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【 CASE REPORT 】

Successful Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome with Chronic Febricula Using the Traditional Japanese Medicine Shosaikoto

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Abstract:

We herein report the case of a 14-year-old girl who had been experiencing chronic fatigue, febricula, and social withdrawal for 20 months. No notable abnormalities were identified during routine checkups at a general pediatric hospital; symptomatic treatments did not affect her condition. She was diagnosed with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Based on the concepts of Japanese traditional medicine, she was administered shosaikoto-based treatment. After several weeks of treatment, all of the symptoms had been dramatically alleviated, consequently resolving the issue of non-attendance at school. Shosaikoto-based medication may be a therapeutic option for treating ME/CFS in patients presenting with chronic febricula.

Key words: myalgic encephalomyelitis/chronic fatigue syndrome, chronic febricula, neuroinflammation, shosaikoto, Kampo medicine, late yang stage pattern

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Introduction

Myalgic encephalomyelitis (ME), also known as chronic fatigue syndrome (CFS), is a disease characterized by chronic, unexplained fatigue, usually accompanied by a low-grade fever, myalgia, sleep disturbance, depression, headaches, dizziness, anorexia, and other miscellaneous symptoms (1). Infection-related episodes were reported at onset in 64% of patients with ME/CFS (2). Thus far, no effective strategies for treating ME/CFS have been established.

We herein report the case of a young woman with ME/CFS and an accompanying persistent intermittent fever who was successfully treated with traditional Japanese (Kampo) medicine.

Case Report

A 14-year-old girl started experiencing intermittent febricula and fatigue after an episode of acute pharyngitis with a fever (>38.5℃) 20 months before her first consultation with us. She could only bear to attend school (junior high) for a short time once or twice a week due to recurrent fatigue, a low-grade intermittent fever, and sleep disturbance. She visited pediatric and psychiatric clinics, but routine medical checkups showed no abnormalities. The administration of antipyretics, antibiotics, and antidepressants, along with Kampo formulas (e.g., hochuekkito), did not affect her condition.

Gradually, her condition worsened, and she was referred to our department when in her third year of junior high

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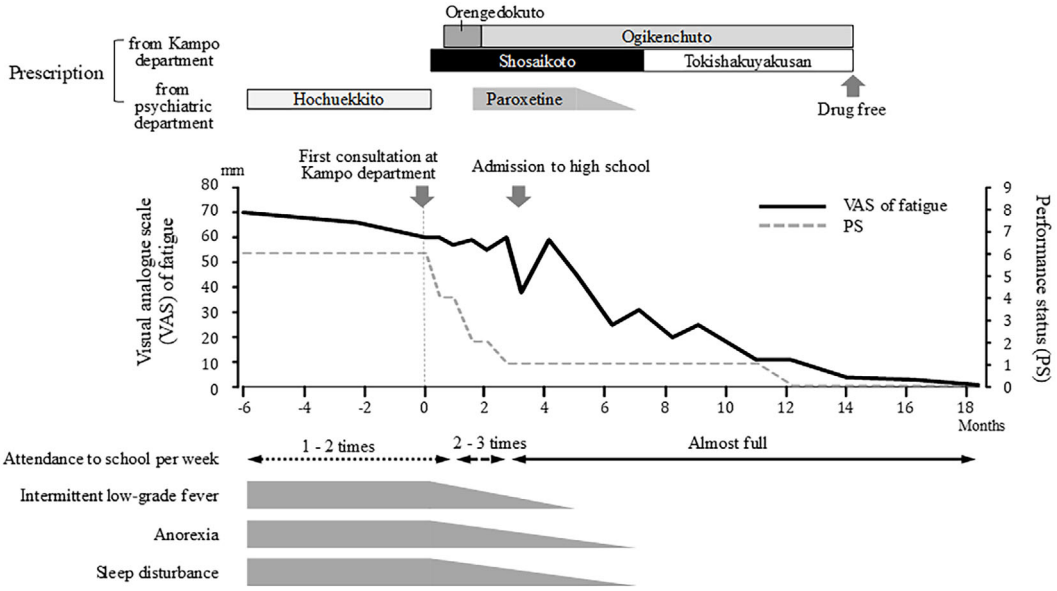

Figure 1. Clinical course of the presented case. After treatment with shosaikoto, the patient's chronic fatigue and other accompanying symptoms were gradually alleviated. The patient maintained a good performance status and attended school every day even after ceasing the treatments.

school. She reported post-exertion malaise, impaired concentration, dizziness, headache, anorexia, weight loss, an intermittent low-grade fever, sleep disturbance, abdominal pain, and breathlessness. Her interpersonal relationships were not affected. She had an episode of urticaria at 10 years of age, and her family history was unremarkable. Her height (150 cm), weight (39.5 kg), and body temperature (36.5℃) were recorded. No notable abnormalities were identified on routine physical examinations, chest radiography, blood tests including blood cell counts, or biochemical examinations, including thyroid hormone assessments.

Based on these findings, we suspected ME/CFS. Her self-reported visual analogue score for fatigue was 61 mm, and the severity of fatigue measured by the performance status score (0-9 integer scale) was 6. She required rest, without work, at home for over half of the week, and she was able to do light tasks in good health (Fig. 1) (3). Her complicated symptoms, such as an intermittent low-grade fever, dizziness, and anorexia, matched the indications of shosaikoto (SST) based on the Kampo concept. We therefore prescribed 6.0 g of SST per day. Two weeks later, she reported the alleviation of several of the above-described symptoms. We further added 6.0 g of orengedokuto (OGT) to SST to treat the remaining low-grade fever and fatigue. Four weeks after the first consultation, she was diagnosed with definite ME/CFS based on the diagnostic criteria (4).

Six weeks after the first consultation, her malaise, intermittent fever, and sleep disturbance were gradually resolved, although she retained a poor appetite. We prescribed 18 g/day of ogikenchuto instead of OGT for her appetite loss and fatigue. She subsequently was able to eat adequate meals and felt less fatigued. A psychiatrist prescribed paroxetine for five weeks after starting the Kampo formulas. However, her symptoms did not improve with paroxetine, and it was tapered and subsequently discontinued.

When she returned to school, her performance status score decreased to grade 1. Although she was able to do normal activities, she sometimes experienced fatigue. She was able to attend school every day. Seven months after the first consultation, the symptoms of ME/CFS (e.g., intermittent fever, sleep disturbance, and poor appetite) were mostly resolved. She had had infrequent and irregular menstruation since menarche as well as leg swelling. To improve these symptoms, we prescribed 5.0 g of tokishakuyakusan daily instead of SST. After starting tokishakuyakusan, her menstrual cycle stabilized to every two months, and she reported less fatigability.

As her symptoms were gradually alleviated, we reduced the dose of the Kampo formulas. Sixteen months after the first consultation, she became almost symptom-free. Therefore, all Kampo treatments were terminated.

The compositions of the Kampo formulas are described in the supporting information.

Discussion

We encountered a case of ME/CFS that was successfully treated with SST-based Kampo formulas, suggesting that SST can effectively treat ME/CFS and accompanying chronic inflammation, including neuroinflammation in the central nervous system.

Recently, neuroinflammation has been shown to be associated with the pathophysiology of ME/CFS. A positron emission tomography-based study demonstrated that findings suggestive of neuroinflammation existed in several cerebral areas in patients with ME/CFS (5). Among the seven herbal ingredients in SST, *Bupleurum falcatum* root (BR) and *Scutellaria baicalensis* root (SR) are reportedly effective in

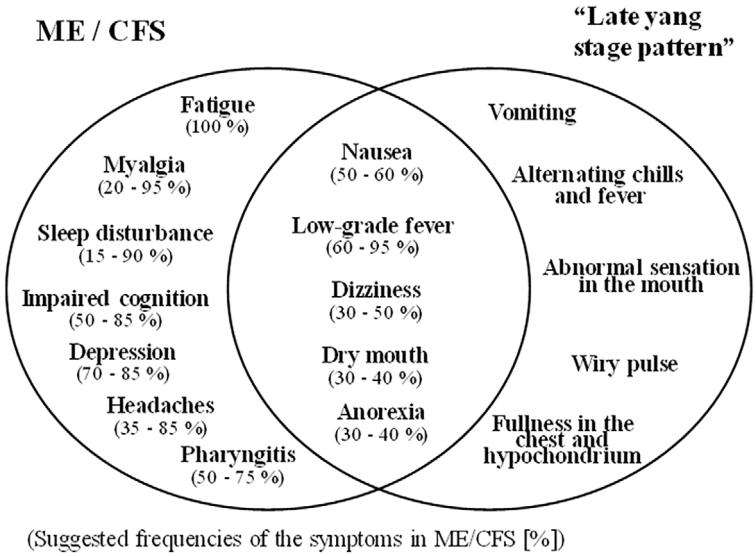

Figure 2. Common symptoms between ME/CFS and "late yang stage pattern". The symptoms that are common between ME/CFS and "late yang stage pattern" are shown in this figure. The bracketed numbers are the suggested frequencies (%) of symptoms in patients with ME/CFS based on a previous review (ref. 1). ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome

treating neuroinflammatory processes. The ethanol extract of BR reportedly attenuates the lipopolysaccharide-induced activation of microglia and astrocytes in the hippocampus and substantia nigra of mice (6). Reportedly, SR extract reduces brain damage by suppressing the production of inflammatory cytokines (e.g., tumor necrosis factor-α, interleukin-6) and regulating glial-cell activity in the striatum in a dose-dependent manner (7).

We added OGT to SST to decrease neuroinflammation, which presented as an intermittent fever. OGT contains SR, as does SST. Furthermore, berberine, which is a major component of OGT, is reported to decrease the elevation of hippocampal cytokines and microglia activation induced by chronic stress (8). The addition of OGT to SST treatment might enhance the anti-inflammatory effect and promote the improvement of the ME/CFS symptoms in this case.

After resolving the intermittent fever, her appetite loss and infrequent and irregular menstruation persistent. Ogikenchuto was prescribed for the treatment of fatigability and appetite loss. A previous study showed that ogikenchuto aided in the recovery from fatigue (9). For the treatment of oligomenorrhea and leg swelling, we prescribed tokishakuyakusan, which is reported to stimulate the selection of 17 beta-estradiol and ovulatory processes (10). In Kampo medicine practice, a holistic approach is usually adopted. Recovery of the appetite and menstruation were necessary for the improvement of the general condition of this patient. Following treatment with these Kampo formulas, her fatigue diminished.

Regarding other Kampo treatments, some cases with ME/CFS that were successfully treated with hochuekkito have been reported. In a retrospective case series, hochuekkito treatment reduced the performance status in 41% of the patients, although a low-grade fever still remained in 70% of patients (11). Another case series reported that patients with CFS were classified into seven categories according to the Kampo diagnoses, and the therapeutic effects after a half year differed significantly among the categories (12). Williams et al. reported the heterogeneity of CFS using a principle component analysis and latent class analysis (13). We speculated that ME/CFS has multiple phenotypes, for which patients may need personalized Kampo treatment approach.

From the perspective of Kampo medicine, SST was the most suitable Kampo formula for the symptoms of this patient. SST is known as a representative formula for the treatment of "late yang stage pattern", which is characterized as an acute febrile condition followed by alternating chills and a fever, anorexia, and dizziness (14, 15). These symptoms overlap with the symptoms of ME/CFS with an intermittent low-grade fever (Fig. 2). In the present case, the onset of pharyngitis, an intermittent fever, loss of appetite, and dizziness were similar to the symptoms of "late yang stage pattern." In contrast, hochuekkito is more suitable for general fatigue with appetite loss and gastrointestinal dysfunction without an acute febrile condition in its original concept. These facts may support treating ME/CFS using SST in patients with intermittent febricula.

No adverse effects of Kampo treatment were observed in this case. Previously reported adverse effects of SST include interstitial pneumonia, pseudoaldosteronism, and liver injury. Periodic chest radiography and liver function tests are therefore needed to ensure the safe use of SST.

In conclusion, SST-based Kampo treatments may be a viable therapeutic option for patients with ME/CFS presenting with chronic febricula.

The authors state that they have no Conflict of Interest (COI).

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