

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

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

## 7) Psychogenic Fever

Masatoshi Takahashi, Takakazu Oka, and Sadatoshi Tsuji\*

### Introduction

Psychogenic fever is a psychosomatic disease often noted in adolescent and middle-aged people. Fever associated with infection or inflammation is caused by signal transmission to the brain by proinflammatory cytokines including interleukin (IL)-1 and IL-6 produced in peripheral tissues. In this process, the principal mediator in the brain is prostaglandin E<sub>2</sub> (PGE<sub>2</sub>). Therefore, fever can be reduced if cyclooxygenase, a rate-limiting enzyme for PGE<sub>2</sub> production, is inhibited. However, a temperature increase in patients with psychogenic fever cannot be suppressed by cyclooxygenase inhibitors; psychogenic fever is considered different in terms of mechanism from fever associated with inflammation. For treatment of the psychogenic fever, psychotherapy and psychotropic drugs are often combined. In this article, we evaluated the usefulness of Kampo prescriptions for psychogenic fever.

### 1. Investigation methods

A search was performed using search expression “shininseihatsunetsu OR humeinetsu” and kanpou (or prescription name) at Japan Medical Abstracts Society website and Tsumura’s website Kampo Square, and search expression “psychogenic fever OR FUO” and Kampo (or prescription name) at PubMed and Cochrane library.

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. In principle, reports that involve at least 10 cases were included, but case reports were also included for (5) Refractory case and (8) Psychosomatic study.

### 2. Results

#### 1) Current situation

As of April 2008, 30 reports were obtained by the above-mentioned search.

#### 2) Usefulness

Among reports evaluating the usefulness of Kampo therapy for psychogenic fever (or fever of unknown origin [FUO]), there were no reports on [1] a double-blind randomized controlled trial with placebo, [2] a randomized controlled trial with placebo, or [3] a case series study that involves at least 10 cases. Among case reports that involve less than 10 cases, there are a report<sup>1)</sup> that shosaikoto, hochuekkito, and rikkunsito were effective in 8 teenage patients with suspected psychogenic fever, and a report<sup>2)</sup> that ninjinyoeito, kamishoyosan, saibokuto, hochuekkito, shigyakusan, saikokeisikankyoto, saikokeisito, hachimijiogan, shokenchuto, and rokumigan were effective in 8 patients with psychogenic slight fever among 182 patients with climacteric disorder. As for reports on single cases, there is a case report that kamikihito was effective in a patient with stress-induced hyperthermia<sup>3)</sup>. As drug products that were effective against FUO, there are case reports on kamishoyosan, saikokeisikankyoto, ninjinyoeito, shosaikoto, saikokeisikankyotokaryukotsu, hochuekkito, rikkunsito, chikujountanto, daisaikoto, saikokaryukotsuboreito, shakanzoto, byakkokaninjinto, jumihaidokuto, and shosaikotokakikyosekko, though it is unclear whether those cases of fever were psychogenetic or not.

#### 3) Effect on QOL

There are currently no reports investigating the effects of Kampo prescriptions on QOL of patients with psychogenic fever in a large number of patients.

#### 4) Study of comparison with western medicines

There are currently no reports comparing Kampo medicines with western medicines.

#### 5) Study of effect on refractory cases

There are reports that kamikihito<sup>3)</sup> was effective in patients with stress-induced hyperthermia in whom treatment with antidepressants and non-steroidal anti-inflammatory drugs (NSAIDs) had failed, that saikokeysikankyoto<sup>4)</sup> was effective in FUO patients in whom NSAIDs had failed, that byakkokaninjinto<sup>5)</sup> was effective in FUO patients in whom anti-bacterial drugs had failed, and that shosaikoto<sup>6)</sup> was effective in FUO patients in whom anti-bacterial drugs and steroid drugs had failed.

#### 6) Study of concomitant use with western medicines

There are currently no reports evaluating the usefulness and safety of combination of Kampo prescriptions and western medicines in a large number of patients.

#### 7) Study that takes Shou into account

The Kampo medicine-based condition of pediatric patients with psychogenic fever is mainly attributable to Kikyo in many cases, and patients with significant Kiutsu and Oketsu were also seen.<sup>1)</sup> According to a report,<sup>2)</sup> it was inferred that the oriental medicine-based pathology of psychogenic slight fever complicating climacteric disorder is mainly a condition of Jinkyō, Kikyo, Hikyo, or Kiinryoukyo complexly combined with Kankikekkyo or Kankiukketsu.

When hochuekkito and rikkunsito were given to 7 pediatric patients (5 and 2 patients, respectively) with psychogenic fever in whom Kikyo was considered the central condition, 5 patients reportedly achieved complete response;<sup>1)</sup> however, there are no reports investigating in a large number of patients whether effects of Kampo prescriptions differ in case where Shou is taken into account.

#### 8) Psychosomatic study

There is a report<sup>7)</sup> that since patients with psychogenic fever have tendency to over-adjustment in many cases, it is essential to instruct patients on relaxation method and to combine psychotherapy. Also there is a case report that in a course of psychotherapy for a female child with psychogenic fever and enuresis, Kikyo turned out gradually, and treatment with rikkunsito was effective when given at that timing.<sup>8)</sup> As shown in the treatment course of the patient, when psychotherapy is given to patients with psychosomatic disease who have strong tendency to over-adjustment, there is a time during the treatment course when Kikyo becomes apparent, and thus when Kampo therapy is performed, care should be taken to "Kikyo as Sensho."<sup>8)</sup>

#### 9) Mechanism

There are currently no reports investigating the mechanism of action of Kampo prescriptions on psychogenic fever.

#### 10) Grades of recommendation

Judgment of grades of recommendation is not possible because the sample size is currently small.

#### 11) Future problem

Since any of the reports involve only less than 10 patients, further case series are required in future to evaluate the usefulness.