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Biologic basis of TCM syndromes and the standardization of syndrome classification

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Abstract Traditional Chinese medicine (TCM) syndrome is an integral and essential component of TCM theory, and goes beyond philosophic concepts. This article reviews the concept of TCM syndromes and summarizes research findings on the biologic foundation of syndromes. In addition, insight is provided into the promotion of standardization of syndrome classification by enforcing uniformity of TCM terminology, applying standardized diagnostic criteria and operating procedures to minimize subjective effects. Also incorporating interdisciplinary approaches such as data mining and structure modeling, as well as integrating findings on biomarker research are discussed. Consideration is made of the fundamental TCM aspects of syndrome elements, symptoms, phenotypic features, as well as diseases, to form an integral process in the diagnostic path. We believe that better understanding of the biologic basis of the TCM syndrome and standardization of syndrome classification will improve diagnosis, which in turn will enhance therapeutic efficacy and disease prognosis.

Introduction

With a history of more than 3 000 years, traditional Chinese medicine (TCM) has been widely accepted as an effective folk medical practice by Asian medical systems and is gaining position over the world. Syndrome (*zheng*) classification is an essential component of TCM theory. Although traditionally considered to rely primarily on experiential

Abbreviations: TCM, traditional Chinese medicine; RA, rheumatoid arthritis.

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and phenotypic-enriched insights, as summarized in this review article, considerable advancement has been made in elucidating the biologic foundation of the TCM syndrome and to move toward standardization of syndrome classification.

What is TCM syndrome

A syndrome, or pattern, is an integral and essential part of TCM theory. A syndrome is an outcome of analysis of TCM information by the TCM practitioner, as well as what TCM treatments rely on.

A syndrome can be defined as a categorised pattern of symptoms and signs in a patient at a specific stage during the course of a disease. In TCM it is said 'different syndromes for one disease'. Each disease has a natural course of development for a certain period from occurrence, initial, intermediate, and advanced stages, to recovery, relapse, or deterioration. TCM syndrome classification may change as the disease goes through each stage.

A syndrome may be affected by various factors including gender, age, constitution, climate, weather, living and working conditions. The syndrome is classified based on categorization of TCM signs and symptoms under the guidance of TCM theory, while considering disease diagnosis, environment and patient profile (Fig. 1). For example, in a study,[1] of menopausal women in Germany and China, TCM diagnosis was performed by the same investigator. Syndrome differentiation demonstrated that German women experienced more from kidney-yang deficiency, whereas Chinese women were more prone to kidney-yin deficiency syndrome. Thus, factors of climate, constitution, and living conditions may have contributed to the differences in syndromes between the German and Chinese women.

How is a TCM syndrome identified? In brief, a TCM syndrome is a combination of signs and symptoms with internal relationships. First, information on presenting signs and symptoms is gathered through the TCM diagnostic methods of inspection, auscultation and olfaction, inquiry, and palpation. Next, the information is analyzed by the TCM doctor using the TCM theory of pathogenesis, or etiology. Signs and symptoms closely linked to the current state of illness are extracted, correlations among them are analyzed and conclusions are drawn. Eventually, diagnostic results can be made in terms of the TCM syndrome. Thus,

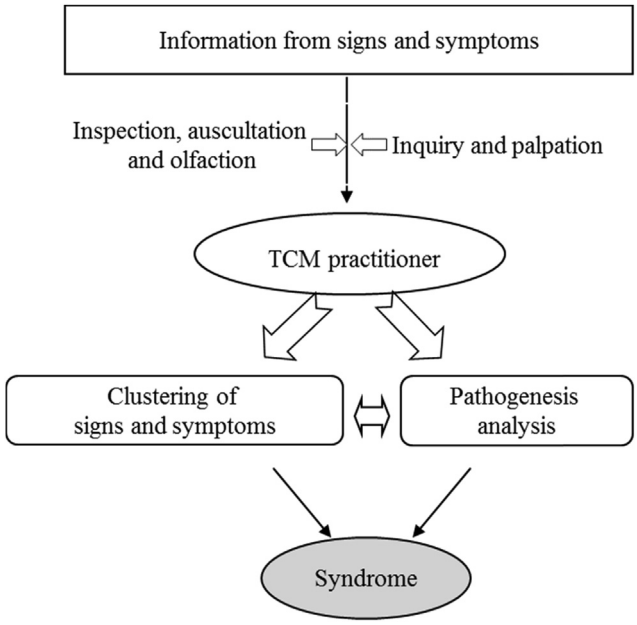

Figure 2 Key information used for TCM pattern classification.

syndrome identification is performed by finding a group of inner-linked signs and symptoms and their internal relationships, based on TCM theories. Signs and symptoms are the key information used for TCM pattern classification. They are gathered through the diagnostic methods of inspection, auscultation and olfaction, inquiry, and palpation. These factors are later classified and defined as a syndrome (Fig. 2).

The practice of TCM depends on accurate diagnosis and procedures known as treatment based on syndrome differentiation (*bian zheng lun zhi*) (Fig. 3). Fundamental TCM theories, including yin-yang, five elements, visceral manifestation, and channels have generated several syndrome differentiation criteria, such as syndrome differentiation according to eight principles, visceral manifestation, and six-channel. Through these differentiation methods, basic TCM theories are thus linked to the syndromes.

Syndrome differentiation is also used to guide the prescribing of herbal medicine, acupuncture/moxibustion, and massage therapies. Thus, syndrome differentiation is the key process for integrating basic theories and clinical

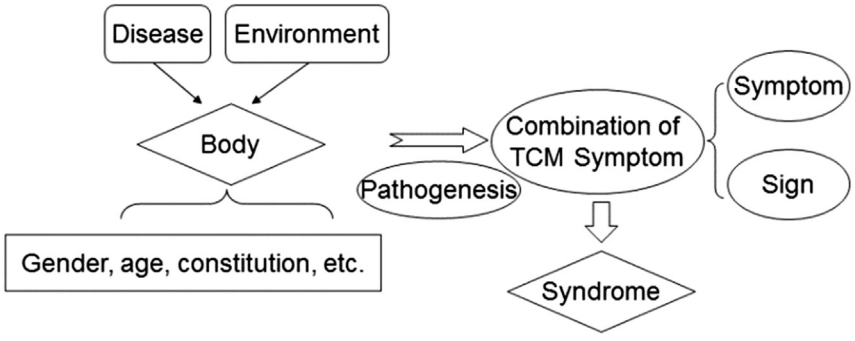

Figure 1 Concept of a TCM syndrome.

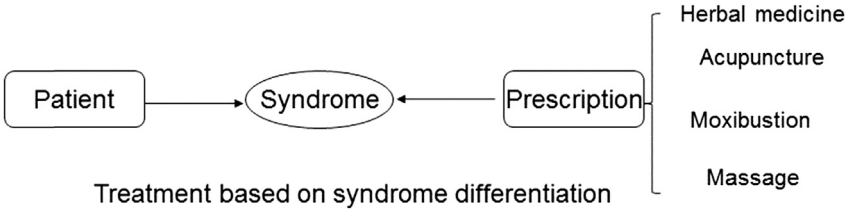

Figure 3 Concept of treatment based on syndrome differentiation.

practice. The syndrome is the central concept of TCM, with the focuses of which are TCM theory, diagnostic methods, treatment modalities, and the clinic itself (Fig. 4).

Does the TCM syndrome actually exist?

Is the TCM syndrome a factual phenomenon of correlation or is it merely a hypothesis formulated by the TCM practitioners? To answer this question, many studies have been performed to validate the TCM syndrome through its biomedical mechanisms and clinical manifestations.

Cellular and molecular studies

Considerable effort has been devoted to investigating the biomedical explanations of syndromes and to reveal the molecular features of different TCM syndromes for one disease, as well as the same TCM syndrome for different diseases. Zhao et al.[2] and Qiu et al.[3] studied proteomics and gene expression profile characteristics of patients with blood stasis (*xue yu*) syndrome, and both researchers determined that this syndrome may be correlated with inflammatory reactions. Guo et al.[4] identified the molecular mechanisms for liver-gallbladder dampness-heat syndrome (*gan dan shi re*) and liver depression and spleen deficiency syndrome (*gan yu pi xu*) using microarray samples from chronic hepatitis B and liver cirrhosis patients. Gu et al.[5] used microarray technology to reveal gene expression profiles and metabolic phenotypes from RA patients with either cold (*han bi*) or hot syndrome (*re bi*). Different gene expression levels and metabolic phenotypes were observed in patients who experienced the two different syndromes.

Xiong et al.[6] studied wind syndrome caused by liver yang hyperactivity (*gan yang hua feng*) at the protein expression level in patients with different diseases. Peripheral blood mononuclear cells were isolated from patients with cerebral hemorrhage, cerebral infarction, or Parkinson disease who were diagnosed with the aforementioned syndrome. Analyses found that compared to healthy subjects, patients with any of the three conditions exhibited the same expression in different diseases of the same syndrome. Thus, patients with a certain syndrome arising from different diseases seemed to share the same biologic basis at the protein expression level.

Although we are still far from reaching a full understanding of the inherent mechanisms of the TCM syndromes, these representative studies appear to show that biologic differences exist between several syndromes arising from a given disease; conversely, the same syndrome arising from different diseases may share the same biologic basis.

Data mining

TCM syndromes can also be demonstrated through data mining from epidemiological surveys or the literature. The presence of a syndrome can be supported by classification of clinical manifestations, the result of which is identical to the collection of symptoms during syndrome differentiation.

In a multi-center randomized controlled study of patients with rheumatoid arthritis (RA), 18 common symptoms were detected. Symptom clusters could be classified into four factors (symptom combinations) using factor analysis. The symptom combinations were notably similar to the syndromes differentiated by TCM theory in RA patients, which divides RA into three basic syndromes: cold (*han*), heat (*re*), and deficiency (*xu*) syndromes.[7]

In a study of menopausal women, factor analysis was used to reveal that symptoms could be grouped according to their mutual relationships. Results coincide with those of kidney-yin deficiency syndrome (*shen yin xu*) and kidney-yang deficiency syndrome (*shen yang xu*).[5]

In Chinese medicine, the process of diagnosis is to establish co-relationships of evident variables, such as the symptoms, and underlying variables, such as syndromes. To simulate this process, Zhang et al proposed employing latent structures to study syndromes.[8,9] Data for the occurrence of symptoms were collected through

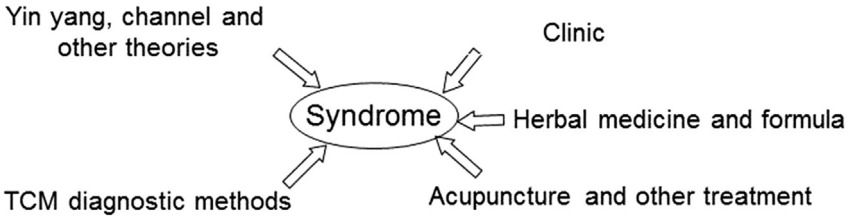

Figure 4 Central concept of TCM.

epidemiologic surveys of patients with depression, and multidimensional clustering analysis was performed using latent structure models. Next, classifications were made based on the clustering of symptoms. Interestingly, the classifications could be explained using TCM theory and were similar to differentiation of syndromes.[10] Using this method, studies were performed in patients with chronic gastritis, as well as type 2 diabetes, chronic obstructive pulmonary disease, psoriasis vulgaris, and cardiovascular disease. Results of these studies all indicated that there are classifications of symptoms in certain diseases that are consistent with TCM syndromes.[11–14]

What are the subjective factors in the process of syndrome differentiation?

Because each syndrome exists as an underlying pattern, what are the subjective factors that affect identification of the right pattern? Two independent studies evaluated subjectivity in syndrome differentiation by TCM practitioners. The degree of agreement among TCM practitioners may be improved through a training process and a questionnaire-based diagnostic process. These results suggest that syndrome classification is often influenced by subjective factors.[15,16]

This situation is related to several factors, but primarily to personal experience and a lack of standardization of syndrome terminology. The process of syndrome differentiation is often subjective because it usually depends on the practitioner's experience and interpretation of presenting signs and symptoms. As stated, syndrome differentiation involves gathering and assessing large quantities of information and logical reasoning. Many practitioners tend to use personal experience while diagnosing without strictly following syndrome differentiation theory. Thus in reality, simple and handy diagnostic methods are practiced in the clinic, such as differentiation according to the main symptoms, constitution, and climate/weather.

Among the many signs and symptoms, focusing on the primary symptom can help determine the syndrome. *Discussion on Cold Damage* (*Shang Han Lun*) recorded this method two thousand years ago, 'Once knowing the main symptom, the syndrome can be determined, no need to collect all symptoms'. A syndrome is the consequence of a struggle between vital qi and pathogenic factors. Under certain circumstances, vital qi plays the leading role in the struggle. Thus, the internal environment has much more of an influence on the syndrome. As examples, plump people may be prone to excessive phlegm, while slim individuals may be prone to excessive internal heat. Children are of pure-yang constitution; therefore, they easily experience heat syndrome. On the other hand, older people are susceptible to cold due to a lack of kidney yang. Under other circumstance, the effect of the external environment, such as social factors, geology, climate, and weather dominates the syndrome. Many traditional practitioners use the five movements and six climates (*wu yun liu qi*) theory for syndrome classification of epidemics because the theory helps identify the external etiologic factors.

The differentiation methods mentioned above emphasize the importance of certain information. However, these types of methods are not advantageous for TCM practitioners to pass on and disseminate, let alone validate. During their long careers, eminent herbalists may have accumulated considerable and valuable experience, which is often not easy for young practitioners to learn quickly. Conversely, practitioners whose perspective on syndrome differentiation is curbed by their limited experience are unable to transmit competent knowledge to others.

Another reason for subjectivity in differentiation is a lack of standard terminology. This refers to lack of standardization of both syndrome names and important elements of the syndromes. Some traditional syndromes are ambiguous because they only feature the pathogenesis with necessary details. For example, with the syndrome qi deficiency, the name of the syndrome itself is not sufficient to guide a clinician in the choice of formula and herbs. In this scenario, diagnostic information was not fully collected and expressed using adequate nomenclature. As such, the treatment may be disconnected from syndrome differentiation. Thus, lack of standard terminology and objective criteria for differentiation adversely affects TCM practice, especially for clinical trials across multiple centers.

Classifying syndromes objectively

Syndrome elements

Syndrome elements are the principal components of a syndrome. A syndrome should include the main aspects of a disease, such as its site in the body, pathogenesis, and etiologic factors. Since combinations of these factors can lead to a large number of syndromes, objectification of syndrome differentiation should have standard syndrome elements.

At present, approximately 50 syndrome elements are divided into two categories. One category is the site of the disease, which is the organ or channel. The other category includes the pathogenic/etiologic factors, such as the excesses (exogenous wind, summer heat, etc.) (Supplemental Materials).

Compared with the various syndrome names in use and in current textbooks, syndrome elements are concentrated and easy to use. Furthermore, the syndrome elements can be combined in a flexible manner. Once the features and criteria of the syndrome elements are clear, the syndrome can be identified based on the patient's condition.

Diagnosis based on both diseases and syndromes

Integrating the differentiation of diseases with that of syndromes is becoming an important trend for clinical diagnosis. This mode of diagnosis considers the specificity of the disease while embodying the flexibility of syndrome differentiation. This approach is suitable for clinical practice. The method also facilitates the understanding of TCM diagnosis with that of Western medicine. Chen et al[17] applied this approach by establishing a scale of syndromes to automatically generate a diagnosis for patients based on their phenotypes through analyzing phenotype networks of coronary heart disease.

Standardized syndrome diagnostic criterion and process

With definitive syndrome elements and confirmed diagnosis of disease, the following steps can be executed to standardize syndrome differentiation:

Step 1. Understanding common syndrome elements of certain diseases.
Step 2. Identifying symptom groups related to common syndrome elements.
Step 3. Acknowledging the contribution of the signs and symptoms to diagnostic syndrome elements.
Step 4. Forming a preliminary diagnostic criterion for the syndrome.
Step 5. Evaluating and verifying the syndrome criterion.

With sufficient epidemiologic surveys, symptoms and their weights can be determined using statistical methods with the ultimate goal of establishing the syndrome criterion based on sound data.

This method is compatible with Chinese medical theory and is helpful for the establishment of a standard syndrome differentiation criterion, which will be the agreed foundation for clinicians and researchers, TCM practitioners and Western doctors.

Wang et al.[10] applied latent structure models as an objective and quantitative method for the standardization of syndrome differentiation. Other studies have used aforementioned methods to establish syndrome differentiation criteria for such diseases as depression, chronic hepatitis B, chronic renal failure, chronic obstructive pulmonary disease, menopausal syndrome, ulcerative colitis, and ischemic stroke.[11–14] These criteria are being verified in clinical practice.

Diagnostic standards are also being developed for TCM diagnostic techniques such as for the various pulse types and tongue presentations.[18,19] In addition, patients' symptoms can be measured more accurately using such instruments as scales and questionnaires.[10]

Biologic indicators

An attempt has been made to identify biologic indicators of syndromes and to use them to facilitate syndrome differentiation.[20] However, biologic indicators cannot entirely replace clinical information for identification of syndromes. They may serve as important information and as physical signs to be considered along with the symptoms.

Conclusions

The concept of TCM syndromes serves as an essential element in Chinese medicine theory. Considerable research has been directed toward improving standardization of syndrome classification. Systems biology approaches have provided informative insight into the biologic basis of TCM syndromes and should be further explored to facilitate defining and interpreting syndromes biomedically. While TCM diagnostics partially relies on subjective phenotypic features, such as pulse presentation, as perceived by the practitioner, these diagnostic variables should be evaluated and subjective factors that may confound the diagnosis should be controlled. Further investigations would promote deeper understanding of the TCM syndrome and improve diagnosis and therapeutic efficacy.[21] Standardization of syndrome classification will also catalyze standardization of outcome measures and training of the next generation of medical professionals.

Contributors

Qingguo Wang obtained funding and supervised this study. Fafeng Cheng conducted the review and wrote the manuscript. Xueqian Wang and Wenting Song collected reference articles and contributed to the first two sections of this article. Yi Lu and Xiaoguang Sun offered advice relevant to the last two sections. Xiaoli Li proofread the manuscript.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jtcms.2014.09.005.

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