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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.
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The Relationship Between Magnetic Resonance Imaging and Electrodiagnostic Studies in Patients with Ulnar Neuropathy at the Elbow

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Objective: This study investigated the correlations between magnetic resonance imaging (MRI) and nerve conduction studies (NCS) in patients with ulnar neuropathy at the elbow (UNE).

Methods: In total, 46 patients who underwent elbow MRI and NCS at a single center from 2014 to 2018 were included. Motor studies, including segmental and inching tests, and sensory NCS were performed. The 5-point severity score was evaluated based on the signal change and swelling in the fat-suppressed T2 weighted sequence. The findings of MRI and NCS were grouped into 3 categories. The Spearman rank test was used to evaluate correlations between the severity score on MRI and electrodiagnostic parameters.

Results: The locations of the lesions on MRI and NCS were correlated in 20 of the 46 patients with UNE, while the other 20 patients had no correlations. Six patients who could not be categorized according to the location showed various findings. The severity score based on MRI showed significant negative correlations with amplitude on the segmental study ($r = -0.423$, $p = 0.002$) and the inching study ($r = -0.456$, $p = 0.002$), and with conduction velocity in the segmental study ($r = -0.526$, $p < 0.001$) and the inching study ($r = -0.548$, $p < 0.001$).

Conclusion: Electrodiagnostic outcomes had negative correlations with the severity score, reflecting the structural changes seen on MRI. Combining electrodiagnostic studies and MRI could make the diagnosis and localization more precise.

Keywords: Electrodiagnosis; Magnetic resonance imaging; Ulnar neuropathies

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Introduction

Ulnar neuropathy at the elbow (UNE) is the second most common mononeuropathy after carpal tunnel syndrome [1]. Neurophysiologic studies, including motor nerve conduction studies (NCS) and needle examinations, are commonly used to confirm the diagnosis of UNE. Although short segmental incremental studies have played a role in the localization of demyelinating UNE [2,3], this method of diagnosing UNE has several limitations. First, localization is not easy in some patients with mild lesions or in those who have severe axonal injuries with low distal compound muscle action potential (CMAP) amplitudes [1,4]. Second, there can be errors in distance and latency measurements [3,4]. Third, the sensitivity and specificity of this method are not very high [2,4].

Ultrasonography can also be used for the diagnosis of ulnar

neuropathy, but its sensitivity and specificity are likewise lower than ideal [5,6]. Magnetic resonance imaging (MRI) has become increasingly important for the evaluation of UNE. Previous studies evaluating the diagnostic value of MRI findings of hyperintensity and nerve swelling showed varying results for sensitivity and specificity [5,7].

Although there have been many studies on UNE, few have investigated the relationship between MRI and electrodiagnostic studies in patients with UNE using segmental and inching studies to localize the location and determine its severity. The aim of this study was to investigate the correlations between MRI and NCS, especially segmental and inching studies, in patients with UNE.

Materials and Methods

1) Subjects

Electronic medical records were searched for 194 patients diagnosed with or suspected of having UNE through electrodiagnosis from 2014 to 2018. In total, 46 patients who underwent elbow MRI and NCS were included in this retrospective study conducted at a single center. Patients who did not have a formal MRI reading or for whom the location of the lesion was difficult to identify through electrodiagnosis were excluded from the study. This study was exempt from Asan Medical Center Institutional Review Board review (No. 2022-0619).

2) Localization

The location of the lesion, based on both MRI and NCS, was divided into 3 sections. Section 1 included the area from 2 cm above the elbow to 6 cm above the elbow, section 2 included the area from 2 cm above the elbow to 2 cm below the elbow, and section 3 included the area from 2 cm below the elbow to 6 cm below the elbow. The location was categorized as "undetermined" if there was a broad lesion or if there were multiple lesions across the sections. A cross-sectional study design was used to evaluate the correlations of the localizations.

3) Electrodiagnostic studies

Neurophysiological testing was performed using an Oxford Synergy apparatus (Oxford Instruments; Medelec, Surrey, United Kingdom). Motor and sensory NCS were performed by electrical stimulation of the bilateral ulnar nerves, with the elbow flexed at 90°. For the motor NCS, CMAPs were recorded from the abductor digiti minimi muscle with surface electrodes, with filter settings of 3 Hz to 10 kHz, sensitivity of 5 mV for amplitude and 500 mV for onset latency determination, and sweep of 20 ms.

With clinical suspicion of UNE, both segmental and inching studies were conducted on the symptomatic side, and routine conduction studies were conducted on the wrist and the ulnar groove of the asymptomatic side [3]. In the segmental studies, 3 points (the wrist, below the elbow, and above the elbow) were stimulated. The diagnosis of UNE was based on electrophysiological criteria [3,8]. In the inching studies, 5 points of the ulnar nerve were stimulated at successive 2-cm intervals from 4 cm below to 6 cm above the medial epicondyle. Latency of more than 0.4 ms was as a positive finding [9]. The inching study was analyzed because it had shorter segments than the segmental study, leading to the possibility that it could yield more significant values for certain parameters, such as the conduction velocity.

Sensory nerve action potentials (SNAPs) were obtained antidromically from the fifth finger, with filter settings of 20 Hz to 2 kHz, sensitivity of 20 μV, and sweep of 10 ms. The needle examination included the first dorsal interosseous muscle and other ulnar innervated forearm flexors.

4) MRI

T2-weighted fat-saturated axial images focused on the radio-humeral joint were analyzed by 2 musculoskeletal radiologists, who reached consensus regarding their interpretation. The severity of each lesion was determined based on increased T2 signal intensity and nerve swelling in a cross-sectional image of the ulnar nerve through a qualitative image analysis. T2 signal intensity was qualitatively analyzed throughout the entire image. T2-weighted images without any hypersignal changes were considered "normal," while those with a hypersignal change in the ulnar nerve were considered "abnormal" and further evaluated in terms of whether the change in the signal intensity was mild or severe. Mild swelling was defined as a more than 20% increase of the nerve caliber in relation to the proximal and distal segments, while severe swelling was defined as a more than 50% increase in the nerve caliber. The severity scoring for each section was conducted by 2 radiologists using a 5-point score from 0 to 4, which was based on the signal alteration and/or swelling on the fat-suppressed T2 weighted axial images [1,10]. Fig. 1 shows representative image sections.

5) Statistical analysis

Statistical analyses were performed using IBM SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA). The Spearman correlation method was used to evaluate the correlation between the severity score on MRI and each electrodiagnostic parameter. Values of $p < 0.05$ were considered to indicate statistical significance.

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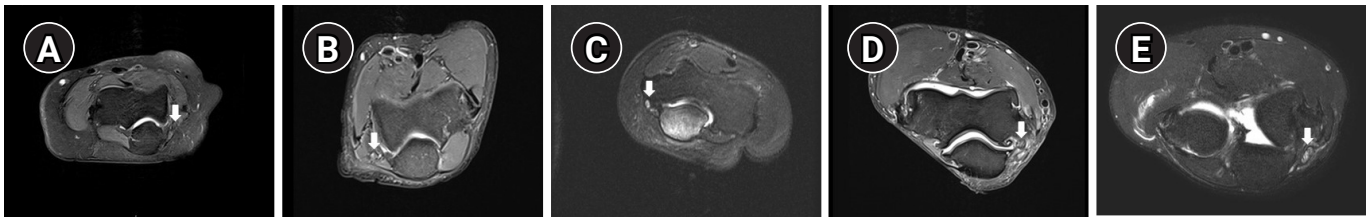

Fig. 1. The severity based on the magnetic resonance imaging (MRI) findings using a 5-point score was evaluated based on the signal alteration and/or swelling on the fat-suppressed T2 weighted axial sequences. The images around the elbow were divided into 3 sections from 2 to 6 cm above the medial epicondyle (section 1), from 2 cm below the medial epicondyle to 2 cm above the medial epicondyle (section 2), and from 2 to 6 cm below the medial epicondyle (section 3). Fig. 1 shows representative images for the evaluation of ulnar neuropathy in section 2, and the ulnar nerve is indicated with white arrows. (A) Axial MRI on the right side depicts score 0 with a normal finding of the ulnar nerve. (B) Axial T2 fat-suppressed image shows a mild signal change (score 1). (C) Axial T2 fat-suppressed image on the left side presents a severe signal change (score 2). (D) MRI of the right elbow shows a signal change with mild swelling (score 3). (E) Axial MR on the right side depicts severe swelling with a severe signal change (score 4).

Results

We reviewed 46 patients (28 males and 18 females) with available elbow MRI and NCS findings. The clinical and electrophysiologic findings of the 46 patients are described in Table 1. The mean age of the patients was 45.1 ± 16.9 years. On the day of the electrophysiologic study, 29 patients (63.0%) complained of sensory symptoms and signs without muscle weakness. Five patients (10.9%) had weakness of the ulnar-innervated muscles without sensory symptoms and signs. Twelve (26.1%) patients reported both sensory symptoms and muscle weakness. All studies were consistent with UNE. There were no absent findings of CMAP, and the ulnar CMAP was reduced in 12 patients (26.1%). Meanwhile, the ulnar SNAP was absent in 9 patients (19.6%) and reduced in 14 patients (30.4%). The absolute motor nerve conduction velocity from above-elbow to below-elbow was less than 50 m/s in 38 patients (82.6%).

The MRI findings of 46 patients revealed ulnar nerve abnormalities at the elbow in 43 (93.5%) patients. Eighteen patients had isolated ulnar nerve hyperintensity, including 15 patients with a mild T2 signal change (score 1) and 3 patients with a severe T2 signal change (score 2). A combination of ulnar nerve hyperintensity and mild swelling of the ulnar nerve at the elbow was the most common abnormality, seen in 18 patients (score 3), while 7 patients (score 4) had both signal changes and severe swelling of the ulnar nerve.

Table 2 shows the relationship of the lesion localization between MRI and the electrodiagnostic study for 46 patients. Six patients were classified as having an "undetermined" location based on the MRI findings, while 20 patients showed correlated locations between the MRI and electrodiagnostic studies. Three patients had normal MRI and abnormal electrodiagnostic findings, and 4 patients had normal electrodiagnostic and abnormal MRI findings.

Table 3 and Fig. 2 show some correlations between the severity score on MRI and the parameters on the segmental and inching studies. The amplitude of sensory NCS showed a negative correlation with the MRI-based severity score ($r = -0.421$, $p = 0.004$). In the segmental studies, the severity score based on MRI was correlated with the amplitude and conduction velocity in the same section of the lesion. In the inching studies, the severity score based on MRI was correlated with the amplitude and the conduction velocity in the matched section of the lesion. The severity score based on MRI was also correlated with the minimum values of the amplitude and the conduction velocity among the 5 points that we stimulated.

Discussion

This is the first study to reveal a correlation between MRI and NCS findings, including segmental and inching studies, in an investigation of the location and the severity of UNE. Most cases of UNE occur at the level of the retroepicondylar groove, which is called the cubital tunnel. This nerve may also be compressed at the humeral-ulnar aponeurosis between the 2 heads of the flexor carpi ulnaris (FCU) or at the point of the exit from the FCU [11]. Identifying the location of the entrapment helps with therapeutic decisions, because operative interventions such as resection of the arcuate ligament, medial epicondylectomy, and anterior transposition of the ulnar nerve can resolve cubital tunnel syndrome in some cases [12].

The ulnar nerve signal on T2 imaging has diagnostic importance in lesion localization since it is correlated with the segmental study of NCS. Increased signal intensity on T2 imaging indi-

Table 1. Clinical and Electrophysiologic Findings of 46 Patients with Ulnar Neuropathy at the Elbow

Characteristic	Value
General characteristic	
Age (y)	45.1 ± 16.9 (18-78)
Sex (male:female)	28 (60.9):18 (39.1)
Affected side (left:right:both)	23 (50.0):22 (47.8):1 (2.2)
Duration of symptoms (mo)	33.8 ± 39.3 (1-120)
Etiology	
Trauma	18 (39.1)
Osteoarthritis at the elbow	13 (28.3)
Tendinopathy of FCU	4 (8.7)
Ulnar nerve subluxation	3 (6.5)
Medial epicondylitis	1 (2.2)
Unknown	7 (15.2)
Clinical findings	
Sensory symptom only	28 (60.9)
Motor symptom only	5 (10.9)
Sensory and motor symptoms	13 (28.2)
Definite atrophy of ulnar-innervated muscles	6 (13.0)
Sensory NCS	
Absent SNAP	9 (19.6)
Low SNAP amplitude	14 (30.4)
Normal SNAP amplitude	23 (50)
Motor NCS	
Absent CMAP	0 (0)
Low CMAP amplitude stimulated at the wrist	12 (26.1)
Normal CMAP amplitude stimulated at the wrist	34 (73.9)
Conduction block only	2 (4.3)
Conduction slowing only	22 (47.8)
Conduction block and conduction slowing	22 (47.8)
MRI severity scoring in the section of the lesion	
Score 0	3 (6.5)
Score 1	15 (32.6)
Score 2	3 (6.5)
Score 3	18 (39.1)
Score 4	7 (15.2)
Surgery	14 (30.4)

For the age and the duration of the symptoms, the mean ± standard deviation and range are shown, while for the other parameters, number (%) are presented.
FCU, flexor carpi ulnaris; NCS, nerve conduction study; SNAP, sensory nerve action potential; CMAP, compound muscle action potential; MRI, magnetic resonance imaging.

cates the presence of UNE, and the magnitude of nerve caliber enlargement distinguishes between mild and severe neuropathy [10]. Our study included both segmental and inching studies to determine the correlation between MRI and NCS results of UNE.

A previous study showed that ultrasonographic abnormalities due to UNE might not be maximal at the site of the nerve dysfunction based on the segmental and inching studies [13]. However, our study showed a correlation of severity between MRI and NCS based on the segmental and inching studies, without a significant difference between the segmental and inching studies..

The findings of high signal intensity and nerve swelling on MRI represent focal demyelination. Previous studies reported that MRI was more sensitive than segmental NCS studies, especially in patients with non-localizing UNE. A previous study found no significant differences in MRI findings according to different scores of UNE severity [1]. However, our study confirmed that MRI and NCS produced similar findings and that the UNE severity based on the NCS was correlated with the MRI findings, as in the 25 patients who showed abnormal spontaneous activity on needle EMG.

Furthermore, in a comparison between 2 subgroups, this study also revealed that more significant signal changes on elbow MRI were observed in patients with non-traumatic etiologies. Subgroup A included 18 patients with trauma and 3 patients with ulnar nerve subluxation. All 3 patients with ulnar nerve subluxation and 6 patients with traumatic history showed mild signal changes, with an MRI severity score of 1. Two patients with normal findings on MRI were confirmed to have UNE based on NCS. More than half of the patients with an MRI severity score of 3 and all patients with a score of 4 belonged to subgroup B, without traumatic etiology or subluxation. In particular, all patients with a severity grade of 4 showed severe osteophytes and bony spurs on elbow MRI. Therefore, it is inferred that MRI signal changes are more closely correlated with non-traumatic etiologies.

Among 20 patients with discrepancies in the location between the NCS and MRI, 9 had a previous history of orthopedic surgery. Among these patients, 6 had MRI findings superior to those of NCS, while 3 patients had NCS findings superior to those of MRI. Among 6 patients in the undetermined group based on MRI imaging, 5 patients had undergone previous orthopedic surgery and showed multiple lesions across the sections. Although there was a clinical correlation between the location of the lesion on MRI and NCS in 50% of the patients, the other patients had discrepancies that may have been related to the differences in the patient's position during NCS and MRI. A moderately flexed position (about 70° to 90°) has been recommended to ensure that surface skin measurements more closely reflect the true nerve length. An extended elbow position often causes an underestimation of the true nerve length, leading to artifactual delayed conduction velocity across the elbow. However, MRI is usually performed in the elbow-extended position [9,14,15].

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Table 2. Relationship of the Lesion's Location Between MRI and Electrodiagnostic Studies in Diagnosing Ulnar Neuropathy at the Elbow (n = 46)

MRI	Category	NCS			
		Normal (n = 4)	Abnormal (n = 42)		
			Section 1	Section 2	Section 3
Normal (n = 3)			0	3	0
Abnormal (n = 43)	Section 1	0	0	0	0
	Section 2	4	3	18*	9
	Section 3	0	0	1	2*
	Undetermined		2†	2†	2†

MRI, magnetic resonance imaging; NCS, nerve conduction study.
*Twenty patients showed a correlated location between MRI and electrodiagnostic studies (20/40 = 50.0%). †Among the 46 patients, 6 were classified as the 'undetermined' group based on MRI findings.

Table 3. The Relationship Between the Severity Score on MRI and the Parameters on Nerve Conduction Study

Study	Parameter	Spearman correlation coefficient (rho)	p-value
Sensory study	The amplitude of the sensory nerve conduction study	-0.421	0.004*
Segmental study	The amplitude at the lesion on MRI	-0.423	0.002*
	The conduction velocity at the lesion on MRI	-0.526	< 0.001*
Inching study	The amplitude at the lesion on MRI	-0.456	0.002*
	The conduction velocity at the lesion on MRI	-0.548	< 0.001*
	The minimum amplitude	-0.512	< 0.001*
	The minimum conduction velocity	-0.583	< 0.001*

MRI, magnetic resonance imaging.
*$p < 0.05$ by Spearman correlation analysis.

Furthermore, another limitation is that the interval of the sections on MRI and the inching study were not exactly matched.

We did not conduct any further analyses of the SNAP amplitude because it is a limited parameter that depends on distance. In addition, the onset or peak latencies of SNAP could not be analyzed for quantitative correlations with the severity score based on the MRI findings because there were several patients with no SNAP responses. Although a previous study reported abnormalities on sensory NCS with normal findings on MRI, abnormalities on sensory NCS usually suggest the possibility of axonal degeneration [16]. This study showed a negative correlation between SNAP and MRI findings. To be more concrete, 4 patients had a score of 4 on MRI with hyperintensity and severe swelling of the ulnar nerve, and 3 of the 9 patients with absent SNAP findings had the lowest score on MRI, with mild hyperintensity.

This study has several limitations. First, the relatively small sample size made it difficult to determine the correlation of the location of the lesion based on NCS and MRI with the operative findings. Although the medical records of 194 patients with NCS were reviewed, only 46 patients underwent MRI for ulnar neuropathy, and only 14 patients had surgical records that confirmed the exact location of the lesion. Additional studies with larger sample sizes would reveal more definite correlations. Second, unblinded radiologists evaluated the MRI and qualitatively scored the severity of ulnar nerve entrapment. It would be preferable to correlate the severity of NCS and the quantitative scoring of MRI after measuring the interrater and intrarater reliabilities. Furthermore, it was not feasible to determine the clinical relationship of patients' subjective symptoms with the severity and the location of the lesion based on NCS and MRI due to the insufficient symptomatic data in the medical records. Additional prospective studies including precise information on the distribution and the severity scales of the symptoms would give more useful information for the diagnosis of UNE.

Conclusion

Although some discrepancies about the location of the UNE existed between the electrodiagnostic studies and MRI, this study demonstrates that the electrodiagnostic outcomes have correlations with the severity score, which reflects the structural changes on MRI. In conclusion, using a combination of electrodiagnostic studies and MRI improves diagnostic accuracy, including the lesion localization and assessment of the severity of

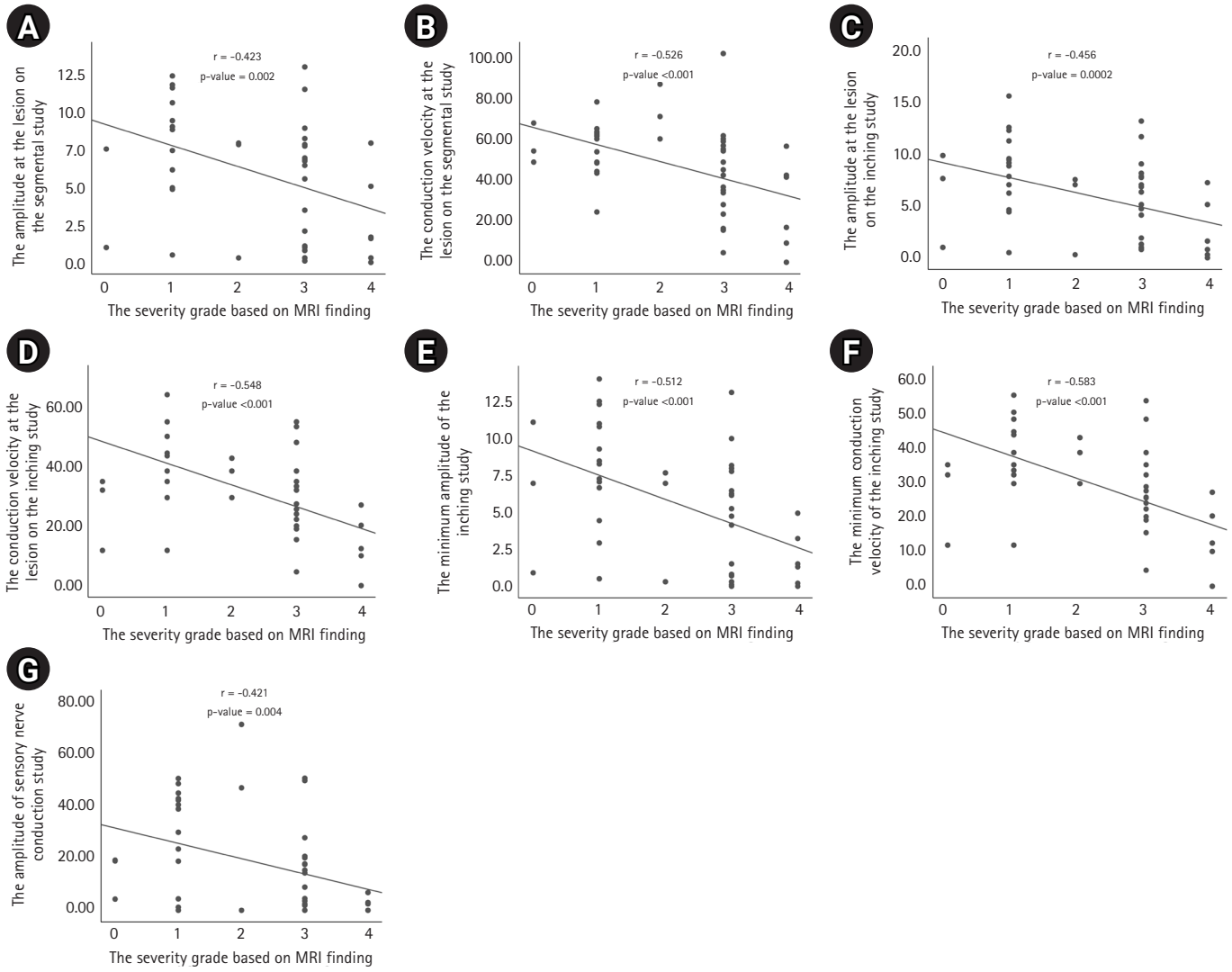

Fig. 2. Relationships between the severity score on magnetic resonance imaging (MRI) and the parameters of nerve conduction studies. The severity score on MRI showed correlations with (A) the amplitude at the lesion of the segmental study, (B) the conduction velocity at the lesion of the segmental study, (C) the amplitude at the lesion of the inching study, (D) the conduction velocity at the lesion of the inching study, (E) the minimum amplitude of the inching study, and (F) the minimum conduction velocity of the inching study. (G) The severity score on MRI was correlated with the amplitude of the sensory nerve conduction studies.

UNE. It is necessary to verify the relevance and localization of patients' symptoms through additional prospective studies.

Conflict of Interest

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

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Clinical and Pathological Findings of Korean Patients with Selenoprotein N-Related Myopathy

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Objective: This study investigated the clinical, pathological, and genetic characteristics of 5 Korean patients with selenoprotein N-related myopathy (SELENON-RM).
Methods: Five unrelated patients were genetically diagnosed with SELENON-RM by whole-exome or targeted gene panel sequencing. We then analyzed their clinical, pathological, and genetic spectra.
Results: The median age at symptom onset was 3 years (interquartile range, 2–10 years). The most common clinical finding was proximal muscle weakness in all 5 patients, followed by spinal scoliosis and respiratory distress in 4 patients and delayed motor development in 2 patients. Other uncommon clinical findings were winged scapula in one patient and cardiomegaly in one patient. Magnetic resonance imaging of muscles revealed that fatty replacement was predominant in the paraspinal muscles, adductors, semimembranosus, semitendinosus, long head of the biceps femoris, and medial gastrocnemius. Muscle biopsies in 2 patients showed type 1 predominance and multiple eccentric cores within the fibers. We identified 5 pathogenic variants of *SELENON*. The most common variant was the c.1574T > G variant in 5 alleles (50%) in 4 patients (80%).
Conclusion: In the first report of SELENON-RM in Korea, we identified 5 SELENON-RM patients and expanded existing knowledge on the clinical and genetic spectrum of these patients.

Keywords: *SELENON*; SELENON proteins; Myopathies, structural, congenital

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Introduction

Congenital myopathies are a clinically and pathologically heterogeneous group of genetic myopathies characterized by hypotonia, muscle weakness from birth, and a slowly progressive clinical course [1]. Congenital myopathies have been classically categorized based on muscle pathologies such as nemaline rods, cores, central nuclei, and selective hypotrophy of type 1 fibers [2,3]. The application of next-generation sequencing has made it possible to identify the genetic causes of congenital myopathies quickly and easily, and nearly 50 causative genes have been identified to date [4]. Recent advances in molecular diagnosis have shown that the relationship between genotype and phenotype is highly complex. The same gene can cause different phenotypes and muscle pathologies, and multiple genes can result in the same clinicopathological findings [5].

Selenoprotein N-related myopathy (SELENON-RM), caused by pathogenic variants of *SELENON*, is an autosomal recessive congenital myopathy. SELENON-RM clinically presents with slowly progressive proximal muscle weakness, spinal scoliosis, and respiratory insufficiency [6,7]. Multi-minicores are the main histopathological features of SELENON-RM, but congenital fiber-type disproportions and Mallory body-like inclusions have also been reported [7,8]. There have been large international

case series in Europe [7], and some smaller case series in Asia [9–11]. However, there are no reports demonstrating the detailed clinical phenotypes of SELENON-RM patients in Korea. We evaluated the characteristics of SELENON-RM in a Korean population by analyzing clinical, pathological, and genetic data obtained from 5 unrelated patients with pathogenic variants in *SELENON*.

Materials and Methods

We reviewed the medical records from the myopathy database from January 2002 to December 2021 at Gangnam Severance Hospital. Five unrelated patients who had been diagnosed with *SELENON* pathogenic variants (MF27, MF88, MF1467, MF1481, and MF1949) were identified and included in this study. We previously reported one variant (c.619delC) as a novel pathogenic variant in *SELENON* in the MF88 patient, but did not present the detailed clinical and pathological phenotypes [12]. Clinical, laboratory, and pathology data were retrospectively obtained by reviewing patients' medical records. Data from before patients visited our institution were extracted from medical records submitted by patients from other hospitals. Clinical information included the age at symptom onset, motor development, muscle impairment, respiratory distress, scoliosis, and joint contractures. The laboratory analysis included serum creatine kinase (CK) levels. Whole-body muscle magnetic resonance imaging (MRI) was available for one patient (MF1467). Muscle biopsies were performed on 2 patients (MF27 and MF1467) at Gangnam Severance Hospital. Frozen muscle sections obtained from specimens were stained with hematoxylin and eosin, modified Gomori trichrome, and reduced nicotinamide adenine dinucleotide-tetrazolium reductase. The muscle biopsies of 2 other patients (MF88 and MF1481) had been conducted previously at other hospitals, and we analyzed their pathology reports.

This study was approved by the institutional Review Board of Gangnam Severance Hospital, Korea (IRB no. 3-2022-0011). All participants had previously provided informed consent for their involvement in this study and genetic analysis.

Results

The clinical and pathological phenotypes of the 5 patients with *SELENON* pathogenic variants are summarized in Table 1. All patients had 2 pathogenic variants of *SELENON*. All variants were classified as likely pathogenic or pathogenic according to the guidelines of the American College of Medical Genetics and Genomics/Association for Molecular Pathology (Table 2) [7,10,12–14].

A 5-year-old boy (MF27, II-1 in Fig. 1A) presented to our clinic with a 1-year history of respiratory insufficiency and proximal muscle weakness. He presented with delayed motor development; unsupported sitting was achieved at 12 months and independent gait at 18 months. When he was 4 years old, he was admitted to another clinic due to acute respiratory failure, and he was referred to our clinic 1 year later. He underwent a neurological examination that showed muscle hypotrophy and severe scoliosis with spinal rigidity. Laboratory studies revealed a CK level

Table 1. Clinical Characteristics of Patients with Selenoprotein N-Related Myopathy

Patient	Sex	Age at onset (y)	Age at diagnosis (y)	Clinical presentation	Scoliosis	Respiratory distress	CK (IU/L)	Muscle pathology	Other clinical features
MF27	Male	1	22	Delayed motor development and proximal muscle weakness	Yes	Yes	42	Type 1 fiber predominance	None
MF88	Female	3	19	Early pulmonary distress, followed by proximal muscle weakness	Yes	Yes	66	Myopathic changes	High-arched soft palate
MF1467	Female	19	29	Proximal muscle weakness in adolescence	No	No	182	Minicores	Long face, bilateral facial palsy, high-arched soft palate, and winged scapula
MF1481	Male	2	27	Delayed motor development and proximal muscle weakness	Yes	Yes	555	Chronic myopathic changes	None
MF1949	Male	10	18	Proximal muscle weakness, followed by respiratory distress	Yes	Yes	230	NA	Neck contracture, cardiomegaly, and pericardial effusion

CK, creatine kinase; NA, not available.

Table 2. Pathogenic and Likely Pathogenic Variants in *SELENON* in the Present Study

Type	Nucleotide changes	Amino acid changes	Patient	Other studies reporting this variant
Frameshift	c.13_22dup	p.Gln8ProfsTer78	MF27	Silwal et al. [14]
Frameshift	c.234delC	p.Leu79TrpfsTer21	MF1467	Park et al. [12]
Nonsense	c.565C > T	p.Arg189Ter	MF1467	Villar-Quiles et al. [7]
Frameshift	c.619del	p.Gln173SerfsTer22	MF88, MF1481	Park et al. [12]
Missense	c.1574T > G	p.Met525Arg	MF27, MF88, MF1481, and MF1949	Izawa et al. [10]

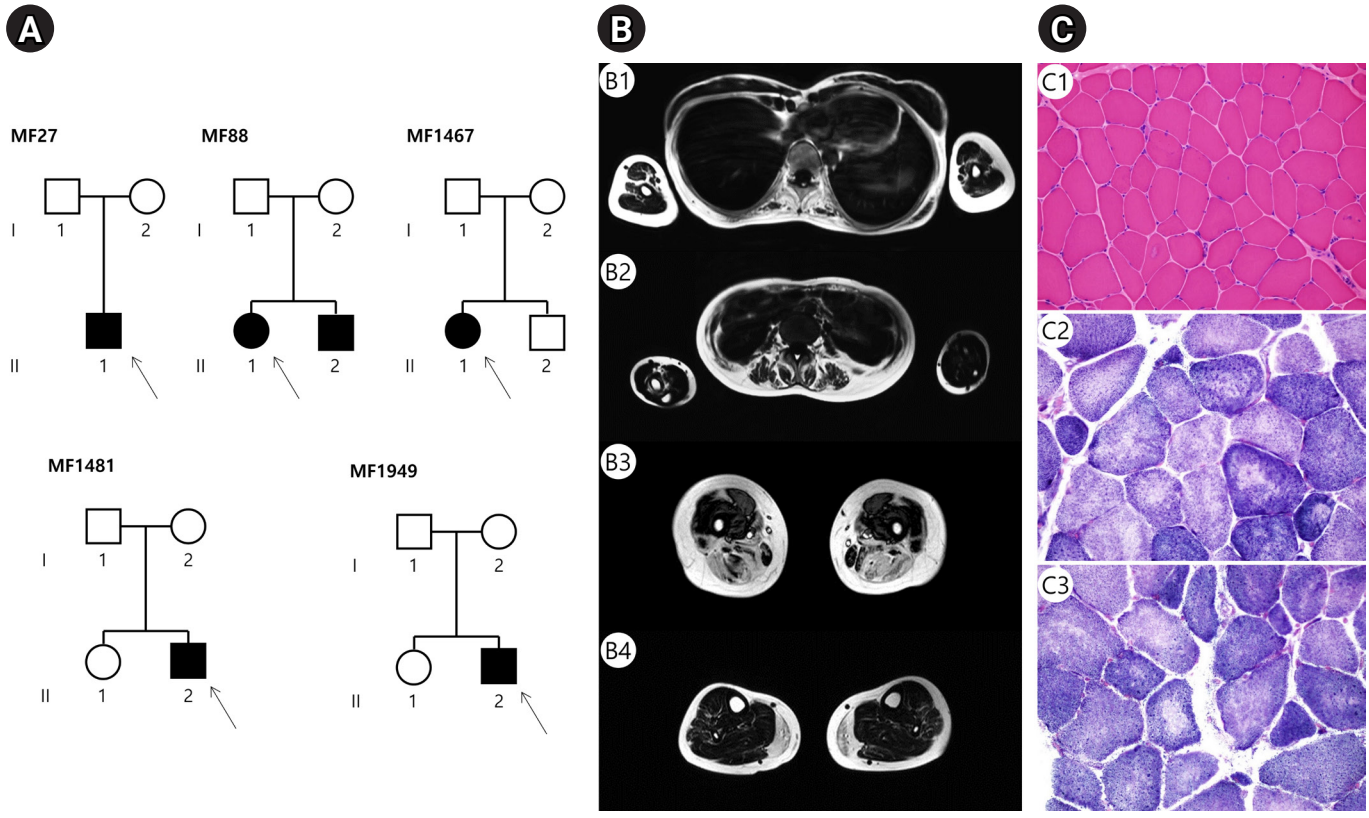

Fig. 1. Pedigrees, muscle magnetic resonance imaging (MRI), and muscle biopsies in Korean families with SELENON-related myopathy. (A) Pedigrees of 5 families with *SELENON* pathogenic variants. Arrows indicate the probands (square, male; circle, female; filled, affected; unfilled, unaffected). (B) Muscle MRI findings of patient MF1467. Axial T1-weighted imaging revealed that fatty replacement was predominant in paraspinal muscles at the thoracic level (B1, B2), the adductor, semimembranosus, semitendinosus, and the long head of the biceps femoris at the thigh level (B3), and the medial gastrocnemius at the calf level (B4). (C) Muscle biopsy samples of the biceps brachii in MF1467. Mild muscle fiber size variation and little local necrotic fibers on hematoxylin and eosin staining (C1, ×200). Nicotinamide adenine dinucleotide staining, demonstrating multiple focal areas that are not stained (i.e., multiple eccentric cores) (C2, C3, ×400).

of 45 IU/L (reference value, < 135 IU/L). Needle electromyography was consistent with myopathic changes. A muscle biopsy was performed from the right vastus lateralis when the patient was 5 years old. It showed mild to moderate muscle size variation with type 1 fiber predominance, consistent with congenital fiber-type disproportions. One year later, he underwent tracheostomy and full-time non-invasive positive-pressure ventilation. At 15 years of age, the patient underwent corrective spinal surgery. He became unable to walk independently when he was 19 years old and was in a bedridden state. Whole-exome sequencing identified a compound heterozygous variant (c.13_22dup + c.1574T > G) in *SELENON*.

A 15-year-old girl (MF88, II-1 in Fig. 1A) was born to healthy parents at 40 weeks of gestation, weighing 2.5 kg. Her brother presented with pulmonary insufficiency and muscle weakness, and was previously diagnosed with muscular dystrophy. At 3 years of age, she experienced acute respiratory distress, but recovered within a few days. However, she had difficulty climbing

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stairs or getting up from sitting since the age of 5 years. Since the age of 11 years, she complained of spinal rigidity, scoliosis, and the aggravation of muscle weakness. The serum CK level was 66 IU/L, and needle electromyography showed generalized myopathy. According to the pathology report, she had undergone muscle biopsy when she was 14 years old from the left vastus lateralis, and it showed moderate-size variation in myofibers and a few degenerating fibers. When she was referred to our clinic at 15 years of age, she exhibited a high-arched soft palate, and a severe restrictive pattern on pulmonary function testing. She had forced vital capacity values below 35% of that predicted for height, which worsened every year. When she was 20 years old, she became unable to sit or walk alone. Targeted sequencing of 598 neuromuscular disorder genes identified a compound heterozygous variant (c.619del + c.1574T > G) of *SELENON*.

A 29-year-old woman (MF1467, II-1 in Fig. 1A) presented with a 10-year history of progressive muscle weakness. Her family history was unremarkable, and her initial psychomotor development was normal. She had an elongated face, bilateral facial paralysis, a high-arched palate, and winged scapula. A neurological examination revealed proximal and axial muscle weakness with the Gower's sign. The serum CK level was mildly increased (182 IU/L). Needle electromyography revealed generalized myopathy. Whole-body MRI showed that fatty replacement and muscle atrophy were predominantly observed in the paraspinal muscles, adductors, semitendinosus, semimembranosus, the long head of the biceps femoris, and the medial gastrocnemius muscles (Fig. 1B). Histopathological examination of the left biceps brachii revealed increased variations in muscle fiber sizes and multiple eccentric cores within the fibers (Fig. 1C). At the age of 33 years, she could walk independently for about 100 m and did not complain of respiratory difficulty. Targeted sequencing of 598 neuromuscular disorder genes identified a compound heterozygous variant (c.234delC + c.565C > T) of *SELENON*.

A 19-year-old boy (MF1481, II-2 in Fig. 1A) was born to healthy parents at 40 weeks of gestation, weighing 3.2 kg. He presented with motor developmental delay, having achieved head control at 8 months and autonomous gait at 20 months. At the age of 13 years, he suffered from acute respiratory failure, and had been wearing a non-invasive ventilator. One year later, the patient underwent corrective spinal fusion surgery at another hospital. He underwent muscle biopsies from the quadriceps and paraspinal muscles at the ages of 13 and 14 years, respectively. Both muscle biopsy findings were recorded as nonspecific myopathic changes. When he visited our clinic at the age of 19 years, he was able to walk independently for up to 5 m. A neurological examination revealed diffuse muscle weakness and marked neck flexor weakness. Laboratory findings showed that the serum CK level had increased to 555 IU/L. Needle electromyography revealed generalized myopathy. Targeted sequencing of 598 neuromuscular disorder genes identified a compound heterozygous variant (c.619delC + c.1574T > G) of *SELENON*.

A 13-year-old boy (MF1949, II-2 in Fig. 1A) visited our clinic with pulmonary insufficiency and proximal muscle weakness. His family history was unremarkable. At the age of 10 years, he noticed difficulty climbing stairs and running. At the age of 11 years, he underwent general medical and orthopedic examinations. The patient exhibited severe contractures of the neck extensors with spinal scoliosis, and demonstrated weakness of the axial and proximal muscles. The serum CK level was 100 IU/L, and electromyography revealed generalized myopathy. According to his medical records, cardiomegaly was observed on chest radiography and pericardial effusion on echocardiography. The electrocardiogram demonstrated a normal sinus rhythm. Because of proximal weakness, including neck contracture with cardiac involvement, the patient was initially suspected of having Emery-Dreifuss muscular dystrophy. When he was 13 years old, he experienced acute respiratory distress requiring a tracheostomy with ventilator support. At the age of 21 years, he was able to walk up to 50 m with assistance and intermittent non-invasive ventilator use, especially at night. Targeted sequencing of 598 neuromuscular disorder genes identified a homozygous variant (c.1574T > G) of *SELENON*.

Discussion

We analyzed the genetic, clinical, and pathological spectra of 5 Korean patients with SELENON-RM. The present study identified 5 pathogenic variants in 5 unrelated Korean patients. Four variants were classified as pathogenic according to the guidelines of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology and have been previously reported [7,12,15].

SELENON is an endoplasmic reticulum (ER) protein that plays an important role in oxidative stress protection and redox-related calcium homeostasis [8]. Although the precise pathogenic mechanism of SELENON-RM is not fully understood, SELENON deficiency affects excitation-contraction coupling in muscle [16], mitochondrial physiology, and energy metabolism [8]. In addition, it has been reported that depletion of SELENON increases susceptibility to metabolic disorders, including insulin resistance or lipotoxicity of saturated fatty acids, as a secondary change to ER stress [17]. Based on the pathophysiology of SELENON-RM, it is necessary to evaluate the

changes in muscle mass and overall nutritional status as the disease progresses.

In agreement with previous studies [6,7,14,18], we found that in most patients, the onset of clinical symptoms was in the first decade, except for one patient who developed symptoms at the age of 19 years. According to the largest cohort studies with SELENON-RM [7], the first signs were noticed before the age of 15 years in all patients, and the proportion of patients with symptom onset after the age of 8 years was approximately 8%. In addition, all 5 patients predominantly had proximal muscle weakness. The most common phenotype in our study was spinal scoliosis with respiratory distress, consistent with the commonly known features of SELENON-RM. However, there are several differences between this study and previous reports. First, limb joint contractures or hyperlaxity, as one of the main clinical features, was not observed in our study. Second, the present study identified one patient who presented with a winged scapula without any spinal deformity (MF1467). There are no previous reports that the winged scapula is associated with SELENON-RM. Winged scapula may appear, but it is considered pseudo-winging due to dorsal hyperlordosis associated with spinal scoliosis [7]. Third, cardiac involvement is not known to be a clinical manifestation of SELENON-RM. If there is involvement, it is not as severe as mild ventricular hypertrophy, or it develops secondary to respiratory insufficiency [6,18]. However, we found a patient with a phenotype predominantly characterized by cardiac abnormality (MF1949).

Whole-body muscle MRI in the MF1467 patient showed that fatty replacement was predominant in the paraspinal muscles, adductor, semimembranosus, semitendinosus, long head of the biceps femoris, and medial gastrocnemius. These findings are consistent with the previously reported MRI data [14,19]. These selective muscle involvements may depend on the clinical distribution of muscle weakness and the presence of scoliosis.

Muscle pathology showed congenital fiber-type disproportion and multiple eccentric cores in MF27 and MF1467, respectively. These pathological findings are among the most common pathological findings of SELENON-RM [7,8]. However, we found medical records of nonspecific myopathic features of muscle biopsies in 2 patients (MF88 and MF1481) who underwent biopsies at other hospitals.

Our study identified 5 different pathogenic variants in *SELENON*. There were 3 frameshift variants (c.13_22dup, c.234del, and c.619delC), one nonsense variant (c.565C > T), and one missense variant (c.1574T > G). The most common variant was the c.1574T > G variant, which was found in 5 alleles (50%). This variant is located in exon 12, which modifies the nonpolar amino acid methionine into the acidic amino acid arginine. It was first reported in Japan [10]. Subsequently, a pathogenic variant was identified in a few cases in Asia [11,15]. However, in a large, wide-ranging case series in European countries, the c.1574T > G variant was found in only one of 132 patients. Ethnic variation in hotspots for *SELENON* or environmental factors may have contributed to these varied findings.

We did not find a correlation between the genotype and phenotype in patients with SELENON-RM. It is difficult to establish a rare disease, and we lack patients with the same pathogenic variants. A previous study reported that some exon 1 variants, including c.13_22dup, found in one of our patients (MF27), were associated with a severe phenotype [14]. Although this patient presented with clinical manifestations at the youngest age among our patients, it was not associated with disease severity. Null variants are usually correlated with a more severe phenotype than other types [14]. In our study, MF1467, with 2 null variants of *SELENON* (c.234del and c.565C > T), showed the mildest phenotype without respiratory distress and scoliosis. We identified the c.1574T > G missense mutation, which was the most common variant, in 5 alleles in 4 patients.

Conclusion

Our study represents the spectrum of clinical, pathological, and genetic findings in Korean SELENON-RM patients. We have outlined the clinical diagnostic clues of early axial and proximal muscle weakness, spinal scoliosis, and respiratory failure in SELENON-RM. In addition, we also observed one patient with a mild phenotype, suggesting that there is inter-individual variability in SELENON-RM. In conclusion, diagnosing and verifying the pathogenicity of genetic variants in SELENON-RM requires a comprehensive approach that integrates clinical characteristics, histological findings, muscle imaging, and genetic findings. This study is the first in Korea to analyze the various clinicopathological characteristics and genetic spectrum of SELENON-RM, which will contribute to improving the diagnosis and management of this condition and increasing disease awareness and recognition of its specific clinical characteristics.

Conflict of Interest

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

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CASE REPORT

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Acute Transverse Myelitis after Varicella-Zoster Virus Infection in an Immunocompetent Patient: A Case Report

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Herpes zoster is caused by reactivated varicella-zoster virus (VZV) and characterized by a painful skin rash with vesicles that affects the adjacent dermatomes. Transverse myelitis is a rare complication of VZV infection that may even occur in immunocompetent patients. Here, we report a 60-year-old male patient admitted with right lower-extremity weakness and hypesthesia. Spine magnetic resonance imaging (MRI) revealed transverse myelitis at the C3–C4 and T6 levels. A month prior to admission, the patient was diagnosed with herpes zoster involving the right T2-T4 dermatome. Considering his history of VZV infection, he was treated with intravenous steroids and acyclovir. Eleven days after hospitalization, paraplegia developed to Medical Research Council grade 0/5 despite performing plasmapheresis. MRI confirmed the aggravation of the cord lesion between T4 and T7. Acute transverse myelitis after VZV infection is a rare disease that can cause serious sequelae in immunocompetent patients. Therefore, clinicians should be cautious of this situation.

Keywords: Varicella zoster virus; Transverse myelitis; Immunocompetence

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Introduction

Varicella-zoster virus (VZV) infection is clinically common in otherwise healthy individuals and is characterized by skin rashes and neuropathic pain along the dermatome. After the first infection, the virus becomes latent in the ganglia and reactivates in an immunosuppressed state, causing neurological complications such as postherpetic neuralgia [1,2]. Complications involving the central nervous system such as encephalitis and myelitis, are relatively rare, especially in immunocompetent patients [3]. Here, we report a case of transverse myelitis after VZV infection in an immunocompetent patient.

Case Report

This study was conducted with informed consents of the patient.

A 60-year-old male patient was admitted to our hospital with motor weakness and sensory dysfunction of the right lower extremity. On admission, his vital signs were stable, and he showed normal cranial nerve and cerebellar function. The muscle strength of the upper and left lower extremities was normal, but that of the right lower limb decreased to Medical Research Council (MRC) grade 4/5. Sensation in his right lower extremity also decreased. Despite the motor weakness and sensory dysfunction, he was able to walk independently. Deep tendon reflexes (DTRs) were normal in both upper extremities, but were increased in both the knees and ankles. The Babinski sign was ob-

served on both sides, and the Hoffman sign was observed on the right upper limb.

Magnetic resonance imaging (MRI) indicated nodular enhancement of the spinal cord at the right C3–C4 level (Fig. 1) and hyperintensity of the spinal cord at T6 on T2-weighted imaging (Fig. 2). No other specific brain lesion was observed on brain MRI.

The laboratory findings for complete blood cell count, liver function, kidney function, infection markers, and urine analysis were normal. A cerebrospinal fluid (CSF) study showed an increase in protein (36 mg/dL) and myelin basic protein (4.8 μg/L) levels with an opening pressure of 18 cmH_2O. All bacterial antigens, polymerase chain reaction (PCR) tests, culture studies, and antigen tests, including VZV, were negative (Table 1). All autoimmune antibody tests performed to exclude autoimmune myelitis were also negative (Table 2).

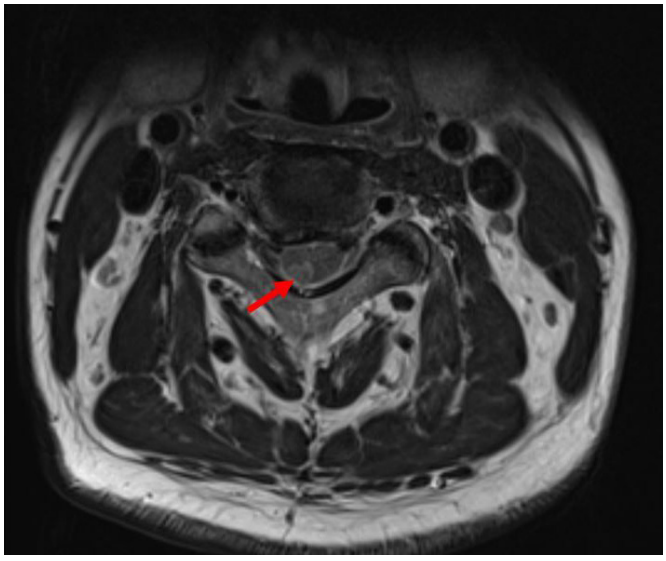

Fig. 1. Image showing the nodular enhancement of right C3-C4 level (arrow) on axial T2 weighted magnetic resonance imaging.

A month prior to admission, the patient had a painful erythematous vesicle on the right T2–T4 dermatome. He was diagnosed with VZV infection of the right T2–T4 dermatome based on clinical symptoms and treated with oral valacyclovir (1,000 mg) for 7 days. After 5 days of valacyclovir administration, the vesicles and pain improved. However, erythematous skin lesions persisted for more than 1 month until his hospitalization for motor weakness and sensory dysfunction. Upon admission, an erythematous skin lesion measuring 4 to 5 cm was observed on the right T2–T4 dermatome.

Considering the history of VZV infection, we diagnosed the patient with acute transverse myelitis (ATM) caused by VZV and started acyclovir (2,100 mg/day) for 14 days, along with steroid pulse therapy (intravenous methylprednisolone [1,000 mg] for 5 days and oral prednisolone 300 mg for 5 days, tapered for 4 days).

On the second day of hospitalization, a somatosensory potential (SEP) test was performed. The SEPs of the left median nerve and bilateral tibial nerves were normal. However, the SEP of the right median nerve had decreased by more than half compared with that on the left side.

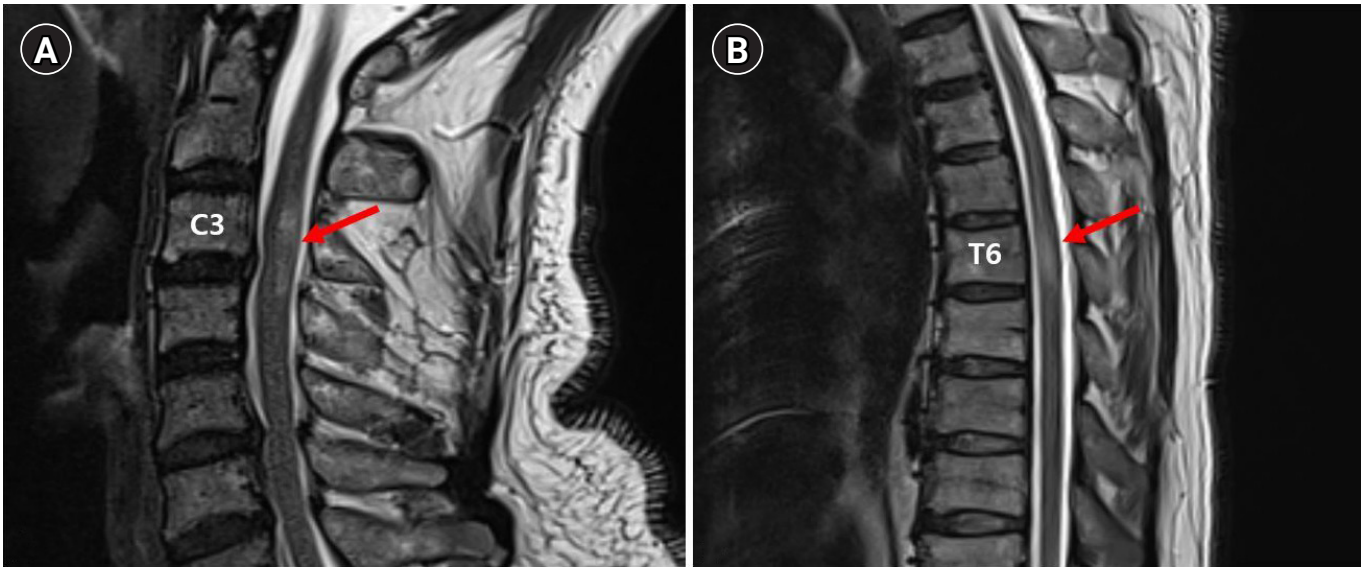

Fig. 2. (A) Image showing high signal intensity between C3 and C4 level (arrows) at day 2 on T2 weight magnetic resonance imaging (MRI). (B) Image showing high signal intensity on T6 level at day 2 on T2 weight MRI.

Table 1. Culture Study, Bacterial and Viral Polymerase Chain Reaction Study and Antibody Test for Cerebrospinal Fluid

Parameter	Result (normal value)
Varicella-zoster virus culture	No virus isolated.
Cytomegalovirus culture	No virus isolated.
HSV culture	No virus isolated
Fungus culture	No growth
Cryptococcus antigen	Negative
Herpes IgM	Negative
Streptococcus pneumoniae	Negative
HIB	Negative
Neisseria meningitidis	Negative
Group B *Streptococcus*	Negative
Listeria monocytogenes	Negative
Epstein-Barr virus	Negative
Human herpes virus-8	Negative
Human herpes virus-6	Negative
Varicella-zoster virus	Negative
Cytomegalovirus	Negative
Enterovirus	Negative
Mumps virus	Negative
HSV type 1	Negative
HSV type 2	Negative
Tuberculosis	Negative

HSV, herpes simplex virus; HIB, Haemophilus influenzae type B.

Table 2. Autoimmune Antibody Study

Parameter	Result
Anti SS-A/Ro Ab	Negative
Anti SS-B/La Ab	Negative
Anti Nuclear Ab	Negative
ASCA	Negative
ANCA	Negative
CH50 (U/mL)	54 (32-58)*
Anti ds-DNA Ab IgG	Negative
Anti ds-DNA Ab IgM	Negative
Anti Cardiolipin IgA	Negative
Anti Cardiolipin IgM	Negative
Anti B2 GPI IgG	Negative
Anti Mitochondrial Ab	Negative
Anti Cardiolipin IgG	Negative
Anti CCP Ab (U/mL)	< 0.5 (0-5)*
Lupus anticoagulant	Negative

ASCA, Anti-Saccaromyces cerevisiae antibodies; ANCA, anti-neurophil cytoplasmic antibody.
*Abnormal values are represented.

On the third day of hospitalization, the patient complained of voiding difficulty. A Foley catheter was inserted, and 950 mL of urine was drained. His lower extremity muscle strength started to deteriorate gradually. On the seventh day of hospitalization, the muscle strength of the lower extremities decreased to MRC grade 2/5. The patient complained of decreased sensation of the C3–C4 dermatomes of the right upper extremity, and no sensation was felt at the dermatome lower than the T6 level. Cervical and thoracic spine MRI, which was performed on the 10th day of hospitalization, confirmed the aggravation of the cord lesion between T4 and T7 (Fig. 3). Nevertheless, the muscle weakness of the lower extremities worsened to MRC grade 0/5, although plasmapheresis was performed. The patient lost perianal sensation and voluntary contraction of the anal sphincter, and the DTRs of the lower extremities disappeared on the 11th day of hospitalization. Upper and lower extremity nerve conduction studies performed on the 13th day of hospitalization were normal. However, needle electromyography (EMG) showed increased insertional activity and positive sharp waves on both sides of the gastrocnemius, tibialis anterior, peroneus longus, vastus medialis, tensor fasciae latae, and thoracic paraspinal muscles, which were compatible with complete thoracic cord lesions [4]. There were no abnormal findings in the muscles of the right upper extremity, such as the biceps, abductor pollicis brevis, and first dorsal interosseous muscle.

After progressing to complete paraplegia, additional plasmapheresis was performed seven times with steroid therapy. However, there was no recovery of motor or sensory function. Motor evoked potential (MEP) and SEP tests were performed to predict the prognosis. The MEP and SEP tests of the lower extremities performed on the 52nd day of hospitalization showed no response (Tables 3, 4), although those of the upper extremities were normal. At that time, the DTRs of both lower extremities showed hyperreflexia, whereas the upper extremity showed normoreflexia.

After 1 year, the patient revisited the outpatient clinic for an evaluation of his disability grade. The muscle strength of the lower extremities remained at MRC grade 0/5, and follow-up MEP and SEP tests of the lower extremities still showed no response (Tables 3, 4).

Discussion

Although VZV infection is common, transverse myelitis caused by VZV is rare, particularly in immunocompetent patients. The pathophysiology of transverse myelitis due to viral infection is known to involve systemic reactions post-infection and the direct invasion of the virus [5,6]. However, the VZV PCR test of CSF is negative in most cases, and the diagnosis is made according to history of viral infection and clinical features [2].

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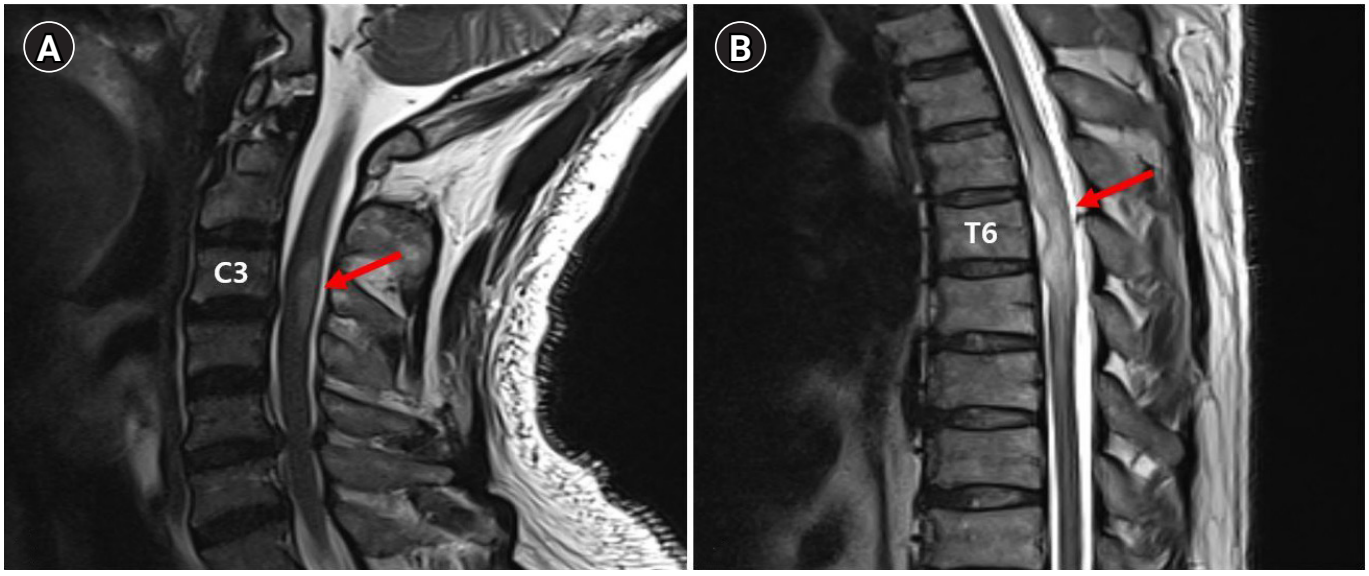

Fig. 3. (A) Image showing high signal intensity between C3 and C4 level (arrow) at day 10 on T2 weight magnetic resonance imaging (MRI). (B) Image showing aggravation of lesion between T4 and T7 (arrow) at day 10 on T2 weighted MRI.

Table 3. Results of the Motor Evoked Potential Study

Nerve	Day 52		After 1 year	
	Latency (ms)	Amplitude (mV)	Latency (ms)	Amplitude (mV)
Abductor pollicis brevis right/left				
100%	22.60/21.46	5.6/6.5	20.99/19.17	9.9/8.4
90%	23.44/23.33	5.4/5.5	21.41/20.42	8.8/7.1
80%	24.27/23.54	5.1/4.6	21.46/21.15	7.8/5.4
70%	25.42/24.27	1.9/1.1	22.08/22.08	1.0/1.1
60%	25.38/24.90	0.2/0.1	23.18/23.21	0.1/0.1
50%	NR/NR	NR/NR	NR/NR	NR/NR
Abductor hallucis right/left				
100%	NR/NR	NR/NR	NR/NR	NR/NR

NR, no response.

Table 4. Results of the Motor Evoked Potential Study

Nerve	Day 5	Day52	After 1 year
Median right/left			
N20 (ms)	20.20/19.00	21.77/19.22	21.04/20.10
P25 (ms)	23.34/26.45	28.23/25.26	26.51/26.15
Amplitude (μV)	2.21/0.64*	3.3/4.4	4.5/3.4
Tibial right/left			
P37 (ms)	40.6/41.1	NR/NR	NR/NR
N45 (ms)	45.98/49.91	NR/NR	NR/NR
P60 (ms)	56.61/59.84	NR/NR	NR/NR

NR, no response.
*Abnormal values are represented.

Likewise, in our case, all viral PCR, culture, and antigen tests were negative in the CSF study, and the diagnosis was made considering the patient's history of VZV infection and clinical presentation.

Steroid pulse therapy is the primary treatment option for ATM. In addition, antiviral agents may improve the prognosis of transverse myelitis caused by viral infection. If severe motor weakness is present, plasmapheresis can be performed, along with steroid pulse therapy [7]. Cyclophosphamide is also an option for patients with acute exacerbations [8]. In this case, steroid pulse therapy was administered along with an antiviral agent, but the patient showed no symptom improvement. Cyclophosphamide was not administered in our case, but it could be considered as a treatment option in the future if a patient shows deteri-

oration during conventional steroid pulse and antiviral treatments. Aggravation of the lesion was confirmed on MRI, and dysuria and lower extremity muscle weakness continued to worsen despite steroid and antiviral treatments. We confirmed complete thoracic cord lesions by a nerve conduction study, EMG, and motor- and sensory-evoked potential tests.

In a previous case report, myelitis caused by viral infections in immunocompetent patients showed a good response to steroid treatment and a good prognosis [2,9]. However, in our case, the patient had a poor prognosis, with complete paraplegia. Definitive prognostic factors for ATM remain unclear, but a poor prognosis is associated with complete paraplegia, rapid disease progression, and abnormal SEP findings [10,11]. Necrosis of the motor tract and sensory tract of spinal cord also has a poor prognosis. In contrast, edema and demyelination of the spinal cord tend to resolve quickly and show a better prognosis than necrosis. If more than 6 months have elapsed since onset, EMG can be used to distinguish between necrosis and edema or demyelination. Therefore, the severity of weakness and abnormal spontaneous activity on EMG is the most specific prognostic factor if more than 6 months have elapsed since onset. However, in the early stage, where denervation has not progressed, it is difficult to differentiate between necrosis, edema, and demyelination using EMG. In this situation, MEP and SEP tests could be helpful [12].

In our case, we performed MEP and SEP tests to predict the prognosis on the 52nd day of hospitalization. No response was observed in the MEP and SEP tests performed on the lower extremities. There was also no recovery of motor or sensory function after 1 year. Although the MEP and SEP tests performed on the upper extremity were normal on the 52nd day of hospitalization, the patient complained of sensory dysfunction in the right upper extremity. After 1 year, the function of the upper extremity had fully recovered, possibly in response to the treatment of transverse myelitis with steroids and antiviral agents. However, thoracic lesions were present.

Furthermore, the symptoms worsened rapidly even with steroids and antiviral drugs. This could have been the natural course of the disease, but it is also possible that the lesions were exacerbated by the steroid treatment. Spinal dural arteriovenous fistula (SDAVF) is a rare cause of transverse myelitis. In cases of SDAVF-induced transverse myelitis, symptoms may be exacerbated by steroid treatment and lumbar puncture [13,14]. We diagnosed VZV-induced ATM with a history of VZV infection and myelopathy at a level similar to that of the dermatome, where the zoster was present. However, it was not possible to confirm the diagnosis because the VZV PCR test and CSF culture were negative. The possibility of SDAVF cannot be completely disregarded because thoracic MRI showed the enlargement of spinal blood vessels at the T4–T7 level (Fig. 4) and the exacerbation of lesions after steroid pulse therapy. However, we could not identify specific findings of SDAVF on MRI, such as prominent serpiginous intradural extramedullary flow voids. Magnetic resonance angiography and spinal angiography could have been helpful for the diagnosis, but they were not performed.

Even in patients with normal immunity, ATM can occur due to VZV and result in a poor prognosis, such as complete paraplegia. Therefore, an active intervention should be considered in the presence of poor prognostic factors such as abnormal MEP and SEP. Myelitis due to SDAVF should also be considered prior to steroid pulse therapy, and any aggravation of symptoms should be noted.

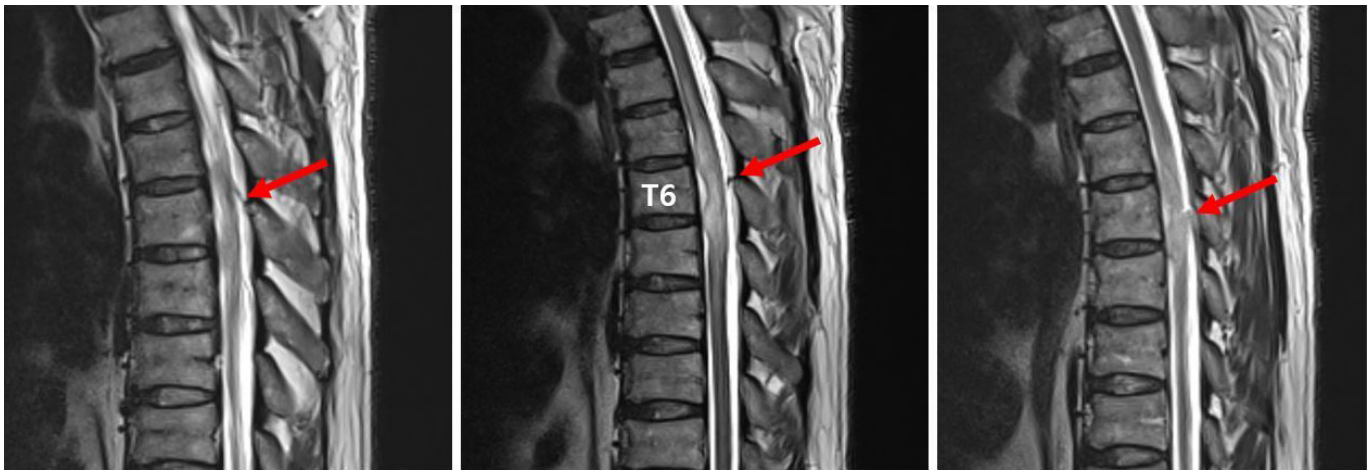

Fig. 4. Image showing the enlargement of perimedullary vessels (arrows) at day 10 on T2 weighted magnetic resonance imaging.

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Conflict of Interest

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Rectus Sheath Hematoma after Contralateral Intercostal Neuropathy as a Complication of Video-Assisted Thoracoscopic Surgery in a Patient with Asthma: A Case Report

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Rectus sheath hematoma (RSH) in patients who have undergone video-assisted thoracoscopic surgery (VATS) has not been reported to date. This report describes a case of RSH in a patient with right abdominal muscle atrophy due to an intercostal nerve injury following VATS. A 61-year-old male patient complained of a bulge in the right upper abdominal quadrant after undergoing VATS. Computed tomography (CT) revealed atrophied right abdominal muscles, including the rectus abdominis, and the electrodiagnostic findings were compatible with right 8th and 9th intercostal neuropathy. The patient visited the emergency room 444 days after undergoing VATS, complaining of a left abdominal mass and pain. He had a severe cough 2 weeks prior due to underlying asthma. CT revealed an RSH in the left abdomen that shrank after 4 weeks of observation. In cases of abdominal muscle weakness due to intercostal neuropathy following VATS, the precipitating factors for RSH must be managed thoroughly.

Keywords: Video-assisted thoracoscopic surgery; Rectus abdominis; Hematoma

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Introduction

Sensory abnormalities are generally the primary symptoms of intercostal nerve injury due to thoracic surgery and usually resolve within a few months [1]. Video-assisted thoracoscopic surgery (VATS) has a lower incidence of intercostal nerve injury than conventional thoracotomy [2]. In extremely rare cases, permanent paralysis of the rectus abdominis (RA) can occur due to intercostal neuropathy after VATS [1,3].

Rectus sheath hematoma (RSH) is an acute or chronic accumulation of blood in the sheath of the RA or within the muscle due to the rupture of an epigastric vessel or muscle. Precipitating factors for the formation of RSH include coagulation abnormalities, trauma, hypertension, pregnancy, and actions that increase intra-abdominal pressure (e.g., coughing, sneezing, vomiting, defecation, or urination) [4]. In cases of delayed RSH diagnosis, unnecessary invasive diagnostic studies or surgery may be performed, and severe bleeding may cause hypotension and even death [5].

To our knowledge, no cases of RSH after abdominal muscle atrophy due to VATS have been reported to date. Therefore, we present a case of RSH that spontaneously occurred in the contralateral abdomen of a patient who presented with symptoms of right abdominal muscle atrophy and pseudohernia due to intercostal neuropathy following VATS.

Case Report

A 61-year-old male patient underwent VATS for a solitary pulmonary nodule biopsy of the right lung. VATS was performed

with the three-port technique. The port insertion sites were in the right sixth intercostal space (ICS) along the posterior axillary line, the 8th ICS along the mid-axillary line, and 9th ICS along the posterior scapular line (Fig. 1A). On the first day after surgery, the patient complained of severe pain and a bulge in the right upper quadrant of the abdomen. The pain partially improved thereafter; however, the bulge did not, and the patient was discharged 1 week later. The bulge was still present at the patient's hospital visit on the 38th day after VATS (Fig. 1A, B). It was not visible in the supine position, but protruded when the patient was sitting or standing. The patient also complained of hypoesthesia and pain in the right abdomen ranging from the xiphoid process to the umbilical level. Abdominopelvic computed tomography (CT) revealed atrophy of the right abdominal muscle, including the RA, from the level of the 9th thoracic vertebra (T9) to the first lumbar vertebra (L1), and no specific mass was observed in the muscle or subcutaneous layer (Fig. 2A).

A nerve conduction study performed 166 days after VATS revealed that compound muscle action potentials were absent in the right 8th and 9th intercostal nerves. In cases of intercostal neuropathy, there are no standardized electrodiagnostic studies other than needle electromyography; therefore, the examination was conducted using the method introduced by Pradhan and Taly [6]. Abnormal spontaneous activities of fibrillation potential and positive sharp waves were observed on needle electromyography at the supraumbilical level of the RA. The electrodiag-

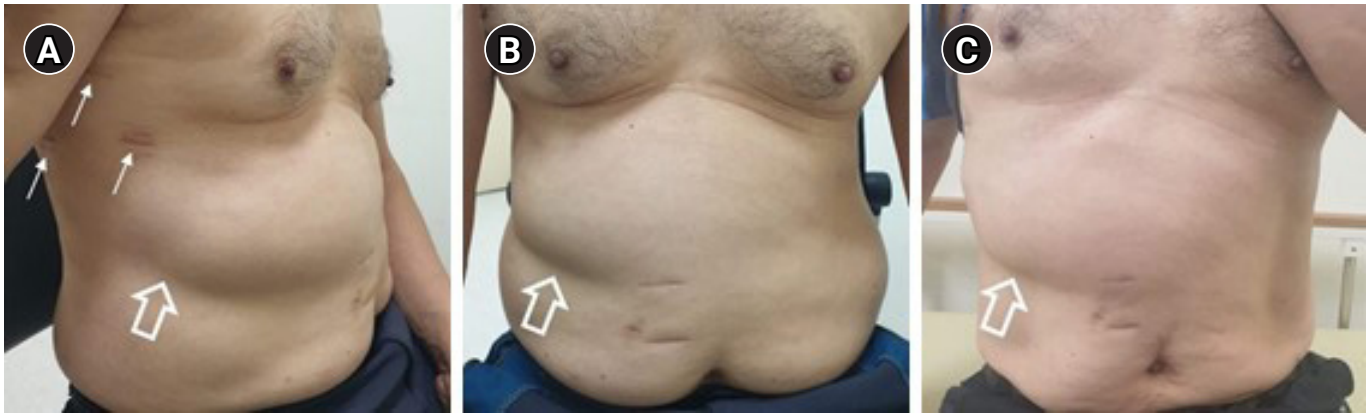

Fig. 1. Photograph of the patient. The photograph shows the video-assisted thoracoscopic surgery (VATS) port insertion site (arrows) (A) and abdominal bulge (open arrows) in the right upper quadrant (A, B) on the 38th day after VATS. The port insertion sites were in the right sixth intercostal space (ICS) along the posterior axillary line, the 8th ICS along the mid-axillary line, and the 9th ICS in the posterior scapular line (A). The abdominal bulge had not changed after 1 month of electrical stimulation therapy on the 185th day after VATS (C). We received the patient's consent form about publishing all photographic materials.

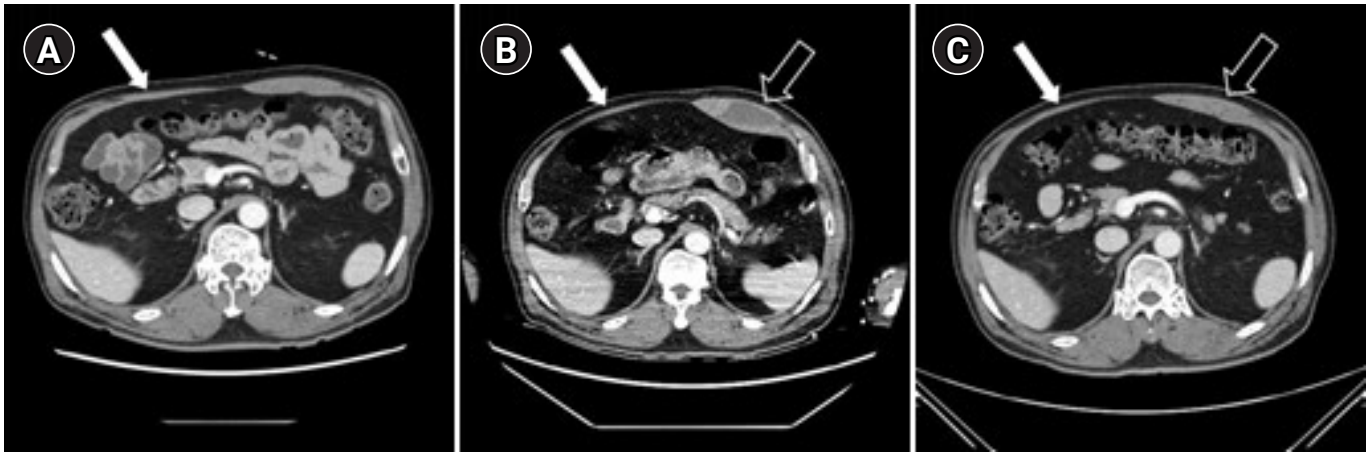

Fig. 2. Abdominal computed tomography (CT) findings of the patient on the 38th day (A), 444th day (B), and 468th day (C) after video-assisted thoracoscopic surgery. CT revealed atrophied abdominal muscles (arrows) in the right upper quadrant (A-C) and rectus sheath hematoma (open arrows) in the left upper quadrant (B) at the level of the 11th thoracic vertebra (T11). The size of the hematoma decreased 24 days later (C).

nostic findings observed in the patient were compatible with right 8th and 9th intercostal neuropathy (Tables 1, 2).

Subsequently, electrical stimulation therapy (EST) was applied primarily to the right RA for 1 month. A study conducted by Lalingkar et al. [7] indicated that performing EST on the RA is beneficial in patients with RA muscle diastasis. EST was delivered at the following settings: frequency, 45 Hz; current, 45 mA; rise time, 1 second; stimulus time, 3 seconds; decay time, 1 second; and relaxation time, 10 seconds. The intervention was conducted for 30 minutes per day, three times a week, for 4 weeks in total. Abdominal muscle atrophy did not improve even after EST, and the patient was lost to outpatient follow-up.

On the 444th day after VATS, the patient visited the emergency room complaining of a left abdominal mass and severe abdominal pain. He had been diagnosed with asthma approximately 20 years ago and was on inhaled corticosteroids. His asthma symptoms were usually well controlled, but he had had a severe cough 2 weeks previously. At the time of the patient's hospital visit, his vital signs were within the normal range and the cough had improved. His laboratory test results were as follows: hemoglobin, 14.6 g/dL; leukocytes, 7,470/mm^3; platelets, 150,000/mm^3; activated partial thromboplastin time, 26.5 seconds; prothrombin time, 10.6 seconds; and international normalized ratio, 0.92. The values were within normal ranges.

Abdominopelvic CT revealed an RSH measuring 80 × 27 × 60 mm in the left abdomen at the le vel of the 11th and 12th thoracic vertebrae (T11 and T12) (Fig. 2B). The medical staff recommended hospitalization; however, the patient refused and was discharged. He visited an outpatient clinic after taking tranexamic acid and acetaminophen for 3 days, and he decided to receive follow-up after 4 weeks without additional treatment after consulting with his doctor in charge. CT performed 24 days later revealed that the size of the RSH had decreased to 30 × 7 × 26 mm (Fig. 2C). However, the atrophy of the right abdominal muscles had not changed (Fig. 2B, C). Subsequently, the patient did not visit the hospital again, and long-term follow-up was not possible.

Discussion

In this article, we report a case of intercostal neuropathy through an electrodiagnostic study in a patient who showed symptoms of abdominal muscle atrophy and pseudohernia after VATS; the patient later developed an RSH. The abdominal muscle atrophy did not improve, but the RSH improved after 4 weeks of follow-up with no further treatment. Cases of abdominal muscle atrophy due to intercostal neuropathy following VATS are very rare [3]. Additionally, no cases of RSH after abdominal muscle atrophy due to intercostal neuropathy have been reported to our knowledge.

Although RA rupture during severe coughing or increased abdominal pressure has frequently been reported, most of these cases have occurred in patients taking anticoagulants [8]. In the present case, no anticoagulants were administered and no obvious hemodynamic abnormalities were found in the results of the laboratory tests performed at the time of admission to the emer-

Table 1. Results of the Intercostal Nerve Conduction Study

Side	Stimulation site (intercostal space)	Recording site of the RA	Latency (ms)	Amplitude (mV)
Right	7th	0–1 cm above the level of the xiphoid process	4.10	2.3
	8th	1–3 cm below the level of the xiphoid process	NR	NR
	9th	2–5 cm above the level of the umbilicus	NR	NR
	10th	1 cm above to 4 cm below the level of the umbilicus	6.70	0.7
Left	7th	0–1 cm above the level of the xiphoid process	3.60	2.5
	8th	1–3 cm below the level of the xiphoid process	4.05	1.3
	9th	2–5 cm above the level of the umbilicus	4.70	1.0
	10th	1 cm above to 4 cm below the level of the umbilicus	6.40	0.7

RA, rectus abdominis; NR, no response.

Table 2. Results of Needle Electromyography

Muscle	IA	Spontaneous activities		MUAPs			Interference pattern
		Fibrillation	PSW	Amplitude	Duration	Polyphasia	
Right rectus abdominis (upper)	Increased	1+	1+	Large	Long	Present	Single
Right rectus abdominis (middle)	Increased	2+	2+	Large	Long	Present	Discrete

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

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gency room. We did not identify any other factors that could induce RSH, except for coughing caused by underlying asthma. Therefore, it is likely that the RA muscle contracted excessively due to severe coughing caused by underlying asthma, thereby damaging the RA and causing RSH [9].

According to a study by Bolser et al. [10], coughing is a defensive reflex characterized by coordinated bursts of activity in the inspiratory and expiratory muscles. Additionally, the anterolateral abdominal muscles (RA, external oblique, internal oblique, and transversus abdominis) act as a unit. However, coordination was impaired in this patient due to atrophy of the right abdominal muscle, and greater pressure was applied to the left abdominal muscle to create abdominal pressure for coughing, which is presumed to have affected RSH formation. However, as mentioned in the study by Lee et al. [5], since RSH can occur, albeit rarely, as a result of severe coughing due to underlying asthma, the possibility that RSH occurred independently without the influence of the contralateral intercostal neuropathy cannot be excluded.

In most cases, conservative treatment, such as rest, analgesic therapy, fluid resuscitation, and anticoagulation reversal, is appropriate for RSH treatment; however, transfusion, angioembolization, and surgical intervention should be considered if necessary [9]. If asthma is a precipitating factor, the general management of bronchospasm, including the appropriate use of corticosteroid medications, should be performed [5]. In the present case, the patient did not receive anticoagulants. The patient refused hospitalization, and the hematoma shrank after 24 days, even though no additional treatment was administered. Additionally, long-term follow-up was not possible. Nevertheless, this case report is meaningful in that it reports a rare clinical condition and emphasizes the need for thorough management of the precipitating factors of RSH in similar situations.

In summary, if the abdominal muscles are paralyzed because of intercostal neuropathy caused by VATS, RSH may occur due to RA damage. Therefore, in similar cases, the precipitating factors of RSH, such as respiratory diseases, must be managed thoroughly.

Conflict of Interest

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

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Neoplastic Lumbosacral Plexopathy in Untreated Cervical Cancer: A Case Report

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In this report, we present the case of a patient with cervical adenocarcinoma with progressive right lower-extremity pain and weakness. Electromyography of the lower extremities and subsequent ultrasonographic imaging complementarily demonstrated findings considered suspicious for the perineural spread of malignancy to the lumbosacral plexus and sciatic nerve. This possibility was confirmed by magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) scanning. This case report suggests that in addition to MRI and FDG PET/CT scans, electromyography and ultrasonographic imaging are valuable modalities for the diagnosis of perineural malignancy.

Keywords: Lumbosacral plexus; Electromyography; Ultrasonography

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Introduction

Although the morbidity of cancer is increasing, its involvement in the peripheral nervous system is relatively uncommon. In particular, neoplastic lumbosacral plexopathy (NLP), which typically manifests as painful neuropathy, is a rare complication that is generally associated with prostate cancer.

According to a previous study, the frequency of cancer metastasis to the lumbosacral plexus is 0.71% [1]. Another research reported the incidence of histologically confirmed parametrial perineural invasion as 7.53% in early-stage cervical cancer patients and that of perineural invasion as 12.5% in the cervical stroma [2,3]. The prevalence of NLP may have been underestimated in previous studies. Therefore, a thorough investigation of metastatic neural invasion is needed.

Computed tomography (CT) or magnetic resonance imaging (MRI) scans are commonly considered as the initial modalities to diagnose NLP [4]. However, these modalities are expensive, and the radiation exposure during CT scans cannot be ignored. In this report, we discuss the case of a patient who was diagnosed with NLP and suggest electromyography (EMG) and ultrasonography as cost-effective and less invasive tools for the early diagnosis of NLP.

Case Report

A 40-year-old female patient complained of rapidly progressive right lower-extremity pain and weakness that had developed over approximately 5 months. Although the patient had been diagnosed with micro-invasive cervical squamous cell carcinoma 1.5 years previously, she declined further examinations and appropriate treatment, such as chemoradiation therapy. Approximately 1 year after the initial diagnosis, the patient started to experience pain, hypoesthesia, and weakness in the right hip and leg. She chose alternative medicine preferentially and received honey bee venom needle therapy for 6 months. However, the symptoms were not relieved; thus, the patient visited a pain clinic and was diagnosed with lumbar disc herniation based on MRI and underwent disc decompression and percutaneous epidural neuroplasty with ballooning; however, this did not alleviate her pain.

Finally, she experienced right foot drop and visited our clinic for an examination.

The initial physical examination revealed that motor function was 0 in both flexors and extensors of the right ankle and toes and poor in the knee flexors and the hip extensors. Motor strength was normal in the other limbs. Hypoesthesia was observed from the right posterior and medial leg to the foot. Vibration sensation and joint positioning of the right toes were diminished. The right ankle reflex was absent. Upper motor neuron signs, including the Babinski sign, were not evident. The patient did not have any urinary or bowel symptoms.

An electrophysiological study suggested severe right multiple lumbosacral radiculoplexopathy from the L5–S4 roots with considerable involvement of the sciatic nerve (Table 1). Nerve conduction studies demonstrated the absence of a motor response from the peroneal and tibial nerves and the absence of a sensory response from the sural nerve in the right lower limb.

On ultrasonography, a remarkably enlarged right sciatic nerve was identified from the gluteal fold to the thigh (Fig. 1A, B). MRI of the pelvis revealed enlargement of the right lower lumbosacral

Table 1. Needle Electromyography in Right Lower Extremity

Muscle	Insertion activity	Abnormal spontaneous activity	Motor unit action potentials			Recruitment
			Polyphasic	Amplitude	Duration	
Right						
Iliopsoas	Normal	-	Normal	Normal	Normal	Complete
Vastus lateralis	Normal	-	Normal	Normal	Normal	Complete
Tibialis anterior	Increased	F&P(+)	No MUAP			
Peroneus longus	Increased	F&P(++)	No MUAP			
Gastrocnemius medial head	Increased	F&P(++)	No MUAP			
Flexor digitorum longus	Increased	F&P(++)	No MUAP			
Flexor hallucis brevis	Increased	F&P(+)	No MUAP			
Tensor fascia lata	Increased	F&P(+)	Inc. polys			Reduced
Gluteus maximus		F&P(+)				Single
Semitendinosus		F&P(++)	Inc. polys			Reduced
External anal sphincter		CRD	Inc. polys			Reduced
L4/5, L5/S1 PVMs	Increased	-				
S1/2, S2/3 PVMs	Normal	-				

F&P, fibrillation potentials and positive sharp waves; MUAP, motor unit action potential; Inc., increased; polys, polyphasic motor units; CRD, complex repetitive discharges; PVM, paravertebral muscle; -, electrodiagnostic test showing right severe right multiple lumbosacral plexopathy from L5 root to S4 root with severe involvement of the sciatic nerve.

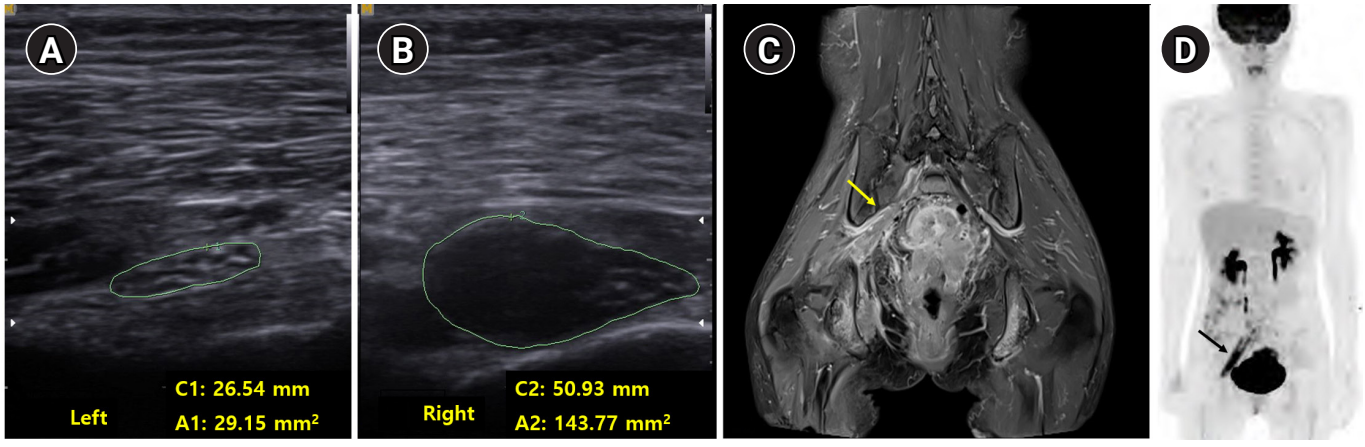

Fig. 1. (A, B) Cross-sectional ultrasonographic image of bilateral sciatic nerve. The area of the sciatic nerve is significantly larger on the right-side (B) than on the left-side (A). C1, C2, circumferences of the sciatic nerve; A1, A2, areas of the sciatic nerve. (C) Magnetic resonance imaging (MRI), (D) Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) images of sciatic nerve. (C) The right lumbosacral plexus (yellow arrow) is remarkably enlarged with a low-signal mass in MRI. (D) Linearly increased FDG uptake (black arrow) is found in the right pelvis on PET/CT.

plexus from the L5–S3 nerve roots to the right sciatic nerve (Fig. 1C). A subsequent fluorodeoxyglucose positron emission tomography/CT (FDG PET/CT) scan demonstrated linear asymmetric hypermetabolic activity in the right pelvis, compatible with swelling of the lumbosacral plexus identified on MRI (Fig. 1D). These findings suggested neural metastases from the L5–S3 nerve roots along the right sciatic nerve.

The patient was clinically diagnosed with stage III C1 cervical cancer (5.4 cm × 5.7 cm × 6.3 cm) with invasion of the right pelvic wall and multiple lymph node metastases. She started concurrent chemoradiation therapy (CCRT) using a cisplatin and 5-fluorouracil regimen and external beam radiation of 63.7 Gy. After completion of 3 cycles of CCRT, the cancer showed partial regression on MRI, and the motor function in the right knee flexors and hip extensors improved from poor to good. However, the foot drop did not show significant improvement.

In a follow-up EMG study, decreased insertional activities with no motor unit action potential were noted in the right tibialis anterior, peroneus longus, gastrocnemius medial head, biceps femoris short head, and tensor fascia lata muscles, and there was no significant interval change.

Discussion

NLP results from the direct neural invasion of tumors or other metastatic diseases. Based on previous studies, the perineural spread of malignancy progresses through the direct infiltration of the perineural space, instead of via lymphatics. Pelvic malignancies, such as uterine, prostate, and rectal cancers, are common causes of NLP. Local perineural invasion can also occur in patients with cervical cancer and has a poor prognosis. Invasion of cervical adenocarcinoma and cervical epidermoid cancer to the sacral nerve roots occurs by a mechanism similar to that of prostate cancer spreading to the sciatic nerve [5].

The innervation of the uterus and the cervix has been defined well in gynecology owing to the development of nerve-sparing surgery, and a direct neural pathway to the sciatic nerve has been discovered. Lateral to the uterosacral ligament, the hypogastric plexus provides both sympathetic and parasympathetic nerves to the uterus, bladder, and rectum [6]. The splanchnic plexus, which originates from the S2–S4 roots, provides sympathetic innervation. The entire sciatic nerve and lumbosacral plexus become prone to metastases after cancer invades the S2–S4 roots.

In this patient with untreated cervical cancer, the EMG study suggested right severe multiple lumbosacral plexopathy from the L5–S4 roots with severe involvement of the sciatic nerve. Subsequent ultrasonographic imaging also demonstrated significant swelling of the right sciatic nerve. Therefore, considering the clinical history of cervical cancer, along with the electrophysiological and ultrasonographic findings, a metastatic lesion of the right lumbosacral plexus was suggested.

Finally, MRI demonstrated an asymmetrical linear thickening, which was supported by increased FDG activity in the PET/CT scan, reflecting the L5–S3 nerve roots and right sciatic nerve invasion.

Frequently, neuropathy or neuritis due to chronic radiation can be incorrectly diagnosed as the perineural spread of malignancy; since the majority of pelvic cancer patients receive radiation therapy, a careful differential diagnosis is important. Thomas et al. [7] compared 20 cases of radiation neuropathy and 30 cases of malignant lumbosacral plexopathy. The radiation neuropathy group reported weakness and numbness as the most common symptoms; however, for the NLP group, pain was the chief complaint.

On EMG, myokymic discharges are frequently observed in patients with radiation-induced neuropathy or plexopathy patients; thus, these discharges are an important electrophysiological characteristic of radiation injury [8]. In this case, no myokymic discharge was observed on EMG. Malignant neuropathy can also be distinguished from radiation neuritis based on MRI. Radiation neuritis is usually restricted to the radiation area and typically shows a thin peripheral "tram-track" pattern of enhancement without irregularity [9]. Concurrently, when the perineural spread of malignancy occurs, it presents comparatively thicker enhancement around the individual nerves and may be asymmetrical, as in the patient in this study [10].

In conclusion, intraneural metastasis in the lumbosacral plexus caused by malignancy is a rare condition, and the majority of cases occur in patients with prostate cancer. In this study, a patient with untreated cervical cancer who experienced lower-extremity weakness and pain was finally diagnosed with neural metastases after several procedures. The study revealed that in addition to MRI and FDG PET/CT scans, EMG and ultrasonographic imaging can be relevant modalities for the diagnosis of perineural malignancy.

Conflict of Interest

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

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Hirayama Disease Diagnosed after COVID-19 mRNA Vaccination in an Adolescent Patient: A Case Report

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Hirayama disease is characterized by initially progressive muscular weakness and wasting of the distal upper limbs in young people. It has a male predominance, and its progression spontaneously arrests within several years. Here, we report the case of a 15-year-old girl with findings of Hirayama disease on spinal magnetic resonance imaging (MRI) after she visited the hospital with unilateral muscle weakness that occurred after coronavirus disease 2019 mRNA vaccination. She was asymptomatic for 3 weeks after vaccination; however, starting the night before hospitalization, her right limb began to lose strength. MRI demonstrated typical Hirayama disease findings.

Keywords: Amyotrophy, monomelic; COVID-19 vaccines; Adolescent

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Introduction

Hirayama disease, also known as benign focal amyotrophy, is characterized by initially progressive muscular weakness and distal upper limb wasting that predominantly affects young men in their 20s and 30s, with spontaneous arrest of disease progression occurring within a few years [1]. Hirayama disease is a self-limiting disorder, but an early diagnosis is needed to prevent deterioration. Although the pathophysiology of Hirayama disease is unknown, circulatory disorders in the spinal cord are hypothesized. Neck flexion tightens the dura and damages the intramedullary microcirculation, causing nerve damage [2]. Therefore, other causes of circulatory and neurological problems might directly or indirectly affect Hirayama disease, and medical staff have noted the coronavirus disease 2019 (COVID-19) vaccine as a possible cause. Its neurological side effects include headache, Guillain-Barré syndrome (GBS), venous sinus thrombosis (VST), transverse myelitis, facial nerve palsy, small-fiber neuropathy, newly developing multiple sclerosis, and others that have been reported only in a few patients [3]. Although the mechanism by which these diseases occur is unknown, hypotheses include antibodies to the COVID-19 vaccine forming a complex causing thrombosis or hyperviscosity of the patient's blood [4].

Here we report a case of Hirayama disease observed on spine magnetic resonance imaging (MRI) in a 15-year-old girl who complained of unilateral muscle weakness after COVID-19 mRNA vaccination.

Case Report

On December 27, 2021, a 15-year-old girl visited a pediatric outpatient clinic. She had received a Pfizer-BioNTech COVID-19 vac-

cine 3 weeks prior. She was asymptomatic at that time, but her right leg began to lose strength the night before the hospital visit. Her symptoms persisted until the following morning, when she visited the hospital. At the outpatient visit, the left upper and lower extremities were asymptomatic, but the right upper and lower extremities showed a manual muscle test grade of fair to good, and the distal muscles were weaker than the proximal muscles. The light touch sensation on the right half of her body, excluding the face, was decreased. The patient was admitted to the Department of Pediatrics for a differential diagnosis of cervical myelopathy, GBS, and a brain tumor. After hospitalization, brain MRI, nerve conduction studies (Table 1), and somatosensory evoked potential studies (Fig. 1) were performed in collaboration with the neurologists at the hospital. Most of the test results were within the normal range. However, contrast-enhanced spinal MRI showed enlargement of the posterior epidural space with epidural venous plexus engorgement and enhancement at the cervicothoracic junction to the T8 level. The prominent posterior epidural vessels appeared consistent with the imaging findings of Hirayama disease (Fig. 2). It is known that Hirayama disease does not usually invade the lower extremities. Therefore, this patient had an atypical presentation. Regarding the reason for the involvement of the lower extremities, the medical staff kept in mind the possibility that it was accompanied by conversion disorder. The MRI showed typical Hirayama disease findings, and the final diagnosis was Hirayama disease.

On December 30, the patient was referred to the Department of Rehabilitation Medicine, where an evaluation revealed the following: Berg Balance Scale score, 45 points; K-Modified Barthel Index score, 61 points; a full range of motion; motor assessment scale scores, 52 points on the right side and 54 points on the left side; Motricity Index: upper extremity, 59.0 points and lower extremity, 56.0 points; functional ability assessment, 18 points; Fugl-Meyer Assessment (FMA) of the upper body, 116 points on the right side and 126 points on the left side; FMA of the lower body, 73 points on the right side and 86 points on the left side; and weakness of right finger extension and adduction, a "fair plus" result in manual muscle tests. In addition, in a blood test conducted on December 31 to differentiate other diseases that cause muscle weakness, such as GBS, Miller Fisher syndrome, and neuromyelitis optica, negative results were obtained for anti-GM1 immunoglobulin G (IgG) isotype, anti-GD1B IgG isotype, anti-GQ1b IgG, and anti-aquaporin 4 IgG. In the COVID-19 antibody assays, the Roche total antibody value was 201 U/mL and the Abbott IgG value was 4,621 AU/mL, 7.5 times higher than the maximum Roche antibody value (26.7 U/mL) measured 1 month after vaccination and 6.3 times higher than the maximum Abbott IgG antibody value (732.8 AU/mL) [5]. In short, the increase in the antibody load after the COVID-19 vaccination was abnormally high. Although the exact mechanism was difficult to determine, the medical staff assumed that the elevated antibody load may have affected the development of Hirayama disease in some way.

Discussion

This is the first report of Hirayama disease after COVID-19

Table 1. Nerve Conduction Studies of This Case

Nerve	Stimulation site	Recording site	Amplitude (mV or μV)		Latency (ms)		Conduction velocity (m/s)		F-wave latency (ms)	
			Right	Left	Right	Left	Right	Left	Right	Left
Motor										
Median	Wrist	APB	17.6	15.6	3.0	2.9	-	-	24.7	23.6
	Elbow	APB	17.2	15.1	6.8	6.6	61.8	62.2	-	-
Ulnar	Wrist	ADM	16.4	13.9	2.0	2.2	-	-	23.7	23.2
	Below elbow	ADM	15.4	13.3	5.6	5.4	61.1	62.5	-	-
Peroneal	Ankle	EDB	12.0	12.6	3.3	2.8	-	-	NR	40.4
	Below fibular	EDB	11.2	12.0	9.0	8.8	52.6	52.5	-	-
Tibial	Ankle	AHB	36.0	34.2	4.0	3.6	-	-	43.5	42.7
	Popliteal fossa	AHB	31.1	28.3	11.0	10.6	52.9	52.9	-	-
Sensory										
Median	Wrist	Second finger	31.6	36.5	2.2	2.2	-	-	-	-
Ulnar	Wrist	Fifth finger	23.2	25.9	2.0	2.1	-	-	-	-
Sural	Calf	Lateral malleolus	31.9	30.6	2.6	2.5	-	-	-	-
H-reflex	Popliteal fossa	Soleus	-	-	24.4	25.0	-	-	-	-

APB, abductor pollicis brevis; ADM, abductor digiti minimi; EDB, extensor digitorum brevis; AHB, abductor hallucis brevis; NR, no response; -, not applicable.

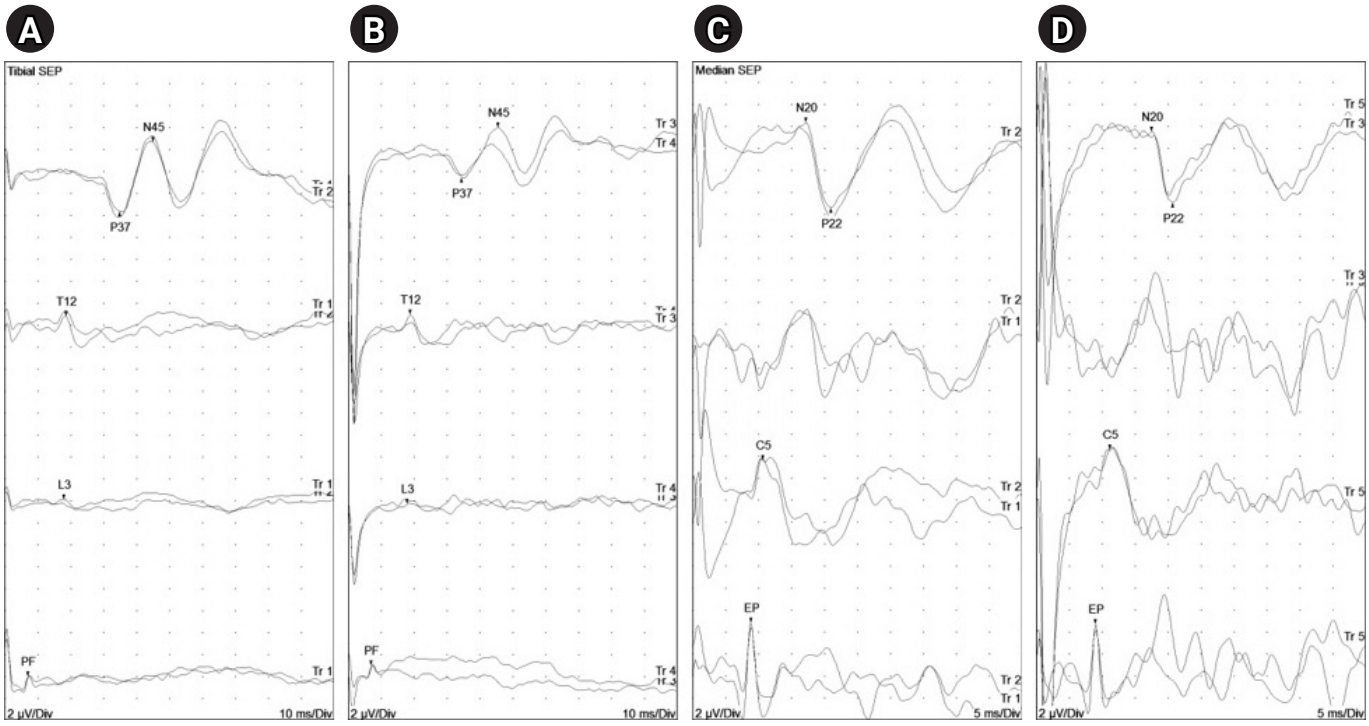

Fig. 1. (A) Left tibial somatosensory evoked potentials (SEPs). (B) Right tibial SEP. (C) Left median SEP. (D) Right median SEP.

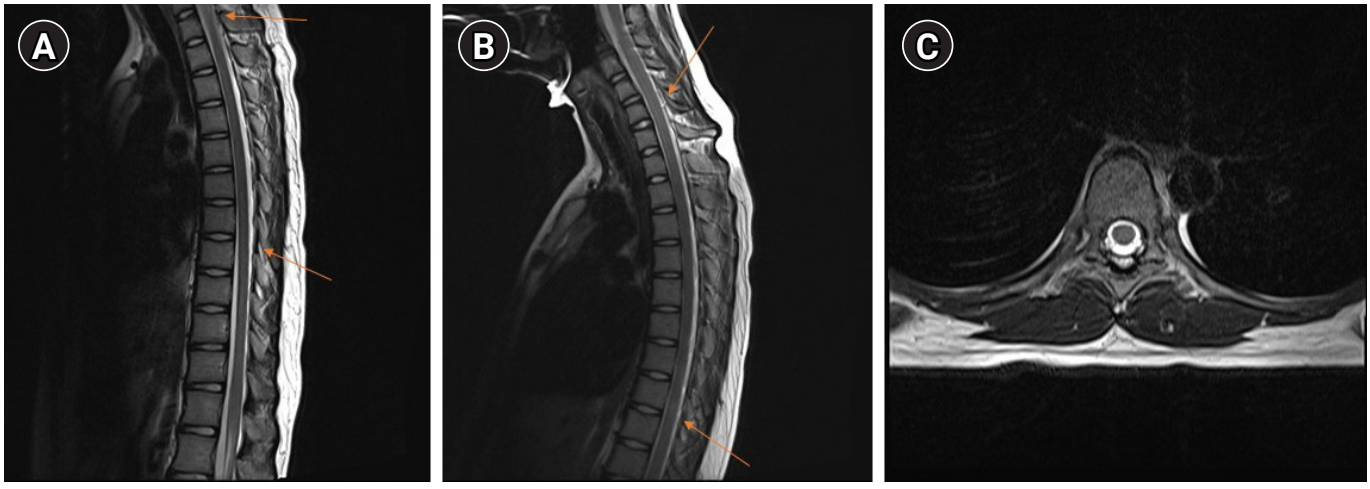

Fig. 2. (A) Cervical magnetic resonance imaging (MRI) in the neutral position revealed an enlarged posterior epidural space with epidural venous plexus engorgement (arrows) and enhancement at the C-T junction to the T8 level. (B) Cervical MRI with neck flexion showed prominent posterior epidural vessels (arrows). (C) Axial T2-weighted MRI in the neutral position.

mRNA vaccination in a female adolescent. Hirayama disease occurs in young people in their 20s and 30s and much more often in male than in female patients at a ratio of 20:1 [1]. It shows an insidious onset and slow progression of muscular atrophy in the distal upper limbs, including the thenar, hypothenar, interossei muscles, and wrist flexors and extensors, but it spares the brachioradialis muscles [6]. The amyotrophy is unilateral in most patients, but it can be bilateral. Most patients show "cold paresis" symptoms, in which the finger muscles weaken in cold environments. Paresthesia is uncommon; however, in some patients, local sensation is lost in both hands. Most (73%) patients stop developing symptoms within 5 years [1]. Amyotrophic lateral sclerosis, spinal muscle atrophy, C8–T1 radiculopathy, compressive myelopathy, cervical spondylotic myelopathy, syringomyelia,

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post-polio syndrome, multifocal motor neuropathy, and toxic neuropathy should be considered in the differential diagnosis [7]. To differentiate Hirayama disease from the above-mentioned diseases, nerve conduction velocity, electromyography (EMG), motor-evoked potentials (MEPs), and cerebrospinal fluid (CSF) tapping can be performed, and MRI yields the most characteristic findings. In previous research, EMG showed acute and chronic denervation of the atrophied muscles [8], while the findings of nerve conduction velocity and CSF tapping analyses were almost normal [2]. If MEPs are measured after transcranial magnetic stimulation is performed with neck flexion, the latency increases and the amplitude decreases, suggesting the pathogenic role of neck flexion in this disease [9]. Neck flexion on MRI is diagnostic for Hirayama disease, with characteristic findings of focal hyperintensities on T2-weighted images of the anterior caudal segments of the cervical spinal cord [10]. Our patient had no symptoms of muscle atrophy, but MRI showed a typical pattern of Hirayama disease, including an enlarged posterior epidural space with epidural venous plexus engorgement, enhancement at the cervicothoracic junction to the T8 level, and prominent posterior epidural vessels in the flexion view.

In response to the current COVID-19 pandemic, vaccines are being administered to minimize complications. However, neurological complications can occur from the vaccination itself, including headache, GBS, VST, transverse osteomyelitis, facial neuropathy, small nerve neuropathy, and multiple sclerosis, as mentioned earlier [3]. In our patient, spinal cord damage occurred due to the immune response to the vaccination; the diagnosis of Hirayama disease was made based on the MRI findings, despite the lack of full consistency with the clinical features. Given the observation of an excessively increased COVID-19 antibody load, this overreaction may have affected the blood vessels of the spine via thrombosis, hyperviscosity of the blood, or other unknown mechanisms by forming an immune complex.

Further research is needed, but considering the findings of the current case, attention should be paid to the possibility of Hirayama disease in the current circumstances of widespread Pfizer-BioNTech COVID-19 vaccination among Asian adolescents. Although no cases have been reported, if the above symptoms occur after vaccination, the possibility of Hirayama disease should be considered.

Conflict of Interest

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

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Severe Isolated Peripheral Polyneuropathy without Myelopathy after Nitrous Oxide Abuse: A Case Report

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Nitrous oxide (N_2O) abuse induces vitamin B_{12} deficiency, resulting in complications in the central and peripheral nervous systems. Some cases related to subacute combined degeneration or myeloneuropathy after N_2O abuse have been reported. However, isolated peripheral polyneuropathy without spinal cord involvement has rarely been reported in South Korea. We describe a 29-year-old woman who had inhaled "happy balloons" daily (1,000 balloons/day) for recreational purposes over 3-month period, and presented with acute symmetrical hypoesthesia, paresthesia, and motor weakness on the bilateral lower limbs. Serologic tests showed megaloblastic anemia and vitamin B_{12} deficiency. Magnetic resonance imaging of the brain and spine showed no abnormalities. An electrodiagnostic study confirmed lower limb-dominant axonal sensorimotor polyneuropathy due to vitamin B_{12} deficiency from N_2O abuse. The patient was treated with intramuscular vitamin B_{12} replacement. A follow-up electrodiagnostic study 4 months after the initial study showed only partial improvement. Despite the legal efforts of the Korean government to ban the use of N_2O other than for medical purposes, cases of complications from its abuse are on the rise, especially among young adults. Physicians should recognize the strong possibility of N_2O abuse as an underlying cause of vitamin B_{12} responsive polyneuropathy with or without spinal cord involvement.

Keywords: Nitrous oxide; Polyneuropathy; Vitamin B 12 deficiency

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Introduction

Nitrous oxide (N_2O) has been used historically for anesthetic purposes in medical treatment for a long time. However, an increasing number of young adults misuse so-called "happy balloons" as a way to consume this gaseous agent for recreational purposes, resulting in various medical complications among abusers. N_2O is known to inactivate vitamin B_{12}, interfering with the methionine synthase cycle, which is vital for stabilizing the myelin sheath. Cases have been reported in the literature of vitamin B_{12} deficiency leading to axonal degeneration and demyelination in both the central and peripheral nervous systems, ultimately resulting in subacute combined degeneration (SCD) or myeloneuropathy [1–5]. In South Korea, isolated peripheral polyneuropathy (PN) induced by N_2O abuse without myelopathy has been rarely reported; moreover, detailed electrodiagnostic study data and information on the associated amount of inhalation have also been deficient [3]. Herein, we report a case of a patient who developed isolated acute sensorimotor axonal PN after heavy N_2O intoxication, including electrodiagnostic study findings. The study was approved by the Ethics Committees of the Presbyterian Medical Center (approval number: E2022-09).

Case Report

A 29-year-old woman with history of clinical depression presented to our department with a 3-month history of symmetrical hypoesthesia, paresthesia, and motor weakness of the bilateral lower limbs. She complained of voiding difficulty along with intermittent fecal incontinence; and required assistance in ambulating due to gait disturbance. In general, the patient was in otherwise good health. Her social history showed that she worked as a professional cheerleader and had engaged in a daily habit of inhaling "happy balloons" (total usage: 1,000 balloons) for 3 months until the sudden presentation of the aforementioned symptoms. The patient's past medical history was significant for a recent short-term inpatient admission at another hospital due to poor oral intake accompanied by episodes of melena with epigastric pain, which was treated with a proton pump inhibitor.

On a manual muscle test, motor weakness was evident on ankle dorsiflexion (grade: 1 out of 5), plantarflexion (grade: 2 out of 5), and in other lower limbs (grade: 3 out of 5) bilaterally and symmetrically, while the upper limbs were both normal (grade 5 out of 5). Pain and temperature sensation were normal, but the sense of light touch and pinprick was markedly reduced below the bilateral knees. Deep tendon reflexes at the bilateral ankles were diminished. Although the patient required assistance during ambulation, her coordination was normal; there were no pathologic reflexes nor Lhermitte's sign, and Romberg's test was negative.

The initial serologic test showed anemia and vitamin B_{12} deficiency: hemoglobin, 8.0 g/dL (normal range, 12–16 g/dL); red blood cell count, 2.61 × 10^6/mm^3 (normal range, 3.8–5.4 × 10^6/mm^3); mean corpuscular volume, 91 fL (normal range, 79–100 fL); and vitamin B_{12}, 135.8 pg/mL (normal, 197–771 pg/mL). The vitamin B9 level was normal (5.6 ng/mL; normal range, 3.9–26.8 ng/mL). Follow-up laboratory testing performed after 2 weeks showed a hemoglobin level of 9.4 g/dL (normal range, 12–16 g/dL), a red blood cell count of 2.87 × 10^6/mm^3 (normal range, 3.8–5.4 × 10^6/mm^3), a mean corpuscular volume of 102 fL (normal range, 79–100 fL); and a peripheral blood smear consistent with megaloblastic anemia. Brain and full-spine T2-weighted sagittal magnetic resonance imaging was negative, excluding any evidence of cervical nervous system involvement. Urodynamic studies, assessments of anal contraction, deep anal pressure, and perianal sensation could not be elucidated as the patient declined these components of a comprehensive physical examination and diagnostic workup.

An electrodiagnostic study was performed 3 months after the initial onset of symptoms. Motor nerve conduction studies (NCS) demonstrated delayed onset latencies and low amplitudes for the bilateral tibial and right median compound muscle action potentials (CMAPs) with decreased nerve conduction velocities. The bilateral peroneal CMAPs were unobtainable. Sensory NCS showed delayed latencies and low amplitude of bilateral superficial peroneal and tibial sensory nerve action potentials (Table 1). F-wave, H-reflexes, and evoked potentials were not tested due to patient's poor compliance with the study. Needle electromyography (EMG) demonstrated abnormal spontaneous activity (ASA) and decreased interference patterns in both tibialis anterior and peroneus longus muscles, and ASA with unobtainable motor unit action potentials in both extensor digitorum brevis muscles (Table 2). The results of the test were compatible with severe sensorimotor PN (mainly axonal injury) involving the lower extremities.

To treat her vitamin B_{12} deficiency, the patient received daily intramuscular injections of 1 mg of vitamin B_{12} (Actinamide; Shin Poong Pharm Inc., Ansan, Korea) for 7 days, with recommendations to taper down to once a week for a month and lifelong maintenance of monthly injections along with 1 mg of oral cyanocobalamin supplement (Vitamedin; HK innoN, Seoul, Korea). The patient's serum vitamin B_{12} level after 3 months of supplementation increased to 539.1 pg/mL (normal range, 197–771 pg/mL). As the patient refused an assessment of voiding difficulty, her subjective symptoms of urgency with hesitancy were managed pharmaco-therapeutically, using a cholinergic agonist, which led to partial resolution of these urinary symptoms.

Seven months after the initial onset of symptomatology, motor strength in ankle dorsiflexion showed partial improvement from grade 1 to 2, while a sensory examination, including proprioception, remained abnormal. However, the patient could walk without assistance using bilateral foot orthoses. In a follow-up electrodiagnostic study, there was no significant improvement. Bilateral peroneal and tibial CMAPs were unobtainable; the bilateral superficial peroneal muscles showed prolonged amplitudes and latencies, while the tibial muscles continued to show no response on NCS (Table 3). Needle EMG demonstrated ASA in both the tibialis anterior and gastrocnemius muscles (Table 4). The result was still consistent with known sensorimotor PN (mainly axonal injury) involving the lower extremities.

Discussion

Vitamin B_{12} is a cofactor for methionine synthase and methylmalonyl-CoA mutase, which are involved in the production of DNA and myelin. N_2O, by inactivating cobalamin, interferes with the methionine synthase cycle and affects both the central and peripheral nervous systems, resulting in demyelination and axonal degeneration of the dorsal and lateral columns of the spinal cord,

Table 1. Findings of the Initial Nerve Conduction Study

Nerve site	Latency (ms)		Amplitude (mV)		CV (m/s)	
	Right	Left	Right	Left	Right	Left
Motor NCS						
Median						
Wrist	3.7	3.3	8.8	10.3		
Elbow	8.0	7.3	5.0	6.4	46.5*	52.5
Ulnar						
Wrist	2.4	2.3	11.7	13.4		
Elbow	6.5	6.3	12.4	12.4	51.2	50.0
Peroneal						
Ankle	NR*	NR*	NR*	NR*		
Fibular head	NR*	NR*	NR*	NR*	NR*	NR*
Tibial						
Ankle	7.9*	4.7*	0.1*	0.1*		
Popliteal fossa	18.2*	14.2*	0.1*	0.1*	32.8*	35.7*
Sensory NCS						
Median						
Index-wrist	2.3/2.9	2.2/2.8	35.6	36.5		
Ulnar						
Finger-wrist	1.8/2.6	1.8/2.4	37.0	39.9		
Superficial peroneal						
Ankle	4.4/5.0*	3.9/4.9*	5.7*	7.1*		
Sural						
Calf	4.4/5.2*	3.8/4.5*	9.1*	9.9*		

Amplitudes are measured in millivolts (mV, motor) and microvolts (μV, sensory); onset/peak latency is used in sensory nerve conduction.
CV, conduction velocity; NCS, nerve conduction study; NR, no response.
*Abnormal value.

Table 2. Initial Findings of Needle Electromyography in the Bilateral Lower Extremities

Muscle	Insertion activity	Spontaneous activity			Motor unit action potential		
		Fibrillation	PSW	Fasciculation	Duration/ amplitude	Phases	Recruitment
Right							
Tibialis anterior	Normal	0	1+	0	Normal	Increased	Reduced
Peroneus longus	Normal	1+	1+	0	Normal	Normal	Markedly Reduced
EDB	Normal	0	2+	0	Absent	Absent	Absent
Left							
Tibialis anterior	Normal	0	1+	0	Normal	Increased	Reduced
Peroneus longus	Normal	0	1+	0	Normal	Normal	Reduced
EDB	Normal	0	1+	0	Absent	Absent	Absent

PSW, positive sharp wave; EDB, extensor digitorum brevis.

white matter in the brain, peripheral, and cranial nerves [6]. Bouattour et al. [7] reported that patients with vitamin B_{12} deficiency showed sensorimotor neuropathy, mainly of the axonal type, with demyelinating features as the major electrodiagnostic findings.

Patients who engage in N_2O abuse often complain of acute onset of motor weakness and hypoesthesia, which are more severe in the distal lower limbs, and this pattern appears to be associated with electrodiagnostic study findings of axonal sensorimotor neuropathy mainly in the lower extremities in a dose-dependent manner [8–10]. Our patient had an admitted history of daily inhalation, totaling 1,000 happy balloons, for 3 months with sudden evident motor and sensory deficits, likely attributable to axonal sensorimotor PN in the lower extremities. Interestingly, our case showed no involvement of the central nervous system on imaging.

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Table 3. Findings of the Follow-Up Nerve Conduction Study

Nerve site	Latency (ms)		Amplitude (mV)		CV (m/s)	
	Right	Left	Right	Left	Right	Left
Motor NCS						
Median						
Wrist	3.0	2.9	9.6	9.6		
Elbow	6.8	6.8	9.3	9.4	55.2	53.8
Ulnar						
Wrist	2.3	2.2	11.9	12.9		
Elbow	6.3	6.0	13.3	13.1	55.0	55.2
Peroneal						
Ankle	NR*	NR*	NR*	NR*		
Fibular head	NR*	NR*	NR*	NR*	NR*	NR*
Tibial						
Ankle	NR*	NR*	NR*	NR*		
Popliteal fossa	NR*	NR*	NR*	NR*	NR*	NR*
Sensory NCS						
Median						
Index-wrist	2.3/2.9	2.2/2.7	34.0	36.4		
Ulnar						
Finger-wrist	1.8/3.1	1.7/2.9	31.3	37.9		
Superficial peroneal						
Ankle	2.4/3.1	4.3/5.1*	8.0*	8.5*		
Sural						
Calf	4.6/5.7*	4.8/5.8*	8.0*	5.9*		

Amplitudes are measured in millivolts (mV, motor) and microvolts (μV, sensory); onset/peak latency is used in sensory nerve conduction.
CV, conduction velocity; NCS, nerve conduction study; NR, no response.
*Abnormal value.

Table 4. Findings of Follow-Up Needle Electromyography in the Bilateral Lower Extremities

Muscle	Insertion activity	Spontaneous activity			Motor unit action potential		
		Fibrillation	PSW	Fasciculation	Duration/ amplitude	Phases	Recruitment
Right							
Tibialis anterior	Normal	0	2+	0	Normal	Increased	Reduced
Peroneus longus	Normal	0	1+	0	Normal	Increased	Reduced
EDB	Normal	0	0	0	Normal	Normal	Reduced
Left							
Tibialis anterior	Normal	0	2+	0	Normal	Increased	Reduced
Peroneus longus	Normal	0	2+	0	Normal	Normal	Reduced
EDB	Normal	0	0	0	Normal	Normal	Reduced

PSW, positive sharp wave; EDB, extensor digitorum brevis.

Lee et al. [3] reported two cases of isolated PN from N_2O intoxication; however, the duration of intoxication was within a month, no information was presented regarding the amount of inhalation, and sensory rather than motor symptoms were the chief complaint.

In determining the main cause for vitamin B_{12} deficiency in our case, several limitations are considered. These include (1) the patient's history of taking a proton pump inhibitor to address the episode of melena; (2) poor intake during the gaseous agent abuse period, which could have also contributed to low vitamin B_{12} levels; and (3) failing to check serum levels of homocysteine and methylmalonic acid, which can also reflect deficiency levels. However, vitamin B_{12} deficiency is known to be related to long-term adherence to a strict vegan diet and prolonged use of proton

Table 5. Cases of Polyneuropathy Following Nitrous Oxide Abuse Reported in Korea

Study	Age (y)	Sex	Amount of inhalation	Duration of inhalation	Signal change in MRI	Initial electrodiagnostic study	Follow-up study
Lee et al. [1]	22	Female	> 100	6 wk	+	Mixed type motor dominant PN	Partial improvements in H-reflex, CMAP of median nerve
	33	Male	2, 3 per week (20 at a time)	7 mo	+	Axonal motor dominant PN	No significant change
Kwon et al. [4]	22	Female	> 100	2 mo	+	Axonal motor dominant PN	Not done
	33	Male	Up to 5 L (daily)	6 mo	+	Axonal motor dominant PN	Not done
Kim et al. [5]	26	Male	400	3 wk	+	Normal NCS, abnormalities in SEPs	Not done
Choi et al. [2]	24	Male	Daily inhalation	5 mo	+	Sensorimotor PN of lower limbs	Not done
	22	Female	Daily inhalation	3 mo	+	Sensorimotor PN of lower limbs	Partial improvements in tibial SEPs
Current case	29	Female	> 1,000 (daily)	3 mo	-	Sensorimotor PN of lower limbs	No significant change

MRI, magnetic resonance imaging; PN, polyneuropathy; CMAP, compound motor unit action potential; NCS, nerve conduction study; SEP, somatosensory evoked potential.

pump inhibitors. Our patient had a history of a significantly higher amount of N_2O than other reported cases of SCD from N_2O abuse in Korea, as presented in Table 5 [1,2,4,5]. Considering the amount of gas inhalation and the acute onset of presentation of sensorimotor impairment in our patient, we can infer that N_2O abuse was a major factor contributing to vitamin B_{12} deficiency in this patient.

N_2O abuse has long been a social issue in Korea. After escalating overuse and deaths associated with its abuse, in 2017 the Korean government banned the use of N_2O other than for medical purposes, as was the case in the United Kingdom under the Psychoactive Substances Act in 2016. Despite legal efforts, case studies related to the harmful effects of N_2O abuse continue to be reported, and there is likely to be a larger public health crisis involving victims of N_2O abuse among young adults in their 20s and 30s (Table 5), who are unaware of the potentially serious complications of abuse.

In conclusion, our report presents a case of isolated sensorimotor PN of the lower extremities following a short period of N_2O abuse. Clinicians should suspect and firmly consider the underlying possibility of N_2O abuse to prevent serious complications, especially in young adults presenting with vitamin B_{12} deficiency PN, and actively promote efforts to improve social awareness of its abuse as a potential public health crisis.

Conflict of Interest

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

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Instructions for Authors

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

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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.

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