



Case Report / 증례보고

Lambert–Eaton myasthenic syndrome 환자의 만성 변비 및 복통에 대한 난간전을 포함한 한방 치료 증례보고

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Korean medicine treatment, including Nangan-jeon, of chronic constipation and abdominal pain in Lambert-Eaton myasthenic syndrome : A case report

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ABSTRACT

This case study reports the effects of complex Korean medicine treatment, including Nangan-jeon, on Lambert-Eaton myasthenic syndrome (LEMS) accompanied by chronic constipation and abdominal pain as the main symptoms. A 39-year-old woman diagnosed with LEMS with major symptoms, including chronic constipation and acute abdominal pain, received Western treatment. The treatment efficacy was weak and symptoms recurred, so the patient received

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outpatient treatment and 13 days of hospitalization for active Korean medicine treatment, including Nangan-jeon. During outpatient treatment and hospitalization, defecation frequency and the numeric rating scale (NRS) for abdominal pain and abdominal cold feeling were measured. The NRS for abdominal pain and cold decreased from 8 at admission to 3 and 0, respectively, at discharge. Defecation frequency increased significantly from once or twice a month to once every 2-3 days during hospitalization. This study results that complex Korean medicine treatment, including Nangan-jeon may be useful for treating patients who mainly complain of autonomic neurological symptoms, among patients diagnosed with LEMS. In addition, it is believed that it could be basic data applicable to more LEMS patient treatment cases.

Key words : Nangan-jeon, Lambert-Eaton myasthenic syndrome, chronic constipation, abdominal pain, Korean medicine treatment.

I. Introduction

Lambert-Eaton myasthenic syndrome (LEMS) is a neuromuscular autoimmune disease associated with autoimmunity, oncology, and immunology. The characteristic muscle weakness of LEMS is considered to be caused by pathogenic autoantibody activity against the voltage-gated calcium channels (VGCCs) at the pre-synaptic nerve terminals¹⁾.

Proximal muscle weakness, autonomic features, and parareflexia are three typical clinical symptoms of LEMS. Autonomic dysfunction has been reported in 80-96% of LEMS patients. Both the sympathetic and parasympathetic systems are affected. Dry mouth is the most common complaint by patients regarding symptoms of the autonomic nervous system. Other symptoms include erectile dysfunction in men, constipation, urination difficulties, dry eyes, and altered perspiration²⁾.

As with many autoimmune disorders, unknown factors contribute to the onset of LEMS. Recent research on the treatment of LEMS has focused on improving motor weakness by using 3,4-diaminopyridine to block the efflux of potassium ions and increase the depolarization time³⁾. However, a lack of research exists on the treatment of various symptoms of autonomic dysfunction in patients suffering from LEMS.

In this case study, a LEMS patient with major

autonomic symptoms of chronic constipation and acute abdominal pain received Western treatment, but it did not work. But we report this study because autonomic symptoms of LEMS improved after Korean medicine treatment with Nangan-jeon at the Department of Acupuncture & Moxibustion, College of Korean Medicine, Daegu Haany University.

II. Case Report

1. Patient

Female, 39 years old

2. Chief complaints

Abdominal pain

The patient reported sudden and extreme abdominal pain in the lower left and upper abdomen. The pain would worsen when the patient would strain to defecate or before and after menstruation. As the abdominal pain would worsen, the patient's abdominal cold feeling would also increase. When the abdominal pain became severe, the patient visited the emergency room and was given a narcotic pain killer, but the pain relief effect was weak. The patient complained of frequent gas in the abdomen, and a large amount of gas was observed when abdominal percussion was performed. The numeric rating scale (NRS) of abdominal

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pain at the time of the patient's first outpatient visit was 7–8.

Constipation

Before receiving inpatient treatment, the patient would defecate twice a month, before and after menstruation. Usually, the patient would have a heavy feeling in the lower abdomen and complain of residual changes even after she had a stool. The stool was usually normal when she would naturally defecate before and after menstruation, but it is often harder when she would strain to defecate.

3. Onset

End of February 2020

4. History

The patient was diagnosed with LEMS in 2010 and began 3,4-diaminopyridine three times a day after meals.

5. Presenting illness

The patient complained that the number of bowel movements had been few since adolescence, about once or twice a month, but that there was no particular inconvenience. When the patient was first diagnosed with LEMS in 2010, it was noted that the chronic constipation and weak bowel movements might be due to autonomic dysfunction caused by LEMS. At that time, the patient stated that there were also muscle weakness of lower extremities. In addition, for about half a year from the summer of 2015, the patient had abdominal pain on every start date of menstruation and visited the emergency room once a month to receive treatment with painkillers. In the summer of 2017, bowel movements deteriorated, and since then, the patient had visited the emergency room twice due to abdominal pain.

On February 27, 2020, the patient's abdominal pain suddenly deteriorated without any special cause, and the patient was taken to the emergency room of ○○ Hospital for admission. An abdominal Computed

Tomography (CT) and blood test were conducted, but no special abnormalities were found except for swelling of the colon and stomach. At the time, ○○ Hospital tried to conduct a colonoscopy for further examination, but the test could not be conducted because the patient had severe abdominal pain. During the hospitalization from February 27 to March 4, the worsening abdominal pain was treated with a painkiller, but the pain recurred. A colonoscopy was conducted on March 3, a day before discharge, and no special cause was found other than edema of the colon.

On March 27, 2020, the patient's severe abdominal pain recurred, and she went to the emergency room of □□ University Hospital for an abdominal CT and blood tests. As no abnormality was found, she received painkillers. Afterwards, the patient had abdominal pain again, and she received a colonoscopy on April 1 and an ultrasonic test on April 10. Neither test result found abnormalities, and the abdominal pain recurred. Thus, the patient considered Korean medical treatment for a recurring abdominal pain and visited College of Korean Medicine, Daegu Haany University on April 28.

6. Duration of treatment

April 28, 2020: Outpatient treatment

May 7–19, 2020 (13 days): Hospitalization

7. Treatments

Herbal medicine

Nangan-jeon was prescribed from April 28 to May 13, 2020. Nangan-jeongami was prescribed from May 14 to May 19. Considering the patient's condition, Nangan-jeongami was prescribed with the addition of 4g *Pinelliae Rhizoma*, 3g *Aurantii Immaturus Fructus*, and 2g *Coptidis Rhizoma*. Then, 120cc were consumed three times a day after meals (Table 1).

Acupuncture

The KMD performed acupuncture at acupoints CV4, CV10, CV12, ST25, LI11, ST36, LI5, SI5, LI4, PC6, LR3⁴⁻⁵). Disposable 0.20 × 30mm stainless-steel needles (Dongbang Acupuncture Inc. Korea) were used.

Acupuncture was performed twice a day Monday through Saturday and once a day on Sunday. The session duration was about 15 minutes.

Moxibustion

Indirect moxibustion (Shinkigu, Haetnim Inc. Korea) was performed on two acupoints (LI-11 and LI-10) once a day Monday through Saturday during the hospitalization period.

Physiotherapy

A hot pack was used on the patient's abdomen twice a day from May 7 to May 19.

8. Evaluation

Numeric rating scale

The patient's abdominal pain and abdominal cold feeling were measured every day using the NRS. A score of 0 indicated no pain and no abdominal cold feeling. A score of 10 indicated unbearable pain and extreme abdominal cold feeling (Fig. 1).

Frequency of defecation

During the hospitalization, at 7:00 AM every day, we asked about and recorded the patient's defecation frequency for the previous day (Fig.1).

9. Progress

Outpatient treatment period

The patient complained of abdominal pain during her first visit on April 28, 2020. Degree of abdominal pain at the time of outpatient treatment was measured as NRS 7-8. When it deteriorated, it was accompanied by an etched abdominal cold feeling. The patient defecated twice a month before and after her menstrual cycle. The stool looked like mud and sometimes needed a finger enema. There was no abdominal cold feeling after defecation, and abdominal pain increased when straining to defecate. Along with abdominal acupuncture, Nangan-jeon was prescribed three times a day for 10 days. After taking Nangan-jeon, patient had a bowel movement on April 29, 2020. The intensity of the

abdominal pain, which had been sustained before being hospitalized on May 7, decreased to an NRS score of 3, and no sudden abdominal pain occurred.

Hospitalization period

On May 7, 2020, the patient was admitted to the hospital for intensive Korean medicine treatment and abdominal radiography was performed (Fig. 2). On May 8, 2020, blood tests were also performed (Table 2). A large amount of feces was observed in the abdominal radiography performed, and no unusual problems were found in the blood test. Abdominal pain decreased after outpatient treatment, so the patient's abdominal pain level at the time of hospitalization was NRS 3. The most recent defecation at the time of hospitalization was on the afternoon of April 29. Except for on day 4 of hospitalization, the patient's abdominal pain was well maintained at a reduced state of less than NRS 4 during the 13-day hospitalization. On days 3 and 4 of hospitalization, the abdominal pain and abdominal cold increased, and on days 4 and 5, the patient continuously defecated. After that, the NRS of abdominal pain and abdominal cold continued to decrease to 3.5 and 1.5, respectively, for day 7. However, on the afternoon of day 7, the patient's abdominal pain slowly began to worsen, with the NRS for abdominal pain and abdominal cold feeling rising to 4 and 1.5, respectively, on day 8. On day 8, the patient was prescribed herbal medicine of Nangan-jeongami, as the patient had abdominal gas and pyrosis the afternoon before. During hospitalization, the patient had a total of six bowel movements on days 2, 4, 5, 7, 11, and 12. We assumed that there was a decrease in intestinal activity in light of the patient's sudden deterioration of abdominal pain. Therefore, on day 8, to increase intestinal motion and address the patient's complaints of nausea and regurgitating acid caused by worsening abdominal pain, herbal medicine was replaced with a Nangan-jeongami with the addition of *Aurantii Immaturus Fructus*, *Pinelliae Rhizoma*, and *Coptidis Rhizoma*. After that, there was no increasing abdominal pain and abdominal cold

feeling, and the nausea and heartburn also improved. The patient had continuous bowel movements on days 11 and 12. The NRS for abdominal pain and abdominal cold at the time of discharge on day 13 was measured at 3 and 0, respectively.

III. Discussion

LEMS is a rare neuromuscular autoimmune disease with a global prevalence of around 3 – 4 per million population. LEMS can most commonly occur as small cell lung cancer (SCLC), and it can also occur as an autoimmune disease (non-tumor NT-LEMS) regardless of tumor⁶. As with many autoimmune disorders, it is unknown which factors contribute to the onset of LEMS. In patients with related tumors, the immune response to the antigenic determinants of the tumor surface induces autoantibody production, and these antibodies may interact with VGCCs in the neuronal terminal to induce neurological diseases⁷. In LEMS patients without tumors, the original trigger of the autoimmune reaction is unknown. The first option for treating proximal muscle weakness in LEMS patients is 3,4-diaminopyridine⁸. The most frequent serious side effect of this medication is seizures. This risk appears to be dose-dependent and is accounted for at a dose of about 100mg per day. Rituximab has been reported to be effective in LEMS patients with severe amyotrophic weakness¹. In addition to chemotherapy, most patients can be sufficiently treated with symptomatic treatment combined with prednisone and azathioprine, but these medications have been reported to be ineffective at times.

Extensive autonomic dysfunction occurs in LEMS, and studies have reported symptoms and signs suggesting the involvement of the intestinal, sympathetic, and parasympathetic divisions of the autonomic nervous system⁹. To date, most studies have examined symptomatic therapy for myasthenia gravis of LEMS, but there are few therapeutic studies on autonomic nervous system symptoms, such as constipation, sexual dysfunction, and dry mouth, in LEMS patients. Symptoms are

usually improved by increasing nerve terminal calcium levels, interfering with the immune response, or treating paraneoplastic LEMS for underlying cancer⁹. However, there is no research model on how LEMS affects the autonomic nervous system and manifests symptoms. Therefore, further study is needed on the calcium channels required for release of autonomic neurotransmitter and LEMS antibodies for physiological function of organs.

In this study, the patient was diagnosed with LEMS and there are also findings of proximal muscle weakness, but the symptoms that usually complain in daily life are chronic constipation and chronic abdominal pain corresponding to a high NRS score. Whenever the patient had sudden abdominal pain, she was taken to the emergency room for radiography and painkillers, but no special cause was found and the pain relief was minimal. Therefore, the patient visited the Outpatient Department to receive active Korean medicine treatment without Western medical treatment for abdominal pain.

Nangan-jeon is a herbal medicine originally used for “lower abdomen cold pain (少腹冷痛)” and infertility with the effects of “warm liver and kidney (暖肝溫腎)” and “move the qi to relieve pain (行氣止痛)”. However, there are no clinical reports of railing except for reports of “Genital Cold Syndrome (陰冷)”¹⁰. We prescribed Nangan-jeon because it was determined into “yin cold and internal exuberance (陰寒內盛)” and “qi movement obstruction (氣機阻滯)” in consideration of abdominal cold feeling, abdominal pain, constipation complained by this patient and weak pulse in pulse diagnosis and white coated tongue in tongue diagnosis. For Nangan-jeon, Lycii Fructus, Angelicae Gigantis Radix, Foeniculi Fructus, Cinnamomi Cortex, Aconiti Lateralis Preparata Radix, Evodiae Fructus were used to induce “warm liver and kidney (暖肝溫腎)”, and Linderae Radix, Aquilariae Resinatum Lignum, Hoelen were used to induce “move the qi to relieve pain (行氣止痛)”¹¹.

We considered the patient's deterioration of abdominal pain on day 8 to be due to decreased intestinal activity.

In addition, we prescribed Nangan-jeongami with the addition of Aurantii Immaturus Fructus, Pinelliae Rhizoma, and Coptidis Rhizoma in consideration of nausea and regurgitating acid caused by the patient's worsening abdominal pain. Extracts of Aurantii Immaturus Fructus have been found to increase the contraction effect of the large intestine¹²⁾, and nausea and regurgitating acid have been treated with Pinelliae Rhizoma by "resolving phlegm and checking vomiting (化痰止嘔)" and with Coptidis Rhizoma by "heat-clearing and dampness-drying (清熱燥濕)"¹³⁾.

Acupuncture was performed at local and distal acupoints, which were chosen to alleviate abdominal pain and improve chronic constipation by activating intestinal activity in patients^{4,14)}. During hospitalization of the patient, who had nontumorous LEMS accompanied by abdominal pain and chronic constipation, acupuncture treatments were performed twice a day on the abdominal local and distal acupoints, along with Nangan-jeon three times a day.

After the complex Korean medicine treatment, the defecation frequency increased significantly from the patient's usual once or twice a month. In addition, reduction of abdominal pain and abdominal cold feeling could be observed as the patient's defecation frequency increased.

Currently, even though LEMS is a rare disease, there are no reports of direct treatments that improve chronic constipation and abdominal pain complained of by LEMS patients. This study reported that it has been effective as a combination of Korean medicine focusing on Nangan-jeon in LEMS patients who mainly complain of autonomic neurological symptoms. In addition, it is believed that it can be a basic data applicable to more patients' treatment cases.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Table 1. The Composition and Amount of Nangan-jeon

Herb name	Pharmacognostic name	Amount(g)
枸杞子	Lycii Fructus	12.0
當歸	Angelicae Gigantis Radix	10.0
小茴香	Foeniculi Fructus	8.0
烏藥	Linderae Radix	8.0
肉桂	Cinnamomi Cortex	8.0
茯苓	Hoelen	8.0
桂枝	Cinnamomi Ramulus	6.0
玄胡索	Corydalis Tuber	4.0
附子	Aconiti Lateralis Preparata Radix	4.0
川芎	Cnidii Rhizoma	4.0
沉香	Aquilariae Resinatum Lignum	4.0
吳茱萸	Evodiae Fructus	3.0

On the day 8 of hospitalization, Pinelliae Rhizoma 4g, Aurantii Immaturus Fructus 3g, Coptidis Rhizoma 2g were added to the Nangan-jeon

Table 2. Blood test on 2020.05.08

Index	value
Red blood cell count	3.8
White blood cell count	7.5
Hemoglobin	11.8
Hematocrit	36.0
Erythrocyte sedimentation rate	5.0
Aspartate aminotransferase level	15.0
Alanine aminotransferase level	20.0
Blood urea nitrogen level	8.0
Creatinine level	0.5
Serum sodium level	140.0

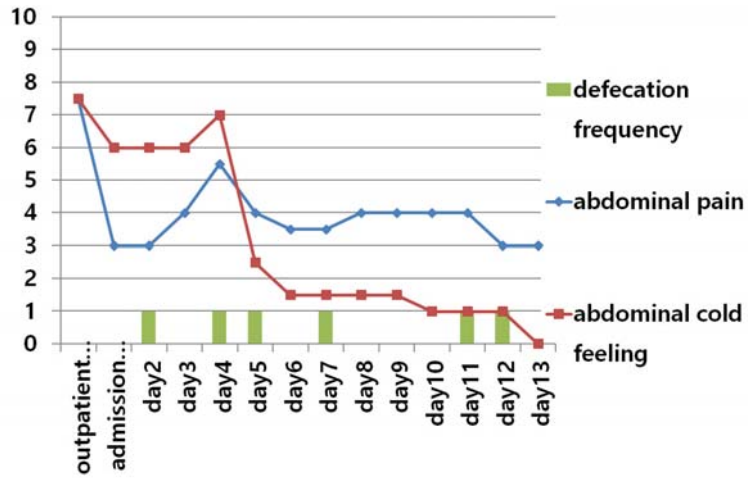


Fig. 1. Changes in defecation frequency and NRS for abdominal pain (abd.pain) and abdominal cold feeling (abd.cold)



Fig. 2. Erect view of abdomen on May 7, 2020 (admission day) – Much feces material are observed in each abdominal erect view