pISSN: 2733-6581
eISSN: 2733-659X

JEND

Journal of Electrodiagnosis and Neuromuscular Diseases

VOL. 25
NO. 1
APRIL
2023

JEND
Journal of Electrodiagnosis and Neuromuscular Diseases

VOL. 25, NO. 1 APRIL 2023
Pages 1-50

JEND
Journal of Electrodiagnosis and Neuromuscular Diseases

KOREAN ASSOCIATION OF EMG
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e-jend.org

pISSN 2733-6581
eISSN 2733-659X

Vol. 25, No. 1 April 2023

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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Publisher
Korean Association of EMG Electrodiagnostic Medicine

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#805, 26 Sangwon 1-gil, Seongdong-gu, Seoul 04779, Korea
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Published on April 30, 2023

JEND Journal of Electrodiagnosis and Neuromuscular Diseases

Editorial Board

pISSN: 2733-6581 · eISSN: 2733-659X

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pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2023;25(1):1-18
https://doi.org/10.18214/jend.2022.00227

Etiopathogenesis of Fibromyalgia

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Fibromyalgia is characterized by chronic widespread pain, and it is often accompanied by various symptoms such as fatigue, sleep disturbance, mood changes, cognitive dysfunction, and several somatic symptoms. The etiopathogenesis of fibromyalgia remains poorly understood, but it is thought to be caused by complex interactions among genetic predisposition, environmental factors, and biological factors. Emerging evidence suggests that central sensitization, which is characterized by impairment in the processes of pain perception, transmission, and modulation, plays an important role in fibromyalgia. Although various treatments have been used for fibromyalgia, patients still suffer from uncontrolled symptoms. Fibromyalgia still has many challenges to be solved. In this review, we discuss existing evidence on the etiopathogenesis of fibromyalgia.

Keywords: Fibromyalgia; Central nervous system sensitization; Pain

Received: November 29, 2022
Accepted: March 29, 2023

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Introduction

Fibromyalgia (FM), as the name implies, it is a disease accompanied by musculoskeletal pain throughout the body. This pain is chronic and widespread, with multiple tender points. In addition to pain, the disease is characterized by stiffness, fatigue, sleep disturbance, mood disorder, cognitive dysfunction, and various somatic symptoms. FM is the third most common musculoskeletal disease after low back pain and osteoarthritis. It is more common in women than in men, and its prevalence has been reported to be 2% to 5%, with some variation among studies. FM may also appear concurrently with other diseases such as infection, rheumatic disease, and neurological/psychiatric diseases, among others [1-4].

Although numerous studies have been conducted regarding the etiopathogenesis of FM, there are still many gaps in our understanding. There is no evidence that a single factor causes FM; instead, it is thought that FM is induced by a combination of genetic predisposition, environmental factors (such as physical and psychological stressors), and biological factors (such as sleep disorders, immunological abnormalities, neuroendocrine dysfunctions, psychiatric comorbidities, and neuroinflammation, among others) (Fig. 1). Central sensitization, which refers to abnormal hypersensitivity to pain due to errors in pain recognition and processing in the brain, is considered to play an important role in FM (Fig. 2) [5-7].

For the diagnosis of FM, the 2016 revised FM diagnostic criteria based on the 1990 American College of Rheumatology criteria are most commonly used [8]. However, since there is no specific biomarker for the diagnosis of FM and the diagnosis is made clinically, early diagnosis remains a challenge.

The diversity of clinical manifestations and underlying problems of each patient makes FM difficult to treat in clinical practice. In order to overcome these problems, clinicians have used combinations of non-pharmacological and pharmacological treatments, but the results remain disappointing. More effective

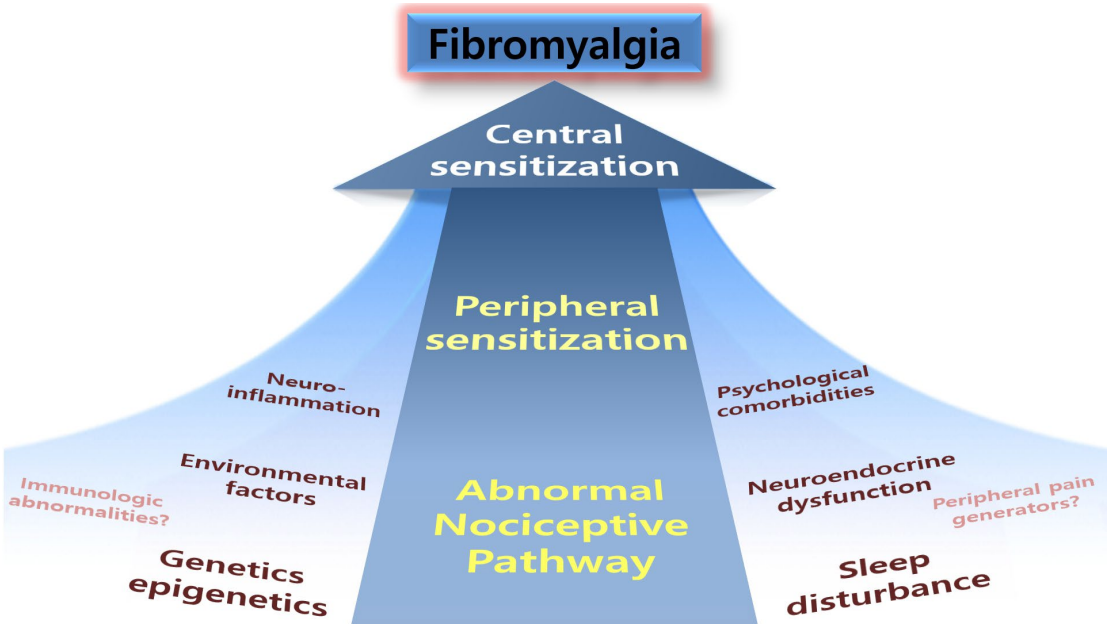

Fig. 1. Etiopathogenesis of fibromyalgia.

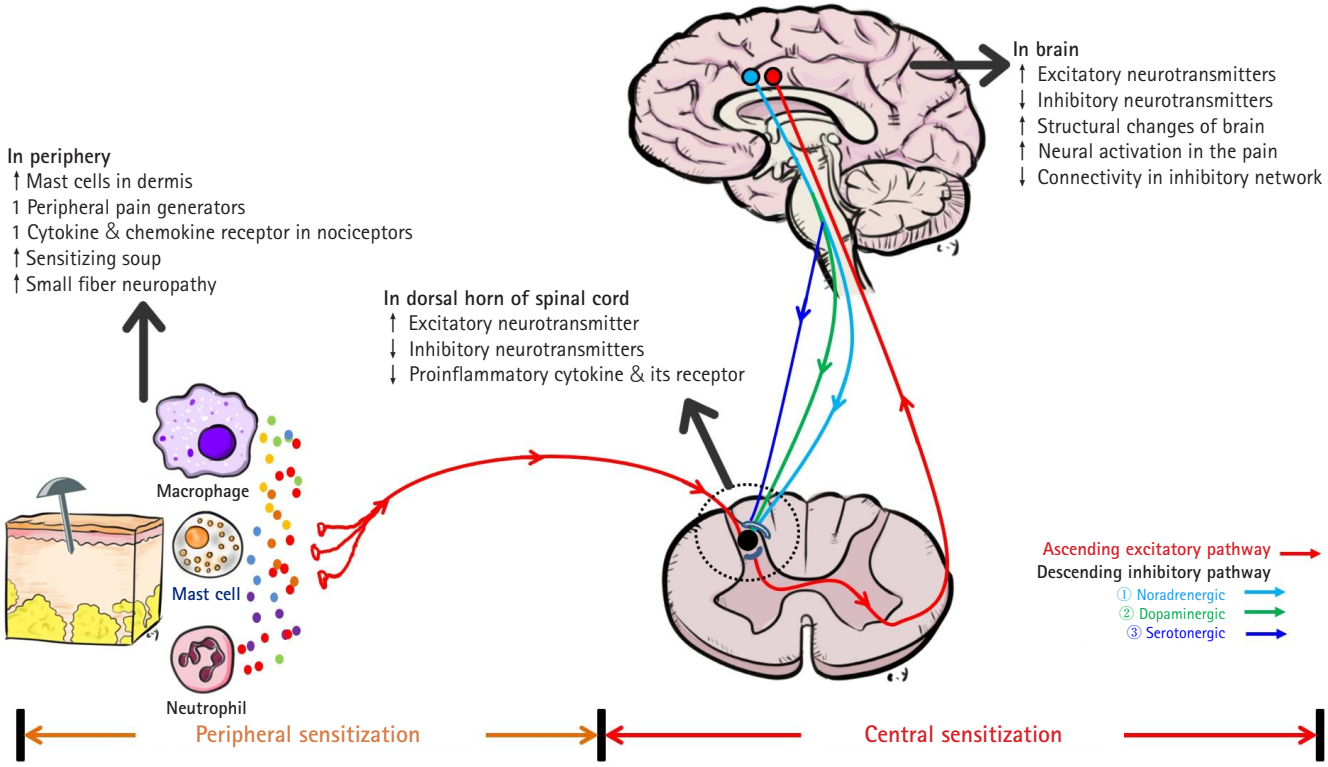

Fig. 2. Pain mechanisms in fibromyalgia.

and appropriate treatment is needed because many FM patients do not reach treatment targets and their daily lives are severely restricted. To this end, a better understanding of the etiopathogenesis of FM is required to facilitate the development of effective treatments.

Here, we aim to provide an overview of the etiopathogenesis of FM by reviewing studies to date.

 https://doi.org/10.18214/jend.2022.00227

Etiopathogenesis of Fibromyalgia

1) Genetics and epigenetics

(1) Genetic factors

The fact that epidemiological studies of FM show a distinct familial tendency suggests that genetic predisposition may play an important role in the pathogenesis of FM. The first-degree relatives of patients with FM were 8.5 times more likely to have FM than the first-degree relatives of patients with rheumatoid arthritis [9].

In a genome-wide association study with 116 families from the Fibromyalgia Family Study , the prevalence of FM in the general population was 2%, but its prevalence in siblings of patients with FM was 13.6%, indicating familial aggregation. Associations were observed in D17S2196 (empirical P [Pe] = 0.00030) and D17S1294 (Pe = 0.00035) in the chromosome 17p11.2-q11.2 region. This chromosome 17p11.2-q11.2 region matches the serotonin transporter (*SLC6A4*) and transient receptor potential vanilloid 2 (*TRPV2*) genes, which are potential candidate genes for FM [10]. In a genome-wide expression profiling study comparing 70 FM patients with 70 healthy controls, FM patients showed differential expression of 421 genes related to the pain pathway compared to the control group [11]. A genome-wide association study was conducted on 6,914 patients complaining of chronic widespread musculoskeletal pain registered with the UK Biobank and 242,929 control subjects. Loci for ring finger protein 123 (*RNF123*), which is involved in calcium regulation, and ATPase secretory pathway Ca2+ transporting 1 (*ATP2C1*) showed statistically significant associations in FM patients [12].

Genetic predisposition accounts for about 50% of disease susceptibility in chronic widespread pain, including FM [13]. Many genes associated with pain may also be involved in the pathogenesis of FM. Representative candidate genes include genes involved in the catecholaminergic, serotonergic, and gamma-aminobutyric acid (GABA)ergic pathways, μ-opioid receptors, and voltage-gated sodium channels [14-16].

In a single-nucleotide polymorphism (SNP) study, the GABA A receptor, beta 3 (*GABRB3*), trace amine associated receptor 1 (*TAAR1*), and guanylate binding protein 1 (*GBP1*) genes, which are associated with chronic pain, showed significantly different allelic frequencies in FM patients compared to the control group [14]. Next, we will examine the genes associated with neurotransmitters and receptors that play an important role in the pain pathway.

Serotonin and serotonin receptors play diverse roles in regulating the central nervous system. Dysregulation of the serotonergic system is involved in the pathogenesis of neurological disorders and pain, as well as psychiatric disorders such as anxiety, depression, schizophrenia, and autism [17-19]. Several studies have shown that specific genes related to the serotonergic system are also involved in the pathogenesis of FM. The frequency of carriers of the 102C allele of the 2A serotonin receptor gene (*HTR2A*) was significantly higher in patients with FM than in the control group, and FM patients had worse perceptions of environmental factors [20]. A meta-analysis also confirmed that the 102T/C polymorphism of the 5-HT2A receptor was linked to FM [21]. The frequency of the S/S genotype in the promoter region of the gene encoding the serotonin transporter (5-HTT) was significantly higher in patients with FM than in the control group, and depression and psychological distress were higher in the S/S subgroup [22].

Dopamine, epinephrine, and norepinephrine are catecholamine neurotransmitters that play an important role in various neurological disorders and pain control. Catechol-O-methyltransferase (COMT), a catecholamine-degrading enzyme, regulates the catabolism of catecholamine neurotransmitters. The activity of the COMT enzyme is regulated by major genotypic polymorphisms of alleles (Val/Val, Met/Met, Val/Met). Among homozygotes, the Val/Val genotype has the highest enzymatic activity and the Met/Met genotype has the lowest enzymatic activity, while heterozygotes, with the Val/Met genotype, exhibit moderate enzymatic activity [23,24]. The homozygous low activity (Met/Met) and heterozygous low activity (Val/Met) genotypes of *COMT* were predominant in FM patients compared to controls [25]. Among polymorphisms of the *COMT* gene, the Val158Met polymorphism has been studied the most, and has been found to be involved in various clinical symptoms including FM pain [26-28]. However, in a large-scale retrospective study examining the effect of the *COMT* gene on FM in 2,713 patients, no direct association between pain sensitivity-associated *COMT* haplotypes and FM pain was observed [29]. The *COMT* gene is the most studied gene in terms of FM susceptibility, but additional research is needed to clarify its association with FM.

Dopamine is involved in pleasure, motivation, and motor control, as well as pain modulation [30,31]. Dysregulation of the dopaminergic system is presumed to play an important role in the pathogenesis of FM [32]. FM patients showed a lower frequency of a dopamine D4 receptor polymorphism that had been reported to be related to novelty seeking than controls [33].

The dopamine receptor D3 (*DRD3*) Ser9Gly polymorphism was associated with lower thermal pain thresholds and diffuse noxious inhibitory control efficacy in patients with FM than in controls [34]. In a study evaluating the A118G rs1799971 polymorphism in the opioid receptor μ1 (*OPRM1*) gene, the 118G

allele frequency was significantly lower in the FM patient group than in the control group, and pressure pain thresholds were also lower. This suggests that the 118G polymorphism may have a protective effect against FM [35]. In addition, it was found that the functional polymorphism of *OPRM1* was associated with alterations in the fronto-parietal network, as well as with increased activation of the posterior cingulum during pain induction in patients with FM, suggesting that OPRM1 may play a role in pain processing [36].

Translocator protein (TSPO) is upregulated during glial activation in chronic pain patients. The high-affinity binding genotype (rs6971) of *TSPO* in FM patients was associated with higher pain intensity and more severe symptoms [37].

TRPV channels play an important role in pain signaling pathways. In a study of Korean FM patients, the GTA haplotype of *TRPV2* played a protective role against FM. Polymorphisms of *TRPV3* were reported to be associated with FM symptom severity [38]. In another study of Korean subjects, SNPs and haplotypes of the brain-derived neurotrophic factor (*BDNF*) gene, which is involved in the survival, growth, and differentiation of neurons during the development of the central and peripheral nervous system, have also been found to increase susceptibility to FM and contribute to symptoms [39].

In addition, in a large candidate gene association study, the *TAAR1*, regulator of G protein signaling 4 (*RGS4*), cannabinoid receptor 1 (*CNR1*), and glutamate ionotropic receptor ampa type subunit 4 (*GRIA4*) genes were associated with FM [14].

These studies show that genetic factors can influence both susceptibility to FM and the severity of symptoms. However, since genetic factors do not completely explain the pathogenesis of FM, additional research is needed not only on individual genes, but also on the effects of combinations of various genetic mutations and interactions with environmental factors.

(2) Epigenetics

Gene-environmental associations have recently attracted attention as an etiology of FM. Epigenetics is the study of how environmental factors affect gene operation without altering the DNA sequence. Unlike genetic changes, epigenetic changes are reversible and can alter the expression of DNA sequences through mechanisms such as DNA methylation, histone modification, and non-coding RNA. It has been reported that these epigenetic changes in pain-related regions frequently occur during inflammation and nerve damage [40-42].

In a study examining genome-wide methylation patterns of female FM patients, *BDNF*, N-acetyltransferase 15 (*NAT15*), histone deacetylase 4 (*HDAC4*), protein kinase C, alpha (*PRKCA*), reticulon 1 (*RTN1*), and protein kinase, cGMP-dependent, type I (*PRKG1*) were identified as genes associated with differentially methylated sites in patients [43]. In a study examining changes in DNA methylation profiles, FM patients showed 1,610 differentially methylated positions, which were related to DNA repair pathways, mitochondria-related processes, synaptic signaling, MAPK signaling pathway, regulation of actin cytoskeleton, and focal adhesion. It was related to the cytoskeleton and focal adhesion. FM patients also showed hypomethylation DNA patterns in regions rich in genes involved in stress response and DNA repair/free radical clearance [44]. Patients with FM and chronic fatigue syndrome had significantly higher serum *BDNF* levels and lower *BDNF* DNA methylation than the control group. This was related to patients' symptoms and widespread hyperalgesia [45].

MicroRNAs are short non-coding RNA molecules composed of approximately 20 to 22 nucleotides and can regulate gene expression in disease processes and physiological pathways. About 30% of human genes are regulated by microRNAs, and each microRNA can repress hundreds of genes [46,47]. In a study evaluating the genome-wide profile of microRNAs in the cerebrospinal fluid (CSF) of patients with FM, the expression levels of nine microRNAs (miR-21-5p, miR-145-5p, miR-29a-3p, miR-99b-5p, miR-125b-5p, miR-23a-3p, 23b-3p, miR-195-5p, miR-223-3p) were significantly lower than those in the control group. Among them, miR-145-5p showed a statistically significant positive correlation with Fibromyalgia Impact Questionnaire pain and fatigue scores [48]. In a study examining 374 circulating microRNAs in 20 female FM patients and healthy women, those with FM had lower levels of seven microRNAs (miR-103a-3p, miR-107, let-7a-5p, miR-30b-5p, miR-151a- 5p, miR-142-3p, and miR-374b-5p) and higher levels of miR-320a. Among them, miR-103a-3p showed a correlation with pain and sleep quantity in patients with FM, and miR-320a and miR-374b-5p showed inverse correlations with pain and the pain threshold, respectively [49].

The pathogenesis of FM is presumed to be caused by the complex interaction of various factors. Epigenetics is a very attractive possible explanation for the interaction between genetic predisposition and environmental factors [50], and it seems to be an area that requires further research.

2) Environmental factors

The environmental factors presumed to be involved in the pathogenesis of FM can largely be divided into physical and psychological stressors. Physical stressors include infection, repeated stimulation, mechanical/physical trauma, surgery, and accidents,

https://doi.org/10.18214/jend.2022.00227

among others, and psychological stressors include chronic stress, mental abuse, emotional trauma, and sexual abuse. These environmental factors are presumed to contribute to the pathogenesis of chronic pain, such as FM, through stimulation of the neuro-endocrine system [51-55].

In animal studies using rats and mice, repeated exposure to cold stress, swim stress, and sound stress induced thermal hyperalgesia and persistent deep mechanical hyperalgesia, which were relieved by antidepressant treatment [56-59]. In addition, repeated forced swimming stress reduced basal and pain-evoked release of GABA in the spinal cord [60]. Another study confirmed that the use of gabapentin and pregabalin inhibited the secretion of glutamate, an excitatory neurotransmitter [61]. Blocking N-methyl D-aspartate (NMDA) receptors in the central nervous system has been shown to block exercise-induced hyperalgesia [62].

Some infections, such as hepatitis C virus, hepatitis B virus, human immunodeficiency virus, and *Borrelia burgdorferi*, have been reported to be associated with the development of FM [63]. A cohort study conducted on the prevalence of FM 10 years after a *Giardia lamblia* outbreak was recently published. The prevalence of FM was approximately three times higher in the group exposed to *G. lamblia*, and FM was associated with irritable bowel syndrome and chronic fatigue. Although this result alone cannot prove a causal relationship, there did seem to be a close relationship [64].

Physical trauma is a trigger for FM and chronic pain, but it is difficult to prove a causal relationship. In some studies, the prevalence of FM after a car accident was reported to be between 1% and 22% [65-67]. In addition, physical stressors such as surgery, terrorism, or war experiences contribute to the onset of FM [68-70]. Stress is presumed to play an important role to the extent that FM is considered a stress-related disease, but this may vary depending on intensity, type, and exposure time of stress. In a community-based study, significant tenderness in FM was strongly associated with psychological distress and somatization [71]. In the British Birth Cohort Study, which was conducted from 1958 onward, chronic widespread pain in adulthood was more common among participants whose childhood experiences included hospitalization due to a traffic accident, residence in institutional care, maternal death, and familial financial hardship [72]. In addition, sexual or emotional assault/abuse can contribute to the onset of FM [73,74].

These psychological/physical stressors can cause various changes in the body. In the normal response to stress, the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis are activated [75-78]. However, if stress is excessive or lasts for a long time, dysregulation occurs, leading to FM and other chronic diseases [79-81]. Chronic stress can lead to neuroendocrine abnormalities such as HPA axis dysregulation, which can lead to a relative decrease in cortisol. It has been reported that metyrapone-induced hypocortisolism significantly lowers pain thresholds and amplifies the temporal summation of pain [82]. It was confirmed that taking 40 mg of orally administered hydrocortisone significantly reduced capsaicin-induced pain and neurogenic hyperalgesia, such as that in response to pinprick stimuli [83]. In addition, it has been reported that negative emotions such as anger and sadness directly amplify pain regardless of the presence or absence of FM [84].

3) Biological factors

(1) Dysfunction of the neuroendocrine system

The HPA axis is an important component of adaptive responses to stress, and dysfunction of the HPA axis has been found in patients with FM [85]. The HPA axis regulates neurotransmitters through interactions with the brain's serotonergic, noradrenergic, and dopaminergic systems, as well as stress. The final product, cortisol, acts on various tissues, among which the hypothalamus is an important target and can regulate the expression of various neurotransmitters [86,87]. Plasma cortisol levels in patients with FM have shown various results depending on the study, but there are many reports of dysregulation of circadian changes. FM patients have a lower cortisol response to corticotropin-releasing hormone (CRH) than normal controls [75]. In a study using patients with rheumatoid arthritis as a control group, a significant loss of diurnal variation in plasma cortisol levels was observed in patients with FM [88]. Another study reported that patients with FM had less diurnal fluctuation in cortisol than normal controls, indicating that the elasticity of the HPA axis had been lost [89]. In patients with FM, the concentration of CRH in the CSF was associated with pain [90]. Chronic stress also reduced total cortisol release by decreasing adrenal reactivity in patients with FM [91].

Growth hormone is mainly secreted during non-rapid eye movement (NREM) sleep, and is involved in not only growth, but also repair of micro-damage to muscle tissue. Growth hormone also promotes the production of Insulin-like growth factor 1 in the liver, and it has been found that both of these hormones are present in lower levels in patients with FM than in controls [92,93]. However, it is not yet clear whether these changes affect the development of FM or whether they are secondary changes caused by sleep disturbance in FM.

The ANS maintains homeostasis largely by regulating balance between the sympathetic nervous system and the parasympa-

thetic nervous system. In FM, abnormal findings in the sympathetic nervous system are observed, contributing to several clinical features. Sympathetic hyperactivity is accompanied by increased emotional distress and decreased heart rate variability in FM. FM patients showed decreased nighttime heart rate variability, which indicated sympathetic predominance, a feature significantly correlated with FM symptoms such as pain intensity, constipation, and depression [94].

Overactivation of the sympathetic nervous system is associated with several symptoms of FM, but it remains unclear whether it is the cause.

(2) Sleep disturbance

Patients with FM often complain of feeling tired and not refreshed when they wake up in the morning, even after sleeping for a long time. Daytime sleepiness is also frequent. Sleep disturbance is very common in FM, occurring in about 90% of patients [95], and it may simply be a symptom of FM, but it can also be viewed as an etiological factor. There is evidence that sleep disturbance usually precedes the onset of pain [96].

An 11-year prospective cohort study targeting the general population reported that poor sleep, obesity, and chronic disease could predict widespread chronic pain [97]. In early studies, patients with FM exhibited NREM sleep disturbance, but even in healthy subjects, sleep disturbances have been found to induce muscle pain and tenderness similar to FM [98,99]. In a longitudinal study of 12,350 Norwegian women who had never been diagnosed with FM, 327 were diagnosed with FM on follow-up. There was a dose-dependent association between sleep problems and the risk of FM, and the adjusted relative risk of FM was reported to be 3.43 (95% confidence interval, 2.26 to 5.19) in women with a high frequency of sleep disturbance [100]. These findings strongly suggest that sleep disturbance may contribute to the onset of FM.

Sleep disturbance is associated with the exacerbation of various FM symptoms, including pain severity, tenderness point, fatigue, and depression [101-106]. Sleep also plays an important role in the pain pathway. Even in healthy individuals, sleep disorders inhibit the descending inhibitory pain pathway [107-109].

The mechanism by which sleep disturbance contributes to the exacerbation of symptoms of FM, especially pain, is as follows. First, In patients with FM, it is often observed that the alpha activity abnormally intrudes into the delta activity region in slow-wave sleep (stage 3 of NREM sleep). Slow-wave sleep has been found to reduce pain through synaptic downscaling [110,111]. Disrupted slow-wave sleep not only increases the pain response by lowering the musculoskeletal pain threshold, but is also associated with FM-like symptoms such as discomfort, fatigue, and decreased energy [101]. Therefore, it is presumed that alpha activity interferes with the pain suppression effect of normal delta activity, resulting in increased pain in FM [112]. Second, the thalamus plays an important role in sensory transmission pathways. Meanwhile, the thalamocortical circuit controls sensory information and NREM sleep [113]. In FM patients, reduced connectivity has been observed in the thalamus and premotor areas, right insula and primary sensorimotor areas, and supramarginal and prefrontal areas [114]. This reduced connectivity of the thalamic pathway or dysfunctional primitive thalamus lowers the restorative function of sleep, which can trigger somatic and psychological symptoms of FM [115]. Third, substance P (SP) was found to cause sleep disturbance in animal studies. Elevation of SP in plasma and CSF was observed in FM patients, suggesting that it may be a possible cause of sleep disturbance in FM patients [116-118]. Fourth, sleep disturbance can promote nociception through an increase in proinflammatory cytokines, such as interleukin 6 (IL-6) [119]. Last, sleep disturbance is also closely related to other fibromyalgia symptoms. The pain caused by fibromyalgia activates the sympathetic nervous system and causes various symptoms, which also reduces sleep efficiency, and eventually has adverse effects each other [120].

Both experimental and epidemiological studies suggest that sleep dysfunction can cause FM and is also closely associated with various FM symptoms. Conversely, FM can further promote sleep disorders, creating a vicious cycle through mutual influence.

(3) Psychiatric and psychological comorbidities

In total, 30% to 60% of FM patients have accompanying psychiatric disorders, such as anxiety or depression [121,122]. In a recent meta-analysis, the most common comorbidities in patients with FM were depression and major depressive disorder, with prevalence rates of 43% and 32%, respectively [123]. On functional magnetic resonance imaging (fMRI) in patients with FM, depression was associated with the magnitude of pain-evoked neuronal activation in brain regions associated with affective pain processing (the amygdala and contralateral anterior insula) [124]. Depression and FM are highly correlated in terms of genetic predisposition. A serotonin transporter promoter region (5-HTTLPR) polymorphism associated with anxiety-related personality traits has also been observed in FM [125]. Forebrain regions related to pain control include the limbic system, which is also involved in stress response and mood regulation [126]. In addition, HPA axis abnormalities, microglial activation, and proinflammatory cytokines, which are involved in the pathogen-

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esis of FM, may be commonly involved in the pathogenesis of depression [127-131]. Various symptoms of FM severely interfere with the patients' daily and work life, which can lead to additional psychosocial problems, such as anxiety and social isolation.

(4) Immunological abnormalities

Recent studies have reported that immunological mechanisms may be involved in the pathogenesis of FM. When serum immunoglobulin G (IgG) extracted from FM patients was intraperitoneally injected into mice, mechanical and cold hypersensitivity, reduced locomotion, reduced skin innervation, and increased nociceptor excitability were observed in the mice. In addition, biopsies showed that the patients' IgG was bound to satellite glial cells in the mouse lumbar dorsal root ganglia (DRG), and showed higher immunoreactivity than IgG from healthy individuals. The activation of satellite glial cells induces chronic pain through increased neural activity. This suggests that autoantibodies from patients with FM can bind to antigens in the DRG of mice without systemic inflammation [132].

It has also been reported that antibodies to 5-hydroxytryptamine (5-HT), gangliosides, and phospholipids are detected at high frequency in patients with FM and chronic fatigue syndrome [133,134]. FM was confirmed to be associated with thyroid disease. Thyroid disease can exacerbate the symptoms of FM, and the frequency of thyroid autoantibodies has been confirmed to be high in FM patients [135,136]. Some studies have reported that immunological mechanisms may play an important role in FM, but overall evidence is lacking.

(5) Neuro-inflammation

A) Cytokines

Several studies have reported that proinflammatory cytokines are involved in the pathogenesis of FM. Serum concentrations of proinflammatory cytokines, IL-6, IL-8, IL-1β, and tumor necrosis factor α (TNFα) are increased in FM, while the concentrations of anti-inflammatory cytokines are decreased [137-140]. In a recent meta-analysis, the levels of TNF-α, IL-6, and IL-8 (proinflammatory cytokines) and IL-10 (an anti-inflammatory cytokine) were significantly higher in peripheral blood in FM patients than in healthy controls. This study suggests that cytokines may be involved in the pathogenesis of FM [141]. Peripheral nociceptors express various cytokine and chemokine receptors [142]. When these are stimulated, neuronal activity is activated and can play an important role in peripheral sensitization [143,144]. Spinal dorsal horn neurons also express various proinflammatory cytokine receptors [145]. Proinflammatory cytokines can enhance excitatory synaptic transmission in neurons of the spinal cord and suppress inhibitory synaptic transmission [141]. Patients with FM exhibit higher IL-8 levels in CSF than healthy controls [146]. IL-8 is synthesized in microglial cells and astrocytes and is involved in pain control [147]. Blocking IL-8 receptors relieved pain in a mouse model [148]. This suggests that IL-8 may also be an important target for treatment in FM patients.

Proinflammatory cytokines can induce the sensitization of peripheral neurons by increasing reactivity to nitric oxide and prostaglandin E2 [149]. It may also be involved in the pathogenesis of FM by affecting the HPA axis, the sympathetic nervous system, and immune cells [150,151]. Although several studies on cytokines were limited by various types of bias, they generally suggested that cytokines can contribute some extent to the pathogenesis of FM.

B) Neuropeptides

Neuropeptides are small chains of amino acids synthesized and secreted by neurons, and are defined as various neuroactive substances responsible for communication between neighboring neurons. More than 100 different neuropeptides have been identified that regulate nerve activity and function in tissues such as the intestine, muscle, and heart [152].

Nerve growth factor (NGF), calcitonin gene related peptide (CGRP), SP, glutamate, serotonin, norepinephrine, GABA, and dopamine are representative neuropeptides related to pain. They play a very important role in peripheral sensitization and central sensitization, which will be described later. Adrenomedullin, neurokinins, and vasoactive intestinal peptide are also neuropeptides contributing to pain pathways [153].

SP is secreted from the terminals of specific sensory nerves and contributes to the inflammatory response and pain in the brain and spinal cord, as well as peripheral nerves. When the SP level increases, the sensitivity to pain increases as well. It was found that the concentration of SP in the CSF of patients with FM was two to three times higher than that of normal controls [154,155].

CGRP regulates motor, sensory, and integration systems in the central nervous system, as well as synaptic transmission through inhibition of acetylcholine esterase expression at the neuromuscular junction in the peripheral nervous system. It is a neuropeptide that plays a very important role in peripheral and central sensitization in the pain pathway [156-158]. Serum CGRP and CGRP receptor protein levels were significantly elevated in FM patients compared to healthy controls [159].

Glutamate is a representative excitatory neurotransmitter that

plays an important role in brain metabolism [160]. Glutamate is found at high levels in the insula and posterior cingulate, which control pain and emotion processing in the cerebrum of patients with FM [161-163].

NGF is a neuropeptide involved in the growth, maintenance, and survival of neurons and also plays an important role in pain regulation. Compared to normal controls, a significant increase in the concentration of NGF was observed in the CSF of patients with FM [163]. In a study comparing plasma BDNF and NGF levels between FM patients and healthy controls, no significant difference was observed between the two groups [164]. Further studies are needed to explore these conflicting results.

Serotonin, which is also known as 5-HT, is a monoamine neurotransmitter that plays an important role in pain control as well as mood, cognition and memory. In patients with FM, lower levels were observed than in normal controls, and were associated with pain, fatigue, and depression. This decrease in serotonin may also contribute to the development of FM [165].

Dopamine, another important neurotransmitter, has been found to be involved not only in pleasure, motivation and motor control, but also in the descending inhibitory modulation of pain in the brain [166]. Because dopamine is involved in both pain regulation and affective processing, impaired dopaminergic neurotransmission may play a particularly important role in the pathogenesis of FM.

The CSF concentration of the opioid peptide nociceptin was found to be significantly higher in FM patients than in healthy controls. Nevertheless, it was reported that FM patients had a significantly lower pressure threshold and more tender points than the control group. This may be helpful in explaining the mechanism by which the endogenous opioid system is already fully activated in FM patients, and thus exogenous opioids are ineffective [167,168].

Decreased levels of inhibitory neurotransmitters, such as serotonin, norepinephrine, and dopamine, and elevations in excitatory neurotransmitters such as SP, glutamate, and NGF are key pain amplification mechanisms. An imbalance in these neurotransmitters may be a cause of the onset of FM (Fig. 2) [163,169,170].

4) Other factors

(1) Peripheral pain generators

Local abnormalities such as osteoarthritis, enthesopathies, meniscal injury, bursitis, neuropathy, myofascial trigger points, ligamentous trigger points, or osteoarthritis of the joints and spine are common in patients with chronic widespread pain, including FM. These abnormalities act as a peripheral pain generator and can be involved in the initiation and persistence of chronic pain [171-173]. However, the role of peripheral pain generators in the onset of FM and induction of central sensitization remains a matter of debate [174].

(2) Small fiber neuropathy

Several studies have reported that FM is associated with small fiber neuropathy (SFN), which is defined as abnormally reduced epidermal nerve fiber density. FM patients without depression were significantly more likely to have small fiber dysfunction accompanied by increased cold and warm detection thresholds when compared to healthy controls [175]. In another study, a significantly higher incidence of small fiber polyneuropathy was observed in patients with FM than in healthy controls [176]. A meta-analysis of 222 FM patients reported that the prevalence of SFN in FM was 30% to 76%, and that 49% of FM patients had structural abnormalities of small nerve fibers [177].

Although SFN does not fully explain the chronic widespread pain, chronic fatigue, or mood and sleep disturbances commonly seen in FM, it can be assumed that these abnormal neuronal changes at the peripheral level may contribute to the activation of pain pathways.

(3) Muscle abnormalities

Although evidence for structural muscle abnormalities in FM is lacking, some studies have reported changes in muscle metabolism. In a study that evaluated muscle metabolism using magnetic resonance spectroscopy, patients with FM had significantly higher muscle fat content in the quadriceps muscle than the control group, while the concentrations of adenosine triphosphate (ATP) and phosphocreatinine (PCr) were significantly lower. Decreased muscle concentrations of ATP and PCr were also associated with reduced physical capacity in the leg and the hand [178]. In other studies, light microscopy and histochemical and immunoenzymatic methods did not find definitive evidence of muscle disease in the skeletal muscle of patients with FM. However, microscopic abnormalities such as empty basement membrane sleeves, many lipofuschin bodies, and other degenerative changes were observed on ultrastructural evaluations [179].

Pain Mechanisms in FM

1) Peripheral sensitization in FM

Extrinsic and peripherally generated stimuli activate nociceptors in nerve endings, and the action potentials generated reach the dorsal horn of the spinal cord through Aδ-fibers or C-fibers and are transmitted to the brain through the spinothalamic tract.

https://doi.org/10.18214/jend.2022.00227

When stimulation is continuous and repeated, the production of mediators (e.g., neuropeptides, proinflammatory cytokines, eicosanoids) is promoted in non-neural cells (such as mast cells, basophils, platelets, macrophages, neutrophils, endothelial cells, keratinocytes, and fibroblasts) through tissue damage or inflammatory response. Increased concentrations of these mediators form an "inflammatory soup," which results in greater activation of nociceptors. Most of the impulses generated in the nociceptor proceed toward the spinal cord, but some are transmitted to other terminal branches and secrete several neuropeptides, including SP, at the nerve endings. The secreted neuropeptides trigger the secretion of histamine and serotonin through vasodilation, stimulation of nearby mast cells and platelets, and form a vicious cycle in which nociceptors are stimulated again through the formation of an additional inflammatory soup. This series of processes is called peripheral sensitization [143].

In patients with FM, a significant increase in mast cells in the papillary dermis was confirmed by skin biopsy (5 to 14 times more than controls). Since symptoms such as fatigue, headache, flushing, abdominal discomfort, hypotension, and tachycardia, which are common in FM, are also frequently observed in mast cell degranulation, it is assumed that there is a correlation between them. Increased mast cell degranulation in patients with FM may play an important role in peripheral sensitization [180,181]. Meanwhile, the aforementioned peripheral pain generators can further contribute to peripheral sensitization by providing additional input to the sensitized nociceptive pathway. This can be explained by some studies showing that treatment with peripheral pain generators in patients with conditions such as myofascial pain syndrome increased the pain threshold and reduced remote secondary heat hyperalgesia [182,183]. To sustain and extend central sensitization, persistent peripheral nociceptive input may be important (Fig. 2) [184].

Active management of these peripheral pain generators can help manage FM symptoms by decreasing central sensitization. However, since the symptoms of FM often do not resolve even if these peripheral factors are removed, central sensitization is assumed to play a more important role in the pathogenesis of FM.

2) Central sensitization in FM

Central sensitization is defined as the amplification of nerve signals in the central nervous system, resulting in hypersensitivity to pain [185]. Several studies have demonstrated that central sensitization by abnormal pain processing (i.e., abnormal ascending and descending pain pathways), is a key component of the pathophysiology of FM (Fig. 2). Various mechanisms are involved in this process. As a result, hyperalgesia, allodynia, and hypersensitivity to various external stimuli such as sound or light appear in FM [186-190].

(1) Abnormally activated ascending excitatory pathways in FM

Excitatory neurotransmitters such as glutamate, SP, and NGF are present at increased levels in the CSF of patients with FM [154,163,191]. In animal models of FM, superficial dorsal horn neurons are strongly sensitized, and an increase in excitatory postsynaptic input and a decrease in inhibitory input are also observed in the superficial dorsal horn [192]. This helps explain the ascending nociceptive hypersensitivity at the spine level in FM.

(2) Structural and functional changes of the brain in FM

fMRI enables the evaluation of active areas of the brain, the degree of connection between brain areas, and morphological evaluation of the brain. This is very helpful in studying the pathogenesis of FM. In a study using fMRI, when the same amount of pressure was applied, FM patients showed greater neural activation in the pain processing area of the brain than the control group [193]. The brain regions that consistently showed greater activation were the secondary somatosensory cortex, insula, and anterior cingulate cortex [194]. This suggests that patients with FM are much more sensitive to pain than healthy subjects, as the activation of pain-related brain regions is induced even with less pressure.

In patients with FM accompanied by depression, increased blood flow can be observed in the amygdala and anterior insula, which are important areas for the emotional pain response [124]. FM patients also exhibit less activation in the ventral segmental area, which controls sensory, affective, cognitive, and pain-modulatory processes, than controls [195]. This may also help explain the central sensitization of pain. In a study that evaluated brain activity caused by spontaneous chronic pain during rest, patients with FM had increased insular connectivity to the default mode network, and these changes were correlated with pain intensity [196].

In voxel-based morphometric analysis of fMRI, FM patients showed a significant decrease in total gray matter volume, and a 3.3-fold greater age-associated decrease in gray matter compared to healthy controls. Gray matter loss was more severe as disease duration increased, suggesting that FM can accelerate brain aging [197]. This gray matter volume loss was observed not only in areas related to stress and pain processing, but also in areas related to cognitive function [198]. In a study comparing FM patients and pain-free controls using proton magnetic resonance spectroscopy, FM patients showed a higher concentration of gluta-

mate in the posterior insula than the control group [160]. In a study investigating white matter changes with diffusion-weighted imaging, patients with FM had significantly increased damage to white matter microstructure in the body of the corpus callosum associated with pain intensity than healthy controls [199]. Due to these changes observed in the brain, central sensitization is presumed to play an important role in the pathogenesis of FM.

(3) Abnormal descending inhibitory pain pathways in FM

Pain perceived by the brain is appropriately regulated through the descending inhibitory pathway. Representative descending inhibitory pathways include the serotonergic (5-HT-containing), noradrenergic, and dopaminergic inhibitory pathways. Serotonin and norepinephrine, key neurotransmitters in the descending inhibitory pathway, were decreased in the CSF of patients with FM [169,200]. A study used positron emission tomography to evaluate endogenous release of dopamine for experimental pain in FM patients and healthy controls. In the control group, dopamine was secreted from the basal ganglia during pain stimulation, but this finding was not observed in FM patients [32]. This suggests that pain suppression mechanisms are also impaired in FM.

fMRI is also useful for assessing the degree of connectivity between brain regions. In one study, the rostral anterior cingulate cortex, a brain region connected to the descending inhibitory pathway in patients with FM, exhibited reduced activity in response to pain induction [201]. In another study, patients with FM showed more abnormal resting state functional connectivity of the periaqueductal gray than healthy controls [202], and exhibited less connectivity in the brain's pain inhibitory network for pressure pain than healthy controls [203]. These findings suggest that there is an impairment of the descending inhibitory pathway for pain in patients with FM. fMRI also revealed significant impairment of brainstem/spinal cord network connectivity in patients with FM compared to healthy controls [204]. These connectivity problems make the transmission of endogenous pain inhibitory signals impossible even when the brain recognizes pain, which can aggravate central sensitization.

In another study using proton magnetic resonance spectroscopy, a decrease in the concentration of GABA, a pain inhibitory neurotransmitter, was observed in the insula of FM patients compared to healthy controls [205]. In a study using μ-opioid receptor positron emission tomography, a decrease in μ-opioid receptor binding potential was observed in regions involved in pain modulation, such as the nucleus accumbens, the amygdala, and the dorsal cingulate, in FM patients compared to healthy controls [168]. However, FM patients showed higher opioid levels in CSF than healthy controls [167]. Patients with FM generally show less response to exogenous opiates, which is presumed to be due to altered endogenous opioid receptor activity.

In an fMRI study of spinal cord and brainstem activation, patients with FM showed abnormal temporal-summation-of-second pain for repetitive heat stimuli compared to the control group [206]. This is presumed to be due to pain modulation dysfunction in FM.

Taken together, the results of several studies suggest that central sensitization plays a very important role in the pathogenesis of FM. However, it is unclear whether the ascending excitatory pathways or descending inhibitory pathways play a more important role (Fig. 2).

Conclusion

Here, we reviewed several findings related to the etiopathogenesis of FM. Our understanding of the pathogenesis of FM has improved over several decades through genetic, psychophysiological, and neuroimaging studies. FM is presumed to be caused by complex interactions of various factors, including genetic and environmental factors, neuroendocrine system abnormalities, sleep disorders, psychiatric problems, immunological abnormalities, neuroinflammation, peripheral pain generators, and SFN. Through mutual interactions, these factors can be involved in the exacerbation of various clinical symptoms, as well as the development of FM (Fig. 1).

Central sensitization in FM has been reported, with evidence suggesting enhancement of ascending excitatory pathways, suppression of descending inhibitory pathways, and structural/functional abnormalities of the brain. This leads to a decrease in the pain threshold, and FM patients suffer from chronic hyperalgesia and allodynia. It also seems to be responsible for the non-pain features of FM (Fig. 2).

Because various factors are involved in the etiopathogenesis of FM, treatments are often insufficient. It may be helpful to subclassify patients with FM according to etiopathogenesis and take a tailored approach. To achieve this, further scientific and clinical studies on the etiopathogenesis, diagnosis, and treatment of FM are needed.

Conflict of Interest

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

https://doi.org/10.18214/jend.2022.00227

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 https://doi.org/10.18214/jend.2022.00227

JEND Journal of Electrodiagnosis and Neuromuscular Diseases

CASE REPORT

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2023;25(1):19-24
https://doi.org/10.18214/jend.2022.00129

Electrodiagnosis of Multiple Cranial Neuropathies and Lumbosacral Polyradiculopathy in Tuberculous Meningitis: A Case Report

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Cranial neuropathy and radiculopathy are common complications of tuberculous meningitis. However, the co-occurrence of these complications and the corresponding electrodiagnostic findings have rarely been reported. We report a patient diagnosed with tuberculous meningitis who presented with difficulty in smelling, facial paralysis, hearing loss, and severe weakness in the bilateral lower extremities. A neurological examination confirmed impaired function of the olfactory nerves. Electrodiagnostic studies, including a nerve conduction study, electromyography, and brainstem auditory evoked potential, revealed multiple cranial neuropathies involving the left facial nerve and bilateral vestibulocochlear nerves, as well as bilateral lumbosacral polyradiculopathies. In patients with tuberculous meningitis, multiple cranial neuropathies and polyradiculopathies can occur simultaneously as complications, and electrodiagnostic studies can enable an accurate diagnosis of these complications and an assessment of their severity.

Keywords: Tuberculosis, meningeal; Cranial nerve diseases; Polyradiculopathy

Received: July 27, 2022
Revised: September 26, 2022
Accepted: September 27, 2023

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Introduction

Cranial neuropathy and radiculopathy can occur as complications of tuberculous meningitis [1-3]. However, the co-occurrence of multiple cranial neuropathies and polyradiculopathies has rarely been reported. Furthermore, to our knowledge, studies reporting the electrodiagnostic findings of these complications are extremely rare [4]. Herein, we report a case of a patient diagnosed with tuberculous meningitis with patchy involvement of multiple cranial nerves and lumbosacral polyradiculopathy.

Case Report

A 61-year-old woman visited a university hospital 4 hours after the onset of fever. Five months prior, she had been hospitalized for a fever that lasted 6 months. Her only underlying disease was dyslipidemia. On admission, arthralgia was observed in the bilateral shoulder, wrist, metacarpophalangeal, proximal interphalangeal, knee, and ankle joints, without skin lesions. She underwent abdomen-pelvis and chest computed tomography which showed no infectious fever focus. A bone scan revealed arthritis in multiple joints, including the bilateral shoulder, elbow, wrist, and knee joints (Fig. 1), and whole-body positron emission tomography suggested reactive hypersplenism and inflammatory reactive lymph nodes. Serum laboratory testing showed leukocytosis (16,740/mm^3) with neutrophil dominance (94.7%), a high C-reactive protein (CRP) level (18.77 mg/dL), a high erythrocyte sedimentation rate (ESR, 102 mm/h) and positive rheuma-

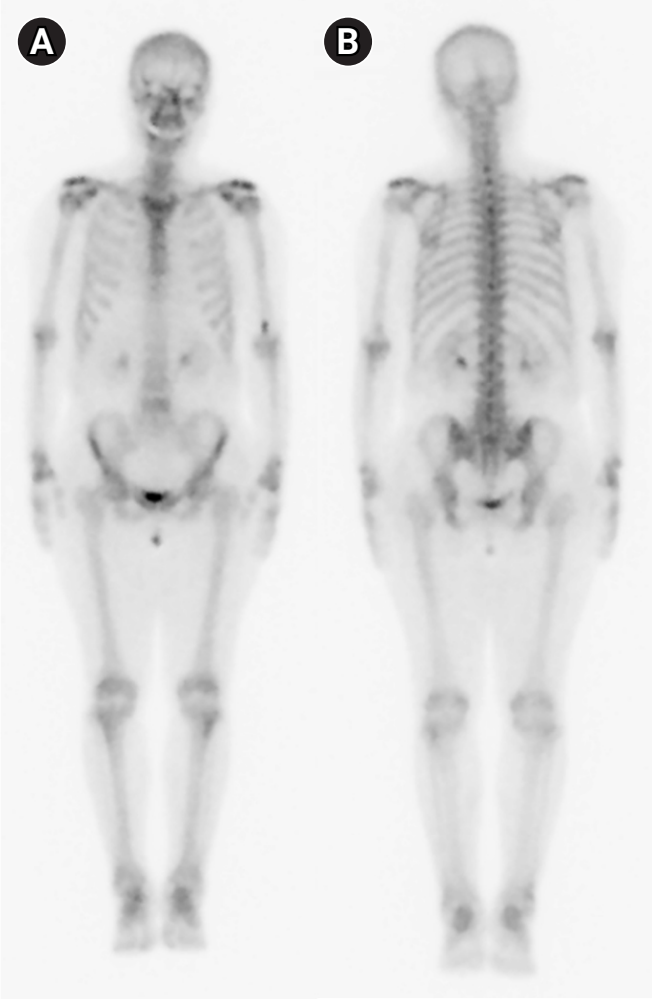

Fig. 1. Bone scan (A: anterior view; B: posterior view) performed during the previous hospitalization, showing mildly increased uptake in the bilateral shoulder, elbow, wrist, and knee joints.

toid factor. Anti-cyclic citrullinated peptide and anti-nuclear antibody were negative, and creatine kinase (108 IU/L) was not elevated. Based on these results, the patient was diagnosed with seropositive rheumatoid arthritis or adult-onset Still's disease. She was prescribed methotrexate, hydroxychloroquine, cyclosporine, prednisolone, and cyclophosphamide based on these diagnostic possibilities.

Afterward, she had a mild fever; however, 5 months later, a more severe fever of > 38°C occurred; this was accompanied by a confused mental state, vomiting, and general weakness. On a neurological examination, she was confused and her orientation to time and place was impaired. She also showed bilateral hearing impairment and left facial palsy of the peripheral type with House-Brackmann grade 2. Appropriate oral feeding was impossible because of her confused state; therefore, a nasogastric tube was inserted. She had bilateral flaccid weakness of the lower extremities (grade 1 of 5 on the Medical Research Council scale). In addition, severe neuropathic pain was present in her bilateral lower extremities.

Brain magnetic resonance imaging (MRI) revealed diffuse sulcal enhancement with small nodular enhancing foci in a gadolinium-enhanced T1 sequence, suggesting a diagnosis of meningoencephalitis associated with tuberculosis, neurosyphilis, or granulomatous inflammation. Whole-spine MRI showed extensive irregular leptomeningeal thickening and enhancement along the spinal cord, as well as cauda equina (Fig. 2A-D).

Serum complete blood counts showed a normal white blood cell count (9,410/mm^3) with a high neutrophil proportion (96.6%). Elevation of the CRP level (2.85 mg/L) and ESR (49 mm/h) was observed, but the results were lower than those observed in the previous hospitalization. A cerebrospinal fluid (CSF) study revealed a high adenosine deaminase level (27 IU/L) with pleocytosis (456 white blood cells per mm^3) of mononuclear cell dominance (87.1%) and a high protein level (3,848 mg/dL), suggestive of tuberculous infection despite negative culture results for *Mycobacterium tuberculosis*. An absence of arthralgia aggravation and salmon-colored rash, combined with a normal liver function test, suggested that a flare-up of adult-onset Still's disease was unlikely. On the day the patient was transferred from the emergency room to the Department of Neurology, which was 2 days after the onset, she commenced taking anti-tubercular medications (rifampin, isoniazid, pyrazinamide, and ethambutol) for tuberculous meningoencephalitis. Follow-up spine MRI performed 26 days after the first spine MRI revealed clumped and adherent cauda equina to the dural sac and multifocal obliteration of the subarachnoid space, suggestive of adhesive arachnoiditis (Fig. 2E, F). A videofluoroscopic swallowing study performed 1 month after the onset showed no definite penetration or aspiration for all tested foods; thus, the nasogastric tube was removed. After the removal of the nasogastric tube, she had no difficulty eating a regular diet.

After acute management in the Department of Neurology, the patient was transferred to the Department of Rehabilitation Medicine, 35 days after the onset. A follow-up neurologic examination revealed impairment of olfactory function, left peripheral type facial palsy, bilateral hearing impairment, and severe bilateral lower-extremity weakness. The muscle strength of the right and left lower extremities was 0/0 for hip flexors, 0/1 for knee extensors and knee flexors, and 1/1 for ankle dorsiflexors, big toe extensors, and ankle plantar flexors. Knee jerks were decreased bilaterally. In addition, voluntary anal contraction was absent, and the sensory function of the S4-5 dermatome was impaired. A Foley catheter that had been inserted in the emergency room

https://doi.org/10.18214/jend.2022.00129

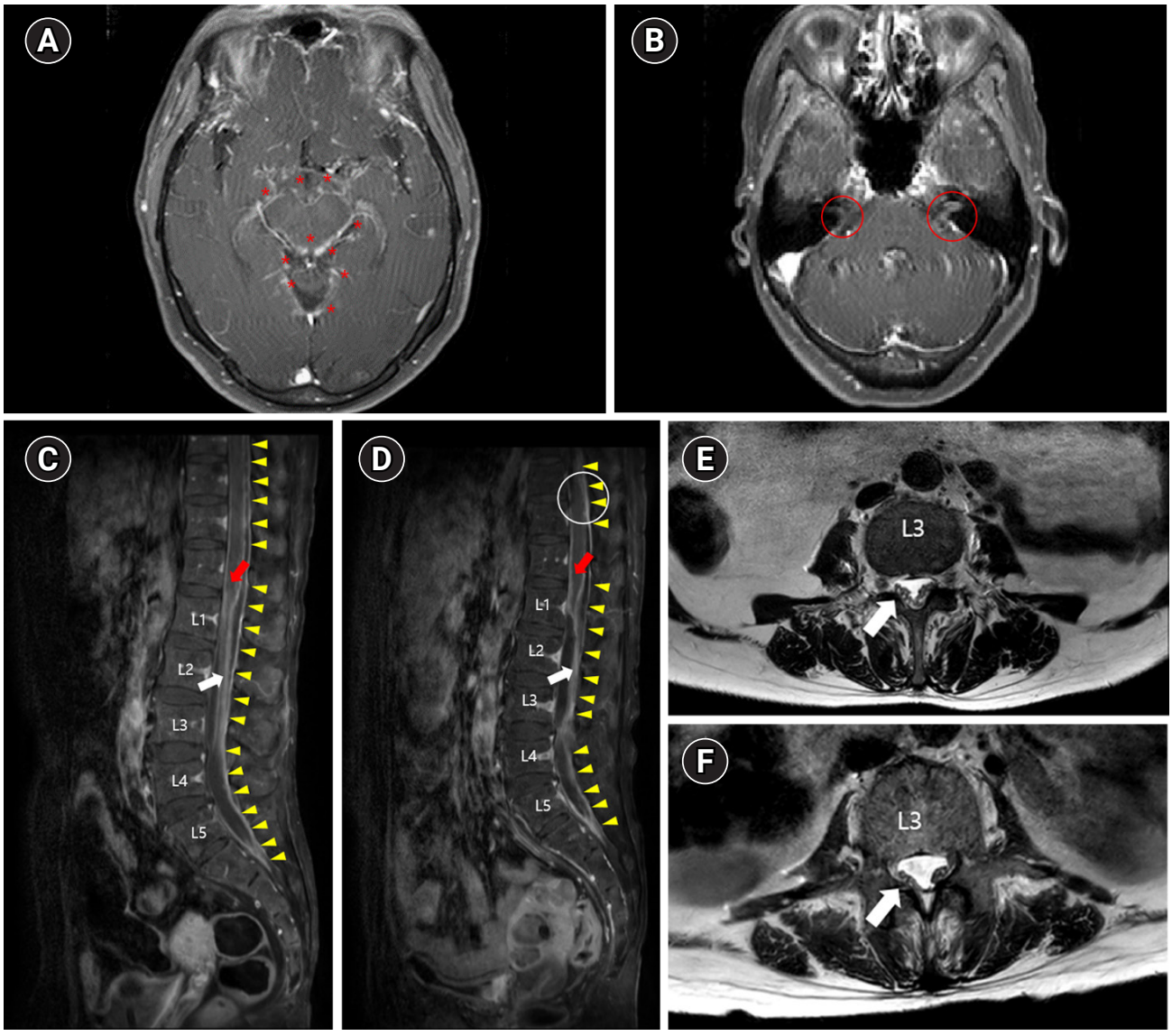

Fig. 2. Brain (A, B) and spine (C, D, E, F) magnetic resonance imaging (MRI) of the patient. (A) Gadolinium-enhanced T1 axial view at the midbrain level. Asterisks (*) indicate small nodular enhancing foci of the diffusely enhanced meninx. (B) Gadolinium-enhanced T1 axial view at the pons level. Red circles indicate the right and left facial-vestibulocochlear nerve complexes with perineural enhancement. (C) Gadolinium-enhanced T1 sagittal view of the first spine MRI. The red arrow indicates conus medullaris with surface enhancement, and the white arrow indicates cauda equina with irregular leptomeningeal thickening and enhancement. Yellow arrowheads indicate dural enhancement along the spinal canal. (D) T2 axial view at the L3 level of the first spine MRI. The white arrow indicates the cauda equina with irregular leptomeningeal thickening and enhancement at the L3 level. (E) Gadolinium-enhanced T1 sagittal view of the follow-up spine MRI. Compared to the first spine MRI (C), the cauda equina (white arrow) is clumped and adherent to the dural sac, and obliteration of the subarachnoid space (white circle) was observed. (F) T2 axial view at the L3 level of the follow-up spine MRI. The white arrow indicates the cauda equina with more adhesion to the dural sac than the first spine MRI (D).

was removed, but self-urination was not possible and clean intermittent catheterization was performed.

One day after transfer, comprehensive electrodiagnostic studies were performed to evaluate the involvement of the cranial nerves and peripheral nervous system.

In a motor nerve conduction study (NCS), the amplitudes of bilateral peroneal, right tibial, and left facial compound muscle action potentials were diminished (Table 1). Sensory NCS showed no abnormalities, and F-waves of the bilateral peroneal nerves and H-reflex tests for bilateral tibial nerves showed no response. The blink reflex test showed no response on the left side.

Electromyography showed denervation potentials in several

Table 1. Nerve Conduction Study, Late Response, and Blink Reflex

Motor nerve conduction study					
Nerve	Stimulation site	Recording site	Latency (ms)	Amplitude (mV)	Conduction velocity (m/s)
Rt. peroneal	Fibular head	TA	4.77	3.4*	NA
	Ankle	EDB	4.1	0.8*	47.4
	Fibular head	EDB	10.65	0.7*	
Lt. peroneal	Fibular head	TA	4.83	3.5*	NA
	Ankle	EDB	3.85	0.8*	47.5
	Fibular head	EDB	10.38	0.7*	
Rt. tibial	Ankle	AH	4.13	2.1*	44.7
	Knee	AH	12.06	1.8*	
Lt. tibial	Ankle	AH	4.21	5.3	42.5
	Knee	AH	12.21	4.2	
Rt. facial	Postauricular	Frontalis	3.33	1.7	NA
	Postauricular	Orbicularis oculi	2.83	3.1	NA
	Postauricular	Nasalis	2.94	2.8	NA
	Postauricular	Orbicularis oris	2.98	4.1	NA
Lt. facial	Postauricular	Frontalis	4.9	0.2*	NA
	Postauricular	Orbicularis oculi	4.52	0.2*	NA
	Postauricular	Nasalis	4.85	0.2*	NA
	Postauricular	Orbicularis oris	5.25	0.2*	NA
Sensory nerve conduction study					
Nerve	Stimulation site	Recording site	Latency (ms)	Amplitude (μV)	Conduction velocity (m/s)
Rt. sup peroneal	Lateral leg	Foot dorsum	2.81	16.3	NA
Lt. sup peroneal	Lateral leg	Foot dorsum	2.9	14.7	NA
Rt. sural	Calf	Lateral malleolus	2.83	14.1	NA
Lt. sural	Calf	Lateral malleolus	2.88	14	NA
F-wave					
Nerve	Simulation site	Recording site	Min latency (ms)	Max latency (ms)	Mean latency (ms)
Rt. peroneal	Ankle	EDB	NR*	NR*	NR*
Lt. peroneal	Ankle	EDB	NR*	NR*	NR*
Rt. tibial	Ankle	AH	51.1	52.1	51.7
Lt. tibial	Ankle	AH	52.4	55.3	53.3
H-reflex					
Nerve	Simulation site	Recording site	Min latency (ms)	Max latency (ms)	Mean latency (ms)
Rt. tibial	Knee	Soleus	NR*	NR*	NR*
Lt. tibial	Knee	Soleus	NR*	NR*	NR*
Blink reflex					
Nerve	Simulation site	Recording site	R1 (ms)	R2 (ms)	R2–R1 (ms)
Rt. supraorbital	Supraorbital foramen	Rt. orbicularis oculi	11.63	35.65	23.92
Rt. supraorbital	Supraorbital foramen	Lt. orbicularis oculi		NR*	
Lt. supraorbital	Supraorbital foramen	Rt. orbicularis oculi		39.58	
Lt. supraorbital	Supraorbital foramen	Lt. orbicularis oculi	NR*	NR*	NA

Rt., right; TA, tibialis anterior; EDB, extensor digitorum brevis; NA, not available; Lt., left; AH, abductor hallucis; sup peroneal, superficial peroneal; NR, no response; R1, early latency; R2, late latency.
*Abnormal findings are represented with asterisks; an abnormal finding was defined as non-conformity with our laboratory standards or a greater than 40% reduction of amplitude or 30% delay of latency compared to the contralateral side.

facial and lower-extremity muscles (Table 2). Motor unit action potential (MUAP) analyses showed no MUAP activity or discrete interference pattern in the lower-extremity muscles and a discrete to reduced pattern in the left facial muscles. Brainstem auditory evoked potential testing, which was performed to evaluate auditory function, elicited no response bilaterally.

Overall, the findings of the electrodiagnostic study indicated cranial neuropathies involving the left facial nerve, bilateral vestibulocochlear nerves, and bilateral lumbosacral polyradiculopathies involving the nerve roots at and below the L2 level; this was in addition to the impairment of olfactory nerves found in the neurologic examination.

During the patient's 3-week stay in the Department of Rehabilitation Medicine, rehabilitation therapies, including range-of-

https://doi.org/10.18214/jend.2022.00129

Table 2. Needle Electromyography Findings

Muscle	IA	Spontaneous		MUAP			Interference pattern
		Fib/PSW	Other	Amplitude	Duration	Polyphasic	
Lt. frontalis	N	1+/1+	None	N	N	N	Reduced
Lt. orbicularis oculi	N	1+/1+	None	N	N	N	Reduced
Lt. nasalis	N	1+/1+	None	N	N	N	Reduced
Lt. orbicularis oris	N	1+/1+	None	N	N	N	Discrete
Rt. VM	N	1+/1+	None				No MUAP activity
Lt. VM	N	1+/1+	None	N	N	N	Discrete
Rt. TA	N	2+/2+	None				No MUAP activity
Lt. TA	N	1+/1+	None	N	N	N	Discrete
Rt. GCM	N	1+/1+	None				No MUAP activity
Lt. GCM	N	1+/1+	None				No MUAP activity
Lt. EAS	N	1+/0	None				No MUAP activity

IA, insertional activity; Fib, fibrillation potential; PSW, positive sharp wave; MUAP, motor unit action potential; Lt., left; N, normal; Rt., right; VM, vastus medialis; TA, tibialis anterior; GCM, gastrocnemius; EAS, external anal sphincter.

motion exercises, strengthening exercises, and functional electrical stimulation, were provided; however, lower-extremity motor power and gait function did not show significant improvements. Two months after discharge from the hospital, lower-extremity weakness, gait ability, and urinary function were unimproved, while left facial palsy and hearing impairment of both ears showed partial improvement.

The study was approved by the institute review board of Seoul National University Bundang Hospital (IRB no: B-2208-773-703) and written informed consent was obtained from the patient.

Discussion

This article reports a patient diagnosed with tuberculous meningoencephalitis presenting with difficulty in smelling, facial palsy, hearing loss, and severe lower-extremity weakness. An electrodiagnostic examination demonstrated patchy involvement of multiple cranial nerves and lumbosacral polyradiculopathies.

In tuberculous meningitis, cranial neuropathy and radiculopathy are common complications; however, few studies have reported cases of the simultaneous occurrence of multiple cranial neuropathies and polyradiculopathies [4].

The prevalence of cranial nerve involvement in tuberculous meningitis ranges from 14.8% to 38% [1,2]. The most frequently involved cranial nerves are the oculomotor, abducens, optic, facial, and vestibulocochlear nerves [1,2]. In tuberculous meningitis, the thick gelatinous exudates, which are especially copious in the brain's basilar regions, can entrap the cranial nerve trunks, or increased intracranial pressure can damage them [1]. In our patient, perineural enhancement of the facial-vestibulocochlear nerve complex was observed on brain MRI (Fig. 2B). Together with the electrodiagnostic study results, this suggested injury of these cranial nerves. Cranial nerve involvement has been reported to be associated with the age of onset (< 25 years), hydrocephalus, disability at presentation (modified Rankin Scale [mRS] > 2), altered sensorium, and CSF profile (protein > 250 mg/dL, cell count > 100) [1]. Our patient presented severe disability (mRS 5), altered sensorium (decreased sensation in the S4–5 dermatome), and CSF abnormalities with high cell counts and protein levels. Cranial nerve involvement in tuberculous meningitis is associated with poor outcomes, such as mRS > 2, presence of neurologic sequelae, or decreased consciousness [1,5]; therefore, a precise evaluation and diagnosis of cranial neuropathy are important.

Few studies have reported electrodiagnostic tests performed to diagnose radiculopathy and evaluate disease severity [3,6]. Tuberculous arachnoiditis is generally the cause of radiculomyelopathy associated with tuberculous meningitis. This most characteristic spinal complication is produced by the thick inflammatory exudates surrounding the spinal cord, as in cranial nerve involvement. The thick gelatinous exudates fill the subarachnoid space, encasing the spinal cord and emerging nerve roots, and making them inflamed. The exudates, in late stages, may eventually lead to adhesion and atrophy of nerve roots [3]. The initial spine MRI of our patient showed extensive leptomeningeal enhancement reflective of subarachnoid exudate affecting the spinal cord and cauda equina, and the follow-up MRI demonstrated the development of adhesive arachnoiditis (Fig. 2C-F). A high CSF protein level (> 250 mg/dL) and a low modified Barthel index (< 12) have been reported to be associated with spinal cord and nerve root involvement [6]. The prognosis of tuberculous meningitis with spinal cord or nerve root involvement is not predictable; however, it has been reported that sequelae devel-

oped in 14.2% of patients, and poor outcomes are associated with spinal cord atrophy, syringomyelia, and a multiplicity of complications, such as radiculomyelitis, spinal tuberculoma, or spinal abscess [3].

This case report describes the electrodiagnostic findings of polyradiculopathy and multiple cranial neuropathies caused by tuberculous meningitis, along with the imaging and laboratory findings and the patient's clinical outcomes. Further publications presenting electrodiagnostic findings in tuberculous meningitis may confirm the prognostic value of electrodiagnostic studies in patients with tuberculous meningitis.

In conclusion, multiple cranial neuropathies and polyradiculopathies can occur simultaneously in patients with tuberculous meningitis, and comprehensive electrodiagnostic studies should be considered to evaluate these complications.

Conflict of Interest

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

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https://doi.org/10.18214/jend.2022.00129

JEND Journal of Electrodiagnosis and Neuromuscular Diseases

CASE REPORT

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2023;25(1):25-29
https://doi.org/10.18214/jend.2022.00136

Prolonged Limb and Respiratory Muscle Weakness Associated with Japanese Encephalitis Virus Infection: A Case Report

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Patients diagnosed with Japanese encephalitis (JE) may present with flaccid paralysis. JE has also been reported to be accompanied by anterior horn cell disease or motor axonal polyneuropathy. We report a case of a patient with JE with prolonged limb and respiratory muscle weakness who underwent electrodiagnostic studies, including a phrenic nerve conduction study, 10 months after the onset of paralysis. During that 10-month period, severe weakness of the upper and lower extremities showed no recovery, and the patient required long-term ventilator support through a tracheostomy. Nerve conduction studies and electromyography revealed chronic anterior horn cell disease with abundant denervation potentials involving the craniobulbar, cervical, thoracic, and lumbosacral segments. In addition to the nerves in the upper and lower extremities, the phrenic motor nerves showed abnormalities indicative of diaphragmatic weakness. Therefore, in patients with JE with chronic limb weakness and respiratory difficulty, thorough electrodiagnostic studies should be performed to diagnose the combination of anterior horn cell disease with encephalitis and to evaluate the condition's severity and prognosis.

Keywords: Electrodiagnosis; Motor neuron disease; Encephalitis; Japanese

Received: July 31, 2022
Revised: September 21, 2022
Accepted: October 20, 2022

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Introduction

Japanese encephalitis (JE) is caused by a virus in the family Flaviviridae [1], which can cause flaccid paralysis, even though the main pathophysiology involves the central nervous system and brain. Electrodiagnostic studies (EDXs) have demonstrated anterior horn cell disease or motor axonal polyneuropathy in such cases [2-4]. Herein, we report a case of a patient with JE who underwent EDXs 10 months after onset, revealing an anterior horn cell disease pattern involving the phrenic motor nerve, which is important for respiratory dysfunction.

Case Report

A previously healthy 59-year-old man visited our clinic 5 days after the onset of fever and headache. About 2 weeks before the onset of symptoms, the patient was bitten multiple times by mosquitoes while fishing. Before the hospital visit, limb muscle strength was normal.

Cerebrospinal fluid (CSF) showed pleocytosis (114 white blood cells/mm^3) with monocyte dominance (83.3%), a high protein level (148 mg/dL), and a low glucose level (62.3 mg/dL, 42.1% of serum glucose level), suggesting viral encephalitis. Brain magnetic resonance imaging (MRI) demonstrated diffuse leptomeningeal enhancement along the cerebral sulci and cerebellar folia, consistent with viral meningoencephalitis. One day after admission, the patient's level of consciousness started to decrease, and he was transferred to the intensive care unit (ICU) with intubation and mechanical ventilation.

During the ICU stay, antiviral agent, steroid pulse, and intrave-

nous immunoglobulin therapies were administered, but none of those treatments were effective in preventing respiratory failure and the aggravation of motor weakness. A tracheostomy was performed, and bilevel positive airway pressure (biPAP) ventilation was applied. During this period, JE was diagnosed based on the detection of virus-specific antibodies in the CSF, and ribavirin was administered for 16 consecutive days.

Motor weakness was evaluated as grade 1 in all muscles of the bilateral upper and lower extremities based on the Medical Research Council scale when checked 40 days after the onset. When the patient was transferred to the Department of Rehabilitation Medicine, 70 days after onset, the muscle strength of the bilateral upper extremities was grade 1, and that of the bilateral lower extremities was grade 2. The serum creatine kinase (CK) level was 18 IU/L. The Montreal Cognitive Assessment (MoCA) score was 0, and the patient could obey only simple commands. In contrast to motor weakness, no abnormalities were found in sensory examinations of the extremities, body, and face. The range of motion (ROM) was limited in the bilateral ankle joints, as passive ankle dorsiflexion was limited to a maximum of 0°. A pair of ankle-foot orthoses (AFOs) was fabricated to prevent further aggravation of the bilateral ankle ROM limitation. Neither spasticity nor pathological reflexes were observed. A videofluoroscopic swallowing study showed aspiration into the airway while swallowing 2 mL of free water; moreover, the patient also tried yogurt, but failed to swallow it. Therefore, oral feeding was prohibited.

Ten months after onset, the patient's muscle strength had not even partially recovered despite constant rehabilitation. Because the flaccid paralysis persisted for 10 months, even though the etiology was encephalitis, EDX was performed. At this time, his MoCA score was 14, and his ability to obey commands had recovered enough to perform EDX. In a nerve conduction study (NCS) (Table 1), the sensory nerve action potentials were normal, except for the bilateral superficial peroneal nerves, which showed no response, and the bilateral median nerves, which exhibited mildly decreased conduction velocities. However, in the motor NCS, both the median and ulnar nerves showed low compound muscle action potential (CMAP) amplitudes and delayed onset latencies bilaterally, but more severely on the right side than on the left. The phrenic motor NCS showed no response on the right side and delayed onset latency on the left side. The tibial nerve demonstrated a lower CMAP amplitude on the right side. The peroneal nerve studies at the tibialis anterior muscles revealed delayed onset latency on the right side, and decreased CMAP amplitudes on both sides, but with greater severity on the right side, while those conducted at the extensor digitorum brevis muscles showed no responses bilaterally. F-wave studies showed no response to bilateral median and ulnar nerve stimulation, with normal, minimal-onset latency upon tibial nerve stimulation. Electromyography (EMG) revealed abundant and diffuse denervation potentials in various muscles (Table 2). In motor unit action potential (MUAP) analyses, many muscles showed no or single MUAP interference patterns and/or chronic reinnervation potentials of neuropathic change. All muscles with at least one MUAP interference pattern showed a delayed recruitment pattern. These results suggested chronic ongoing anterior horn cell disease involving the craniobulbar, cervical, thoracic, and lumbosacral segments.

The patient underwent percutaneous gastrostomy for prolonged dysphagia and permanent weakness of pharyngeal and respiratory muscles. Although the patient could be weaned from biPAP ventilation, he experienced recurrent pneumonia and atelectasis, and oxygen was supplied when needed. Phonation was limited due to poor inspiratory strength and ventilation function, even with a fenestrated tracheostomy tube.

This case report was approved by the ethics committee at the Seoul National University Hospital Institutional Review Board (2206-205-1335) and informed consent was obtained from the patient after confirming agreement through repetitive blinking and nodding the head, and the observer who was present throughout the whole process signed the consent on behalf of the participant because of his quadriplegic state.

Discussion

In this case report, EDXs were performed in a patient diagnosed with JE with prolonged limb weakness. Prominent flaccid weakness of the limbs was found after recovery from the decreased level of consciousness, which persisted for a long time (over 10 months) after the presentation of the first symptoms. There was no improvement in motor weakness or pulmonary and swallowing function, which correlated with the EDX results of a widespread motor nerve injury, including the phrenic nerves. As permanent impairment was anticipated, he underwent tracheostomy, gastrostomy, and bilateral AFOs with portable ventilation kept ready for an emergency situation, although he did not receive ventilator support.

Previous articles have suggested JE virus infection as possibility that should be considered in the differential diagnosis of acute flaccid paralysis [2-4] because it attacks both the brain and anterior horn cells. However, there have been no reports of EDXs performed in the chronic stage, several months after onset. In our patient, an EDX, including a phrenic NCS, was performed ap-

 https://doi.org/10.18214/jend.2022.00136

Table 1. Nerve Conduction Study Findings

Nerve	Stimulation site	Recording site	Latency (ms)	Amplitude	Conduction velocity (m/s)
Motor nerve conduction					
Rt. median	Wrist	APB	7.29*	0.1*	50.3
	Elbow	APB	11.67*	0.1*	
Lt. median	Wrist	APB	9.43*	0.7*	52
	Elbow	APB	13.85*	0.4*	
Rt. ulnar	Wrist	ADM	3.85*	0.5*	51.3
	Elbow	ADM	8.33*	0.5*	
Lt. ulnar	Wrist	ADM	5.83*	0.4*	52.4
	Elbow	ADM	9.27*	0.4*	
Rt. phrenic	Posterior to SCM	Xiphoid process	NR*	NR*	
Lt. phrenic	Posterior to SCM	Xiphoid process	9.43*	0.3	
Rt. common peroneal	Ankle	EDB	NR*	NR*	
	Fibular head	EDB	NR*	NR*	
	Knee	EDB	NR*	NR*	
Lt. common peroneal	Ankle	EDB	NR*	NR*	
	Fibular head	EDB	NR*	NR*	
	Knee	EDB	NR*	NR*	
Rt. tibial	Ankle	AH	3.65	9.6*	41.3
	Knee	AH	12.6	6.8*	
Lt. tibial	Ankle	AH	4.06	17.4	50
	Knee	AH	11.67	14.4	
Rt. common peroneal	Fibular head	TA	7.50*	0.3*	57.6
	Knee	TA	8.54*	0.2*	
Lt. common peroneal	Fibular head	TA	2.34	2.4*	41.1
	Knee	TA	3.8	2.4*	
Sensory nerve conduction					
Rt. median	Wrist	Digit II	2.97	19.2	47.1*
Lt. median	Wrist	Digit II	2.92	20.8	47.9*
Rt. ulnar	Wrist	Digit V	2.81	15.4	49.8
Lt. ulnar	Wrist	Digit V	2.71	18.9	51.6
Rt. superficial peroneal	Lateral leg	Foot dorsum	NR*	NR*	
Lt. superficial peroneal	Lateral leg	Foot dorsum	NR*	NR*	
Rt. sural	Calf	Lateral malleolus	2.81	9.3	49.8
Lt. sural	Calf	Lateral malleolus	2.66	8.1	52.6
F-wave					
Rt. median	Wrist	APB	NR*		
Lt. median	Wrist	APB	NR*		
Rt. ulnar	Wrist	ADM	NR*		
Lt. ulnar	Wrist	ADM	NR*		
Rt. tibial	Ankle	AH	52.45		
Lt. tibial	Ankle	AH	53.39		

Amplitudes were measured in millivolts (mV) in the motor nerve conduction study and microvolts (μV) in the sensory nerve conduction study.
Rt., right; APB, abductor pollicis brevis; Lt., left; ADM, abductor digiti minimi; NR, no response; SCM, sternocleidomastoid; EDB, extensor digitorum brevis; AH, abductor hallucis; TA, tibialis anterior.
*Abnormal findings are represented with asterisks; an abnormal finding was defined as non-conformity with our laboratory standards or a greater than 40% reduction of amplitude or 30% delay of latency compared to the contralateral side.

proximately 10 months after the onset to evaluate the cause of prolonged severe limb weakness and impaired ventilation function that had hardly recovered. In the motor NCS study, low CMAP amplitudes and delayed onset latencies were observed in most of the tested motor nerves, including the phrenic motor nerves, in contrast to the sensory NCS results, which showed only mildly decreased conduction velocities in the bilateral median nerves. Furthermore, in the EMG study, abundant and diffuse denervation potentials were observed, with chronic reinnervation potentials and delayed recruitment patterns in several muscles. Therefore, chronic ongoing anterior horn cell disease with widespread distribution, including the craniobulbar, cervi-

Table 2. Needle Electromyography Findings

Muscle	IA	Spontaneous		MUAP			Interference pattern	Recruitment pattern
		Fib/PSW	Other	Amplitude	Duration	Polyphasic		
Rt. APB	N	3+/3+	None				No MUAP activity	
Rt. FCR	N	3+/3+	None				No MUAP activity	
Rt. TB	N	3+/3+	None				No MUAP activity	
Rt. BB	N	2+/2+	None	N	N	Increased	Single	Delayed
Rt. Deltoid	N	3+/3+	None				No MUAP activity	
Rt. VM	N	1+/1+	None	N	N	Increased	Discrete	Delayed
Rt. TA	N	2+/2+	None	N	N	Increased	Discrete	Delayed
Rt. GCM	N	3+/3+	None	N	N	N	Reduced	Delayed
Rt. nasalis	N	1+/1+	None	N	N	N	Reduced	Delayed
Lt. APB	N	3+/3+	None	N	N	Increased	Discrete	Delayed
Lt. FDI	N	3+/3+	None	N	N	N	Single	Delayed
Lt. FCR	N	4+/4+	None	N	N	N	Single	Delayed
Lt. TB	N	3+/3+	None				No MUAP activity	
Lt. BB	N	2+/2+	None	N	N	Increased	Single	Delayed
Lt. deltoid	N	3+/3+	None	N	N	N	Single	Delayed
Lt. VM				N	N	Increased	Reduced	Delayed
Lt. TA	N	3+/3+	None	N	N	Increased	Discrete	Delayed
Lt. GCM	N	1+/1+	None	N	N	Increased	Discrete	Delayed
Lt. nasalis	N	0/0	None	N	N	N/increased	Reduced	Delayed
Lt. masseter				N	N	N	Discrete	Delayed
Lt. genioglossus	N	0/0	None	N	N	N	Complete	N
Lt. C-PSP	N	2+/2+	None					
Lt. T-PSP	N	3+/3+	None					
Lt. L-PSP	N	3+/3+	None					

IA, insertional activity; Fib, fibrillation potential; PSW, positive sharp wave; MUAP, motor unit action potential; Rt., right; APB, abductor pollicis brevis; N, normal; FCR, flexor carpi radialis; TB, triceps brachii; BB, biceps brachii; VM, vastus medialis; TA, tibialis anterior; GCM, gastrocnemius; FDI, first dorsal interosseous; N/increased, normal to increased; C-PSP, cervical paraspinal muscle; T-PSP, thoracic paraspinal muscle; L-PSP, lumbar paraspinal muscle.

cal, thoracic, and lumbosacral segments, was diagnosed.

Although Guillain-Barré syndrome (GBS) could be suspected when acute, flaccid limb weakness first appeared after fever, the features of prolonged severe limb weakness, CSF pleocytosis, and the EDX findings of asymmetric, non-length-dependent motor involvement patterns are not consistent with typical presentations of acute inflammatory demyelinating polyradiculoneuropathy and acute motor axonal neuropathy, which are two forms of GBS. In addition, the sensory NCS results with only mildly decreased conduction velocities of the median nerves did not correspond with acute motor-sensory axonal neuropathy, another variant of GBS, and critical-illness polyneuropathy. A severe axonal injury pattern of EMG and non-responsiveness to immune therapy also ruled out chronic inflammatory demyelinating polyneuropathy. Furthermore, the overall delayed recruitment pattern of MUAPs in the EMG study, the CK level under the lower normal limit, and the disease course with severe flaccid paralysis lasting for more than 10 months with aggravating atrophy, were not consistent with critical-illness myopathy [5].

Although superimposed bilateral carpal tunnel syndrome was suspected considering the differences in motor onset latencies between the median and ulnar nerves and mildly decreased median sensory nerve conduction velocities bilaterally, imaging studies such as ultrasonography or MRI were not performed, which is a limitation of the current study.

Diaphragmatic paresis has rarely been reported in JE [6-8]. A previous study reported a patient with JE who developed diaphragmatic paresis during the disease course, leading to delayed extubation and tracheostomy [7]. Another study reported a patient with JE who developed diaphragmatic paresis caused by longitudinally extensive transverse myelitis involving the C2-6 levels, leading to prolonged mechanical ventilation [8]. Our patient also required long-term tracheostomy and ventilator support, and diaphragmatic weakness was confirmed by abnormal phrenic NCS results and chest radiographs. Permanent phrenic nerve palsy may have resulted from an anterior horn cell disorder caused by JE. Patients who have JE with anterior horn cell involvement may require a thorough examination of pulmonary function to prevent respiratory failure and subsequent hypoxic injury.

Flaccidity has been reported to be an independent prognostic factor for poor outcomes in JE and is attributed to anterior horn

https://doi.org/10.18214/jend.2022.00136

cell involvement [9]. In addition, more severe anterior horn cell involvement is associated with worse recovery [10]. Therefore, EDX may have prognostic value for functional recovery in patients with JE with flaccid paralysis. In conclusion, patients with JE who present with flaccid limb weakness and respiratory difficulty should undergo thorough EDXs, including a phrenic NCS, to diagnose combined anterior horn cell involvement with a brain disorder. EDX results can provide information about the severity and prognosis of motor impairment, making it possible to plan an early intervention for compensations such as tracheostomy, ventilator support, gastrostomy, and/or AFOs.

Conflict of Interest

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

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JEND Journal of Electrodiagnosis and Neuromuscular Diseases

CASE REPORT

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2023;25(1):30-33
https://doi.org/10.18214/jend.2022.00171

Novel Pathogenic Variant in *PIEZO2* in a Korean Patient with Distal Arthrogryposis

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Alterations in *PIEZO2* can result in distal arthrogryposis, which is characterized by non-progressive contracture in two or more areas of the body prior to birth. Here, we present a 29-year-old man born with multiple joint contractures and cleft palate. He showed short stature, low-set ears, macrotia, hearing impairment, micrognathia, a triangular face, blepharophimosis, deep-set eyes, high arched eyebrows, decreased facial expressions, retrognathia, arachnodactyly, absent phalangeal crease, shortening of the first and fifth toes, short stature, pectus excavatum, epicanthus, bilateral ptosis, and ophthalmoplegia. He also complained of dyspnea and severe kyphoscoliosis. Pulmonary function tests showed a severe restrictive pattern. An electrodiagnostic study did not reveal any neurogenic or myogenic features. Next-generation sequencing revealed a novel *de novo* heterozygous pathogenic variant in *PIEZO2* (c.7251G>T; p.Trp2417Cys). Our study is the first report of a pathogenic variant in *PIEZO2* in a Korean patient with distal arthrogryposis.

Keywords: Arthrogryposis; High-throughput nucleotide sequencing; *PIEZO2*

Received: August 30, 2022
Revised: October 9, 2022
Accepted: October 26, 2022

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Introduction

Arthrogryposis multiplex congenita is a term for inherited disorders that present non-progressive contracture in two or more areas of the body prior to birth. It may occur due to chromosomal disorders, single gene disorders, connective tissue disorders, intrinsic muscle disorders, or abnormalities associated with developmental problem of the central and/or peripheral nervous system [1], and it usually involves arm and/or leg joint contractures [1]. It is a congenital condition that can be accompanied by many other conditions including cleft palate, scoliosis, short stature, and joint contractures [1]. Arthrogryposis multiplex congenita is classified into amyoplasia, distal arthrogryposis (DA), and central nervous system or progressive neurological etiology [1]. DA is a subgroup of arthrogryposis multiplex congenita characterized by non-progressive contractures of the distal regions of the hands and feet without primary neurological or muscular disorders. Currently, 10 different types of DA have been clinically classified, and eight causative genes have been identified [1,2]. The symptom presentation of DA varies widely among patients with the same causative gene, even within a single family with the same variant [3]. Among them, alterations in *PIEZO2* can result in DA type 3, DA type 5, DA with impaired proprioception and touch, and Marden-Walker syndrome

(MWS) [4-6]. Pathogenic variants in *PIEZO2* have been rarely reported in Korea. Herein, we present a novel likely pathogenic variant in *PIEZO2* in a Korean patient with DA.

Case Report

A 29-year-old man presented with multiple joint deformities and short stature at an outpatient clinic. He was born at 40 weeks of gestation weighing 2.5 kg to healthy parents, and he displayed multiple joint contractures, particularly in hands and feet (Fig. 1A). He underwent Achilles tenotomy and posterior capsulotomy for the correction of equinus deformity. Surgical procedures to treat cleft lip and palate were also performed. He complained of dyspnea and severe kyphoscoliosis (Fig. 2A). Pulmonary function tests showed a severe restrictive pattern. At 22 years of age, he underwent corrective surgery and began using overnight non-invasive positive-pressure ventilation. At 29 years of age, a physical examination showed multiple contractures of the fingers (including mild camptodactyly), wrists, elbows, toes, ankles, and knees. He exhibited low-set ears, macrotia, hearing impairment, micrognathia, a triangular face, blepharophimosis, deep-set eyes, high arched eyebrows, decreased facial expressions, retrognathia, arachnodactyly (Fig. 2B), absent phalangeal crease, shortening of the first and fifth toes, short stature, pectus excavatum (Fig. 2C), epicanthus, bilateral ptosis, and ophthalmoplegia (Fig. 2D). His touch perception and proprioceptive functions were normal. He did not show ataxia in the extremities or trunk. Although it was difficult to accurately assess motor function owing to the severe joint contractures, there was no definite muscle weakness within the range of motion. Motor function did not change during the 7-year follow-up period. His intellectual function was not impaired. A nerve conduction study showed an amplitude reduction in compound muscle action potential in the lower extremities. Needle electromyography did not reveal any neurogenic or

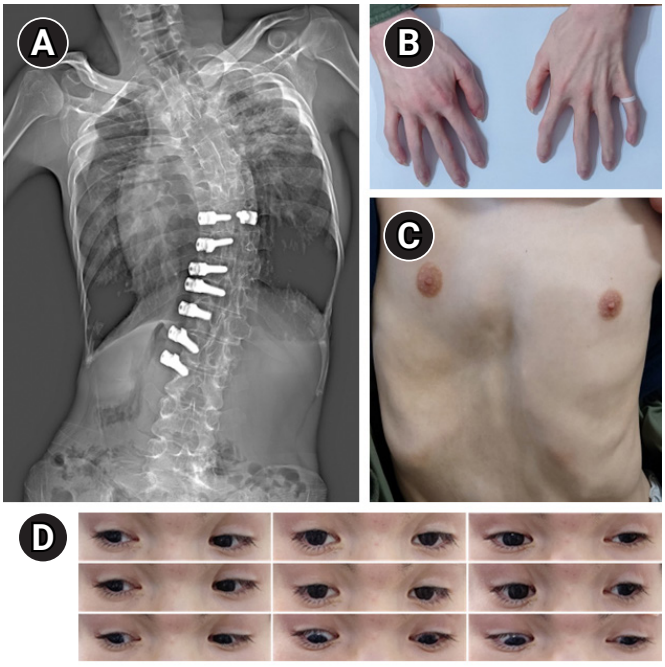

Fig. 2. Clinical features of a patient with a novel *de novo* heterozygous variant in *PIEZO2*. (A) Whole-spine X-ray image. (B) Arachnodactyly. (C) Pectus excavatum. (D) The nine cardinal positions of the gaze.

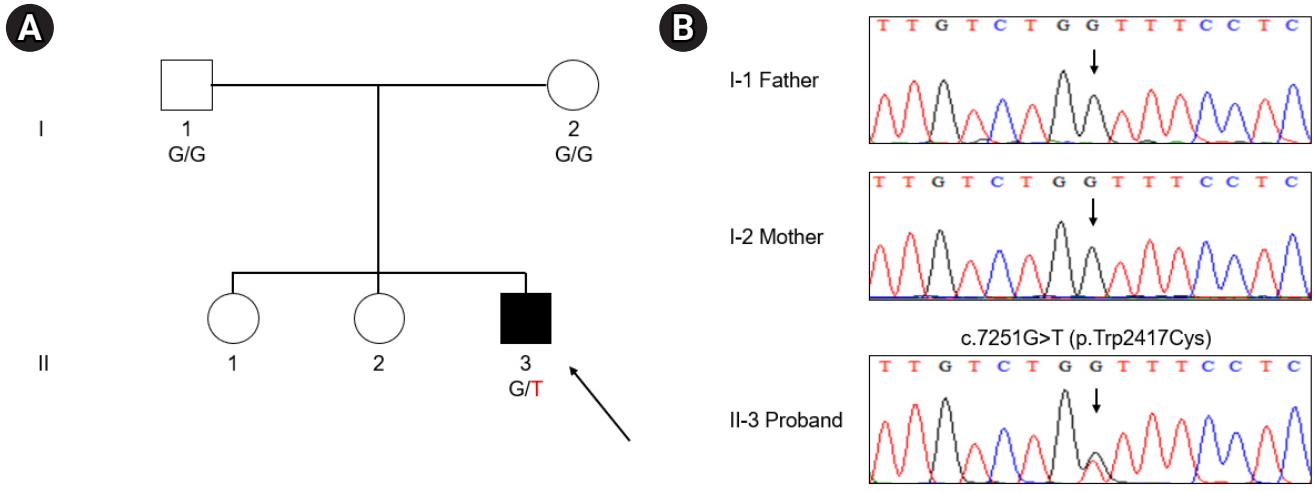

Fig. 1. Pedigree, sequencing chromatogram, and clinical features. (A) Pedigree of a patient with distal arthrogryposis. Arrow indicates the proband (square: male; circle: female; filled: affected; unfilled: unaffected). (B) Sequencing chromatograms of the c.7251G>T variant in *PIEZO2*. The arrow indicates the pathogenic variant site.

myogenic features. His serum creatine kinase level was 136 U/L (reference range, 55 to 170). These clinical features were compatible with DA. To identify the genetic cause, we performed targeted sequencing of 599 neuromuscular genes (Supplementary Table 1). We identified a heterozygous variant in *PIEZO2* (NM_022068.4: c.7251G>T; NP_071351.2: p.Trp2417Cys) (Fig. 1B). The intrafamilial segregation analysis showed that this is a *de novo* variant.

This report was approved for an Institutional Review Board (IRB) exemption by the IRB of the Gangnam Severance hospital (IRB file number 3-2022-0001). The IRB exemption includes a waiver of the need to obtain signed informed consent.

Discussion

In the present study, we identified a likely pathogenic variant in *PIEZO2* in a patient with DA. To the best of our knowledge, this variant has not yet been reported. However, it was classified as a likely pathogenic variant according to the 2015 American College of Medical Genetics and Genomics and the Association for Molecular Pathology guidelines because of the following this evidence: (1) *de novo* occurrence in a patient (maternity and paternity confirmed) with the disease and no family history; (2) absence from the Genome Aggregation Database full exome and genome databases; (3) multiple lines of computational evidence supporting a deleterious effect on the gene (PolyPhen-2 score: 0.999; SIFT score: 0); and (4) a highly specific phenotype for a disease with a single genetic etiology.

There are 10 types of DA (types 1, 2A, 2B, 3, 4, 5, 6, 7, 8, 9, and 10) (Table 1) [1,2]. Patients must meet two or more major diagnostic criteria of DA to be clinically diagnosed. However, when a first-degree family member is clinically diagnosed with DA, other family members only need one major criterion for a clinical diagnosis [1]. The major criteria are camptodactyly or pseudocamptodactyly, hypoplastic and/or absent flexion creases, overriding fingers, ulnar deviation at the wrist, talipes equinovarus, calcaneovalgus deformities, vertical talus, and metatarsus varus [1]. Our patient had two of the major criteria (camptodactyly and absent phalangeal crease). Different DA types share various common features. However, there are some characteristics that represent each DA types. These characteristics are described in Table 1 [1,3]. Because our patient met the diagnostic criteria of DA and had ocular abnormalities, DA type 5 could be considered as the diagnosis based on his phenotype [1]. DA type 5 patients usually show ptosis, oculomotor dysfunction, deep-set eyes, shortening of the first and fifth toes, and restrictive lung failure with multiple joint contractures, as with our patient. DA is not a progressive disorder. Many children who receive treatment generally have a normal life expectancy although it may be altered by heart involvement and some patients might be born with a fatal condition. Treatment focuses on improving quality of life by correcting deformities and strengthening muscles, mainly through surgical correction and rehabilitation [3]. Ventilation support can be used to those who have respiratory difficulties.

Pathogenic variants in *PIEZO2* can result in DA type 3, DA type 5, DA with impaired proprioception and touch, and MWS [4-6]. DA with impaired proprioception and touch is inherited in an autosomal recessive manner [6]. Patients with this type of DA have touch and proprioceptive dysfunction, ataxia, hip dysplasia, finger contractures, foot deformities, and scoliosis [7]. Since our patient did not show misperception of touch sensation, proprioceptive dysfunction, or ataxia, the diagnosis of DA with

Table 1. Typical Characteristics of Distal Arthrogryposis Types

Types of distal arthrogryposis	Typical characteristics (other than multiple joint contractures)
Distal arthrogryposis type 1	Camptodactyly, clubfoot
Distal arthrogryposis type 2A (Freeman-Sheldon syndrome)	Similar to distal arthrogryposis type 1 with oropharyngeal abnormalities, scoliosis, small oral orifice, puckered lips, H-shaped dimple of the chin (whistling face syndrome)
Distal arthrogryposis type 2B (Sheldon-Hall syndrome)	Similar to distal arthrogryposis type 1 with more prominent nasolabial folds, down slanting palpebral fissures, small mouth
Distal arthrogryposis type 3 (Gordon syndrome)	Short stature, cleft palate
Distal arthrogryposis type 4	Scoliosis
Distal arthrogryposis type 5	Ocular abnormalities (ptosis, ophthalmoplegia, strabismus)
Distal arthrogryposis type 6	Sensorineural hearing loss
Distal arthrogryposis type 7 (trismus-pseudocamptodactyly syndrome)	Inability to open the mouth (trismus), pseudocamptodactyly
Distal arthrogryposis type 8 (autosomal dominant multiple pterygium syndrome)	Pterygia involving the neck, axillar, elbows, and knees
Distal arthrogryposis type 9 (congenital contractural arachnodactyly; Beals syndrome)	Abnormally long fingers, scoliosis, scrunched ears
Distal arthrogryposis type 10 (congenital plantar syndrome)	Plantar flexion contractures

https://doi.org/10.18214/jend.2022.00171

impaired proprioception and touch was unlikely. DA type 3, DA type 5, and MWS show autosomal dominant inheritance. The key clinical findings of DA type 3, DA type 5, and MWS are cleft palate, ophthalmoplegia, and intellectual problems, respectively. They also can exhibit blepharophimosis, camptodactyly, short stature, micrognathia, scoliosis, and deep-set eyes, with multiple joint contractures, and the prevalence of various symptoms can be different between diseases [1-4]. Although DA type 3, DA type 5, and MWS have traditionally been considered separate disorders, they can also be considered as different expressions of the same condition [4].

The piezo proteins are nonselective cation channels gated by mechanical forces that participate in cell mechanotransduction [8]. Mechanotransduction is the pathway through which mechanical forces are translated into biological signals [8]. It is important for sensory perceptions, such as pain, hearing, touch, and proprioception, and it is also important for embryonic development [8]. There are two types of piezo proteins. The piezo1 protein participates in sensing shear stress in blood vessels, and it plays a critical role in the regulation of vascular tone and the proper formation of blood vessels [9]. The *PIEZO2* protein, encoded by *PIEZO2*, is a mechanotransducer that is mainly expressed in dorsal root ganglia and Merkel cells in the skin [4,10]. *PIEZO2* signaling regulates morphogenesis and is related to joint extension, lung or thorax expansion, and oculomotor movement [5]. However, further insights into the precise pathophysiology of pathogenic variants in *PIEZO2* causing DA are needed.

In conclusion, a novel *de novo* heterozygous variant in *PIEZO2* was identified in a patient with DA; this is the first reported case in Korea.

Conflict of Interest

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

Acknowledgements

This research was supported by a new faculty research seed money grant of Yonsei University College of Medicine for 2020 (6-2020-0127).

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Supplementary Materials

Further details on supplementary materials are presented online (available at https://doi.org/10.18214/jend.2022.00171).

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JEND Journal of Electrodiagnosis and Neuromuscular Diseases

CASE REPORT

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2023;25(1):34-37
https://doi.org/10.18214/jend.2022.00178

Infantile-Onset *LMNA*-Related Congenital Muscular Dystrophy Presenting as Torticollis: A Case Report

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Lamin A (*LMNA*)-related congenital muscular dystrophy usually presents with hypotonia and severe axial muscle weakness in early infancy. We report a patient who initially presented with torticollis but was finally diagnosed with *LMNA*-related congenital muscular dystrophy. A 7-month-old infant presented to the outpatient clinic with a chief complaint of torticollis. During a thorough physical examination, axial muscle weakness and gross motor delay were noted, and she was admitted to the pediatric rehabilitation department for further evaluation. The serum creatine kinase level was elevated, and electromyography demonstrated the possibility of hereditary myopathy or a motor neuron disorder. A gene study was conducted, and it showed a c.745C>T (p.Arg249Trp) mutation in the *LMNA* gene, which is known to cause congenital muscular dystrophy in rare cases. Since there are few reports describing nerve conduction and electromyography studies in patients with *LMNA*-related congenital muscular dystrophy, this case is meaningful.

Keywords: Electromyography; Muscular dystrophies; Torticollis

Received: August 29, 2022
Revised: November 24, 2022
Accepted: November 25, 2022

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Introduction

Congenital muscular dystrophies are genetic myopathies with hypotonia, muscle weakness, and delayed development from infancy [1]. Lamins are intermediate filament proteins, which are essential for nuclear structure. Laminopathies caused by lamin A (*LMNA*) mutations can be grouped into diseases affecting the striated muscle, peripheral nerve, and adipose tissue. In particular, laminopathies involving striated muscle can cause various types of muscular dystrophy, such as Emery-Dreifuss muscular dystrophy (EDMD), congenital muscular dystrophy, and limb girdle muscular dystrophy type 1B [2].

Congenital muscular dystrophy with *LMNA* mutations associated with congenital onset has been found to be more severe than EDMD with school-age onset [3]. In this case report, we present the clinical and electromyographic features of a patient with congenital muscular dystrophy who initially presented with torticollis.

Case Report

A 7-month-old infant was referred to the pediatric rehabilitation department outpatient clinic with a chief complaint of torticollis. She was the first child of consanguineous parents and was born at term with a birth weight of 3,410 g by cesarean section after an uncomplicated pregnancy. There were no perinatal problems, and at the time of birth, the infant's sucking and crying were strong. No family history of neuromuscular disease was reported.

A physical examination at 7 months of age showed head tilt to the right side when the infant sat with assistance. There was no palpable neck mass, the range of head tilting was 45° on both

sides, and the range of head rotation was 90° on both sides. The head righting reaction was unobtainable on both sides due to weakness of the neck muscles. Unilateral occipital flattening was observed on the right side. The deep tendon reflexes were hypoactive in both the upper and lower extremities. The Babinski sign was equivocal, and there was no ankle clonus. When performing the traction reaction test, head lagging was observed, and during the Landau reaction, the head raised to the trunk level. She could turn over from the supine to prone position, but she could not sit alone and raise her head in the prone position.

Since the patient was hypotonic and presented with gross motor delays, she was admitted to the Department of Pediatric Rehabilitation Medicine for further evaluation. Neck sonography revealed asymmetric thinning of the right sternocleidomastoid muscle without definite evidence of fibromatosis colli (Fig. 1). The serum creatine kinase (CK) level was 2,131 U/L, and brain magnetic resonance imaging revealed enlarged subarachnoid fluid spaces in the supratentorial brain with enlarged subarachnoid fluid in the frontotemporal region and prominent retrocerebellar cerebrospinal fluid. Echocardiography was normal.

A nerve conduction study and electromyography (EMG) were conducted for the hypotonia workup. In the nerve conduction study, left median motor, left sensory, left tibial motor, and sural sensory conduction did not reveal any abnormalities (Table 1). The EMG showed fibrillation potentials in the right gastrocnemius (medial head) and vastus medialis muscles. No abnormal spontaneous activity was observed in the right tibialis anterior muscle (Table 2). It was difficult to accurately evaluate the morphology of the motor unit action potential due to poor cooperation, but there did not seem to be any definite abnormalities, including long or short duration or large or small amplitudes. The clinical findings and electrodiagnostic tests suggested the possibility of hereditary myopathy or a motor neuron disorder. Because the serum CK level was high, muscular dystrophy was more strongly suspected than motor neuron disease or congenital myopathy in this patient.

Based on the above results, we proceeded with genetic testing to confirm the diagnosis. The genetic tests of the *SMN1* gene (for spinal muscular atrophy) and *DMD* gene (for progressive muscular dystrophy) were negative. However, next-generation sequencing for the muscular dystrophy panel with the Illumina MiSeq system (Illumina Inc., San Diego, CA, USA) targeting 30

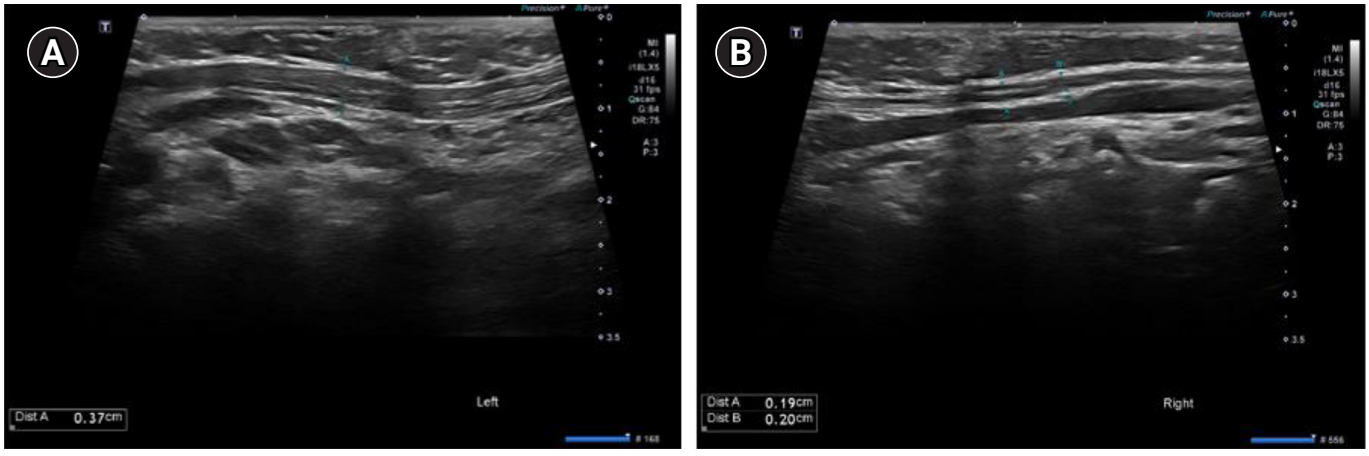

Fig. 1. Ultrasonography findings of the sternocleidomastoid muscle (SCM). (A) The left SCM thickness was measured as 0.37 cm. (B) The right SCM thickness was measured as 0.19 cm. There was asymmetric thinning of the right SCM without any fibromatosis colli.

Table 1. Nerve Conduction Study Findings

Variable	Stimulation site	Recording site	Latency (ms)	Amplitude (μV)	Velocity (m/s)
Motor					
Left median	Wrist	Third finger	1.85	5.1	
Left tibial	Ankle	Abductor hallucis	2.15	9	
	Knee	Abductor hallucis	5.02	8.3	38.3
Sensory					
Left median	Wrist	Third finger	1.97	58.1	32.8
Left sural	Calf	Lateral malleolus	2.23	18.2	31.3

Table 2. Electromyography Study Findings

Muscle	Spontaneous		MUAP			Recruitment	Interference
	Fib	PSW	Amplitude	Duration	Phase		
Rt. gastrocnemius	1+	1+	NL	NL	NL	NT	NT
Rt. tibialis anterior	1+	1+	NL	NL	NL	NT	NT
Rt. vastus medialis	None	None	NL	NL	NL	NT	NT

Fib, fibrillation; PSW, positive sharp wave; MUAP, motor unit action potential; Rt., right; NL, normal; NT, not testable.

genes showed a c.745C > T (p.Arg249Trp) mutation in the *LMNA* gene, which was classified as a pathogenic variant. Genetic testing of the patient's mother was performed, and a very low concentration of mosaicism of the c.745C > T (p.Arg249Trp) (p.R249W) mutation of the *LMNA* gene was found. p.R249W is a mutation reported in patients with congenital muscular dystrophy.

At 8 months of age, intermittent aspiration signs were observed, and the patient was hospitalized for pneumonia, at which point she started nasogastric tube feeding. At 23 months of age, she was assessed with the Bayley Scales of Infant Development-II. While the mental developmental index was 100 (within normal limits), the motor index was < 50 (i.e., more than 3 standard deviations below the mean). She was not able to sit independently or stand with hand support, but was able to flip, crawl, and maintain a sitting position with support. Until 31 months of age, the patient did not need respiratory support requiring a tracheostomy or ventilator.

Written informed consent by the patients was waived due to a retrospective nature of our study.

Discussion

The case described herein is a very rare early form of laminopathy presenting as severe congenital muscular dystrophy; this diagnosis was inferred on the basis of electrodiagnostic and laboratory findings and then confirmed with genetic testing. The *LMNA* gene codes for lamin A, which constitutes the nucleus, and a heterozygous de novo mutation causes severe early-onset congenital muscular dystrophies. A previous report found that all children with *LMNA*-related congenital muscular dystrophy showed rapid weakness in cervical and axial muscle strength that rarely progressed afterward [4].

A recent study showed that about 67% of *LMNA*-related congenital muscular dystrophy patients acquired independent ambulation by the age of 1.2 years; however, 85% of them eventually lost the ability. In contrast, the patient in this case report did not acquire the ability to ambulate until 23 months of age. According to previous reports, the c.745C > T (p.Arg249Trp) mutation is most common (20%), and it is known to be associated with a more severe prognosis [5,6].

Congenital muscular dystrophy is known to present normal electrophysiological findings in motor and sensory nerve conduction studies. In addition, needle electromyographic studies usually show absent or sparse positive sharp waves and fibrillation. Furthermore, polyphasic motor unit action potentials with decreased duration and amplitude appear [7]. In this case, the patient was too young to adequately evaluate the characteristics of motor unit action potentials; however, rare abnormal spontaneous activity was detected. These results suggested congenital myopathy, and congenital muscular dystrophy was suspected due to the high CK level.

Previous reports suggest that *LMNA*-related congenital muscular dystrophy presents with early-onset, life-threatening respiratory insufficiency [4,8]. Ben Yaou et al. [5] reported that non-ambulating patients showed a disease course with more severe progression of respiratory complications early in infancy.

LMNA-related congenital muscular dystrophy is a completely different disease entity from EDMD, where the *LMNA* gene mutation was first identified [9]. EDMD presents as child-onset slowly progressive muscle wasting with preceding contracture [10].

It may be easy to suspect neuromuscular disease in patients with a severe progressing course of *LMNA*-related congenital muscular dystrophy. However, the differential diagnosis is difficult in patients in early infancy before disease progression. In particular, when the chief complaint is torticollis, as it was in this case, clinicians may not consider congenital muscular dystrophy in the differential diagnosis .

There are few reports presenting nerve conduction and EMG studies of *LMNA*-related congenital muscular dystrophy; therefore, this case makes a meaningful contribution to the literature. In addition, this case shows that patients with early-onset congenital muscular dystrophy could present with clinical torticollis due to axial muscle weakness. It is important for clinicians to examine infants with torticollis thoroughly, since it may be the first sign of neuromuscular diseases.

https://doi.org/10.18214/jend.2022.00178

Conflict of Interest

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

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JEND Journal of Electrodiagnosis and Neuromuscular Diseases

CASE REPORT

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2023;25(1):38-41
https://doi.org/10.18214/jend.2022.00185

Myeloneuropathy with Bilateral Foot Pain after Scrub Typhus Infection: An Antibody-Proven Case Report

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Scrub typhus is an acute febrile illness caused by *Orientia tsutsugamushi*. The most common neurological symptoms are headaches presenting with meningitis, meningoencephalitis, or encephalitis; however, transverse myelopathy and polyneuropathy are rare in typhoid infections. Herein, we report a laboratory and electrodiagnostically proven case of subacute myelopathy and polyneuropathy with slow progression after scrub typhus infection. A 64-year-old man complained of truncal numbness and a burning sensation in both feet. Magnetic resonance imaging did not reveal any definite changes in the spinal cord; however, serological tests showed immunoglobulin G antibodies against *O. tsutsugamushi* by enzyme-linked immunosorbent assay. An electrophysiological study showed myelopathy concurrent with polyneuropathy. To the best of our knowledge, this is the first immunochemical detection of antibodies in a patient with delayed neurological manifestations after scrub typhus infection.

Keywords: *Orientia tsutsugamushi*; Scrub typhus; Polyneuropathies

Received: September 6, 2022
Revised: September 26, 2022
Accepted: October 4, 2022

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Introduction

Scrub typhus is an acute febrile illness caused in Southeast Asia by rickettsial infection mediated by the bite of larvae infected with *Orientia tsutsugamushi*. The most common neurological symptoms are headaches presenting with meningitis, meningoencephalitis, or encephalitis [1]. However, transverse myelopathy and polyneuropathy are rare in typhoid infections. Simultaneous involvement of the central nervous system (CNS) and peripheral nervous system is extremely rare [2]. Post-infectious neurological manifestations may arise from an autoimmune phenomenon, as a result of direct infection and as a sequela of the infection. In addition, confirmation through serological tests in the cerebrospinal fluid (CSF) and post-infectious deterioration in the subacute period have not been reported.

We report a case of subacute myelopathy simultaneously accompanied by polyneuropathy resulting from scrub typhus infection, which was confirmed by laboratory antibody testing and responsive to steroid therapy.

Case Report

A 64-year-old man visited a neurology clinic with truncal numbness and a burning sensation in both feet. He had no underlying medical conditions, such as diabetes, alcohol abuse, or vitamin deficiency. He had been admitted to the Department of Infective Medicine at another hospital because of fever and eschar on his right ankle after field activities 2 months ago. He was diagnosed with scrub typhus and empirically treated with doxycycline and steroids as the standard treatment for 1 week after diagnosis. At the time of discharge , the patient did not notice any symptoms. About 1 month before visiting our clinic (3 weeks af-

ter discharge), he had progressive pain in his legs, especially in both feet, numbness in his trunk, and difficulty in defecation, with decreased sensation in the groin and inguinal area. He had gait disturbance with pain and a floating sensation while standing and walking on the ground. He was noted to have a subacute eschar on his right ankle and no fever (Fig. 1). A neurological examination revealed a well-defined truncal sensory level at T4, below which the sensation of pain and temperature was markedly decreased. On both legs, especially the feet, he felt allodynia on touch sensation. Proprioception was impaired and Romberg's sign was positive. He showed a high stepping gait that significantly worsened when he closed his eyes. No motor weakness was noted in either the upper or lower extremities; however, the deep tendon reflex was absent in the bilateral knee and ankle, while the upper extremities showed an intact deep tendon reflex. Magnetic resonance imaging (MRI) revealed no definite changes in signal intensity throughout the spinal cord (Fig. 2). CSF cytology results were normal. Serological tests showed immunoglobulin G antibodies to *O. tsutsugamushi* by enzyme-linked immunosorbent assay (ELISA).

Nerve electrophysiological studies supported the presence of myelopathy concurrent with polyneuropathy, and nerve conduction studies revealed severe sensory-dominant axonal polyneuropathy (Table 1). Sensory evoked potentials demonstrated a central conduction delay (Table 2) [3]. To exclude other inflammatory demyelinating diseases, we checked for oligoclonal bands in the CSF, serum anti-ganglioside antibodies, and anti-aquaporin-4 antibodies, all of which were negative. Immunoglobulin M and immunoglobulin G for *O. tsutsugamushi* were detected in the CSF. Intravenous steroid therapy (1 g/day) was administered for 5 days. After treatment, the numbness, allodynia, pain, and decreased sensation in both legs improved at the time of discharge.

Written informed consent by the patients was waived due to a retrospective nature of our study.

Discussion

Scrub typhus is a rickettsial infection mediated by the bite of larvae infected with *O. tsutsugamushi*. It is known to occur throughout the Asia-Pacific region, including in Korea [4]. An eschar at the site of the bite may help in the diagnosis. Common symptoms of scrub typhus include fever, conjunctival injection, headache, myalgia, and gastrointestinal symptoms [5]. The symptoms and complications vary widely among patients, and some may suffer from neurological symptoms. *O. tsutsugamushi* can invade the CSF and is considered a cause of mononuclear

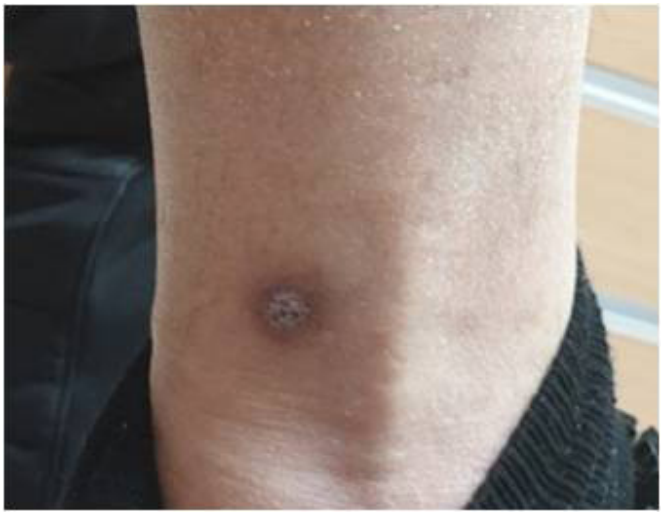

Fig. 1. Subacute phase of eschar on right ankle of the patient.

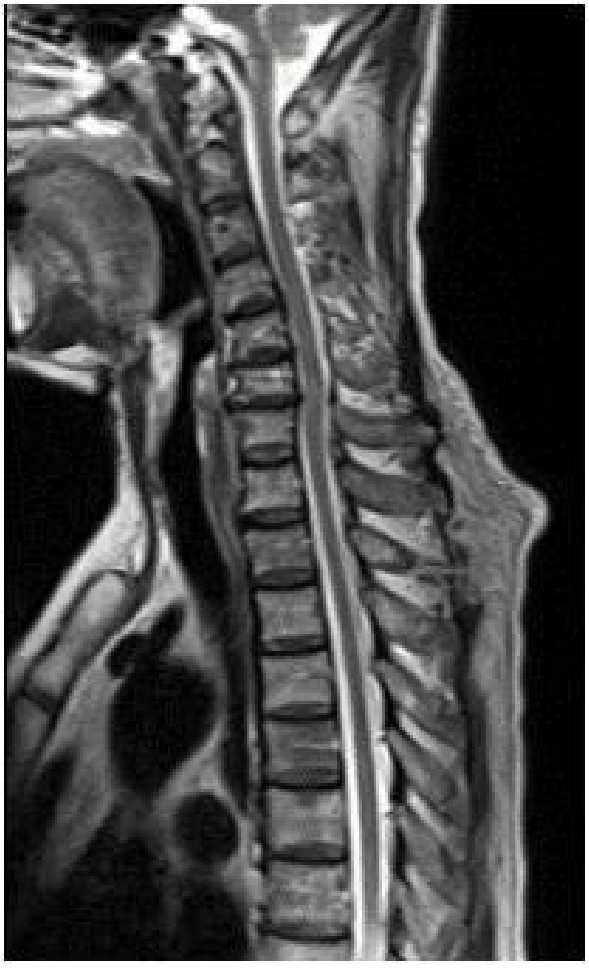

Fig. 2. Spine magnetic resonance imaging mid-sagittal plane at the time of admission.

Table 1. Nerve Conduction Study Showing Severe Sensory-Dominant Axonal Polyneuropathy upon Visiting the Neurology Department

Variable	Stimulation	Latency (ms)*	Amplitude†	CV (m/s)
Motor				
Rt. median	Wrist	3.13	12.88	-
	Elbow	7.92	12.73	47
	Axilla	10.89	12.59	52
Rt. ulnar	Wrist	2.4	17.97	-
	Elbow	6.93	16.15	56
	Axilla	9.58	15.12	60
Rt. peroneal	Ankle	3.33	6.07	-
	Knee	10.21	5.78	44
Lt. peroneal	Ankle	3.91	5.26	-
	Knee	10.47	5.02	45
Rt. tibial	Ankle	3.44	15.59	-
	Knee	13.54	12.63	38
Lt. tibial	Ankle	3.59	13.41	-
	Knee	12.5	8.17	42
Sensory				
Rt. median	Finger-wrist	3.59	4.77†	-
	Wrist-elbow	4.64	8.61†	-
	Elbow-axilla	3.07	25.01	-
Rt. ulnar	Finger-wrist	3.02	4.80†	-
	Wrist-elbow	5.16	12.47	-
	Elbow-axilla	2.86	9.44†	-
Rt. superficial peroneal	Ankle	3.49	7.18	-
Lt. superficial peroneal	Ankle	NR	NR	-
Rt. sural	Ankle	NR	NR	-
Lt. sural	Ankle	NR	NR	-
H-Reflex				
Rt. tibial-soleus	-	35.31§	-	-
Lt. tibial-soleus	-	32.97	-	-

CV, conduction velocity; Rt., right; Lt., left; NR, no response.
*All motor and sensory latencies are onset latencies; †Amplitudes were measured in millivolts (mV, motor) and in microvolts (μV, sensory); †Decreased amplitude compared to the normal range; §Delayed latency compared to the normal range.

Table 2. Sensory Evoked Potentials Revealing Central Conduction Delay upon Visiting the Neurology Department

Nerve	EP (≤ 10.5)*	N13 (≤ 13.7)*	P14	N20 (≤ 20.3)*	N13–N20 (≤ 7.1)*	N21 (≤ 23.2)*	P37 (≤ 41.3)*	N21–P37 (≤ 17.2)*
Rt. median	12.3†	16.6†	18.2	22.9†	6.3	-	-	-
Lt. median	11.5†	17.2†	17.3	22.1†	4.9	-	-	-
Rt. tibial	-	-	-	-	-	28.5†	47.2†	18.6†
Lt. tibial	-	-	-	-	-	27.9†	48.1†	20.2†

EP, evoked potential; Rt., right; Lt., left.
*Adapted from Dumitru et al. [3]; †Delayed latency compared to the normal range.

meningitis. The symptoms are similar to those of leptospirosis, viral meningitis, and tuberculous meningitis [6]. It can also invade the blood vessels in the CNS, which can cause vasculitis [7]. Neurologic manifestations of scrub typhus include altered sensorium, headache, seizures, ataxia, double vision, hyperpyrexia with stiffness of the whole body, and acute bilateral lower limb weakness [8]. Spinal MRI findings may show focal and central high-signal regions extending to three or four segments in the T2 sequence. However, the MRI findings are normal in 40% of cases. In our case, the MRI findings were normal, but they could be differentiated from compressive myelopathy [9].

This is the first immunochemically detected case of delayed neurological manifestations of both myelopathy and polyneuropathy after scrub typhus infection. The detection of *O. tsutsugamushi* using ELISA showed good sensitivity (94%) and specificity (91%) [10]. Clinical features, electrophysiological studies, and serological studies suggested an association of typhoid infection with thoracic myelopathy and sensory-dominant

 https://doi.org/10.18214/jend.2022.00185

axonal polyneuropathy. When a patient complains of numbness in the trunk and a burning sensation in both feet, it may be necessary to recognize the neurological symptoms of delayed typhoid and consider it in the differential diagnosis in order to ensure an accurate diagnosis and proper management.

Conflict of Interest

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

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JEND Journal of Electrodiagnosis and Neuromuscular Diseases

CASE REPORT

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2023;25(1):42-45
https://doi.org/10.18214/jend.2022.00192

Vasculogenic Myoclonus of Peripheral Origin after Whiplash Injury: A Case Report

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Based on the neuroanatomical origin of the electrical discharge, myoclonus could be classified in terms of its etiology as cortical, subcortical, spinal, or peripheral. A 29-year-old female patient experienced a continuous involuntary rhythmic twitching movement of the right elbow for 6 months. This myoclonus occurred immediately after a whiplash injury caused by a rear-end car accident. The patient had no radiological, clinical, or electrophysiological evidence for central nervous system origin. Concentric needle electromyography recordings of the right biceps, brachioradialis, and triceps muscles presented bursts of spontaneous rhythmic activity synchronous to the clinical myoclonus. Doppler ultrasound on the right arm revealed that the biceps and triceps contraction coincided with the vascular pulsation of the brachial artery and vein. This result suggested that myoclonus was caused by vascular stimulation, similar to the pathophysiology of hemifacial spasms. A whiplash injury around the neck or arm may have affected the vascular structures in the upper and middle trunks, resulting in vasculogenic myoclonus. Electromyography can be used to determine the classification and distribution of myoclonic jerks.

Keywords: Brachial plexus; Myoclonus; Electromyography

Received: September 19, 2022
Revised: December 9, 2022
Accepted: December 30, 2022

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Introduction

Myoclonus is sudden, brief, involuntary muscle twitching that induces a simple jerky movement of a body part. Based on the neuroanatomical origin of the electrical discharge, myoclonus could be classified in terms of its etiology as cortical, subcortical, spinal, or peripheral [1]. Myoclonus can be easily diagnosed by clinical observation, but some cases are difficult to distinguish from other involuntary movements such as tremor, dystonia, and chorea. In those circumstances, electromyography (EMG) can be helpful, as one of the most specific characteristics of myoclonus is an abrupt and brief muscle contraction [2].

Information about the synchronization of motor unit discharges can be obtained from EMG [3]. Obtaining EMG recordings simultaneously from multiple muscles is useful, both to demonstrate the distribution of myoclonic jerks and to identify the best muscle for subsequent analysis.

Here, we report a rare case of peripheral origin myoclonus associated with vascular pulsation immediately after a whiplash injury.

Case Report

A 29-year-old female patient experienced continuous involuntary rhythmic twitching movement of the right elbow for 6 months after a whiplash injury due to a rear-end car accident. After the car accident, she was immediately transferred to the emergency department of a tertiary training hospital. There were no symptoms other than posterior neck pain and musculoskeletal pain in the right upper arm, and no other specific injuries or

bone fractures were observed at that time.

However, she soon noticed a continuous painless involuntary movement of the right elbow occurring at rest; this involved a rhythmic twitching movement of the muscles around the elbow, causing rhythmic elbow flexion. The symptom worsened 3 days after the accident.

Magnetic resonance imaging of the cervical spinal cord and brain showed no abnormal findings. Standard electroencephalography also showed no epileptiform activity. As it was difficult to determine the exact etiology, the patient received psychiatric treatment to determine whether there was a psychogenic cause. She was also hospitalized at an oriental medicine hospital and received acupuncture and herbal therapy. Since her symptoms did not improve, she was referred to our outpatient Department of Physical Medicine and Rehabilitation.

A continuous rhythmic movement of the muscles of the arm and forearm was observed, which was considered to be myoclonus (Supplementary Video 1). The patient remained conscious and communicated appropriately. The patient could not suppress the movement intentionally and did not complain of pain or any other discomfort. No motor weakness or sensory changes were observed on the neurological examination. This rhythmic movement occurred only at rest, lasting even during sleep, and was not exacerbated by movement. However, this myoclonic jerk stopped during elbow extension.

A nerve conduction study in both the motor and sensory nerve fibers of the median, ulnar, and radial nerves showed acceptable amplitude and velocity. An F-wave study showed acceptable latency at the bilateral median and ulnar nerves. Concentric needle EMG recordings of the right biceps, brachioradialis, and triceps presented bursts of spontaneous rhythmic activity synchronous to the clinical myoclonus (Fig. 1). Each burst included the activity of several motor unit action potentials. No abnormal activity was noted in other muscles, including the paraspinalis, deltoid, flexor carpi radialis, extensor carpi radialis, abductor pollicis brevis, and abductor digiti minimi (Table 1).

Doppler ultrasound (Philips EPIQ7, Bothell, WA, USA) performed at the right upper arm revealed a rhythmic twitching movement of the biceps and triceps. The muscle contraction coincided with the pulsation of the brachial artery, suggesting that the myoclonus was caused by vascular pulsation (Supplementary

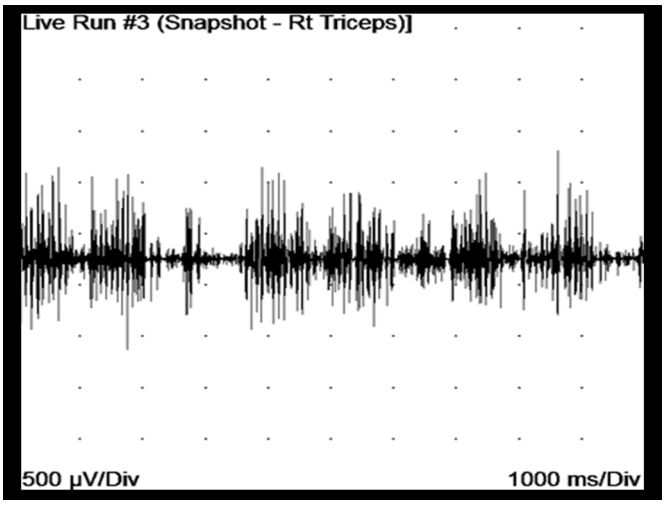

Fig. 1. Electromyography recording of the triceps presents bursts of spontaneous rhythmic activity.

Table 1. Needle Electromyography in the Right Upper Extremities

Muscle	IA	Spontaneous		MUAP			Recruitment pattern/IP
		Fib/PSW	Other	Amplitude	Duration	Polyphasic	
B. C5-T1 paraspinal	None						
Rt. serratus anterior	N	None	None	N	N	N	Complete
Rt. rhomboid major	N	None	None	N	N	N	Complete
Rt. infraspinatus	N	None	None	N	N	N	Complete
Rt. pectoralis major	N	None	None	N	N	N	Complete
Rt. deltoid	N	None	None	N	N	N	Complete
Rt. biceps brachii	N	None	BSRA	N	N	N	Complete
Rt. triceps	N	None	BSRA	N	N	N	Complete
Rt. brachioradialis	N	None	BSRA	N	N	N	Complete
Rt. pronator teres	N	None	None	N	N	N	Complete
Rt. flexor carpi radialis	N	None	None	N	N	N	Complete
Rt. extensor carpi radialis	N	None	None	N	N	N	Complete
Rt. flexor carpi ulnaris	N	None	None	N	N	N	Complete
Rt. abductor pollicis brevis	N	None	None	N	N	N	Complete
Rt. abductor digiti minimi	N	None	None	N	N	N	Complete

IA, insertional activity; Fib, fibrillation; PSW, positive sharp wave; MUAP, motor unit action potential; IP, interference pattern; B., both; Rt., right; N, normal; BSRA, bursts of spontaneous rhythmic activity.

Video 2). Unusually, it was also observed that the brachial vein in the right arm pulsated along with the biceps contraction, which was thought to be a secondary effect of muscle contraction (Supplementary Video 3).

An ultrasound-guided brachial plexus block via the interscalene approach was performed to relieve the myoclonic jerk. An injection of 1 mL of 2% lidocaine along the upper and middle trunks of the right brachial plexus was performed between the anterior and middle scalene muscles. However, this did not alleviate the myoclonus.

Informed consent was obtained for the written case report and video to be published.

Discussion

Myoclonus can be classified based on the neuroanatomical origin of the electrical discharge as cortical, subcortical, spinal, or peripheral myoclonus. Different myoclonic patterns may be expressed depending on the neuroanatomical origin of the abnormal discharge, which can help determine the cause of clinical myoclonus. Cortical myoclonus is usually stimulus-sensitive and is characterized by an extremely short duration of the EMG correlates, usually less than 50 ms [2]. In contrast, spinal myoclonus tends to be rhythmic and involves a group of muscles innervated by a specific spinal segment [2]. Peripheral myoclonus is typically not stimulus-sensitive and is hypothesized to be caused by lesions of the peripheral nerves that may alter the sensory input and induce central reorganization [4].

Our case displayed several unique clinical characteristics. There was no direct trauma to the arm, only a history of whiplash injury to the neck. The myoclonus was confined to a single arm without any radiating pain. The movements were more rhythmic and the EMG bursts were longer in duration than what has been described in classic cortical myoclonus. An EMG study clearly revealed brief muscle jerks (lasting about 800 ms) with bursts of spontaneous rhythmic activity, synchronous to the clinical movement. This myoclonus was strongly supported to be of peripheral origin, as our patient had no clinical, radiological, or electrophysiological evidence of central nervous system origin. Furthermore, Doppler ultrasound revealed that the biceps and triceps muscle contraction coincided with the pulsation of the brachial artery, suggesting that the vascular pulsation caused the muscle contraction. Primary hemifacial spasms have a similar pathophysiology, which is attributed to benign compression of the facial motor nerve by a vessel within or close to its root exit zone from the brainstem [5].

A peripheral generator of myoclonus has been hypothesized in the brachial plexus and, rarely, in peripheral nerve lesions [6]. Kang et al. [7] reported a case of myoclonus of the ipsilateral upper extremity following supraclavicular brachial plexus block, and Hudson et al. [8] reported myoclonus after a routine peripheral nerve block in a healthy patient. Similarly, in our case, the peripheral ectopic activity could have been generated by the vascular structures at the site of these lesions. Considering the pathophysiology of primary hemifacial spasms [5], the history of traumatic whiplash injury might have affected the vascular structures around the upper and middle trunk, inducing vascular pulsation that stimulated peripheral nerves, eventually resulting in vasculogenic myoclonus.

In the case reported here, peripheral nerve trauma or nerve entrapment may have also induced peripheral myoclonus. Assal et al. [4] reported involuntary rhythmic movement following an injury to the cutaneous branch of the deep peroneal nerve. As xylocaine injection to the deep peroneal nerve suppressed the abnormal movement in that previous study [4], we injected lidocaine along the upper and middle trunk levels of the right brachial plexus; however, it had no effect on the myoclonic movement.

There are a few limitations in this case report. First, only a routine nerve conduction study including the median, ulnar, and radial nerves was conducted. A special nerve conduction study including axillary, thoracodorsal, dorsal scapular, musculocutaneous, and suprascapular nerves was not performed, as the myoclonus was limited to the upper extremity, not the shoulder girdle muscle. For this reason, there was a limited ability to accurately assess the possibility of brachial plexus lesion. Furthermore, considering the treatment options for hemifacial spasms, treatments such as botulinum toxin injection and microvascular decompression may also be considered. Unfortunately, as the symptom did not cause functional problems, the patient refused additional treatment before trying those interventions.

This case provides an opportunity to explore the pathophysiology of post-traumatic myoclonus induced by vascular pulsation. Doppler ultrasound revealed that the muscle contraction coincided with the vascular pulsation, suggesting that myoclonus was caused by vascular stimulation. Furthermore, EMG can be successfully used to analyze involuntary muscle activity in myoclonus, as it helps to determine the classification and distribution of myoclonic jerks.

Conflict of Interest

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

https://doi.org/10.18214/jend.2022.00192

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Supplementary Materials

Further details on supplementary materials are presented online (available at https://doi.org/10.18214/jend.2022.00192).

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JEND Journal of Electrodiagnosis and Neuromuscular Diseases

CASE REPORT

pISSN: 2733-6581 · eISSN: 2733-659X
J Electrodiagn Neuromuscul Dis 2023;25(1):46-49
https://doi.org/10.18214/jend.2022.00199

Diagnosis and Treatment of Cauda Equina Arachnoiditis, a Rare Manifestation of Tuberculosis Meningoencephalitis: A Case Report

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Tuberculous meningoencephalitis (TM) is an acute, progressive form of tuberculosis (TB). The epidemiology, clinical signs, and diagnosis of TB are well established, but several atypical forms of tuberculous spinal arachnoiditis can be easily misdiagnosed. We report a rare case of TM with cauda equina arachnoiditis diagnosed by magnetic resonance imaging and an electrodiagnostic study. A 26-year-old otherwise healthy male patient experienced fever, headache, gait disturbance, and bladder and bowel incontinence. Needle electromyography (EMG) recordings were suggestive of bilateral diffuse lumbar and lumbosacral polyradiculopathy, and the pudendal sensory-evoked potential and bulbocavernosus reflex latencies were prolonged. Lumbar arachnoiditis is a rare clinical condition that warrants a heightened index of suspicion. It has diverse etiologies and symptoms, and it can lead to potentially serious and irreversible disorders. This case illustrates the usefulness of nerve conduction, EMG, and pudendal sensory-evoked potential and bulbocavernosus reflex latency studies in the diagnosis of cauda equina syndrome induced by TB arachnoiditis.

Keywords: Cauda equine; Neuroinvasive disease; Tuberculosis

Received: October 12, 2022
Revised: October 17, 2022
Accepted: October 18, 2022

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Introduction

Tuberculous meningoencephalitis (TM) is an acute progressive form of tuberculosis (TB), which accounts for approximately 2% of all infectious diseases affecting the central nervous system [1]. To reduce the risk of mortality and serious complications from TM, a precise diagnosis and prompt prescription of intense treatment are of vital importance [2]. The epidemiology, clinical signs, and diagnosis of TB are well established, but several atypical forms of tuberculous spinal arachnoiditis can easily be misdiagnosed [3].

Arachnoiditis is a rare disorder that causes chronic pain and may even result in long-term disability with paraplegia. Its pathophysiology includes the invasion of fibrinous and oligocellular exudates that result from inflammatory processes in the pia arachnoid layer, causing adhesion of the nerve roots to the arachnoid lining of the meninges. These inflammatory processes may result from spinal trauma, neoplasms, surgery, lumbar puncture, or spinal infections, including TB [4,5].

Here, we report a rare case of TM with cauda equina arachnoiditis diagnosed by magnetic resonance imaging (MRI) and electrodiagnostic study. A loss of sphincter control and weakness of the lower extremities were improved with corticosteroid and anti-TB medication. Several atypical forms of tuberculous spinal arachnoiditis exist, making the diagnosis confusing. Unlike usual TM, this case had symptoms of urinary incontinence and stool incontinence, leading to the suspicion of cauda equina syndrome (CES). We illustrate the difficulties in diagnosing this disease

and the necessity of electrodiagnostic studies for diagnosing TM arachnoiditis-induced CES with bladder and bowel dysfunction.

Case Report

A 26-year-old otherwise healthy male patient experienced fever, headache, and gait disturbance accompanied by bladder disturbances with constipation. The urinary and fecal incontinence progressed, and he was unable to control the anal sphincter. As the symptoms worsened for 1 week, he was transferred to the emergency department of a tertiary training hospital.

Brain MRI revealed meningeal enhancement at the basal meninges. The adenosine deaminase (ADA) level in the cerebrospinal fluid (CSF) was elevated at 22 U/L. Both serum and CSF rapid plasma reagents for syphilis were negative. On the basis of the brain MRI and ADA results, the patient was diagnosed with TM. Intravenous methylprednisolone was initiated at 1 g daily for 5 days, followed by oral prednisolone at 60 mg for another 5 days, with a gradual tapering of the dose over 20 more days. The patient was also given TB medication, including isoniazid (150 mg daily), rifampin (300 mg daily), ethambutol (1,200 mg daily), and pyrazinamide (500 mg daily).

When the patient was medically stable 1 month after the onset of illness, he was transferred to our rehabilitation department. His vital signs were normal upon admission, with no fever, and he demonstrated intact cognitive and cranial nerve function. He showed normal muscle tone in the upper extremities, but weakness in the lower extremities made him unable to stand. He presented grade 2 muscle weakness according to the Medical Research Council (MRC) scale.

The patient remained incontinent for urine and feces. His self-voiding volume was as little as 50 cc, so he started self-catheterization. A urodynamic study revealed an areflexic neurogenic bladder. We added bethanechol chloride and tamsulosin, as the volume of residual urine remained as high as 300 cc. Self-defecation was impossible. Fecal incontinence and constipation continued, so we used a rectal suppository every other day.

Since bladder and bowel impairment is not common in TM, we decided to perform a physical examination for CES, spine MRI, and electrodiagnosis to identify the cause. A sensory examination was normal in temperature and proprioception except in the perianal area. The anal sphincter tone was hypotonic, and the bulbocavernosus reflex (BCR) was equivocal according to our physical examination. MRI of the lumbar spine found an arachnoid cyst at the L4/5 through L5/S1 level (Fig. 1).

An electrodiagnostic study was performed 2 months after onset. A nerve conduction study of both the motor and sensory nerve fibers of the bilateral lower extremities showed acceptable amplitude and velocity (Table 1), while needle electromyography (EMG) recordings suggested bilateral diffuse lumbar and lumbosacral polyradiculopathy. Abnormal spontaneous activity was noted in the muscles, including the paraspinals, iliopsoas, gluteus maximus, tensor fascia latae, vastus medialis, tibialis anterior, gastrocnemius, extensor hallucis longus, anal sphincter, and bulbocavernosus. The sensory-evoked potential (SEP) of the pudendal nerve was prolonged. The bulbocavernosus reflex latency (BCRL) was prolonged, indicating an incomplete sacral reflex arc lesion, such as a cauda equina injury (Table 2).

The patient continued to be treated with antitubercular medication and underwent physical rehabilitation. One month after admission to our rehabilitation center, he demonstrated improved lower extremity muscle power, with the MRC grade improving from 2 to 4. He was able to walk without support but remained incontinent for urine and feces.

Written informed consent by the patients was waived due to a retrospective nature of our study.

Discussion

Adhesive arachnoiditis is a rare condition that has been infrequently described in the medical literature. Therefore, the true incidence of the disease is unknown, and its numbers may be quite underestimated due to the omission of subclinical cases or the presentation of cases that explain it as the cause of paralysis

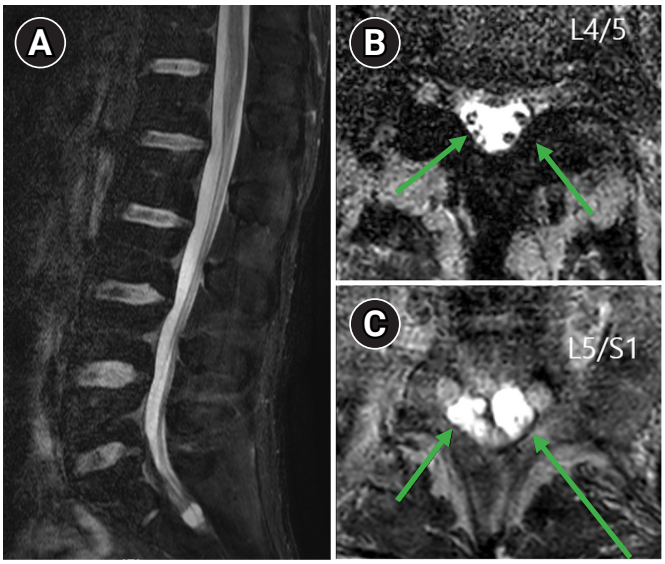

Fig. 1. (A) Lumbar spine midsagittal magnetic resonance imaging showing fatty degeneration of the posterior back muscle at the lower lumbar spine level. (B, C) An arachnoid cyst at L4/5 through L5/S1 (green arrows).

Table 1. Results of the Nerve Conduction Studies

Nerve	Latency (ms)	Amplitude*	Velocity (m/s)
Motor (onset latency)			
Median R/L	3.50/3.81	13.4/12.7	60.8/64.2
Ulnar R/L	2.63/2.50	11.2/8.7	54.0/60.3
Peroneal R/L	4.35/4.44	2.4/3/4	42.6/45.8
Tibial R/L	4.60/4.67	5.8/8.3	40.6/40.9
Femoral R/L	6.46/6.13	-	-
Obturator R/L	5.38/5.69	-	-
Sensory (peak latency)			
Median R/L	2.88/2.92	39.9/47.6	-
Ulnar R/L	2.75/2.73	37.1/42.9	-
Superficial peroneal R/L	2.10/1.990	13.0/14.6	-
Sural R/L	1.77/1.96	17.2/24.7	-
Lateral femoral cutaneous R/L	2.00/1.81	11.5/9.7	-
Saphenous R/L	2.08/2.02	8.1/8.2	-

Onset/peak latency was used for sensory nerve conduction.
R, right; L, left.
*Amplitudes were measured in millivolts (mV, motor) and in microvolts (μV, sensory).

Table 2. Results of Needle Electromyography and the Bulbocavernosus Reflex

Variable	IA	Fib	PSW	Interference pattern	Latency (ms)	Amplitude*
Iliopsoas (R/L)	Increased	-	1+/2+	Complete	-	-
Tensor fasciae latae (R/L)	Increased	-	3+/2+	Complete	-	-
Gluteus maximus (R/L)	Increased	-	2+/1+	Complete	-	-
Vastus medialis (R/L)	Increased	-	1+/2+	Complete	-	-
Tibialis anterior (R/L)	Increased	-	1+/2+	Complete	-	-
Gastrocnemius (R/L)	Increased	-	2+/2+	Complete	-	-
Extensor hallucis longus (R/L)	Increased	-	2+/3+	Complete	-	-
Bulbocavernosus (R/L)	Increased	-	2+/1+	Zero	-	-
Anal sphincter	Increased	-	2+/1+	Partial	-	-
Bulbocavernosus reflex (R/L)					48.81/48.06	0.9/1.8

IA, insertional activity; Fib, fibrillation; PSW, positive sharp wave; R, right; L., left.
*Amplitudes were measured in millivolts (mV, motor) and in microvolts (μV, sensory).

in patients with other, undiagnosed causes of spinal stenosis. The etiology of adhesive arachnoiditis is heterogeneous. The most common causes include infection (bacteria, TB, and syphilis), trauma, tumor, and contamination of a cyst by intraspinal injections [6,7].

The clinical symptoms of arachnoiditis of the lumbar spine are low back pain, sudden paresthesia of both legs, and bladder and bowel sphincter dysfunction. These can be symptoms of compression of the nerve roots of the cauda equina, so they may be explained by other spinal pathologies, such as CES and inflammatory neuropathy. In a clinical review of 63 patients, 83% had lumbar-sacral arachnoiditis, while the rest had thoracic or cervical forms [8].

MRI plays an important role in diagnosing adhesive arachnoiditis, as its sensitivity is about 92%, and its specificity reaches 100% [9]. The most common MRI abnormalities are the presence of arachnoid cysts, displacement and anchoring, swelling of the spinal cord, as well as atrophy of the spinal cord with syrinx formation [6].

In our case, a young man presented with fever, bilateral leg weakness, gait disturbance, and urinary and fecal incontinence. TM was diagnosed, as brain MRI showed meningeal enhancement at the basal meninges and an increased level of ADA in the CSF. The patient started pulse treatment of high-dose intravenous corticosteroid therapy and antituberculosis therapy with a combination of drugs. As urinary and fecal incontinence is not a common symptom of TM, we obtained an MRI scan of the lumbar spine that revealed an arachnoid cyst at the L4/5 through L5/S1 level. A physical examination (anal tone) and manual BCR testing were used as early tools for identifying CES. As the MRI findings and physical examination suggested cauda equina nerve root compression, we performed nerve conduction, EMG, and pudendal SEP and BCRL studies. The report indicated bilateral diffuse lumbar and lumbosacral polyradiculopathy, including abnormal

 https://doi.org/10.18214/jend.2022.00199

spontaneous activity in all key lower extremity muscles and the anal sphincter, as well as prolonged pudendal SEP and BCRL, showing an incomplete sacral reflex arc lesion, such as CES.

The patient in the present case had CES symptoms, but this diagnostic possibility was difficult to recognize, as TM-associated CES is very rare. In New Zealand, among 104 patients with certain or likely TM, myeloradiculopathy that caused sphincter dysfunction, weakness of the lower extremities, and loss of sensation occurred in only three patients [10]. Several atypical forms of tuberculous spinal arachnoiditis that give rise to confusing diagnoses are well known. Anatomically, an L4/5 and L5/S1 arachnoid cyst can cause saddle-type anesthesia, sphincter dysfunction, and reflex and BCR reductions, as observed in this patient. EMG is considered an important dynamic diagnostic procedure for radiculopathy and peripheral neuropathy in TM [11]. In this case, a nerve conduction study, EMG, BCRL, and pudendal SEP helped not only to diagnose CES but also to determine the severity of the condition following the presence of sphincter dysfunction. A previous study showed significant differences in BCR and pudendal SEP outliers in CES patients compared to the control group, confirming that these two parameters have diagnostic value for CES [12].

In conclusion, lumbar arachnoiditis-induced by TM is a rare clinical entity and warrants a heightened index of suspicion. It is a condition with various etiologies and symptoms that can lead to potentially serious and irreversible disorders. This case illustrates the usefulness of nerve conduction, EMG, and pudendal SEP and BCRL studies in diagnosing CES induced by TB arachnoiditis. CES should be suspected in TM patients with bladder and bowel incontinence. Patients with TM rarely develop bladder and bowel impairment, which led to the suspicion of CES in this case. The patient had painless urinary retention with overflow incontinence and loss of the signal to void. MRI and electrodiagnosis may be helpful in the diagnostic process. Through CES diagnosis, rapid self-catheterization was performed to ensure that no residual volume was left after voiding. Pelvic floor exercises can assist in the control of bowel movements. In addition, pressure ulcers can be prevented by repositioning with saddle anesthesia. It should also be emphasized that non-discogenic cauda equina disorder caused by TB arachnoiditis can show rapid improvement of lower limb weakness, but bladder bowel problems may be long-lasting.

Conflict of Interest

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

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Instructions for Authors

JEND
Journal of Electrodiagnosis and Neuromuscular Diseases

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

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

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

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

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Discussion

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

Conclusion

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

Acknowledgment

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Sample References

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

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

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

3) Book chapter

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

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

4) Online resource

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

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

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