Kampo Medicine for the Treatment of Hié (Cold Hypersensitivity) and Pain

CHEOLSUN HAN*1) 2), KAZUO KANEKO*1), HIROYUKI KOBAYASHI*2)

*1)Department of Orthopedics, Juntendo University Faculty of Medicine, Tokyo, Japan, *2)Center for Advanced Kampo Medicine and Clinical Research, Juntendo University Graduate School of Medicine, Tokyo, Japan

Hié or cold hypersensitivity is a form of thermal hyperalgesia that is predominantly localized to hands and feet. It is a subjective symptom that has no clear conception in Western medicine. The pathological process underlying cold hypersensitivity includes various factors such as impaired peripheral circulation in response to cold exposure, decrease in thermogenesis due to age, lifestyle habits such as nutritional deficiency anemia, lack of exercise, and chronic stress, and other organic causes. Modern times have witnessed an increase in cold hypersensitivity among young females. In traditional Oriental medicine, this condition is defined as mibyo or pre-disease state that is classified into five types on the basis of Kampo treatment. Clinically, cold hypersensitivity and painful states are intimately correlated such that cold hypersensitivity is often considered to exacerbate pain. Representative Kampo medicine for the treatment of cold hypersensitivity and pain include tokishigyakukagoshuyushokoyo and bushi.

Key words: cold hypersensitivity, pain, tokishigyakukagoshuyushokoyo, bushi, Kampo

Introduction

In this paper, we will discuss factors that contribute to cold hypersensitivity, recent trends in this condition, as well as effective Kampo medicine for cold hypersensitivity and pain.

Regulation of body temperature

Humans have an innate capacity to adapt their body temperature in accordance with the changes in environmental temperature. As described by Aschoff1, visceral temperature is maintained at 37°C even in cold climates (Figure-1), but the peripheral vasculature preferentially undergoes vasoconstriction upon cold exposure to prevent heat dissipation resulting in greater sensitivity to cold in the periphery, particularly in hand and feet.

Factors that lead to cold hypersensitivity

There are several risk factors and causes, either alone or in combination, which appear to predispose individuals to cold hypersensitivity. Predisposing factors include young females, old age, low BMI, poor nutrition, anemia, sedentary lifestyle, low basal body temperature, stress, and genetic factors. Organic causes include hypothyroidism, pituitary insufficiency, collagen vascular disease, adrenal insufficiency, arteriosclerosis, hormone deficiency, and stroke. These factors set the stage for impaired peripheral circulation in response to cold exposure or a decrease in core temperature due to compromised adaptive thermogenesis. However, the precise mechanisms underpinning cold hypersensitivity remain unknown. This condition has traditionally been more common in postmenopausal
women and elderly patients, but younger females are increasingly affected as well. Recent reports suggest that approximately 50% of young Japanese females complain of cold hypersensitivity. According to the National Health and Nutrition Survey conducted by the Ministry of Health, Labour and Welfare in 2013, the proportion of lean females (BMI 18.5% or less) in Japan was 12.3%, the highest number ever. This has sparked concerns that cold hypersensitivity may continue to rise in parallel with an anticipated increase in the number of women becoming leaner.

Hié from Western medicine perspective

1. Cold hypersensitivity as a subclinical condition is not recognized in Western medicine; however, hypothermia is an accepted medical emergency in which the core body temperature falls dangerously low below 35°C with concomitant impaired consciousness or arrhythmia that are potentially lethal. Meanwhile, patients with cold hypersensitivity in ambulatory care settings frequently report an axillary temperature in the 35°C range, or even lower in the 34°C range. Although core body temperature is usually measured in the rectum or bladder and is maintained at approximately 37°C or higher, considering that the reported mean axillary temperature of Japanese people is 36.89 ± 0.34°C, an average axillary temperature around 35°C may indicate an emerging hypothermic condition presenting as hypersensitivity to coldness.

2. Mechanisms of thermogenesis

1) Thermogenesis during resting and exercise

In humans, the resting (basal) metabolic rate accounts for about 60% of the total daily energy expenditure, while the remaining 30% is accounted for by exercise and 10% by food consumption. The main areas of thermogenesis include thoracoabdominal organs, skeletal muscles, brain, skin, and bone. At rest, 56% of thermogenesis occurs in the thoracoabdominal organs and 18% in the skeletal muscles; however, during the exercise this proportion reverses to 22% in the thoracoabdominal organs and 73% in the skeletal muscles. In other words, heat production at rest occurs mainly in the visceral organs, while skeletal muscles become the main source of heat production during exercise.

2) Thermoregulation in response to cold exposure

a. Shivering thermogenesis

Heat-producing mechanisms caused by ATP (adenosine triphosphate) hydrolysis accompanied with muscle contraction is called shivering thermogenesis. This occurs through simultaneous contraction of the flexor and extensor muscles that liberates heat three to five times greater than that of the basal metabolism. ATP is an important chemical energy source in thermogenesis, producing heat during its synthesis and degradation. Approximately 27% of energy of one glucose molecule is dissipated as heat rather than as ATP during ATP production in glycolysis. Further, 75% of the energy generated from ATP hydrolysis is dissipated as heat, and the rest is used as mechanical energy and for the maintenance of activities of visceral organs.

b. Non-shivering thermogenesis

Upregulation of the sympathetic nervous system in response to cold exposure leads to augmented noradrenaline synthesis. Noradrenaline in turn...
induces peripheral vasoconstriction to prevent heat dissipation from the periphery, and also acts on brown adipocyte tissue (BAT) to produce heat. BAT is primarily innervated by sympathetic nerves and is rich in mitochondria. The mitochondrial inner membrane contains uncoupling protein 1 (UCP 1) that is unique to BAT and functions to stimulate oxidative degradation of fatty acids for thermogenesis without inducing ATP synthesis. This type of heat production involving BAT is called non-shivering thermogenesis. The use of PET (positron emission tomography) has allowed the characterization of active BAT in adult humans, which are present in small amounts. Further, BAT is the main site of adaptive thermogenesis, i.e., it is activated by cold exposure but remains dormant in warmer environments. The number of BAT in men is nearly equivalent to the number in women, and it has been found to decrease with age in both sexes. About 60% of consumed energy is transformed into heat through non-shivering thermogenesis, while the remaining 40% ultimately becomes heat via ATP degradation. On the basis of the discussion thus far, we hypothesize that a dysregulation in shivering and non-shivering mechanisms may predispose some individuals to cold hypersensitivity.

Anemia and low protein status

Premenopausal women have a higher risk of developing anemia due to their menstruation. Modern diet replete with refined carbohydrates triggers deficiencies in vital nutrients such as iron and zinc, vitamins, and protein, leading to a higher incidence of low protein and iron deficiency anemia in young women. Thus anemic patients with cold hypersensitivity in outpatient clinics should be evaluated for not only hemoglobin levels but also serum ferritin levels. The iron storage (combined total of ferritin and intracellular hemosiderin) in healthy adults is approximately 1,000 mg. Provided that 1 ng/ml of serum ferritin in adult corresponds to 8 to 10 mg of stored iron, the optimal serum ferritin level is about 100 ng/ml. Although the standard serum ferritin levels may differ between facilities, the lower limit is approximately 4 to 12 ng/ml. This reference range suggests that a large number of subjects with low serum ferritin levels were included in the sample population to determine this range, which may explain why it is low compared to the so-called optimal levels. If serum hemoglobin level is within the reference range but serum ferritin is low, iron deficiency may be suspected. In anemic patients, cells are deprived of oxygen and ATP synthesis is consequently impaired in mitochondrial systems under anaerobic conditions. Iron is a component of mitochondrial cytochrome enzymes and is also intrinsically involved in ATP synthesis. In addition, hemoglobin and ferritin are both proteins and low protein status can lead to anemia. Thermogenesis that occurs after eating is called diet-induced thermogenesis. Among the three major macronutrients, protein has the highest thermogenic potency and longest lasting effect. For these reasons, if an individual presents signs and symptoms of cold hypersensitivity, dietary deficiencies in addition to organic causes should be carefully evaluated.

Other hormones

Thyroid hormone is closely involved in energy metabolism and temperature regulation. It is certain that thyroid hormone enhances energy metabolism and its target is mitochondria, but these molecular mechanism is unclear in many respects. Recently, thyroid hormone regulates synthesis and utilization of ATP in basal metabolism, and UCP 1 mediated system in BAT is noted in thermogenesis. Progesterone is also involved in thermogenesis in the luteal phase, but the association with cold hypersensitivity has not been clarified sufficiently.

Cold hypersensitivity from a traditional oriental medicine perspective

1. Mibyo (pre-disease state) and preventive medicine

In traditional Oriental medicine, mibyo or pre-disease state marks the earliest stage of a disease trajectory, and cold hypersensitivity is a classic example of mibyo. Although this concept is unique to traditional Oriental medicine, it nevertheless overlaps with the tenets of preventive medicine.

2. Five types of cold hypersensitivity

Traditional Oriental medicine classifies cold hypersensitivity into five subtypes as follows:
(1) Shusoku-kekkan (Cold in hands and feet):
Pathogenic cold in the extremities, particularly hands and feet. Aggravated by cold exposure and correlates with dominance of sympathetic nervous activity.

(2) Jonetsu-gekan (Upper heat and lower cold):
Pathogenic heat in the upper body and pathogenic cold in the lower body. Correlates with hormonal imbalance and dominance of sympathetic nervous activity.

(3) Shinnetsu-kakan (True heat and false cold):
Pathogenic cold in the exterior of body and pathogenic heat in the interior. Aggravated by cold exposure.

(4) Shinkan-kanetsu (True cold and false heat):
Pathogenic heat in exterior of body and pathogenic cold in the interior. Correlates with excessive parasympathetic nervous activity.

(5) Rikan (Interior cold): Pathogenic cold in the entire body including the abdomen. Correlates with decreased digestive function and thermogenesis.

Kampo treatment for cold hypersensitivity

There are many Kampo prescriptions for cold hypersensitivity. In this paper, I will focus on tokishigyakukagoshuyushokoyo and bushi.

1. Tokishigyakukagoshuyushokoyo
This prescription is frequently prescribed to patients with cold hands and feet and a predilection for developing frostbites. It is also given to patients with pathogenic interior cold and decreased gastrointestinal function with signs and symptoms such as headaches, abdominal pain, nausea, vomiting, back pain, menstrual cramps and sciatica. Tokishigyakukagoshuyushokoyo contains toki (Angelicae Radix), keihi (Cinnamomi Cortex), saishin (Asianasari Radix), mokutsu (Akebiae Caulis), shakuyaku (Paeonia Radix), taiso (Zizyphi Fructus), kanzo (Glycyrrhizae Radix), shokyo (Zingiberis Rhizoma), and goshuyu (Evodiace Fructus). Among the constituent herbs, toki, keihi and saishin have strongly warming and analgesic properties and together address the cold hypersensitivity and pain in the hands and feet. Goshuyu, taiso, and shokyo warm the interior cold and augment digestive functions. Shakuyaku and kanzo work in tandem to relieve muscle cramp and pain. Yakubo et al. have reported that the administration of tokishigyakukagoshuyushokoyo in six adult men without cold hypersensitivity reduced peripheral vascular impedance and increased blood flow in the radial artery. Okuda et al. have demonstrated its analgesic and circulatory effects in the periphery in a rat sciatic nerve ligation model. Yoshida et al. have shown that the efficacy rate of this prescription for common orthopedic disease is approximately 42%, while Yamagami et al. have reported a 57.5% efficacy rate in 40 cases of back disorders. Other reports of its clinical effectiveness for painful orthopedic conditions accompanied by cold hypersensitivity include intractable upper extremity pain in postoperative cervical spondylosis and four cases of chronic pain.

2. Bushi (Processi Aconiti Radix)
Bushi is prepared from the root of aconitum, a perennial of Ranunculaceae, and treated with heat to reduce its toxicity before use in humans. In Kampo parlance, bushi disperses cold, relieves pain, and dispels dampness; in other words, it warms the visceral organs, alleviates pain, and regulates body fluids. Pharmacologically it has analgesic, cardiotonic and vasodilatory effects. Some of the major Kampo prescriptions containing bushi include hachimijiogan, goshajinkigan, maobushisaishinto, keishikajyutsubuto, juzentaihoto, and shimbuto. These prescriptions primarily target frail patients with low metabolism, and are suitable for patients with pain with concomitant cold hypersensitivity. In orthopedic surgery, goshajinkigan is frequently used for the treatment of low back pain and lower extremity pain and numbness in elderly patients, and keishikajyutsubuto for arthralgia and neuralgia aggravated by cold hypersensitivity. Aconitum is well known for its potential toxicity, symptoms that start with hot flashes, numbness of the tongue, nausea and vomiting, palpitations, and extrasystole that may progress to motor and sensory paralysis, seizures, dyspnea, and lethal arrhythmia if left untreated. When considering the addition of bushi powder to a Kampo formulation for the extra warming effect, the starting dose should be 1 g/day and incrementally increased by 0.5 to 1 g/day in subsequent dosing. The recommended maximum dose is 4-6 g/day which should be achieved through
judicious vigilance for toxic symptoms. Kampo formulae containing bushi have very small amounts of its detoxified form, and therefore, the risk of toxicity remains extremely small. Nevertheless, when adding bushi powder to the treatment protocol, careful monitoring of toxic symptoms that may appear in a dose-dependent manner is warranted. One of the mechanisms underlying bushi’s analgesic effect as reported by Shibata et al.\(^{18}\) is astrocyte deactivation in the dorsal horn during the chronic phase of pain in a sciatic nerve injury model mouse. In addition, Suzuki et al.\(^{19}\) have reported its analgesic and anti-allodynic effects, contributing to the mushrooming literature of the mechanisms underpinning bushi’s analgesic properties. Taken together, bushi appears to be effective against pain and numbness associated with cold hypersensitivity, and emerges as a feasible therapeutic option for pain relief in clinical practice.

**Conclusion**

In this paper, we have described the factors that contribute to cold hypersensitivity and its differential diagnosis, as well as some of the basic and clinical evidence of Kampo for this condition. It is worth mentioning that cold hypersensitivity can rapidly exacerbate or turn into a more serious condition. Developing healthier lifestyle and dietary habits combined with Kampo treatment can lead to meaningful and lasting improvement of this condition.

**Reference**