

Investigation Report by an EBM Work Team of Japanese Association of Oriental Psychosomatic Medicine

Evidence of Kampo Therapy for Psychosomatic Diseases and Stress-related Diseases

Fatigue and Chronic Fatigue Syndrome

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Introduction

Fatigue is observed when physical or mental load is continuously given. It is a temporary decline in physical or mental performance, and is said to be one of the three alarm signals from the living body, along with pain and fever. According to an estimate by a fatigue study group of the Ministry of Education, Culture, Sports, Science and Technology, Japan's economic loss due to chronic fatigue in particular is said to be 1 trillion and 200 billion yen/year. Especially chronic fatigue syndrome (CFS), characterized by fatigue and malaise as main symptoms lasting long (more than 6 months) enough to interfere with the patient's daily life, is a syndrome of unknown cause that has a combination of infection-like symptoms (pharynx pain, headache, joint pain, and myalgia) and psychoneurotic symptoms (reduced thinking and mental concentration, insomnia, and depressive tendency), often causing difficulty in treatment clinically. It has become clear in recent years that, as a pathophysiology of chronic fatigue syndrome, physical stress (ultraviolet rays etc.), chemical stress (chemical substances), biological stress (infections), and social stress (interpersonal relationship etc.) combine with genetic vulnerability, inducing disorders of the immunoneuroendocrine system. In daily clinical practice, however, chronic fatigue syndrome is still causing difficulty in treatment, and it is hardly said that treatment attempts with various medicines including antivirals, antiphlogistic analgetics, antidepressants, and vitamins have produced certain therapeutic effect. In recent years, attention is attracted to the role of Kampo medicines as a biological response modifier (BRM) for bio balance, and they are expected to produce therapeutic effect against chronic fatigue syndrome that has caused dysfunction of the neuroimmunoendocrine system.

Here, in view of this psychosomatic medical demand, we evaluated the usefulness of Kampo medicines for fatigue with a focus on CFS.

1. Investigation methods

A search was performed for Kampo literature (articles in Japanese and English) by using keywords "manseihiroushoukougun OR kanpou" and "hirou OR kanpou" at Japan Medical Abstracts Society website and Tsumura's website Kampo Square, and "chronic fatigue syndrome OR CFS and Kampo" at PubMed and Cochrane library. In principle, we included reports regarding Kampo extract products that comply with the new formulation standards established after 1986, and excluded those regarding drug solutions of crude drug pieces for decoction, powdered crude drugs, and OTC products. Also, reports that involve at least 10 cases were included in principle, but case reports were included for study of refractory cases and psychosomatic study.

2. Results

1) Overview

As of February 2010, there are no articles evaluating the efficacy of Kampo medicines for CFS in a double-blind randomized controlled trial or randomized controlled trial, but there are five articles on case-series studies that evaluated the efficacy in at least 10 patients.

2) Efficacy

Here, we will introduce major case-control studies, one of which will be introduced in the "7. Study of Shou."

[1] Kuratsune administered TSUMURA Hochuekkito (7.5 g/day for 8 to 20 weeks) to 29 patients 19 to 53 years old who fulfilled the diagnostic criteria for CFS and whose performance status (PS) was 2 or higher at the start of treatment, and investigated various symptoms before and after the administration and natural killer (NK) activity.¹⁾ As a result, effect was observed in 12 (41.4%) of 29 CFS patients. While clinical symptoms such as general malaise, slight fever, photophobia, reduced thinking, and reduced mental concentration improved or disappeared in many patients, infection-like symptoms such as lymphadenopathy, muscular weakness, and headache improved in a limited number of patients. Also, when 10 patients whose NK activity was reduced and 7 patients whose NK activity was not reduced were evaluated, there was a post-dose increase in NK activity in 9 of 10 patients with reduced NK activity as opposed to a decrease in NK activity in 6 of 7 patients with non-reduced NK activity.

[2] Ogawa et al. administered ninjinyoeito (7.5 g/day for more than 1 month) to 35 patients who fulfilled the diagnostic criteria for CFS, and thereafter evaluated cell-mediated immune function (improvement in immune function of patients with reduced NK cell activity, antibody-dependent cell-mediated cytotoxicity [ADCC] activity, and phytohemagglutinin [PHA]-lymphocyte transformation) and improvement in clinical symptoms (enlarged lymph nodes, slight fever, general malaise, and insomnia).²⁾ As a result, clinical effect was observed in 26 (74%) of 35 CFS patients. Of 18 patients with affected cell-mediated immune function, 14 (77%) patients showed improvement in NK cell activity, ADCC activity, and PHA-lymphocyte transformation.

[3] Gohchi et al. administered TSUMURA Hochuekkito Extract and Kamishoyosan Extract (7.5 g/day for 24 weeks) concomitantly to 23 patients with moderate or severe CFS, and investigated clinical symptoms and PS before and after treatment³⁾. As a result, the mean PS was 5.9 before the start of treatment while it improved to 4.8 after 4 weeks of treatment and 4.0 after 24 weeks of treatment. As for infection-like symptoms, only a small number of patients showed improvement in their moderate or severe conditions (pharyngeal pain: 13.6% and muscular weakness: 15.0%). As for psychoneurotic symptoms, remarkable improvement was observed in reduced thinking, reduced mental concentration, and depressive tendency.

[4] Takaya et al. investigated profiles (causative disease, Sho, prescription, progress, and efficacy) and changes in PS before and after treatment of 54 patients with chronic fatigue who did not fulfill the diagnostic criteria for CFS.⁴⁾ As a result, there were 12 patients who received a diagnosis for their feeling of fatigue, 26 patients without any abnormal findings on various tests, and only 2 patients who fulfilled the diagnostic criteria for CFS during the investigation period. As for treatment methods, there were 36 patients who were treated with Kampo formulations, 8 patients with western medicines, and 10 patients without treatment. Most of the prescriptions of Kampo formulations were of hochuekkito, and efficacy defined as improvement or prominent improvement was observed in 71.9% of patients who took Kampo medicines.

3. Improvement in QOL

Since improvement in PS is investigated in most of case-series studies, the above applies to improvement in QOL.

4. Comparison with western medicines

Although there are no reports comparing western medicines with Kampo medicines in terms of efficacy in CFS patients, Madarame et al. reported, after investigating the aggravating factors and alleviating factors in 27 CFS patients who had been followed up for more than 12 months, that there were patients who were considered to have improved by oral psychotropic drugs, oral Kampo drugs, or heating/heat retention (7 patients, respectively).⁵⁾

5. Effect on refractory cases

Mori et al. administered Kampo formulations according to Sho to 9 patients with moderate or severe CFS whose PS was 4 to 9 when first diagnosed, and investigated the effect of Kampo therapy on CFS and whether patients responded to treatment.⁶⁾ Seven out of 9 patients had received various western medicines for a long time and had a history of worsening of PS. The results after 1 year were as follows: prominent improvement in 8 patients, moderate improvement in 1 patient, efficacy rate (moderate improvement or greater) of 100%, and no adverse reaction. The PS after 1 year was 3 or less in all patients, and Terasawa's

Kikyo score was 30 points or less in 6 of 9 patients. A total of 13 Kampo prescriptions were effective: syokentyuto (6 patients), shinbuto, keishininjinto, shimotsuto (4 patients each), bukuryoshigyakuto (3 patients), hangekoubokutou, and ninjinto (2 patients each).

6. Study of concomitant use with western medicines

There are no reports evaluating the efficacy of combination of Kampo formulations and western formulations and the reduction of adverse reactions in a large number of patients. As the precautions to be taken about combination and formulation for CFS, Gohchi recommends the concomitant use of Hozai/Saikozai and NSAIDs in patients with slight fever or intense pharyngeal pain and the combination of Kampo drugs and psychotropic drugs in patients with marked psychoneurotic symptoms.⁷⁾

7. Study of Sho

Horie et al. diagnosed "Sho" based on the interview and tongue examination of 10 CFS patients (3 men and 7 women, suffering period: 7 months to 14 years, PS at the first visit: 3 to 6) who made regular visits to the outpatient clinic of the Department of General Medicine, Nagoya University Hospital, prescribed Kampo formulations based on the Shou, and then investigated prescriptions and efficacy.⁸⁾ Two patients received hochuekkito and one patient each received shosaikoto, hachimijiogan, unseiin, rikkunshito, seishoekkito, tokishakuyakusan, kamikihito, and ninjinto. After treatment for 2 to 3 months, improvement was seen in 70% of patients. Mori emphasizes that since patients with moderate or severe CFS often fall into the state of "Ebyou," treatment with prescriptions corresponding to the Taiinbyou phase to Shouinbyou phase as a basis is more effective.⁹⁾

8. Psychosomatic study

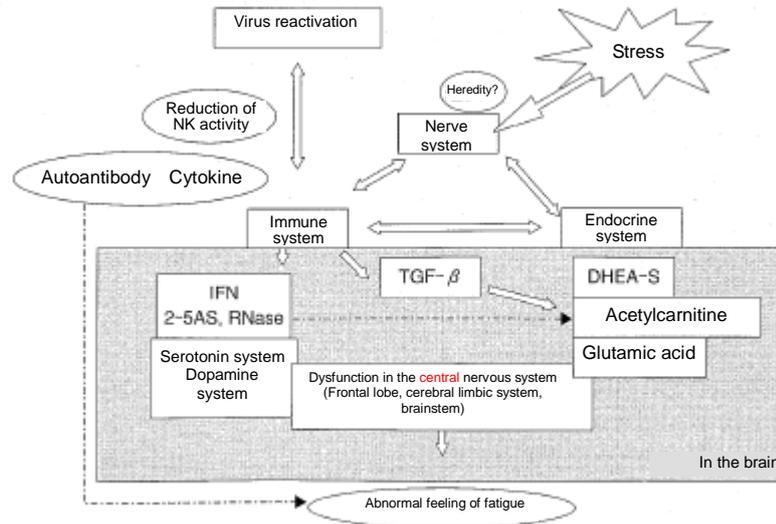
Treatment for chronic fatigue condition includes non-drug therapies such as cognitive behavioral therapy and graded exercise therapy (GET), and oral drug therapies such as Kampo formulations, megavitamins, and psychotropic therapy with antidepressants in particular. Among them, Kampo formulations represented by Hozai such as hochuekkito have had consensus as one of drug-therapies for CFS in Japan; however, there are yet no reports investigating combination of Kampo therapy and psychotherapy or comparing the both therapies in a large number of patients.

Among CFS patients who are considered refractory, there are many patients burdened with various problems in psychosocial background like those with deep-rooted mistrust in medical services and those who have consulted many medical institutions. Therefore, it is extremely important to take a holistic approach both physically and mentally in clinical practice for treatment of CFS, and it may be said that Kampo therapy backed by receptive interview and considerate consultation is itself a high-quality psychosomatic therapy.

9. Mechanism of action

Figure 1 shows the condition of CFS based on modern medicine. According to study results obtained so far, CFS patients has brain dysfunction caused by various cytokine disorders induced by virus reactivation or chronic infection, and behind this lies disturbance in the neuroimmunoendocrine system as a result of a mix of environmental factors related to various stresses and genetic factors.⁹⁾ In recent years, Kampo medicines are receiving attention for its role as a BRM for bio balance, and it is suggested also from a modern medical viewpoint that they form a group of effective drugs in improving fatigue condition. In Kampo therapy for CFS, Jingizai such as hochuekkito and jumentaihoto is often used, and their main crude drugs, ougi, ninjin, and soujutsu are reported to have an inhibitory effect against oxidative damage to the brain in rats.¹⁰⁾ Furthermore, based on the result that when hochuekkito was given to mice daily (500 mg/kg/day), the amount of dopamine and noradrenaline increased in the cerebral cortical tissue, leading to improvement in learning and memory of the mice, hochuekkito is considered to penetrate the blood-brain barrier, exerting effects.¹¹⁾ Xin et al. reported that when hochuekkito was given to CFS model mice prepared by repeated injection of Brucella abortus antigen, daily activity level was significantly higher in treated mice than the control mice while the ratio of the spleen to the body weight and the expression of IL-10mRNA were

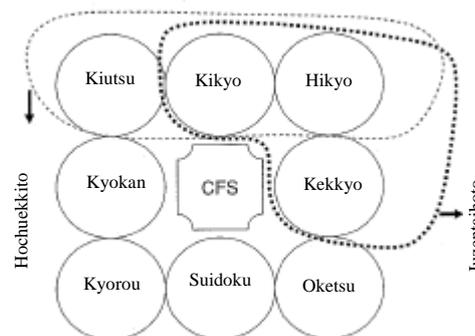
significantly lower.¹²⁾ In addition, in light of Kuratsune's report that NK activity increased in the reduced NK activity group while it decreased in the non-reduced group, hochuekkito is very likely to exert its effect by regulating the immunoneuroendocrine system.



<Figure 1> Condition of CFS Based on Modern Medicine

(Hirohiko Kuratsune: Latest Science behind Fatigue (Saishin Hirou No Kagaku) Figure on page 96 [partially revised])

The condition of CFS from the aspect of Kampo medicine may be described as shown in Figure 2. Reason why hochuekkito and juzentaihoto are frequently used for fatigue may be because they have a wide spectrum that covers Kikyo and other Kampo medicine-based conditions of CFS. However, since the action mechanism of Kampo formulations for chronic fatigue condition remains poorly understood, further analysis is needed from the viewpoints of modern medicine and Kampo medicine in future.



<Figure 2> CFS and its Condition Based on Kampo Medicine

10. Grades of recommendation

Currently, studies of effects of Kampo therapy on CFS are mostly case-control studies with Hozai such as hochuekkito, and the number of reports is still insufficient. Grades of recommendation of Kampo formulations for CFS is considered grade C (Implementation may be considered, but there is not sufficient scientific evidence).

11. Future problems and consideration

Studies of Kampo therapy for CFS are mostly case-control studies, and there were no reports with a high evidence level. Various Kampo formulations are used for CFS, but in case-control studies, Hokizai (especially Jingizai) represented by hochuekkito was most frequently used. For patients refractory to Hokizai, Kampo medicine-based conditions (Oketsu, Suidoku, Rikan, etc.) other than Kikyo should be considered, and those patients are likely to need Sho-based Kampo therapy. For patient with long-standing CFS and those with refractory CFS, it is also important to consult to Kampo specialists early.

As issues to be considered, there is a need for more studies with a high evidence level using objective assessment such as biochemical biomarkers, autonomic nerve function testing, and quantification of physical activity using an actigraph. In CFS patients in whom treatment has failed, there are several Kampo medicine-based conditions, which have often become complicated. It is also necessary to establish EBM that takes Sho into account in order to improve treatment results.