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\* \* \*

RESEARCH ARTICLE

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# Current status of Kampo medicine curricula in all Japanese medical schools

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## Abstract

**Background:** There have been a few but not precise surveys of the current status of traditional Japanese Kampo education at medical schools in Japan. Our aim was to identify problems and suggest solutions for a standardized Kampo educational model for all medical schools throughout Japan.

**Methods:** We surveyed all 80 medical schools in Japan regarding eight items related to teaching or studying Kampo medicine: (1) the number of class meetings, target school year(s), and type of classes; (2) presence or absence of full-time instructors; (3) curricula contents; (4) textbooks in use; (5) desire for standardized textbooks; (6) faculty development programmes; (7) course contents; and (8) problems to be solved to promote Kampo education. We conducted descriptive analyses without statistics.

**Results:** Eighty questionnaires were collected (100%). (1) There were 0 to 25 Kampo class meetings during the 6 years of medical school. At least one Kampo class was conducted at 98% of the schools,  $\geq 4$  at 84%,  $\geq 8$  at 44%, and  $\geq 16$  at 5%. Distribution of classes was 19% and 57% for third- and fourth-year students, respectively. (2) Only 29% of schools employed full-time Kampo medicine instructors. (3) Medicine was taught on the basis of traditional Japanese Kampo medicine by 81% of the schools, Chinese medicine by 19%, and Western medicine by 20%. (4) Textbooks were used by 24%. (5) Seventy-four percent considered using standardized textbooks. (6) Thirty-three percent provided faculty development programmes. (7) Regarding course contents, "characteristics" was selected by 94%, "basic concepts" by 84%, and evidence-based medicine by 64%. (8) Among the problems to be solved promptly, curriculum standardization was selected by 63%, preparation of simple textbooks by 51%, and fostering instructors responsible for Kampo education by 65%.

**Conclusions:** Japanese medical schools only offer students a short time to study Kampo medicine, and the impetus to include Kampo medicine in their curricula varies among schools. Future Kampo education at medical schools requires solving several problems, including curriculum standardization.

**Keywords:** Kampo medicine, Traditional Japanese medicine, Education, Medical school, Curriculum standardization, Questionnaire survey

## Background

Kampo medicine, or traditional Japanese medicine, generally includes not only "Kampo-yaku" (herbal medicine) but also massage, moxibustion, acupuncture, and acupressure [1,2]. The word "Kampo" is a Japanese word meaning "Chinese way" reflecting its origin in China. Since its introduction into Japan from China 1500 years ago, Kampo medicine has greatly developed the way of diagnosis, i.e., "the abdominal examination", by which

the type of Kampo medicine is selected and was practiced in Japan as the primary type of medicine [2]. However, the medical system reform conducted in the 19th century under direction of the Meiji government adopted new curricula of medical education based on Western medicine, resulting in the elimination of Kampo education from the Japanese medical schools' curricula [3,4].

In recent years, an increasing number of people, even in western countries, have been using complementary and alternative medicine (CAM) including Kampo medicine [5], and in parallel there has been a steady increase

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in the number of medical schools that have added CAM therapies to their curricula [6]. The Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) announced in 2001 that instruction of basic Kampo medicine was to be incorporated into the core curricula of all medical schools. Since then, among the 80 Japanese universities with medical schools, a rapidly increasing number of them have integrated Kampo medicine into their curricula [7]. However, regarding the current status of Kampo education in medical courses in Japan, to our knowledge, only a few reports provide basic information on the spread of Kampo education with details on the curricula. The aim of the present study was, therefore, to survey the current status of Kampo education at all the medical schools in Japan and to identify some problems and suggest solutions to implement a standardized Kampo educational system.

## Methods

In July 2011, we conducted a nationwide postal questionnaire survey of all 80 Japanese medical schools (51 national and public universities and 29 private universities). The persons actually responsible for Kampo education in each of the universities were asked to respond to the questions in consultation with the medical curriculum administrator and to declare the names of their universities and the responders. For a precise survey, additional surveys by phone or post were carried out for the universities that did not respond timely or responded inadequately. The questionnaire consisted of eight items specifically related to teaching or studying Kampo medicine, unless otherwise stated: (1) the number of class meetings (taught sessions), target school year or years, and type of classes; (2) presence or absence of a full-time instructor or instructors; (3) curricula contents; (4) textbooks in use; (5) desire for standardized textbooks; (6) faculty development programmes; (7) course contents; and (8) problems to be solved to promote Kampo education (see Additional file 1). When we analyzed the accumulated data, we counted one class meeting as one in which 50% or more of the content was regarding Kampo medicine. Cases of laboratory assignments in the third or fourth year and clinical clerkships in the fifth and sixth years were excluded as class meetings.

The study was funded by a grant from the Ministry of Health, Labour and Welfare. The survey was approved by the Institutional Review Board for Clinical Research of Tokai University and conformed to the principles of the Helsinki Declaration. To prepare the questionnaire, we modified questions from a questionnaire from a similar study conducted by the Liaison Committee of The Japan Society for Oriental Medicine in 2007 [8], after obtaining the author's permission. This study was a survey of the current status of Kampo education in all 80

Japanese medical universities and was not intended to include statistical analyses. The appropriate responsible persons from all 80 medical schools gave written informed consent to participate in this study.

## Results

### Study population

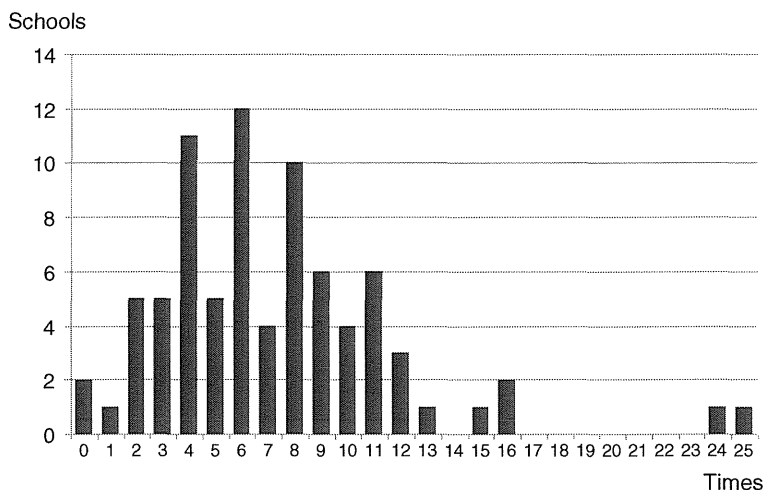
A total of 80 questionnaires were collected, which means that responses were obtained from each of the 80 medical schools in Japan (response rate, 100%).

### Number and length of class meetings and target school year or years

The length of one class meeting ranged from 45 to 100 minutes, with a mean of  $80.5 \pm 13.6$  minutes and a median of 90 minutes. The number of Kampo class meetings as a required subject during the 6 years of medical school ranged from 0 to 25 (at 2 and 1 school, respectively), with a mean of  $7.25 \pm 4.45$  class meetings and a median of 6 class meetings (Figure 1). The total number of required and elective Kampo class meetings ranged from 0 to 37 (at 2 and 1 school, respectively) with a mean of  $8.79 \pm 5.87$  class meetings and a median of 7.5 class meetings (Figure 2). At least 1 Kampo class meeting was conducted as a required subject at 78 medical schools (98%), 4 or more at 67 schools (84%), 8 or more at 35 schools (44%), and 16 or more at 4 schools (5%). Regarding elective classes in addition to these required classes, at least 1 class meeting was taught at 78 schools (98%), 4 or more at 72 schools (90%), 8 or more at 40 schools (50%), and 16 or more at 10 schools (13%). Distribution of the number of Kampo class meetings as a required subject by school year was: 2%, 7%, 19%, 57%, 8%, and 7% for first- through sixth-year students, respectively (Figure 3). Practical training in required Kampo classes was given at 12 schools (15%), and combined required or elective classes at 17 schools (21%). Required clinical clerkships were offered at 10 schools (13%) and required or elective clinical clerkships at 21 schools (26%). Kampo laboratory could be selected in a few-months-long laboratory assignment programmes for third- or fourth-year students at only 2 schools (2.5%).

### Educational systems and contents

Of the 80 medical schools, 23 schools (29%) employed full-time instructors to teach traditional Japanese Kampo medicine, while 57 schools (71%) did not have any such instructors. Teaching was based on traditional Japanese Kampo medicine at 65 schools (81%), traditional Chinese herbal medicine at 15 schools (19%), Western medicine (evidence-based medicine [EBM]) at 16 schools (20%), and "miscellaneous" at 3 schools (4%) (Figure 4). Miscellaneous answers included history, pharmacology, and diversity of medical treatment at 1 school each with



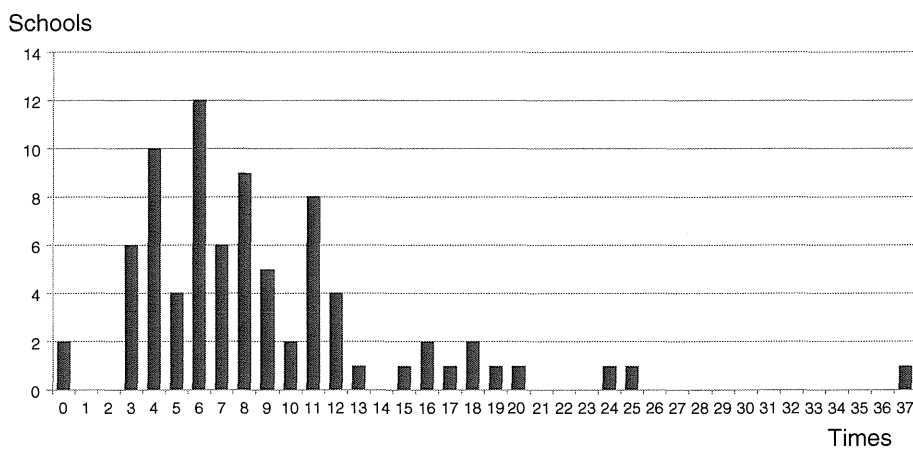
**Figure 1** The number of required Kampo class meetings in all 80 medical schools. Mean,  $7.25 \pm 4.45$  times; Median, 6 times;  $\geq 1$ , 78/80 schools (98%);  $\geq 4$ , 67/80 schools (84%);  $\geq 8$ , 35/80 schools (44%);  $\geq 16$ , 4/80 schools (5%).

multiple responses being allowed. A textbook was used at 19 schools (24%), while no textbook was used at 61 schools (76%). However, 59 schools (74%) wanted to consider the use of standard textbooks, if any were available, 16 schools (20%) were not considering using textbooks, and 5 schools (6%) did not respond. Faculty development programmes were conducted in 26 schools (33%) versus 54 schools (67%) that did not. Regarding the contents to be taught before graduation, characteristics (distinctive features of Kampo medicine, differences between Kampo and Western medicine, etc.) was selected by 94% of the schools, basic concepts (yin and yang, deficiency and excess, etc.) by 84%, explanation of formulae by 43%, practical training for physical examinations (including abdominal, pulse, and tongue examinations) by 53%, case studies by 26%, crude drugs and

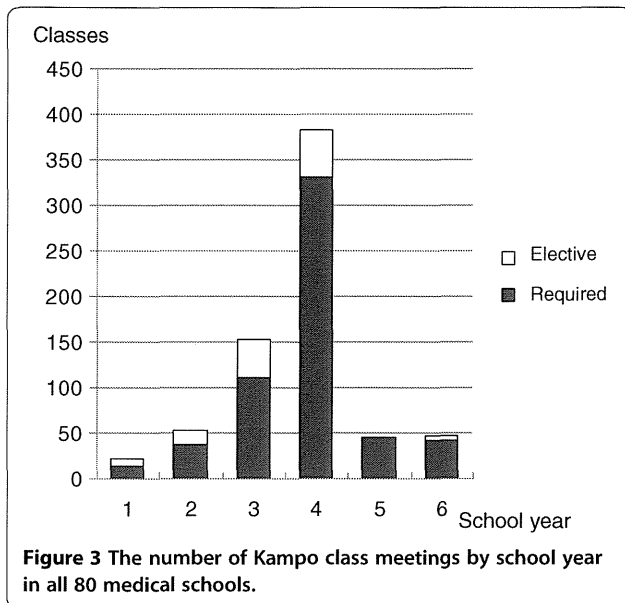
medicinal plants by 45%, history by 45%, EBM by 64%, adverse effects (adverse drug reactions) by 53%, and miscellaneous by 5% (Figure 5). Miscellaneous answers included current status of medical treatment by 3%, clinical topics by 1%, and attitude as a clinician by 1% with multiple responses being allowed.

**Problems**

Among the problems to be solved promptly in the area of Kampo education, curriculum standardization was selected by 63% of the schools, preparation of simple textbooks by 51%, early hands-on learning by 19%, improvement of the Kampo educational environment to promote participatory clinical training by 25%, introduction of Kampo education into both early and late post-graduate clinical training by 33%, fostering instructors



**Figure 2** The number of required and elective Kampo class meetings in all 80 medical schools. Mean,  $8.79 \pm 5.87$  times; Median, 7.5 times;  $\geq 1$ , 78/80 schools (98%);  $\geq 4$ , 72/80 schools (90%);  $\geq 8$ , 40/80 schools (50%);  $\geq 16$ , 10/80 schools (13%).



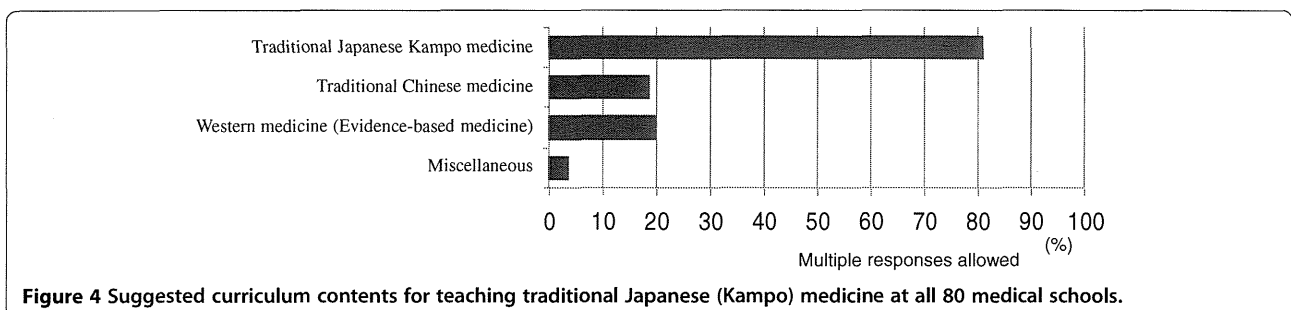
responsible for Kampo education by 65%, and miscellaneous by 6% (Figure 6). Miscellaneous answers included the removal of prejudice against Kampo medicine by 3%, and establishing questions for CBT (Computer-based Testing) and the National Medical Licensing Examination (NMLE) by 3%. These data were acquired with multiple responses being allowed.

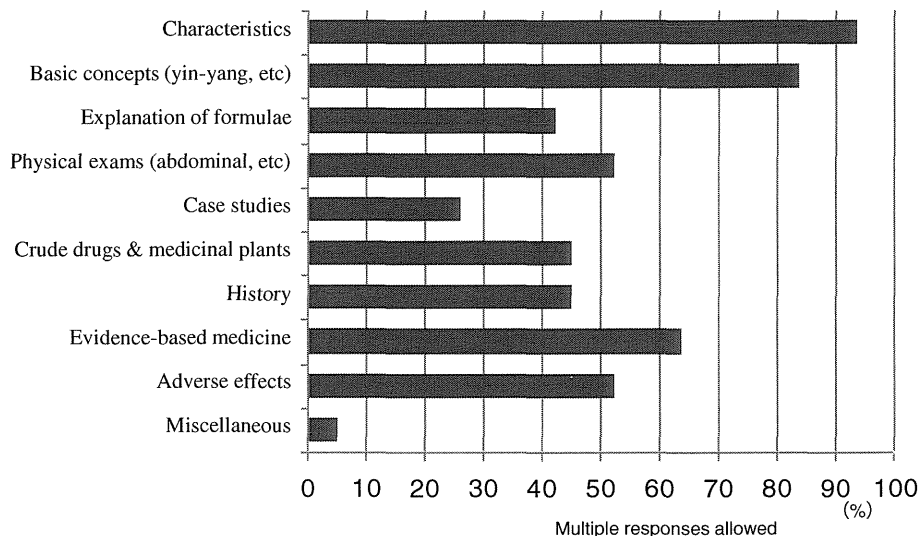
### Discussion

Regarding the status of Kampo education at Japanese medical schools, a nationwide phone survey was conducted in 1998 before incorporation of Kampo medicine into the core medical curricula, reporting that only 18 of the 80 Japanese medical schools had either elective or required classes on Kampo medicine [4]. Thereafter, several survey reports were published on the recent state of Kampo education offered at many medical schools [8,9]. These surveys were, however, incomplete and unsatisfactory because the methods and criteria of the surveys were unclear [8], and not all of the medical schools responded to the questionnaires (response rate, 84%) [9]. In the 10 years since 2001, when Kampo medicine was first integrated into the core medical curricula, the

present study is the first to have retrieved questionnaires from all 80 of the medical schools in Japan (response rate, 100%).

In both China and South Korea, education in traditional medicine is offered at different universities from those that focus on modern Western medicine, and the requirements for qualification as a medical doctor also differ. The formal medical education at universities of traditional Chinese herbal medicine in China requires 5 years of instruction, and students study traditional Chinese medicine along with modern Western medicine in curricula with ratios of each type of medicine from 7:3 to 6:4, respectively [10-12]. Even in schools in China that focus on Western medicine, around 80 class hours of traditional Chinese medicine are provided [13]. In Japan, there is only one qualification required to become a medical doctor, and that is to pass the NMLE after studying Western medicine at medical schools. Any Japanese licensed physician can prescribe Kampo formulations [14]. Therefore, 70% to 97% of Japanese physicians prescribe Kampo medicine according to clinical evidence and mechanism of action or by utilizing simple handbooks from the perspective of modern Western medicine [14-16]. In addition, more extensive scientific evidence of Kampo formulae has been accumulated [17,18], and their quality and safety have been maintained at higher levels with the progress of Kampo extract formulations [19], resulting in their substantial integration into Western medicine [20,21]. Nevertheless, Kampo medicine is primarily characterized by unique concepts of traditional medicine, such as “*sho* (pattern),” diagnostic skill, for example the abdominal examination, and therapeutic modalities [22]. Although it takes many hours of classes and hands-on experience to learn these concepts and modalities, there are no universities specializing in traditional Japanese Kampo medicine in Japan like those in China and South Korea. Moreover, Japanese medical schools only offer students traditional Japanese Kampo medicine education for an extremely limited amount of time. In our opinion, sufficient practical Kampo education based on traditional methods should be provided yearly before attempting any clinical use of Kampo formulae as prospective remedies.



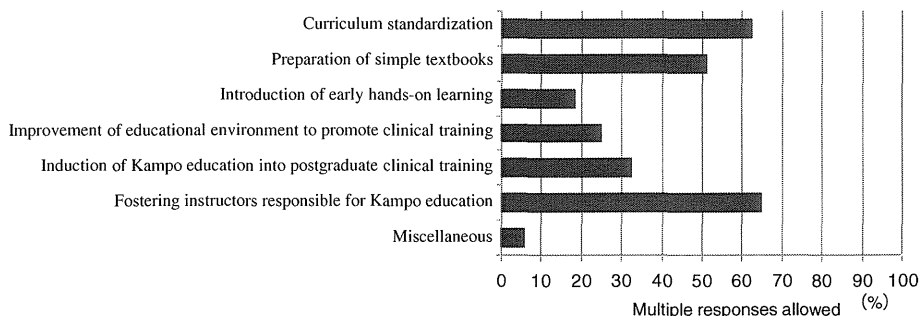


**Figure 5** The contents of Kampo education in 6 years of medical school.

A curriculum for medical students consisting of three different courses (the option of a 110-minute class: 4, 8, or 16 times) for Kampo education has been proposed [23]. Figure 1 shows the numbers of required classes, indicating the impetus of each school to promote Kampo education; while Figure 2 shows the total numbers of both required and elective classes, which is important to know in regard to the number of classes available to students who want to learn Kampo medicine. The present survey revealed that the number of required Kampo class meetings was 4 times or more at 84% of schools, but 8 times or more at less than half of the schools (44%), and 16 times or more at only 4 schools (5%). Although the most Kampo class meetings available to students was 25 times at 1 school, there were 2 schools that did not offer any Kampo classes. Obviously, the impetus to include Kampo medicine in curricula varies widely among universities.

Because the class hours of Kampo education are so limited, providing hands-on learning of Kampo techniques and their effects could improve students'

motivation [24]. However, the actual incorporation into the curriculum of such hands-on practice and clinical training (including clinical clerkships) was reported by less than 20% of Japanese medical schools. Because so many well-trained instructors are needed for the implementation of effective Kampo education, the small number of universities employing full-time instructors responsible for teaching Kampo medicine (29%) seems to greatly hinder the improvement of Kampo education [7]. In the present survey as well, fostering instructors responsible for Kampo education was selected by the largest number of responder schools (65%) as a problem to be dealt with promptly. Moreover, conducting faculty development programmes and the use of textbooks were only reported by 33% and 24%, respectively, of the 80 universities surveyed. These results suggested that only several medical schools in Japan had a good educational environment for Kampo medicine. Major factors that delay the development of Kampo education may include the fact that students must spend many hours preparing for the NMLE, which requires the accumulation of a



**Figure 6** Problems to be solved promptly toward standardization of Kampo education.

large body of knowledge regarding Western medicine, while questions on Kampo medicine have never been asked on the NMLE [25]. The amount of time spent in educating a certain subject is a reflection of the portion of the NMLE questions on that particular subject.

Contrarily, almost all students are interested in Kampo medicine, and feel it necessary to have opportunities to learn Kampo medicine even after graduation [25]. Actually, almost all physicians involved in community health care use Kampo formulae to some extent. Most of them have not had the benefit of taking any classes in their regular medical education on Kampo medicine, but have learned Kampo medicine by self-study [16]. Moreover, Kampo therapy has become increasingly popular among a great number of Japanese [26-28]. Nevertheless, Japan's Kampo education programmes do not fully meet the needs or desires of medical students nor those of physicians from a clinical aspect [16,25].

Kampo classes are offered most frequently for 3rd- and 4th-year students (76%). In our opinion, students are expected to gain diverse views of medical treatment and health care by learning about Kampo medicine along with systematically studying Western medicine in their preclinical years. During their internship, they can be engaged in clinical training on patients with perspectives of both Western and Kampo medicine. In the future Japan, a new type of medical care will be developed that comprises Kampo medicine integrated into Western medicine [29]. Now is a very good time to promote Kampo education to encourage the fostering of physicians able to practice Kampo and Western integrative medicine.

Regarding teaching bases of traditional medicine, more than 80% of Japanese medical schools teach Kampo medicine. As the course content, "characteristics" and "basic concepts" of Kampo medicine were selected by 94% and 84% of the responding medical schools, respectively. Kampo medicine is considered to be a body of wisdom cultivated by the long period of Japanese history and culture [29]. Therefore, many leading physicians responsible for Kampo education may recognize the importance of Kampo medicine as medical practice based on a different medical system from that of Western medicine. Because no national standardized programmes for Kampo education are currently available in Japan [2], traditional Chinese herbal medicine is chiefly being taught instead at 19% of the Japanese medical schools. As pointed out by many educators who participated in the present survey, in order to popularize and spread the use of traditional Japanese Kampo medicine, standardization of educational curricula and the preparation of simple textbooks are greatly desired and will be necessary.

A limitation of this study is that the survey only targeted the 2011 curricula at each medical school, which

proves to be a selection bias, because the curricula on Kampo medicine have varied from year to year. In point of fact, of the two universities that reported offering no Kampo classes, one is now on the road to a new curriculum in which Kampo education is scheduled for all the medical students by the time they graduate; while at the other, although the medical curriculum does not include Kampo education, it is offered in liberal arts and science courses. For an accurate assessment of the current status of Kampo education, it will be necessary to analyze the current status of each university and to discover trends through repeated follow-up surveys.

## Conclusions

In Japan, traditional medicine (Kampo medicine) is incorporated into the medical curriculum at 98% of the 80 medical schools nationwide, and Kampo class meetings are provided 4 times or more by the time of graduation at 84% of them. However, the impetus to include Kampo medicine in their curricula varies widely. The future establishment of Kampo education at Japanese medical schools requires fostering instructors knowledgeable in and responsible for Kampo education, curriculum standardization, and preparation of simple textbooks.

## Additional file

**Additional file 1: Questionnaire on Kampo Education in the Curricula of Japanese Medical Schools.**

### Competing interests

We have no competing financial or non-financial interests in this study, however, the Department of Oriental Medicine, Tokai University School of Medicine, and the Division of Oriental Medicine, Jichi Medical University each received a grant from Tsumura, a manufacturer of Kampo medicine in Japan.

### Authors' contributions

MA and SK conceived the study. MA wrote the manuscript. MA and SK participated in the data collection, data analysis and interpretation of data. SM, TN, TH, and SI carefully revised the manuscript. All authors read and approved the final manuscript.

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We thank Ms. Harumi Hiramoto and Mrs. Eri Kojima for analyzing the data. This study was supported by Health and Labour Sciences Research Grants (Research on Region Medical) by the Ministry of Health, Labour and Welfare. We also thank Robert E. Brandt, Founder, CEO, and CME of MedEd Japan, for editing the manuscript.

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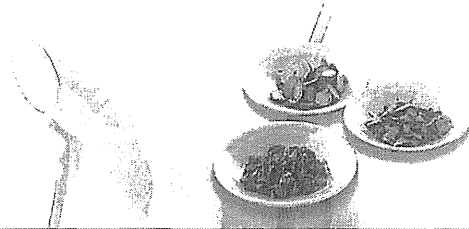


## 頭痛の漢方治療：最新のエビデンス

Novel evidence for Japanese traditional medicines for headache

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◎頭痛の治療薬として多くの漢方薬が経験的・伝統的に有用とされている。片頭痛に対しては、呉茱萸湯、五苓散、桂枝人参湯などが、緊張型頭痛に対しては川芎茶調散、葛根湯、釣藤散などが頻用され、薬物乱用性頭痛をはじめ二次性頭痛にも使用されている。多数の成分を含む漢方薬は作用機序の詳細が未解明で、これまでエビデンスレベルの高い臨床報告は少ない。しかし最近、基礎研究とともに従来の経験則を考慮した臨床治療も進められている。

**Keywords** 漢方, 頭痛, 五苓散, 呉茱萸湯, 川芎茶調散

頭痛は日常診療のなかでよく遭遇する疼痛疾患群である。日本における15歳以上の人口の頭痛有病率は39.6%で、緊張型頭痛の有病率がもっとも高く22.4%、ついで片頭痛が8.4%とされる<sup>1)</sup>。現在、頭痛診療に際しては、国際頭痛分類第2版(ICHD-II)に従った診断と治療が推奨されている<sup>2)</sup>。一次性頭痛(機能的頭痛)は片頭痛、緊張型頭痛など症候により診断され、さしあたり生命に影響のない頭痛である。

片頭痛は10歳代後半から40歳代の女性に多く、緊張型頭痛の約1/5の頻度である。発作性に出現して痛みは強く、体動や力みにより頭痛が増悪するためquality of life(QOL)は著しく低下する。悪心・嘔吐、光・音・臭過敏などの症状を伴う拍動性の頭痛が4~72時間持続する。典型例では、頭痛発作の20~30分前に閃輝暗点などの前兆を認める(表1)。むくみ、嘔気、嘔吐、利尿などは漢方医学の水毒(体内における水分代謝調節異常)の症候である(図1)。片頭痛には肩こり(75%)やストレス(72%)を伴うことも多く、頭痛は両側性(40%)や非拍動性(50%)の場合も少なくないので、緊張型頭痛と誤診しないように注意する。

緊張型頭痛はもっとも頻度が多い。痛みの程度は中等度で日常生活に著しい支障をきたすことは

表1 前兆のない片頭痛の診断基準

頭痛発作>5回
持続時間4~72時間
以下の特徴のうち2項目以上
1. 片側性
2. 拍動性
3. 中等度~重度の頭痛
4. 日常的な動作で増悪
発作中に以下の1項目を満たす
1. 悪心または嘔吐(あるいはその両方)
2. 光過敏および音過敏

ないが、ほぼ毎日起こる。頭部の圧迫感・絞扼感、肩こりとして自覚されることが多い。片頭痛のような発作性や前兆は認めないが、同一患者に緊張型頭痛と片頭痛が併存することはまれではない。

二次性頭痛(症候性頭痛)は器質的疾患を含む他の原因による頭痛である。頭痛診療に際しては二次性頭痛のうち西洋医学的治療が優先される、くも膜下出血、髄膜炎、脳腫瘍などを鑑別することももっとも大切である。初発した頭痛、いつもと違う頭痛、最近増悪している頭痛、発熱・筋力低下・意識の変容などを伴う頭痛などは二次性頭痛を疑う。

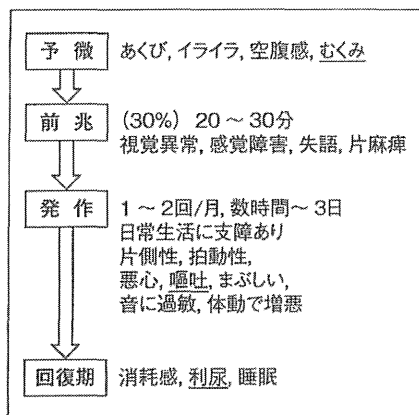


図 1 片頭痛の経過

下線を引いた症候を、漢方医学では水毒(水分代謝調節異常)としてとらえる。

## 頭痛の漢方治療

漢方薬の適応としては、①西洋薬で十分な鎮痛効果が得られない、②西洋薬で副作用がある、③西洋薬の副作用に不安があり、西洋薬とは異なる治療を求める、④西洋薬による薬物乱用頭痛の予防・離脱に使用する、⑤頭痛の背景に心因性の要素を含む、などが考えられる。実際の日常臨床では片頭痛、緊張型頭痛などの一次性頭痛に頻用されているが、器質性疾患に伴う頭痛にも西洋医学的な治療とともに使用される。

## 頭痛の西洋薬治療

片頭痛の急性期治療は、セロトニン受容体(5HT<sub>1B/1D</sub>)作動薬であるトリプタン製剤の登場により急速に進歩した。トリプタン製剤は頭蓋内の血管平滑筋の5HT<sub>1B</sub>受容体と血管周囲に分布する5HT<sub>1D</sub>受容体に結合して神経ペプチドの放出を抑制し、血管を収縮することにより頭痛を頓挫させる。日本では現在、5種類のトリプタン製剤が経口錠、口腔内崩壊・速溶錠、点鼻薬、注射薬の剤型で保険適応となっている。各製剤の特徴を考慮して、頭痛発作の進行が早い症例には最高血中濃度に到達する時間(T<sub>max</sub>)の早いものを、発作

持続時間の長い症例には血中濃度半減期の(T<sub>1/2</sub>)の長いものを使用すれば、片頭痛の急性期治療においてある程度は個別の症例に適した薬の選択が可能となる。しかし、トリプタン製剤は、①血管収縮作用を有するため、虚血性心疾患の既往を有する症例には使用禁忌であり、あらたに虚血性心疾患を惹起する危険がある、②発作時の頭痛を軽減するが予防効果はない、③薬物乱用頭痛の多くは市販薬によって生じるが、トリプタン製剤は他の頭痛薬に比べて薬物乱用頭痛となる期間が短い、④無効例が存在する、⑤高価であり経済的な負担が大きい、など問題点は少なくない。

片頭痛の予防薬として保険適応があるものは、日本で開発されたカルシウム拮抗薬の塩酸ロメリジンのほか、抗セロトニン薬のジメトチアジン塩酸、抑制系神経伝達物質であるγ-aminobutyric acid(GABA)類似作用を有するバルプロ酸と数少ない。外国ではA型ボツリヌス毒素の顔面・頸部への局所投与が片頭痛予防に有用と報告されている<sup>3)</sup>。筋緊張緩和作用のみならず、末梢痛覚神経の神経伝達物質を抑制することにより効果を発揮すると考えられるが、日本では保険適応はない。

緊張型頭痛の治療では、非ステロイド性抗炎症薬(NSAIDs)は胃腸障害、造血器障害などの副作用があり、慢性的な使用により薬剤乱用性頭痛を惹起する可能性がある。また、筋弛緩薬、抗不安薬には眠気、ふらつきなどのQOLを低下させる問題点がある。

## 頭痛に対する漢方薬の頻用処方

片頭痛に対しては、呉茱萸湯、五苓散、桂枝人參湯などが、緊張型頭痛に対しては川芎茶調散、葛根湯、釣藤散などが頻用され、薬物乱用性頭痛をはじめ二次性頭痛にも使用されている(表2)<sup>4)</sup>。

## 基礎研究のエビデンス：五苓散の利水作用とアクアポリン

五苓散は後漢の『傷寒論』と『金匱要略』を原

表 2 頭痛に対する漢方薬の頻用処方

処方	構成生薬
五苓散	沢瀉, 猪苓, 蒼朮(または白朮), 茯苓, 桂皮
呉茱萸湯	呉茱萸, 人參, 大棗, 生姜
川芎茶調散	白芷, 甘草, 羌活, 荆芥, 川芎, 防風, 薄荷, 香附子, 細茶
桂枝人參湯	桂皮, 甘草, 人參, 乾姜, 白朮(または蒼朮)
釣藤散	釣藤鈎, 橘皮(または陳皮), 半夏, 麦門冬, 茯苓, 人參, 防風, 菊花, 甘草, 生姜, 石膏
半夏白朮天麻湯	半夏, 白朮, 陳皮, 茯苓, 天麻, 生姜, 黄耆, 人參, 沢瀉, 黄柏, 乾姜, 麦芽, (神麴), (蒼朮)
苓桂朮甘湯	茯苓, 白朮(または蒼朮), 桂皮, 甘草
当帰四逆加呉茱萸湯	当帰, 桂皮, 芍薬, 木通, 細辛, 甘草, 大棗, 呉茱萸, 生姜
葛根湯	葛根, 麻黄, 大棗, 桂枝, 芍薬, 甘草, 生姜
加味逍遙散	当帰, 芍薬, 蒼朮(または白朮), 茯苓, 柴胡, 牡丹皮, 山梔子, 甘草, 生姜, 薄荷
桃核承気湯	桃仁, 桂皮, 大黄, 芒硝, 甘草
三物黄芩湯	黄芩, 苦参, 地黄
五積散	茯苓, 蒼朮(または白朮), 陳皮, 半夏, 当帰, 芍薬, 川芎, 厚朴, 白芷, 枳殼(実), 桔梗, 乾姜, 桂皮, 麻黄, 大棗, 甘草, (生姜), (香附子)

典とし、沢瀉、猪苓、蒼朮、茯苓、桂皮の5種類の生薬により構成される。元来、急性熱疾患による発汗の後、口渴、嘔吐、下痢、尿量減少のある場合に使用された。消化管内の過剰な水の吸収を促進することで血管内脱水を補正し、さらには排尿により過剰な水分を排出するとされる代表的な利尿剤である。

五苓散は水負荷状態では尿量を増加させ、脱水状態では尿量を減少させる水分代謝調整作用をもつ<sup>5)</sup>が、その薬理作用の詳細は明らかでなかった。一般的な利尿薬の尿量増加の機序としては、腎血圧上昇による腎糸球体濾過量の増加と電解質の再吸収阻害による原尿濃縮作用の2種類が知られているが、五苓散にはこのいずれの作用もみられない。最近、水チャネルのアクアポリン(AQP;「サイドメモ」参照)に対する五苓散の作用が報告されている。生体での水の移動は浸透圧や静水圧に依存し、AQPは細胞膜の水透過性、すなわち水の移動効率の調節を行っている。病的な浸透圧の異常が生じるとそれに伴い過剰に水の移動が起こり、

サイドメモ

アクアポリン(AQP)

1992年、細胞膜の水透過性を調節するアクアポリン(AQP)という水チャネルが発見された。AQPは28 kDaの膜蛋白で細胞膜を貫通する形で存在し、内部に水分子が通過する漏斗状の孔がある。現在までに、ヒトでは13種のアイソフォームが各臓器で確認され、脳では血液脳関門を形成している毛細血管周囲のアストロサイトの足突起などにAQP4が分布している。AQP4欠損マウスでは、急性水中毒状態でも野生型に比べアストロサイト足突起の膨化が著明に軽減され、脳浮腫の発生にAQP4が関与することが示されている。また、視神経脊髄炎の患者血液中にAQP4に対する自己抗体が高頻度に認められ、病態形成に関与していることが推察されてきている。細菌、植物、動物と普遍的に存在し、生命活動に広くかかわる重要な分子AQPを発見したPeter Agreには2003年のノーベル化学賞が贈られた。

その結果として浮腫(水毒)の病態が生じる。マウス肺上皮細胞株とプロテオリポソームを使用した *in vitro* 実験系で五苓散が AQP の働きを阻害して細胞膜の水透過性を抑制することが報告され、この抑制作用は構成生薬の蒼朮に含まれるマンガンが担っている可能性が推察されている<sup>6)</sup>。五苓散が浮腫を抑制(水毒を改善)する利尿作用の、すくなくとも一部は AQP の阻害作用による可能性がある。

脳浮腫の西洋薬による治療では浸透圧利尿薬が使用されるが、脱水、電解質異常、溶血、心不全などの副作用がある。五苓散にはこれらの副作用がないため使用しやすい。現在、慢性硬膜下血腫の保存的治療・再発予防、脳腫瘍や急性期脳梗塞の脳浮腫軽減に臨床応用されている。

## 臨床研究のエビデンス

### 1. 呉茱萸湯・五苓散は慢性頭痛に有用である

呉茱萸湯は後漢の『傷寒論』と『金匱要略』を原典とする。呉茱萸、人参、大棗、生姜の4種の生薬から構成され、血流増加、体温上昇、鎮痛の薬理作用がある。疲労しやすく、手足の冷え、水毒(体内における水分の偏在)による嘔気・嘔吐を伴う頭痛に使用される。これまでに多くの症例報告と症例集積研究があり、頭痛に対して高い有用性が報告されてきた。

漢方医学では生体防御反応を、寒性・非活動性・沈降性の場合を陰証、熱性・活動性・発揚性の場合を陽証と大きく二分する概念などがある。これらの概念と個々の症例の体質、症状、兆候などを総合して得られる証(陰陽、虚实、寒熱などの漢方医学的診断)に基づいて処方が決定される。この証を考慮した頭痛の臨床研究が報告されている。

慢性頭痛 23 例(片頭痛 13 例、緊張型頭痛 2 例、混合型頭痛 8 例)を、個々の症例の陰証と陽証とを考慮して 2 群に分け処方を決定した。陰証 18 例には呉茱萸湯エキス製剤 7.5 g/day を、陽証 5 例には五苓散エキス製剤 7.5 g/day をそれぞれ 4 週間

投与の後に、自覚的な頭痛の改善の程度を、著明改善、改善、やや改善、不変、悪化の 5 段階に分け検討した。その結果、やや改善以上を有効とする有効率は呉茱萸湯群で 72.2%、五苓散群では 80.0%、全体では 73.9%であった<sup>7)</sup>。

さらに、上記の結果を踏まえて最近、慢性頭痛(片頭痛・緊張型頭痛)を対象に、第 1 段階として呉茱萸湯の治療が有効だった症例(レスポnder)を抽出し、続いて対照としてプラセボ群を設定した無作為化二重盲検比較試験が行われた。第 1 段階では慢性頭痛 91 例に呉茱萸湯エキス製剤を 7.5 g/day を投与し、レスポnderを選別した。4 週間休薬の後、このレスポnder 53 例を呉茱萸湯群 28 例とプラセボ群 25 例に分け、それぞれの被検薬を 12 週間投与の後に、頭痛の種類、頻度、随伴症状、その他の頭痛薬の頓服回数などを指標として検討した。その結果、呉茱萸湯群では頭痛発症頻度(日)はプラセボ群と比較して有意に減少し(2.6±3.7 vs. 0.3±1.4,  $p=0.034$ )、頭痛薬の頓服回数はやや減少(2.2±4.0 vs. 1.4±8.2,  $p=0.672$ )していた。また、呉茱萸湯群では冷え、月経痛、肩こりなどの随伴症状が 50% 以上改善していた<sup>8)</sup>。

### 2. 呉茱萸湯は片頭痛予防に有用である

片頭痛予防効果に対する呉茱萸湯と西洋薬・塩酸ロメジリンとを比較した臨床研究において、呉茱萸湯の有効性が報告されている<sup>9)</sup>。片頭痛患者 14 例を、無作為に A 群(前半 28 日間は塩酸ロメジリン 10 mg/day を服用し、2 週間休薬後、後半 28 日間は呉茱萸湯エキス製剤 7.5 g/day を服用する)7 例と B 群(前半 28 日間は呉茱萸湯エキス製剤 7.5 g/day を服用し、2 週間休薬後、後半 28 日間は塩酸ロメジリン 10 mg/day を服用する)7 例に分けたオープン・クロスオーバー研究である。頭痛発作回数、visual analogue scale(VAS)のピーク値で自己評価した頭痛の程度、トリプタン製剤内服錠数、頭痛発作消失までの時間を指標として開始前、第一相、休薬相、第二相、終了時に評価した。この結果、いずれの指標においても呉茱萸湯のほうが塩酸ロメジリンと比較して有意に治療効果が認められた。

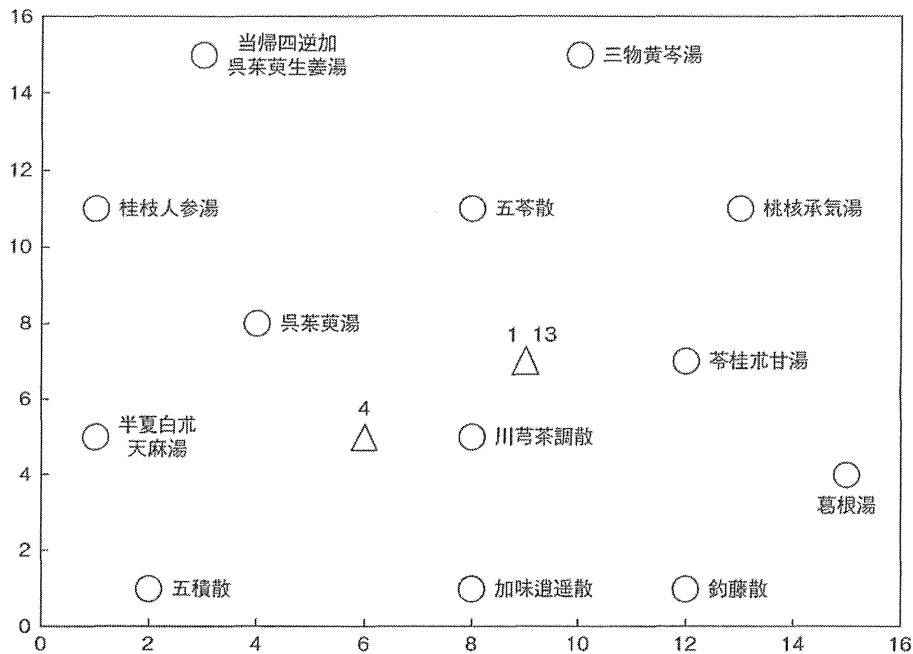


図2 頭痛頻用処方SOM解析<sup>10)</sup>

13処方の類縁関係を適応症候から、自己組織化マップ(SOM)により解析した。図の右側が実証、左側が虚証対応の処方に相当し、川芎茶調散はほぼ中間に位置する。1, 4, 13は川芎茶調散の著効症例の位置。

### 3. 自己組織化マップによる川芎茶調散の適応解析<sup>10)</sup>

川芎茶調散は太平惠民和劑局方の改訂版(宋代)を原典とし、構成生薬は、白芷、甘草、羌活、荆芥、川芎、防風、薄荷、香附子、細茶、(細辛)である。鼻炎を伴う軽度の感冒から女性の生理に伴う頭痛まで頭痛全般に使用される。川芎茶調散は頭痛に頻用される他の漢方薬に比べて特徴的な適応指標(漢方の証)は知られていない。川芎茶調散の中樞神経における作用としてラット線条体のドパミン濃度増加作用が報告されているが、頭痛に対する鎮痛機序は明らかではない<sup>11,12)</sup>。

竹田らは階層型ニューラルネットワークを応用し、藤平の特徴判別表<sup>13)</sup>に基づき教師あり学習を行った漢方処方診断支援システムを開発してきた。これを使用して、川芎茶調散を処方した17例(著効3例、有効9例、無効5例)を対象として他の頻用12処方との類似性を検討した結果では、呉茱萸湯、釣藤散、葛根湯が適応となる頭痛のなか

に川芎茶調散が有効である可能性が示唆された。さらに、各処方との類似性を散布図的に表現できる自己組織化マップ(self-organizing map: SOM)解析を行った結果を示す(図2)。この図で、漢方医学の虚実分類における実証対応の処方は横軸右、虚証対応は左、中間証対応はその間に位置している。川芎茶調散は中間証群に位置づけられた。古典に“いっさいの頭痛に用いる”と記載された川芎茶調散の幅広い適応を反映した結果となっている<sup>14)</sup>。

### おわりに

本稿では、頭痛に使用される漢方薬の基礎と臨床研究を紹介した。日本頭痛学会の慢性頭痛の診療ガイドラインには、「漢方薬は予防薬あるいは急性期治療薬として長期にわたり使用されており、経験的あるいは伝統的には効果・両面から有用である。これらを裏付ける科学的エビデンスも

近年集積されつつあり、漢方薬全般が慢性頭痛予防薬として推奨可能である(グレードB:行うように勧められる)」と記載されている<sup>15)</sup>。

今後、さらに多くのエビデンスレベルの高い研究が実施され、頭痛に対する漢方治療のEBMが確立されることが期待される。

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