shields RW: Electrodiagnostic features of true neurogenic thoracic outlet syndrome. Muscle Nerve 2014;49:724–727.
8. Chang MC, Kim DH: Essentials of thoracic outlet syndrome: a narrative review. World J Clin Cases 2021;9:5804–5811.
9. Lee JH, Choi HS, Yang SN, Cho WM, Lee SH, Chung HH, et al: True neurogenic thoracic outlet syndrome following hyperabduction during sleep: a case report. Ann Rehabil Med 2011;35:565–569.
10. Kim SW, Jeong JS, Kim BJ, Choe YH, Yoon YC, Sung DH: Clinical, electrodiagnostic and imaging features of true neurogenic thoracic outlet syndrome: Experience at a tertiary referral center. J Neurol Sci 2019;404:115–123.

 https://doi.org/10.18214/jend.2022.00094

JEND Journal of Electrodiagnosis and Neuromuscular Diseases

CASE REPORT

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2022;24(3):109-113
https://doi.org/10.18214/jend.2022.00101

# Postoperative Lumbar Plexopathy Secondary to Retroperitoneal Liposarcoma: A Case Report

Kyungmin Kim, Kyeong Eun Uhm

Department of Rehabilitation Medicine, Konkuk University Medical Center, Seoul, Korea

Liposarcoma is a rare malignancy that usually originates in the extremities or the retroperitoneum. The lumbar plexus, a complex neural network formed by divisions of the first four lumbar roots, penetrates the psoas muscle before it exits the pelvis. Owing to their anatomical proximity, neoplasms in the vicinity of the psoas muscle may involve the lumbar plexus. We report a case of postoperative lumbar plexopathy involving the posterior divisions of the lumbar plexus, following the resection of a recurrent retroperitoneal liposarcoma located in the dorsal aspect of the psoas muscle. A 50-year-old man visited a rehabilitation clinic for an evaluation of proximal weakness of the unilateral lower extremity after resection of a recurrent liposarcoma of the left psoas muscle. Physical examination showed weakness of left hip flexion and knee extension accompanied by sensory loss in the left anteromedial thigh and the medial lower leg. An electrophysiological study revealed left lumbar plexopathy with selective involvement of the posterior divisions of the lumbar plexus. The patient could walk independently without a walking aid on level surfaces while he underwent exercise therapy. A comprehensive evaluation, including a physical examination, the use of imaging modalities such as computed tomography for anatomical characterization, and electrophysiological studies, is important for accurate diagnosis.

**Keywords:** Liposarcoma; Lumbosacral plexus; Neoplasms

**Received:** July 5, 2022
**Revised:** October 13, 2022
**Accepted:** October 24, 2022

**Corresponding author:**
Kyeong Eun Uhm
Department of Rehabilitation Medicine, Konkuk University Medical Center, 120-1 Neungdong-ro, Gwangjin-gu, Seoul 05030, Korea
Tel: +82-2-2030-5348
Fax: +82-2-2030-5379
E-mail: 20160130@kuh.ac.kr

## Introduction

The lumbar plexus is formed within the psoas major muscle anterior to the transverse process of the lumbar vertebrae, which lie along the ventral aspect of the pelvis. The terminal branches of the lumbar plexus, including the femoral nerve, emerge from the lateral border of the psoas muscle before passing the groove between the iliacus and psoas muscles [1]. Iatrogenic lumbar plexus injury can be caused by surgical intervention, producing a variety of neurological symptoms. The symptoms range from mild sensory loss at the thigh level to profound weakness of the proximal lower extremity muscles [2].

Liposarcomas are the most common soft tissue sarcomas of mesenchymal origin, which may occur in any part of the body, including the extremities, retroperitoneum, pelvis, and inguinal region [3]. Retroperitoneal sarcoma accounts for 10% to 15% of all soft tissue sarcomas [4]. Retroperitoneal sarcoma originating from the psoas muscle is typically high-grade in nature, meaning that it is characterized by a high rate of distant and local recurrence. Therefore, retroperitoneal sarcoma should be managed with perioperative or postoperative radiation therapy or chemotherapy in many cases [5]. We report a case of postoperative lumbar plexopathy involving the posterior divisions of the lumbar plexus, following resection of a recurrent retroperitoneal liposarcoma located in the dorsal aspect of the psoas muscle.

## Case Report

A 50-year-old man visited a rehabilitation clinic for an evaluation of proximal weakness of the unilateral lower extremity. He underwent surgical resection of a very large (18 cm) retroperitoneal liposarcoma of the left psoas muscle 1 year prior to presentation (Fig. 1). The tumor recurred in the left psoas muscle 10 months postoperatively. The size of the tumor was measured as 4.5 cm on a contrast-enhanced computed tomography (Fig. 2). One month after the imaging study, he underwent repeat tumor resection. His surgical record revealed severe adhesions second-

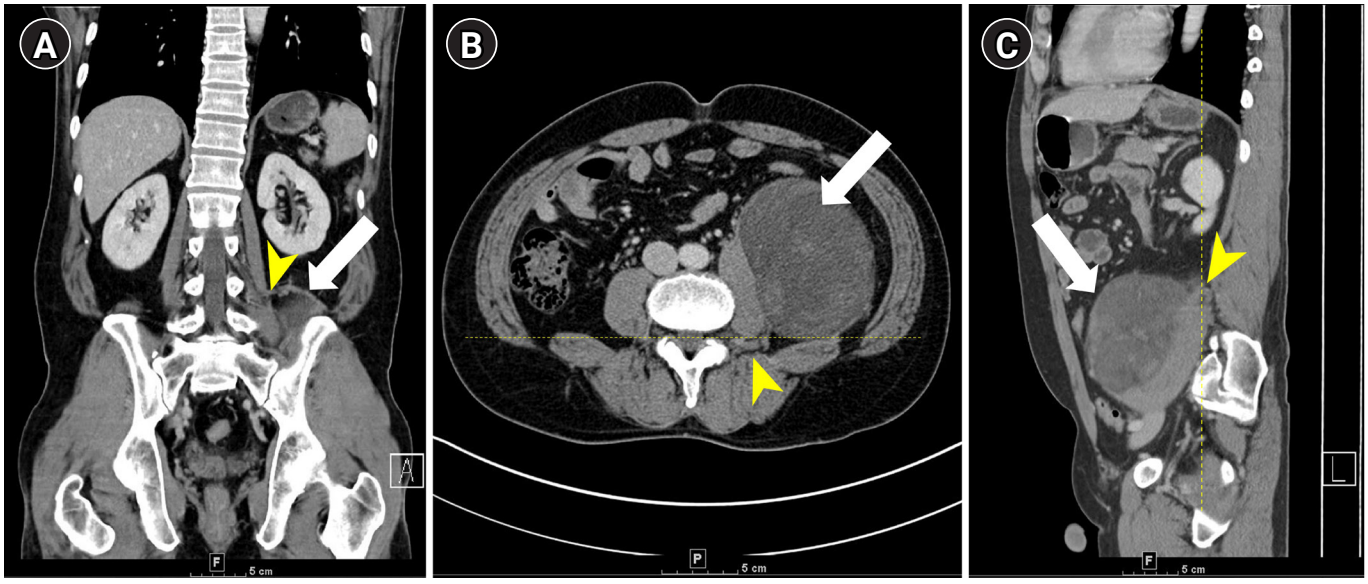


Fig. 1. Contrast-enhanced computed tomography scans of the abdomen and pelvis showing a well-defined, mildly enhancing soft tissue mass suggestive of a liposarcoma (arrows) in the left psoas muscle (maximal 14 cm) and the presumed location of the nerve structures within the psoas muscle (arrowheads). Coronal view (A), axial view at the level of L4 vertebral body (B), and sagittal view (C). The dotted line indicates the coronal plane corresponding to (A).

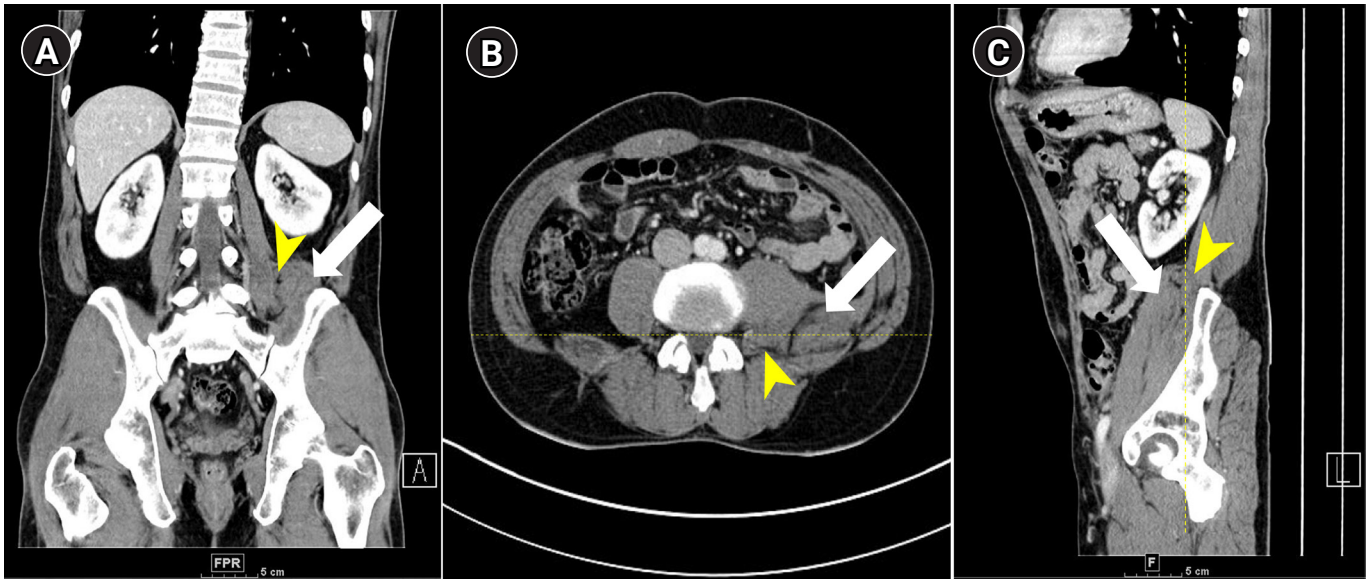


Fig. 2. Contrast-enhanced computed tomography scans of the abdomen and pelvis showing a bulging soft tissue lesion suggestive of a recurrent liposarcoma (arrows) at the posterolateral aspect of the left psoas muscle (maximal 4.5 cm) and the presumed location of the nerve structures within the psoas muscle (arrowheads). Coronal view (A), axial view at the level of L4 vertebral body (B), and sagittal view (C). The dotted line indicates the coronal plane corresponding to (A).


https://doi.org/10.18214/jend.2022.00101

ary to previous surgery, and a well-circumscribed lobulated mass measuring 10 cm was found. The mass was firmly adherent and located inside the dorsal portion of the left psoas muscle at the ventral aspect of the pelvic bone, completely encasing the intramuscular nerves. A histopathological evaluation revealed recurrent myxoid liposarcoma with positive Ki-67 staining in 5% of tumor cells, reflecting rapid growth of the tumor. All resection margins were negative.

The patient experienced proximal left lower extremity weakness and left anterior thigh numbness after the second tumor resection surgery, and he was unable to climb the stairs using alternate feet. A physical examination revealed sensory and motor deficits in the left lower extremity. Left-sided hip flexion and knee extension were classified as grade 3 and 0, respectively, on manual muscle testing using the Medical Research Council scale. Otherwise, normal strength was noted in other muscles of the left lower extremity. We observed hypesthesia in the left anteromedial thigh and medial lower leg with absent left-sided knee jerk. Despite significant weakness of the unilateral proximal lower extremity muscles, the patient could walk independently (without a walking aid) on level surfaces.

An electrophysiological study was performed approximately 50 days after symptom onset; a compound motor action potential was not recordable in the left femoral nerve, and sensory nerve action potentials were undetectable in the left saphenous and lateral femoral cutaneous nerves on nerve conduction studies (Table 1). Other motor and sensory nerve action potentials, F-waves, and the H-reflex were normal. Needle electromyography revealed abnormal spontaneous activity in the left vastus medialis, rectus femoris, and iliopsoas muscles, which showed no motor unit action potentials (MUAPs) (Table 2). The patient was diagnosed with postoperative lumbar plexopathy with selective involvement of the posterior divisions of the lumbar plexus after resection of retroperitoneal liposarcoma in the left psoas muscle.

The patient received postoperative radiation therapy (50 Gy/25 fractions) to the left retroperitoneum after the second surgery. His neurological deficits did not show any change after radiation therapy. The patient showed a slight improvement in left lower extremity weakness at a 2-year follow-up after his initial visit. His left-sided hip flexion was still classified as grade 3, while knee extension improved to grade 2 on a manual muscle test. He additionally developed significant quadriceps atrophy and neuropathic pain in the left anteromedial thigh and medial calf over a period of 2 years. Fortunately, he showed no further deterioration in gait function while he received neuropathic pain medications. A follow-up electrophysiological study performed 2 years after the first study revealed findings similar to those observed on a previous nerve conduction study (Table 1). On needle electromyography, the iliopsoas and rectus femoris muscles showed

**Table 1.** Nerve Conduction Studies

| Nerve and site | Initial | | | Follow-up | | |
|---|---|---|---|---|---|---|
| | Latency (ms) | Amplitude | Conduction velocity (m/s) | Latency (ms) | Amplitude | Conduction velocity (m/s) |
| Motor nerve conduction | | | | | | |
| Rt. peroneal nerve (EDB) | 5.26 | 3.2 | NA | 5.36 | 4.5 | NA |
| Rt. tibial nerve (AH) | 4.11 | 16.4 | NA | 3.85 | 15.8 | NA |
| Rt. femoral nerve (VM) | 5.31 | 11.9 | | 5.26 | 14.1 | |
| Lt. peroneal nerve (EDB) | 4.11 | 3.4 | 46.1 | 3.80 | 5.0 | 46.9 |
| Lt. tibial nerve (AH) | 4.43 | 15.1 | 44.7 | 3.70 | 15.0 | 45.0 |
| Lt. femoral nerve (VM) | No response | | | No response | | |
| Sensory nerve conduction | | | | | | |
| Rt. superficial peroneal nerve | 2.50 | 9.5 | | 2.45 | 14.7 | |
| Rt. sural nerve | 2.71 | 20.5 | | 2.60 | 16.3 | |
| Rt. saphenous nerve | 1.72 | 9.7 | | 1.67 | 7.3 | |
| Rt. LFCN | 1.72 | 8.5 | | 1.77 | 5.6 | |
| Lt. superficial peroneal nerve | 2.76 | 14.1 | | 2.29 | 16.1 | |
| Lt. sural nerve | 3.02 | 18.2 | | 2.76 | 16.2 | |
| Lt. saphenous nerve | No response | | | No response | | |
| Lt. LFCN | No response | | | No response | | |

Amplitudes are measured in millivolt (mV, motor) and microvolt (μV, sensory).
Rt., right; EDB, extensor digitorum brevis; NA, not assessed (proximal stimulation was not performed); AH, abductor hallucis; VM, vastus medialis; Lt., left; LFCN, lateral femoral cutaneous nerve.

Table 2. Needle Electromyography

| Muscle | Initial | | | | Follow-up | | | |
|---|---|---|---|---|---|---|---|---|
| | IA | Fibrillations & PSW | MUAP | Recruitment | IA | Fibrillations & PSW | MUAP | Recruitment |
| Lt. Iliopsoas | - | 3+ | No MUAP | | - | 2+ | Polyphasic | Reduced |
| Lt. adductor longus | - | - | Normal | Normal | - | - | Normal | Normal |
| Lt. rectus femoris | - | 3+ | No MUAP | | - | 3+ | Polyphasic | Reduced |
| Lt. vastus medialis | - | 3+ | No MUAP | | - | 3+ | No MUAP | |
| Lt. tibialis anterior | - | - | Normal | Normal | | | | |
| Lt. tensor fasciae latae | - | - | Normal | Normal | | | | |
| Lt. gluteus medius | - | - | Normal | Normal | | | | |
| Lt. gluteus maximus | - | - | Normal | Normal | | | | |
| Lt. medial gastrocnemius | - | - | Normal | Normal | | | | |
| Lt. mid lumbar paraspinalis | - | - | | | - | - | | |
| Lt. lower lumbar paraspinalis | - | - | | | - | - | | |

IA, insertional activity; PSW, positive sharp wave; MUAP, motor unit action potential; Lt., left.

polyphasic MUAPs, reflecting evidence of reinnervation (Table 2). Currently, he is receiving chemotherapy to manage a second relapse of liposarcoma with peritoneal seeding.

## Discussion

In this report, we present a case of lumbar plexopathy that selectively affected the posterior division of the lumbar plexus in a patient with retroperitoneal liposarcoma. The lumbar plexus is a distinct network of peripheral nerves derived from the L1 through L4 nerve roots. These rami pass downward and laterally along the psoas major muscle, where they eventually form a plexus. During its intramuscular course through the psoas muscle, the lumbar plexus divides into anterior and posterior divisions. The posterior divisions unite to form the femoral nerve. The lateral femoral cutaneous nerve also emerges from the posterior divisions [1]. In this case, liposarcoma recurred at a somewhat different location within the psoas muscle compared with that at initial diagnosis. Initially, the sarcoma developed at the ventral aspect of the psoas muscle, leaving the intramuscular nerve intact, although the size of the tumor was larger. However, the recurrent sarcoma developed deep inside the psoas muscle, involving the dorsal portion of the psoas muscle just ventral to the iliacus, and encased the intramuscular nerves. Despite meticulous fine dissection, it is presumed that the surgical removal of the tumor inevitably caused nerve injury.

Liposarcomas are soft tissue neoplasms that arise from adipose tissue. These are classified into several subtypes, and myxoid liposarcoma is the second most common subtype [6]. Complete surgical resection at the time of initial presentation is the most important prognostic factor for survival in patients with retroperitoneal sarcoma [7]. The risk of recurrence in myxoid liposarcoma was reported to be low, even in large tumors. In contrast to extremity sarcomas, complete resection of a retroperitoneal tumor along with an adequate resection margin is usually challenging owing to the large adjacent neurovascular structures, which frequently cause incomplete tumor resection. Consequently, nearly 70% of patients with retroperitoneal sarcomas develop recurrence [8]. Despite frequent recurrence, palliative debulking surgery may serve as a useful therapeutic approach to improve symptoms and prolong survival in this patient population [7]. Unfortunately, the overall 10-year survival rate was reported to be approximately 60% in patients with metastatic and recurrent myxoid liposarcoma [6]. In the case reported herein, recurrence of the tumor was observed after the surgical removal of the very large initial sarcoma, although all resection margins were negative. A previous study has shown that tumor size and depth are more relevant for the recurrence or metastatic characteristics of a neoplasm than the resection margin status [9].

We observed significant weakness and atrophy of the iliopsoas and quadriceps muscles, and needle electromyography revealed no MUAPs in these muscles. The iliopsoas and quadriceps are the primary hip flexor and knee extensor muscles. The patient was able to produce partial movements of hip flexion and knee extension, and could walk without assistance, although the electrophysiological study findings were compatible with no motor function in the anterior thigh muscles. This can be explained through compensatory action by the completely spared hip adductor and abductor muscles, which are known to play a secondary role in hip flexion and knee extension.

Nerve structures can be directly injured by transection, stretching, suture ligation and diathermy. Several studies have reported


https://doi.org/10.18214/jend.2022.00101

lumbosacral plexopathy after renal transplantation, gynecological surgery, or spinal interbody fusion [10]. Additionally, an abscess or hematoma affecting the psoas muscle can cause lumbosacral plexopathy [1]. However, few reports have described neuropathy associated with the surgical removal of retroperitoneal sarcoma in the psoas muscle. Additionally, retroperitoneal liposarcoma showed frequent recurrence. Therefore, postoperative lumbar plexopathy following repeated surgery might occur inevitably as in this case.

In conclusion, we describe a case of lumbar plexopathy with selective involvement of the posterior divisions of the lumbar plexus after the repetitive surgical resections of a retroperitoneal liposarcoma. A comprehensive evaluation, including physical examination, use of imaging modalities such as computed tomography for anatomical characterization, and electrophysiological studies, is important for an accurate diagnosis, planning treatment, and prevention of complications. Additionally, this case report has significance of the following points. It objectively confirmed the extent and degree of postoperative lumbar plexopathy through an electrophysiological study, which is difficult to diagnose with images alone, reported the progress of recovery, and represents importance of detecting the occurrence of neurological complications.

## Conflict of Interest

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

## ORCID

Kyungmin Kim, https://orcid.org/0000-0001-8198-2955
Kyeong Eun Uhm, https://orcid.org/0000-0003-2714-1092

## References

1. Planner AC, Donaghy M, Moore NR: Causes of lumbosacral plexopathy. Clin Radiol 2006;61:987–995.
2. Moore AE, Stringer MD: Iatrogenic femoral nerve injury: a systematic review. Surg Radiol Anat 2011;33:649–658.
3. Conyers R, Young S, Thomas DM: Liposarcoma: molecular genetics and therapeutics. Sarcoma 2011;2011:483154.
4. Thomas JM: Retroperitoneal sarcoma. Br J Surg 2007;94:1057–1058.
5. Rutkowski PL, Mullen JT: Management of the "Other" retroperitoneal sarcomas. J Surg Oncol 2018;117:79–86.
6. Abaricia S, Hirbe AC: Diagnosis and treatment of myxoid liposarcomas: histology matters. Curr Treat Options Oncol 2018;19:64.
7. Anaya DA, Lev DC, Pollock RE: The role of surgical margin status in retroperitoneal sarcoma. J Surg Oncol 2008;98:607–610.
8. Anaya DA, Lahat G, Wang X, Xiao L, Tuvin D, Pisters PW, et al: Establishing prognosis in retroperitoneal sarcoma: a new histology-based paradigm. Ann Surg Oncol 2009;16:667–675.
9. Stojadinovic A, Leung DH, Hoos A, Jaques DP, Lewis JJ, Brennan MF: Analysis of the prognostic significance of microscopic margins in 2,084 localized primary adult soft tissue sarcomas. Ann Surg 2002;235:424–434.
10. Alsever JD: Lumbosacral plexopathy after gynecologic surgery: case report and review of the literature. Am J Obstet Gynecol 1996;174:1769–1778.

JEND Journal of Electrodiagnosis and Neuromuscular Diseases

CASE REPORT

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2022;24(3):114-119
https://doi.org/10.18214/jend.2022.00108

# Venous Thoracic Outlet Syndrome Combined with Brachial Neuritis Caused by Lymphadenopathy after Vaccination for Coronavirus Disease 2019: A Case Report

Hyun Jeong Lee, Ingi Min, Hyun Sung Lee, Keewon Kim, Sung Eun Hyun

Department of Rehabilitation Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

Thoracic outlet syndrome (TOS) occurs due to compression of the neurovascular bundle exiting the thoracic outlet, through which the brachial plexus and subclavian vessels pass. Here, we report a case of venous TOS combined with brachial neuritis, which was caused by axillary lymphadenopathy after the first dose of the BNT162b2 vaccine against coronavirus disease 2019 (COVID-19). A 17-year-old female patient presented with left upper extremity swelling and pain after inoculation with the BNT162b2 vaccine in the left deltoid muscle. Contrast-enhanced brachial plexus magnetic resonance imaging revealed severe swelling of the left axillary and subclavian lymph nodes, which lie immediately above the subclavian vein. An electrodiagnostic study revealed left brachial plexopathy, mainly involving the lower trunk with mixed demyelinating and axonal injury. The patient received intravenous steroid pulse therapy and oral steroid therapy. A follow-up examination showed complete recovery of muscle strength and function, pain, and swelling in the left upper extremity within 3 months after vaccination against COVID-19.

**Keywords:** Thoracic outlet syndrome; Vaccines; Brachial plexus neuropathies

**Received:** July 19, 2022
**Revised:** September 7, 2022
**Accepted:** September 19, 2022

**Corresponding author:**
Sung Eun Hyun
Department of Rehabilitation Medicine, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-2619
Fax: +82-2-743-7473
E-mail: sechyun@snu.ac.kr

## Introduction

Thoracic outlet syndrome can occur from compression of the neurovascular bundle exiting the thoracic outlet, through which the brachial plexus and subclavian vessels locate. Entrapment of the axillary and subclavian vessels results in vascular TOS, which is subclassified into arterial and venous types [1]. Impingement of the brachial plexus results in neurogenic TOS. The reported incidence of TOS is 3–80/1000 (0.3–8%) and neurogenic TOS accounts for over 90% of all TOS cases [1].

There are a few case reports of acute brachial neuritis following coronavirus disease 2019 (COVID-19) vaccination [2,3]. Several reports have also documented reactive axillary lymphadenopathy as a common adverse effect of mRNA COVID-19 vaccines [4]. If lymphadenopathy is severe enough, subclavian and axillary vascular flow can be compromised, causing venous TOS [5]. No cases of combined venous TOS and brachial neuritis after COVID-19 vaccination have been reported to date. In this case report, we present the clinical manifestations and electromyographic characteristics of a patient diagnosed with both venous TOS and brachial neuritis after receiving an mRNA vaccine against COVID-19. This study was approved by the ethics committee at the Seoul National University Hospital Institutional Review Board (2206-054-1331) and informed written consent was obtained from the patient.

## Case Report

A 17-year-old female presented with left upper extremity swelling and pain after inoculation with the BNT162b2 vaccine

against coronavirus disease 2019 (COVID-19) in the left deltoid muscle. Pain and swelling in the upper arm started approximately 2 hours after the vaccination and spread to the lower arm and hand on the day after vaccination. However, she only observed this symptom and waited for it to subside, knowing that pain and swelling are very common side effects of mRNA vaccines. Although the swelling improved slowly, left arm weakness newly developed 2 weeks later. At that time, only hand swelling below the wrist was noticed, with a reticulated erythematous patch on the dorsum of the hand, implying problems with the peripheral circulation (Fig. 1).

She visited the Department of Pediatrics 2 weeks after the onset of left arm weakness. A neurological examination revealed motor weakness of grade 3 to 4 in the left upper extremity based on the Medical Research Council scale (left shoulder abductor grade 3-, elbow flexor grade 3-, elbow extensor grade 4, wrist dorsiflexor grade 3-, finger abductor grade 3, and finger flexor grade 3-). She reported hypesthesia in the entire left arm and paresthesia in the left palm. Adson's test and Wright's test were positive, while the costoclavicular test was negative. Laboratory investigations, including complete blood count, electrolytes, creatine kinase, and lactate dehydrogenase, were within normal ranges. The results of other autoimmune-related laboratory tests, such as anti-double-stranded DNA, fluorescent antinuclear antibody, lupus anticoagulant antibody, and antiphospholipid antibody, were also unremarkable. Contrast-enhanced left brachial plexus magnetic resonance imaging (MRI) was performed 3 weeks after the onset of left arm weakness. Brachial plexus MRI revealed bilateral—yet left upper extremity predominant—lymphadenopathy, including severe swelling of the left axillary nodes and subclavian lymph nodes, which lie immediately above the subclavian vein (Fig. 2).

A nerve conduction study (NCS) was performed 3 weeks after the onset of weakness to diagnose possible immune-mediated polyneuropathy at the Department of Rehabilitation Medicine. The latency and amplitude of the sensory nerve action potentials (SNAPs) and the compound muscle action potentials (CMAPs) of all examined muscles from bilateral upper extremity were all symmetric (Table 1). No prolongation of the F-wave or the H-reflex was observed.

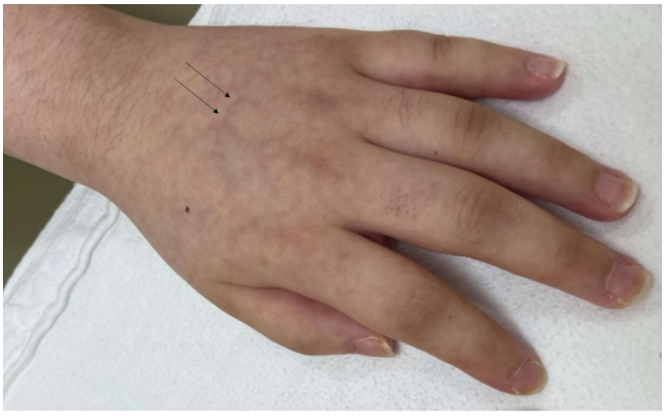

Fig. 1. A reticulated erythematous patch (arrows) and swelling on the dorsum of the left hand 1 month after a vaccine inoculation that was administered in the ipsilateral, left deltoid muscle.

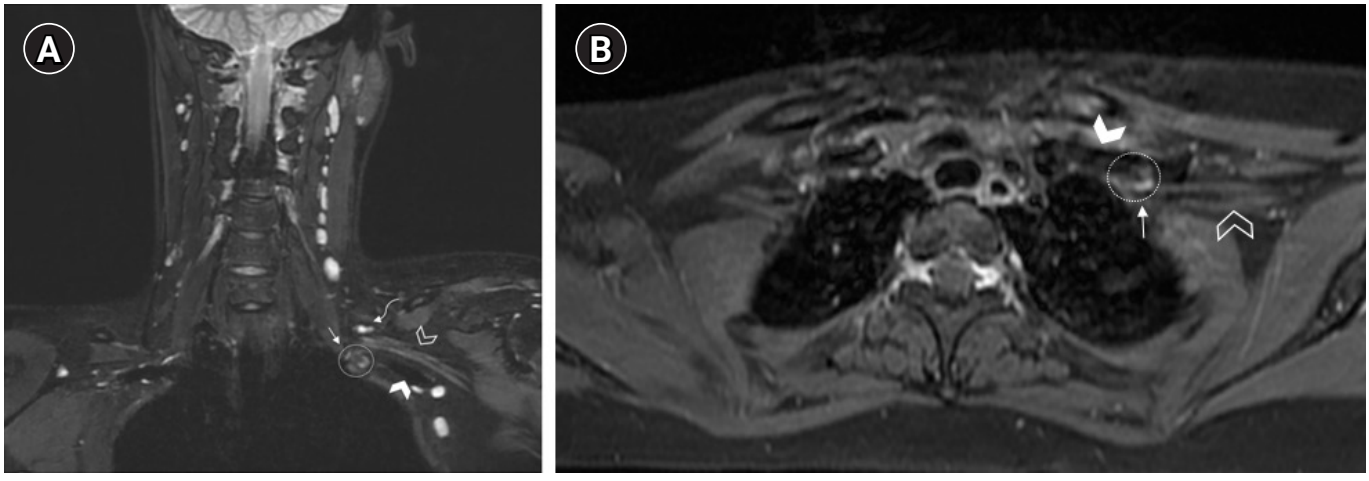


Fig. 2. (A) Coronal view of brachial plexus magnetic resonance imaging (MRI) demonstrating an enlarged subclavian lymph node (straight arrow) compressing the subclavian vein (white arrowhead). An enlarged lymph node (curved arrow) near the left brachial plexus (empty arrowhead) is also apparent, but not compressing the brachial plexus. (B) Transverse view of brachial plexus MRI imaging demonstrating the relationship of the subclavian vein (white arrowhead) with the enlarged subclavian lymph node (straight arrow) and the brachial plexus (empty arrowhead).

Needle electromyography (EMG) revealed prominent denervation potentials and neuropathic motor unit action potentials (MUAPs) in the left extensor indicis, abductor pollicis brevis, and first dorsal interosseous muscles from the lower trunk (Table 2, Fig. 3). The left biceps and deltoid muscles exhibited short duration and polyphasic MUAPs, indicating nascent motor units with relatively less abnormal spontaneous activity than muscles from the lower trunk. These neuropathic MUAPs with denervation potentials indicated axonal injuries in the left brachial plexus. Compared to the symmetric CMAP amplitudes, however, the denervation potentials were extremely prominent, and the interference patterns of MUAPs were reduced, especially in the muscles from the lower trunk, suggesting that proximal demyelination lesions were also present in addition to axonal injuries.

**Table 1.** Nerve Conduction Study Results

| Nerve (recording) | Stimulation | Latency (ms) | | Amplitude | | Duration (ms) | | Area (mV·ms) | | Conduction velocity (m/s) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Right | Left | Right | Left | Right | Left | Right | Left | Right | Left |
| Motor NCS | | | | | | | | | | | |
| Median (APB) | Wrist | 3.07 | 3.54 | 9.9 | 9.6 | 21.3 | 20.16 | 52.2 | 60.6 | | |
| | Elbow | 6.67 | 7.14 | 9.9 | 9.7 | 21.25 | 20.99 | 50.1 | 56.5 | 55.7 | 61.2 |
| | Erb's point | | 11.93 | | 9.3 | - | 21.82 | - | 52.6 | - | 71.0 |
| Ulnar (ADM) | Wrist | 3.03 | 2.55 | 5.6 | 5.9 | 25.99 | 28.91 | 28.30 | 55.3 | | |
| | Below elbow | 5.89 | 5.52 | 5.4 | 5.9 | 26.2 | 28.91 | 26.90 | 47.4 | 67.8 | 64.0 |
| | Above elbow | 7.5 | 7.14 | 5.3 | 5.8 | 26.3 | 29.90 | 27.40 | 53.3 | 61.9 | 61.9 |
| Axillary (deltoid) | Erb's point | 3.07 | 3.02 | 16.9 | 14.8 | 26.2 | 31.65 | 182.80 | 189.80 | | |
| Suprascapular (SST) | Erb's point | 1.82 | 2.50 | 10.8 | 9.4 | 26.25 | 24.79 | 130.90 | 117.50 | | |
| Musculocutaneous (biceps) | Erb's point | 3.96 | 3.39 | 14.3 | 10.5 | 34.43 | 38.28 | 143.80 | 112.90 | | |
| Radial (EIP) | Forearm | 2.45 | 2.76 | 5.1 | 3.8 | - | - | - | - | | |
| | Elbow | 5.47 | 5.99 | 4.0 | 3.1 | - | - | - | - | 59.6 | 55.7 |
| F-wave | | | | | | | | | | | |
| Median (APB) | Wrist | 22.50 | 22.66 | | | | | | | | |
| Ulnar (ADM) | Wrist | 24.32 | 23.44 | | | | | | | | |
| Sensory NCS | | | | | | | | | | | |
| Median (digit II) | Wrist | 2.29 | 2.29 | 42.4 | 43.1 | | | | | | |
| Ulnar (digit V) | Wrist | 2.29 | 2.66 | 25.5 | 26.9 | | | | | | |
| Radial (snuff box) | Forearm | 1.88 | 1.72 | 37.5 | 33.5 | | | | | | |
| LAC (forearm) | Forearm | 1.20 | 1.41 | 26.7 | 29.2 | | | | | | |
| MAC (forearm) | Forearm | 1.56 | 1.35 | 14.9 | 13.5 | | | | | | |

Amplitudes are measured in millivolt (mV, motor) and microvolt (μV, sensory).
NCS, nerve conduction study; APB, abductor pollicis brevis; ADM, abductor digiti minimi; SST, supraspinatus; EIP, extensor indicis proprius; LAC, lateral antebrachial cutaneous; MAC, medial antebrachial cutaneous.

**Table 2.** Needle Electromyography Results

| Muscle | IA | Spontaneous | | MUAP | | | Recruitment pattern/IP |
|---|---|---|---|---|---|---|---|
| | | Fib/PSW | Other | Amplitude | Duration | Polyphasicity | |
| Lt. extensor indicis | Increased | 3+/3+ | None | N | N | N | Discrete |
| Lt. abductor pollicis brevis | N | 4+/4+ | None | | | | No activity |
| Lt. first dorsal interosseous | N | 4+/4+ | None | N | N | Increased | Discrete |
| Lt. biceps brachii | N | 2+/2+ | None | N | Short | Increased | Reduced |
| Lt. deltoid | N | 1+/1+ | None | N | Short | N | Reduced/complete |
| Lt. abductor hallucis | Increased | 0/0 | CRD (1+) | N | N | N | Complete |
| Lt. vastus medialis | N | 0/0 | None | N | N | N | Discrete |
| Rt. extensor indicis | Increased | 0/0 | None | N | N | N | Reduced/complete |

IA, insertional activity; Fib, fibrillation; PSW, positive sharp wave; MUAP, motor unit action potential; IP, interference pattern; Lt., left; Rt., right; N, normal; CRD, complex repetitive discharge.


https://doi.org/10.18214/jend.2022.00108

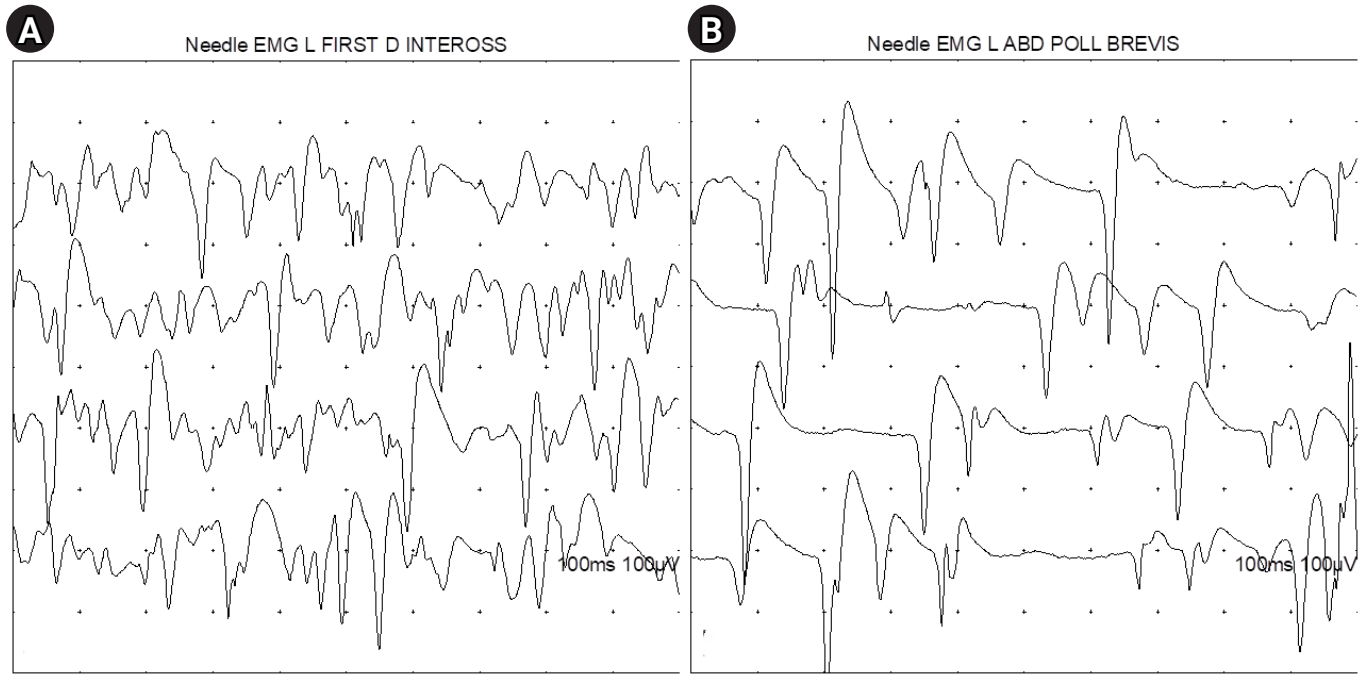


Fig. 3. (A) Abnormal spontaneous activities in the left first dorsal interosseous muscle. (B) Abnormal spontaneous activities in the left abductor pollicis brevis muscle. EMG, electromyography.

Therefore, the electrodiagnostic study concluded that the patient had left brachial plexopathy, mainly involving the lower trunk, with mixed demyelination and axonal involvement.

After intravenous steroid pulse therapy for 3 days and maintenance for 4 months, a follow-up examination showed complete recovery of muscle strength in the left upper extremity, pain, and swelling within 3 months after the vaccination.

## Discussion

The clinical course of brachial neuritis consists of sudden, severe neuropathic pain, fast multifocal weakness, and atrophy of the upper extremities [6], preceded by infection, trauma, or inflammation, including COVID-19 vaccination [2,6]. This patient first presented with left arm swelling and pain after the first dose of the BNT162b2 vaccine, followed by left arm weakness, which is a typical characteristic of brachial neuritis after vaccination. Interestingly, neurogenic motor and sensory symptoms, as well as lymphadenopathy, have been reported to occur more frequently on the same side of the vaccine injection [2,4]. Although there is no proven effective treatment of brachial neuritis, a retrospective study showed that corticosteroid administration in the acute phase shortened pain and accelerated recovery [7]. This patient was also treated with a corticosteroid to reduce pain and promote recovery.

An electrodiagnostic study is one of the examinations for confirming brachial neuritis. Although sensory nerve conduction studies are useful for diagnosing peripheral neuropathies or brachial plexopathies, the sensory NCS is reported to be normal in 80% of patients with brachial neuritis [8]. Although the motor NCS can reveal axonal loss, needle EMG is more sensitive for detecting signs of denervation or reinnervation when clinically affected muscles are examined [9]. In this case, the patient showed nearly symmetric SNAP and CMAP amplitudes, and needle EMG showed an axonal neuropathic injury, which is comparable to brachial neuritis. Denervation potentials, observed at the muscles innervated from lower trunk, could be seen not only in axonal injuries but also in pure peripheral demyelinating neuropathy [10]. This electrodiagnostic study suggested axonal injuries were present, but not very severe depending on NCS result, and both EMG and the patient's inconsistent weakness compared to CMAP supported a presence of combined demyelinating lesions.

The diagnosis of venous TOS requires a comprehensive consideration of the patient's history, a physical examination, and imaging techniques [1]. Venous TOS is characterized by the pathognomonic presentation of acute upper extremity swelling, cyanosis, heaviness, and ultimately pain [1]. This patient also presented with not only acute left upper extremity pain, but also extreme swelling of the entire arm and signs of vascular compro-

mise. She exhibited positive signs on Adson's and Wright's tests, which are provoked by an exaggerated blockage of vascular flow. Brachial plexus MRI confirmed prominent but asymmetric axillary lymphadenopathy, and the swollen left subclavicular lymph node was located at the thoracic outlet (Fig. 2). Several previous studies have reported a correlation between axillary lymphadenopathy and COVID-19 vaccination [4]. Patients receiving the BNT162b2 vaccine demonstrated higher rates of palpable unilateral axillary lymphadenopathy than those receiving placebo [11]. Enlarged subclavian lymph nodes, as in this case, could impede flow through the subclavian vein within the costoclavicular space, resulting in venous TOS.

Although brachial neuritis is usually self-limiting, the previously reported recovery rate is 36% by 1 year, 75% by 2 years, and 89% by 3 years [12], and no prognostic factors are known yet [2]. This case showed relatively early and complete recovery within 3 months after vaccination. As the degree of axonal loss is correlated with CMAP or SNAP and determines the permanent impairment of neuropathy, normal NCS from this case can explain the early recovery [6]. In addition, most cases of reactive ipsilateral axillary lymphadenopathy after COVID-19 vaccination recovered within 10 weeks after vaccination [13]. With the rapid resolution of lymphadenopathy and disrupted venous flow, the clinical symptoms caused by venous TOS could improve within months, which might have also contributed to the patient's early recovery. Since the clinical course could be different among patients, previously reported cases of brachial neuritis after vaccination should also include information about both the amount of axonal loss and any vascular compromise to reveal the possibility of concomitant venous TOS caused by lymphadenopathy. Any supportive evidence of combined venous TOS—more specifically, vascular symptoms, such as swelling, cyanosis, erythematous skin change, and vascular compression provocation tests—should be evaluated to clarify whether brachial neurities with concomitant venous TOS has a different prognosis from brachial neuritis alone.

In conclusion, brachial neuritis combined with an interruption of subclavian vessels and venous TOS followed by lymphadenopathy can occur after COVID-19 vaccination. Therefore, clinicians should evaluate vascular symptoms and neurological examinations to consider the possibility of combined venous TOS before confirming post-vaccine brachial neuritis if sudden weakness with dominant swelling and erythema occurs after a vaccination. Although follow-up electrodiagnostic studies and MRI were not conducted in this study, which would have provided more accurate evidence of the patient's full recovery, this case report suggests the possibility of different pathomechanisms corresponding to diverse prognoses and recovery potentials of brachial neuritis after vaccination.

## Conflict of Interest

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

## ORCID

Hyun Jeong Lee, https://orcid.org/0000-0001-5572-0521
Ingi Min, https://orcid.org/0000-0003-1054-1006
Hyun Sung Lee, https://orcid.org/0000-0003-1467-6063
Keewon Kim, https://orcid.org/0000-0001-6597-578X
Sung Eun Hyun, https://orcid.org/0000-0003-3114-5504

## References

1. Masocatto NO, Da-Matta T, Prozzo TG, Couto WJ, Porfirio G: Thoracic outlet syndrome: a narrative review. Rev Col Bras Cir 2019;46:e20192243.
2. Min YG, Kim JE, Hwang JY, Shin JY, Sung JJ, Hong YH: Parsonage-turner syndrome following COVID-19 vaccination. J Neurol Neurosurg Psychiatry 2022;93:1231–1232.
3. Shields LBE, Iyer VG, Zhang YP, Burger JT, Shields CB: Parsonage-turner syndrome following COVID-19 vaccination: clinical and electromyographic findings in 6 patients. Case Rep Neurol 2022;14:58–67.
4. Lehman CD, D'Alessandro HA, Mendoza DP, Succi MD, Kambadakone A, Lamb LR: Unilateral lymphadenopathy after COVID-19 vaccination: a practical management plan for radiologists across specialties. J Am Coll Radiol 2021;18:843–852.
5. Van Echo DA, Sickles EA, Wiernik PH: Thoracic outlet syndrome, supraclavicular adenopathy, Hodgkin's disease. Ann Intern Med 1973;78:608–609.
6. Al Khalili Y, Jain S, Lam JC, DeCastro A: Brachial neuritis [Internet]. Treasure Island: StatPearls Publishing; 2022 [cited 2022 Aug 28]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499842/.
7. van Eijk JJ, van Alfen N, Berrevoets M, van der Wilt GJ, Pillen S, van Engelen BG: Evaluation of prednisolone treatment in the acute phase of neuralgic amyotrophy: an observational study. J Neurol Neurosurg Psychiatry 2009;80:1120–1124.
8. van Alfen N, Huisman WJ, Overeem S, van Engelen BG, Zwarts MJ: Sensory nerve conduction studies in neuralgic amyotrophy. Am J Phys Med Rehabil 2009;88:941–946.
9. Van Eijk JJ, Groothuis JT, Van Alfen N: Neuralgic amyotrophy: an

update on diagnosis, pathophysiology, and treatment. Muscle Nerve 2016;53:337–350.
10. Kraft GH: Are fibrillation potentials and positive sharp waves the same? No. Muscle Nerve 1996;19:216–220.
11. Skowronski DM, De Serres G: Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2021;384:1576–1577.
12. Tsairis P, Dyck PJ, Mulder DW: Natural history of brachial plexus neuropathy: report on 99 patients. Arch Neurol 1972;27:109–117.
13. El-Sayed MS, Wechie GN, Low CS, Adesanya O, Rao N, Leung VJ: The incidence and duration of COVID-19 vaccine-related reactive lymphadenopathy on 18F-FDG PET-CT. Clin Med (Lond) 2021;21:e633–e638.

# Instructions for Authors

JEND
Journal of Electrodiagnosis and Neuromuscular Diseases

2013. 9. 23 enacted
2015. 5. 29 revised
2015. 12. 14 revised
2019. 2. 23 revised
2020. 6. 24 revised

*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.

The manuscript guidelines for JEND are based on the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals" (http://www.icmje.org/recommendations/), and instructions which are not mentioned in the present guidelines are referred to the guidelines stated in the Recommendations.

Editorial Board will make the final decision on approval for the publication of submitted manuscripts and the publication order of accepted manuscripts. Editorial Board reviews ethics, rationality, originality, and scientific significance in accepting submitted manuscripts, and can request any further corrections, revisions, and deletions of the article if necessary.

## 1. General Guidelines

### 1-1. Qualifications for authorship

Authors should be limited to members of Korean Association of EMG Electrodiagnostic Medicine, associate members of Korean Association of EMG Electrodiagnostic Medicine or those who are associated with clinical practice, experimental and applied research, and education in the field of EMG, electrodiagnostic medicine, and neuromuscular diseases.

Authorship is credited to those who have direct involvement in the study and have made significant contributions to (a) conceptualization and design of the research, or acquisition, analysis, and interpretation of the data, (b) drafting of the manuscript or critical revision, and (c) approval of the submitted and final versions of the manuscript. The primary investigator is designated the first author of the study unless contested by the other authors. The corresponding author is directly responsible for communication and revision of the submitted manuscript.

In the case that more than one author contributed equally as the first author or the corresponding author, the acceptance of co-first or co-corresponding author should be determined through discussion of the Editorial Board. Everyone who is listed as coauthors should have made a substantial, direct, intellectual contribution to the work.

In the case of a change of authorship, a written explanation must be submitted. Change in either the first author or the corresponding author requires approval by the Editorial Board, and any changes of other authors require approval by the Editor-in-Chief.

### 1-2. Types of manuscript

Manuscripts include Original Articles, Case Reports, Brief communications, and Reviews, commissioned by the Editorial Committee on EMG, electrodiagnostic medicine, and neuromuscular diseases.

### 1-3. Duplicate or secondary publication

All submitted manuscripts should be original and should not be considered by other scientific journals for publication at the same time. No part of the accepted manuscript, including the table and the figure, should be duplicated in any other scientific journal without the permission of the Editorial Board. If duplicate publication related to the papers of this journal is detected, the manuscripts may be rejected.

But, if the authors have received approval from the editors of both journals (the editor concerned with secondary publication must have access to the primary version), secondary publication may be allowed only under the conditions for secondary publication stipulated in the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals." The secondary version informs that the paper has been published in whole or in part elsewhere, and the secondary version cites the primary reference.

If the unauthorized duplicate publication is discovered, authors will be announced in the journal, and their institutes will be informed and are subject to penalties and/or unfavorable outcomes including prompt rejection or prohibited submission.

### 1-4. Ethical considerations

For all studies involving human subjects, the principles embodied in the Declaration of Helsinki 2013; https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) should be upheld, informed consent must be obtained from all participants, and must be approved by a recognized Institutional Review Board (IRB) or research ethics committee.

Any information that could have revealed subjects' identities, such as name and initials, should not appear in the text. If a photo is presented, proper measures should be taken not to reveal the subject's identity, or written consent must be presented for the photo and possible disclosure of the subject's identity.

Experiments involving animals should comply with the NIH guidelines for the use of laboratory animals and/or be reviewed by an appropriate committee (Institutional Animal Care and Use Committee, IACUC) to ensure the ethical treatment of animals in research.

All manuscripts should be written with strict adherence to the ethical guidelines recommended by the International Committee of Medical Journal Editors (http://www.icmje.org). If necessary, the Editorial Board could ask for providing patients' written consent and IRB's approval.

Issues of ethical misconduct, plagiarism, and duplicate/redundant publication will be judged and dealt with according to the "Good Publication Practice Guidelines for Medical Journals" (https://www.kamje.or.kr/board/view?b_name=bo_publication&bo_id=13&per_page=).

For the policies on the research and publication ethics not stated in this instructions, International standards for editors and authors (http://publicationethics.org/resources/international-standards-for-editors-and-authors) can be applied.

### 1-5. Copyright transfer

The Korean Association of EMG Electrodiagnostic Medicine is the owner of all copyright to papers published in JEND and has the right to publish, reproduce, distribute, and print the contents in other types of media.

### 1-6. Journal Publication and Manuscript Submission

This journal is published three times a year on April 30, August 31, and December 31, and submission is often allowed. Submitted manuscripts are initially examined for the format, and then appointed a submission date and a submission number. The day of the decision of the publication shall be the day when the manuscript is completed of its reviewing.

### 1-7. Submission of manuscripts

All submitted manuscripts must be accompanied by the official Copyright Transfer and Author Consent Form of JEND and must contain the title page, the title of the manuscript, manuscript, tables, and figures. The files of the title page, main text (the title of the manuscript, manuscript, and figure legends), tables, and figures must be submitted with the online submission system (https://submit.e-jend.org). The official Copyright Transfer and Author Consent Form must be submitted with the online submission system to the Editorial office. This form also should contain the title of the manuscript, date of submission, names of all authors, and written signatures. Note the corresponding author and provide his/her affiliation, email, telephone and fax numbers, and mailing address. Figures should be submitted as an original image (5x7 inches) or jpg file (at least 600 dpi, dots per inch).

Editorial office information (contact us):
Journal of Electrodiagnosis and Neuromuscular Diseases
Department of Physical Medicine and Rehabilitation, Korea University Ansan Hospital, 123 Jeokgeum-ro, Danwon-gu, Ansan 15355, Korea
Tel: 82-31-412-5330
Fax: 82-31-412-4215
E-mail : editjend@gmail.com

### 1-8. Review and revision of manuscripts

Submitted manuscripts will be reviewed by three peer reviewers selected from the Board's database of expert reviewers. Following review, the Editorial Board will decide whether the manuscript will be 1) accepted for publication 2) publication with minor revision, or accepted for publication following revision, 3) subject to major revision, or 4) denied publication.

For manuscripts which are either accepted for publication following revision or subject to major revision, the corresponding author must reply to reviewers' comments point by point and revise the manuscript with changes in red color and explain in detail what changes were made in the manuscript in "summary of revision" as soon as possible.

A manuscript that does not comply with the regulations for submission can be suggested to be adjusted or be reserved to be published or can be adjusted by the Editorial Board, if necessary, without affecting the original contents.

The reviewer and Editorial Board can request correcting English of the manuscript to a considerable level, and the author should accept it.

The manuscripts which are completed reviewing process shall be decided of its publication after reviewing of the Editorial

Board, and a manuscript that does not comply with the regulations for submission can be rejected or delayed the acceptance.

When a manuscript is not resubmitted within two months of notification, it will be considered that the authors have withdrawn the manuscript from submission.

Manuscripts accepted for publication are generally published in order of submission, depending on the category of the manuscript and the date of acceptance for publication.

### 1-9. Charges for reviewing, publication and printing

There are no charges for reviewing, publication and printing, but illustrations that require extraordinary printing processes will be charged to the authors. The corresponding author is also charged a fee for the plate, English proof leading, offprints, and specialty printing.

## 2. Preparation of the Manuscript

### 2-1. Forms of the manuscript

Use Microsoft Office Word (versions after 2003) and ensure correct spelling and grammar. Set up the MS Word document for 1-inch margins on a letter or A4-sized paper. The manuscript must be written in 12-point font, and the sentences must be double-spaced including tables and figure legends. The length of the manuscript should not exceed 20 pages in original articles, 7 pages in the case report, and 30 pages in review article except for the tables and figures.

### 2-2. Use of language and unit

Draw up a manuscript in proper and clear English as per the orthography. When there is no appropriate translation of foreign medical terms, proper nouns, drug names, units, etc., use their originals in the manuscript. If foreign-language words are needed, capital and small letters should be clarified: in principle, proper nouns, place names, and names of persons should be written with a capital letter as the first letter and then small letters for the rest. If an original term has its translation whose meaning is unclear, place the original in a small parenthesis after its translation when it appears for the first time and then uses its translation alone.

Numbers should be written in Arabic numerals, and measurements should be reported using the metric system, and hematologic and biochemical markers should be reported in the International System (SI) of Units. (http://physics.nist.gov/cuu/Units/index.html)

### 2-3. Use of abbreviations

The use of abbreviations should be minimized and restricted to those that are generally recognized. When using an abbreviated word, it should be spelled out in full on the first usage in the manuscript, followed by the abbreviation in parentheses.

### 2-4. Word-spacing

In manuscripts, leave one space for each side, using arithmetic marks as ±, =, +, - (minus), ×, etc. (ex. 25.3 ± 1.2). Leave no space for "-" (hyphen) between words (ex. post-stroke). Leave one space after ",", ";", ":" and ":". Using parentheses, leave 1 space each side in English. And brackets in parentheses, apply square brackets. Ex) ([ ])

### 2-5. Order of manuscripts for original articles

The manuscript for original articles should be organized in the following order: 1) title page as a separate file, 2) Title of the manuscript 3) abstract and keywords, 4) introduction, 5) materials (or subjects) and methods, 6) results, 7) discussion, 8) conflict of interest, 9) acknowledgements (if necessary), 10) references, 11) figure legends 12) tables as separate files, and 13) figures as separate files.

Figures should be submitted with an online submission system as separate files, named as the number of figures of the text and figure legends in JPEG, TIFF, GIF format (ex: Fig1.jpg)..

#### *Title page*

The title page should be uploaded online as a separate file and should describe the title of the article, full names of authors, institutional affiliation(s) with each author. English names should not be described in initials. All authors' ORCIDs should be described.

If authors belong to different organizations, the chief research organization should be specified in the first place, and the other one's shoulder is specified in the order of Arabic numerals (e.g., 1,2,3).

In the title page, the corresponding author must be identified, and his or her contact information (postal address, e-mail, telephone, and fax numbers) should be listed, and if necessary, financial support might be described as a footnote. Running title with 50 spaces maximum should be described.

#### *Title of the manuscript*

The title of the manuscript page should contain the only title. Do not include author information on the title page for a blind peer review. The author names should not appear on this page.

The title should be short, specific, and informative to present clearly the objective of the study and should not use the expressions, such as "study about---" or "clinical study about---." The title should contain less than 20 words. The first letter of words ex-

cept article, preposition, and conjunction should be capitalized. Drug names in the title should be written with generic names, not product names.

### *Title of the manuscript*

Abstract should summarize the content and should not exceed 250 words in the original article and 200 words in the case report. In the original article, a structured abstract with the headings of Objective, Methods, Results, and Conclusion must succinctly describe the paper. Use complete sentences and do not number the results. At the end of the Abstract, list up to 5 relevant Keywords which are in accordance with the Medical Subject Headings (MeSH) in the Index Medicus (http://www.nlm.nih.gov/mesh). Keywords should be written with a capital letter as the first letter and then small letters for the rest and separate each word by a semicolon (;). The abstract of the case report should be non-structured, with no more than 5 Keywords attached. Brief communications should not describe abstract and keywords.

### *Introduction*

Introduction should clearly present the objective of the study, and a brief background to inform the readers of the relevance of the study may be necessary.

### *Materials & Methods*

Describe the participants or research materials of the study, divided by subsection titles, and describe the experimental methods in a logical and systematic manner so that they can be reproducible by another investigator. Explain in detail the inclusion and exclusion criteria for both the experimental and control groups. Experimental drugs should be stated in the generic name. When proprietary brands are used, include the brand name and the name of the manufacturer in parentheses after the first mention of the generic name. When using experimental devices or other products, state the brand name then follow with the name of the manufacturer, city (state), and country in parentheses, e.g., Flow Cytometer (Coulter Electronics Inc., New York, NY, USA). To ensure anonymity during the peer review process, the authors' affiliations or the institutional setting of the study should not be revealed. Subsection titles should be listed in order to 1), (1), A), (A).

Precisely describe the statistical analysis methods, computer programs, and criteria for determining significance.

*(Description of participants)*

Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex or gender. If the study was done involving an exclusive population, for example, in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.

### *Results*

Results should be summarized and described logically the significant findings and trends observed in the results, giving the main or most important objective. Results can be sectioned by subsection titles listed in order to 1), (1), A), (A). Avoid extensive repetition of contents of the tables and figures in the text. In statistical expression, mean and standard deviation should be described as mean ± SD, and mean and standard error as mean ± SE. The letter 'p' in p-value is written in the lower case.

### *Discussion*

Refrain from an excessive review of historical studies, textbook facts, or irrelevant references. Interpret the results with respect to the objective of the study, and describe differences with previous studies and significant findings, which lead to the deduction of the conclusion. Accentuate newly obtained observations from the study and include significant limitations of the study. Do not repeat the results in detail or other information that is given in the Introduction or the Results section.

### *Conclusion*

Conclusions should avoid unqualified statements that are not adequately supported by the data and describe briefly novel findings of the study, according to the purpose of the study.

### *Acknowledgment*

If necessary, persons who have made contributions to the study, but who are not eligible for authorship may be named in this section. Their contribution must be specified, such as data collection, financial support, statistical analysis, or experimentation.

### *References*

References must be written only to the cited body. It is recommended that only important references are recorded, and the number of references is within 40. References should be numbered in order of appearance in the text using Arabic numerals in square brackets such as [1], [2-4], and [5,7,9]. A bracket is placed after the author's name, or before the period in a sentence. In case the author should be mentioned, write only "last name" and list the first two author and add "et al." if the authors are more than three (e.g., one author: Kim, two: Park and Jeong, more than

three: David et al.). The English name is written the last name in conjunction with capital letters of first and middle names. If the reference is Korean, then list the English version in the reference section. List all authors when they are six or fewer; when there are seven or more, list only the first six and add 'et al.". If an article has been accepted but not yet published, the assigned month to be published could be written. Journal titles should be abbreviated in style used in the Index Medicus. If the reference is not listed in Medicus, use the full name of the journal. All other references should be listed, as shown in the "Uniform Requirement for manuscripts submitted to Biomedical Journals" (2008).

Sample References

1) Journals:

Authors: full title of the article. journal name year;volume:the first and last page number.

(e.g., Curr A, Dietz: Traumatic cervical spinal cord injury: relation between somatosensory evoked potentials, neurologic deficit and hand function. Arch Phys Med Rehabil 1996;77:48–53.)

2) Book:

Authors: Book title. edition. place: publisher; year, the first and last page number.

(e.g., Cailliet R: Shoulder pain. 3th ed. Philadelphia: FA Davis; 1991, pp32–35.)

3) Book chapter

Authors: title of the chapter. In: editor. The book title. edition. place: publisher; year, the first and last page number.

(e.g., Kottke FJ: The neurophysiology of motor function. In: Kottke FJ, Lehmann JF, editors. Krusen's handbook of physical medicine and rehabilitation. 4th ed. Philadelphia: Saunders; 1990, pp234–269.)

4) Online resource

National Library of Medicine: Fact sheet: AIDS information resources [Internet]. Bethesda: National Library of Medicine; 2003 [cited 2007 Mar 26]. Available from: http://www.nlm.nih.gov/pubs/factsheets/aidsinfs.html.

### *Tables*

Tables should be uploaded online as separate files and numbered in order of appearance in the main text (Table 1, Table 2, etc.). Table should be easy to understand and unique. The total number of tables should not exceed more than five. Title of table should be briefly written as a phrase or sentence. The first letter except article, preposition, and conjunction, should be capitalized. The title of table is written above the table, and footnote should be described below the table. All abbreviations should be spelled out in footnote in order of abbreviation, colon, and unabbreviated name (e.g., NCS: nerve conduction study). The symbols (*, †, ‡, §, ||, ¶, **, ††, ‡‡) should be superscripts and be used in the indicated sequence (e.g., * $p < 0.05$).

### *Figure legends*

Figure legends must appear on a separate page at the end of the manuscript written in the Microsoft Word file. Write sentences to be understood fully without relying on the main text. Only the first sentence written in capital letters. The second sentence should be set on the starting line of the first sentence. Explain any abbreviation and symbol in the legend. Figures containing histologic slides should be accompanied by legends explaining tissue origin, stain method, and microscopic amplification.

### *Figures*

Figures should be uploaded online as separate files and numbered in order of appearance in the main text (e.g., Fig. 1). If more than two figures are used in the same number, insert the alphabet after Arabic number (e.g., Fig. 1A, Fig. 1B) and record as a single file. Arrows should be inserted to be easily understood. All images should be saved in JPEG, TIFF, GIF or PPT format within 3 MB. The minimum resolutions required are 300 dpi. At online submission, set a file name as the same title as written in main text and legends (e.g., Fig1.jpg).

When already published figures or graphs are inserted, the written consent of the author should be attached and acknowledged in the manuscript.

## 2-6. Articles other than the original manuscript

The general guidelines abide by the original article section.

### *Invited review*

An invited review is a contemplation focused on a certain topic appointed by the Editorial Board. The abstract is limited to less than 250 words, the number of main text less than 30 pages, and the references no more than 60.

### *Case Report*

Case report deal with any unique features, novel diagnosis or treatment, or others accepted in Editorial Board. The abstract should be non-structured and limited to 200 words, with no more than 5 keywords attached. Introduction should be briefly written about background and significance of the case. Main texts are

composed of the course of clinical features, diagnosis, and treatment. Discussion should focus on the significance of the case, and tedious review should be avoided. The number of table and figure is limited to five in total, and the number of references should not exceed more than ten. The maximum word count is limited to 1,500 words, excluding references, tables, and figure legends.

***Brief communication***

Brief communication deal with already reported findings or cases, but with any unusual features, or features that are considered to be important. Abstract and keywords are not required. The text is limited to 700 words. Up to seven references should be listed. Only one table or figure is allowed, and acknowledgment should not be written.

## 3. Copyright Transfer and Author Consent Form

Copyright Transfer and Author Consent must be used the official form made by the Korean Association of EMG Electrodiagnostic Medicine (available and posted at the journal on 'www.kanem.or.kr' or 'www.e-jend.org'). In addition, the title of the manuscript, date of submission, names of all authors, affiliation, and address, and phone number must be recorded with the handwritten signature of all authors. Also, the name and email address of corresponding author should be recorded. Completed Copyright Transfer and Author Consent Form should be submitted at online submission system to the Editorial Office.

# Research and Publication Ethics

JEND
Journal of Electrodiagnosis and Neuromuscular Diseases

The Journal of Electrodiagnosis and Neuromuscular Diseases adheres to the guidelines and best practices published by professional organizations, including ICMJE Recommendations and the Principles of Transparency and Best Practice in Scholarly Publishing (joint statement by the Committee on Publication Ethics [COPE], Directory of Open Access Journals [DOAJ], World Association of Medical Editors [WAME], and Open Access Scholarly Publishers Association [OASPA]; https://doaj.org/bestpractice). Further, all processes of handling research and publication misconduct shall follow the applicable COPE flowchart (https://publicationethics.org/resources/flowcharts).

## Statement of Human and Animal Rights

Clinical research should be conducted in accordance with the World Medical Association's Declaration of Helsinki (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/). Clinical studies that do not meet the Helsinki Declaration will not be considered for publication. For human subjects, identifiable information, such as patients' names, initials, hospital numbers, dates of birth, and other protected health care information, should not be disclosed. For animal subjects, research should be performed based on the National or Institutional Guide for the Care and Use of Laboratory Animals. The ethical treatment of all experimental animals should be maintained.

## Statement of Informed Consent and Institutional Approval

Copies of written informed consent should be kept for studies on human subjects. Clinical studies with human subjects should provide a certificate, an agreement, or the approval by the Institutional Review Board (IRB) of the author's affiliated institution. For research with animal subjects, studies should be approved by an Institutional Animal Care and Use Committee (IACUC). If necessary, the editor or reviewers may request copies of these documents to resolve questions regarding IRB/IACUC approval and study conduct.

## Conflict of Interest Statement

The author is responsible for disclosing any financial support or benefit that might affect the content of the manuscript or might cause a conflict of interest. When submitting the manuscript, the author must describe the conflict of interest statement. Examples of potential conflicts of interest are financial support from or connections to companies, political pressure from interest groups, and academically related issues. In particular, all sources of funding applicable to the study should be explicitly stated.

## Originality, Plagiarism, and Duplicate Publication

Redundant or duplicate publication refers to the publication of a paper that overlaps substantially with one already published. Upon receipt, submitted manuscripts are screened for possible plagiarism or duplicate publication using Crossref Similarity Check. If a paper that might be regarded as duplicate or redundant had already been published in another journal or submitted for publication, the author should notify the fact in advance at the time of submission. Under these conditions, any such work should be referred to and referenced in the new paper. The new manuscript should be submitted together with copies of the duplicate or redundant material to the editorial committee. If redundant or duplicate publication is attempted or occurs without such notification, the submitted manuscript will be rejected immediately. If the editor was not aware of the violations and of the fact that the article had already been published, the editor will announce in the journal that the submitted manuscript had already been published in a duplicate or redundant manner, without seeking the author's explanation or approval.

It is possible to republish manuscripts if the manuscripts satisfy the conditions for secondary publication of the ICMJE Recommendations (http://www.icmje.org/icmje-recommendations.pdf).

## Authorship and Author's Responsibility

Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet these four conditions.

- A list of each author's role should accompany the submitted paper.
- Correction of authorship: Any requests for such changes in authorship (adding author(s), removing author(s), or re-arranging the order of authors) after the initial manuscript submission and before publication should be explained in writing to the editor in a letter or e-mail from all authors. This letter must be signed by all authors of the paper. A copyright assignment must be completed by every author.
- Role of the corresponding author: The corresponding author takes primary responsibility for communication with the journal during the manuscript submission, peer review, and publication process. The corresponding author typically ensures that all of the journal's administrative requirements, such as providing the details of authorship, ethics committee approval, clinical trial registration documentation, and conflict of interest forms and statements, are properly completed, although these duties may be delegated to one or more coauthors. The corresponding author should be available throughout the submission and peer review process to respond to editorial queries in a timely manner, and after publication, should be available to respond to critiques of the work and cooperate with any requests from the journal for data or additional information or questions about the article.
- Contributors: Any researcher who does not meet all four ICMJE criteria for authorship discussed above but contributes substantively to the study in terms of idea development, manuscript writing, conducting research, data analysis, and financial support should have their contributions listed in the Acknowledgments section of the article.

## Registration of Clinical Trial

Clinical trial defined as "any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome" is recommended to be registered to the primary registry to be prior publication. ARM accepts the registration in any of the primary registries that participate in the WHO International Clinical Trials Portal (http://www.who.int/ictrp/en/), NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/), ISRCTN Resister (www.isrctn.org), University Hospital Medical Information Network (www.umin.ac.jp/ctr/index/htm), Netherlands Trial Register (http://www.trialregister.nl/trialreg/index.asp) or The Clinical Research Information Service (http://cris.nih.go.kr/). The clinical trial registration number will be published at the end of the abstract.

## Process for Managing Research and Publication Misconduct

When the journal faces suspected cases of research and publication misconduct, such as redundant (duplicate) publication, plagiarism, fraudulent or fabricated data, changes in authorship, undisclosed conflict of interest, ethical problems with a submitted manuscript, appropriation by a reviewer of an author's idea or data, and complaints against editors, the resolution process will follow the flowchart provided by COPE (http://publicationethics.org/resources/flowcharts). The discussion and decision on the suspected cases are carried out by the Editorial Board.

## Editorial Responsibilities

The Editorial Board will continuously work to monitor and safeguard publication ethics: guidelines for retracting articles; maintenance of the integrity of academic records; preclusion of business needs from compromising intellectual and ethical standards; publishing corrections, clarifications, retractions, and apologies when needed; and excluding plagiarized and fraudulent data. The editors maintain the following responsibilities: responsibility and authority to reject and accept articles; avoid any conflict of interest with respect to articles they reject or accept; promote the publication of corrections or retractions when errors are found; and preserve the anonymity of reviewers.

# Copyright Transfer and Author Consent Form

JEND
Journal of Electrodiagnosis and Neuromuscular Diseases

**Title of manuscript:** _____

_____

I agree to transfer the copyright of this article to the Korean Association of EMG Electrodiagnostic Medicine if it is published in the Journal of Electrodiagnosis and Neuromuscular Diseases.

I warrant that the article is original work that has not been published before and is not being considered for publication elsewhere in its final printed form or electronic form.

I certify that all authors contributed to this manuscript actually and intellectually and have responsibility to this manuscript.

I also declare that my institution has approved the protocol for any investigation involving human subjects or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

I further attest that we have disclosed any and all financial and other relationships that could be construed as a conflict of interest and that all funding sources supporting the work are disclosed in the manuscript.

**Date:** _____

***Corresponding author:** _____ **E-mail:** _____

**Address:** _____

**TEL:** _____ **FAX:** _____

| Author's name (Korean) | Author's name (English) | Signature |
|---|---|---|
| _____ | _____ | _____ |
| _____ | _____ | _____ |
| _____ | _____ | _____ |
| _____ | _____ | _____ |
| _____ | _____ | _____ |
| _____ | _____ | _____ |
| _____ | _____ | _____ |