ACADEMIC EXPLORATION

Study on Correspondence between Prescription and Syndrome and the Essence of Phlegm and Blood Stasis Syndrome in Coronary Heart Disease Based on Metabonomics

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ABSTRACT  Studying the essence of a syndrome has been a key challenge in the field of Chinese medicine. Until now, due to limitations of the methods available, the progress towards understanding such complicated systems has been slow. Metabonomics encompasses the dynamics, composition and analysis of metabolites, enabling the observation of changes in the metabolic network of the human body associated with disease. Being from the point of view of the whole organism, metabonomics provides an opportunity to study the essence of a syndrome to an unprecedented level. Phlegm and blood stasis syndrome is the main syndrome associated with coronary heart disease (CHD), which bring difficulties in clinical treatment due to difficulties associated with differentiation of symptoms and signs. The fundamental differences of material between the two also need to be interpreted. The authors consider that we can use the method of combining a disease (in this case CHD) with associated syndromes (phlegm and blood stasis syndrome) to select patients with phlegm and blood stasis syndrome of CHD, and utilize metabonomics to explore the essence of the syndrome by difference analysis of metabolite spectra. Meanwhile, we can study the syndrome in CM, observe the change regularity of metabolism spectra after the treatment of corresponding and non-corresponding prescription and syndrome, in order to validate the material fundament in the progress of syndrome formation and their differences. This will not only have great significance in enhancing the ability to identify syndrome of phlegm and blood stasis in CHD and to establish the clinical curative criteria, but will also offer a new approach of studying the essence for a syndrome using metabonomics.

KEYWORDS  metabonomics, phlegm and blood stasis syndrome, coronary heart disease, combination of disease with syndrome, correspondence between prescription and syndrome

Due to limitations in methods available, the study of the underlying mechanisms of a variety of syndromes has been slow. Metabonomics encompasses the dynamics, composition and analysis of metabolites, and enables investigation of changes in the metabolic network of the human body associated with disease from the perspective of the whole organism. This provides an opportunity to study the essence of a syndrome. The authors selected patients with phlegm and blood stasis syndrome of coronary heart disease (CHD) as an example of applying the method of metabonomics to study the underlying essence of this syndrome.

The Study of Syndrome in Chinese Medicine—A Technology Breakthrough

Determination of treatment based on disease pathogenesis, obtained through differentiation of symptoms and signs of the disease, is the theoretical core of Chinese medicine (CM), the special way and method to understand, diagnose and treat diseases; while the syndrome is the result and basis of it, also the premise and basis of the diagnosis and treatment in CM. From the point of view of modernizing CM, to understand the essence of a syndrome is necessary to interpret the factors which may produce the syndrome in question, and to establish the particular factors which underlie the change process associated with syndrome development. By inference, studying the factors underlying a syndrome or its physical basis can not focus on a specific organ, and by its nature, it can not be either simple or specific. Therefore, in the final analysis, to study the essence of a syndrome it is necessary to probe many underlying factors. In clinical practice, every syndrome has its extra-
image and connotation. Extra-image is difficult to quantify, and is mostly dependent on the doctor's diagnosis and treatment. It may be semi-quantified, through epidemiological deduction and judgment and evaluation based on expert experience. Extra-image can be obtained by combining the information from four different examinations: inspection, listening and smelling, inquiry, and pulse taking and palpation. Differentiation of symptoms and signs can be affected by subjective factors in both the doctor and patient, and these are difficult to judge objectively and to quantify. Therefore, we must study a syndrome's connotation, i.e., probe the material basis of a syndrome. Studying a syndrome and probing its basis have great theoretical significance and are of much value, not only in enhancing the clinical efficacy of CM, but also promoting the international academic exchange and the internationalization of CM.

Over the years, the CM approach to studying the essence of a syndrome has followed the theoretical framework of modern medicine, dedicated to probing highly specific and sensitive indices of the syndromes in question, in order to identify a single "golden" laboratory diagnostic index. However, due to complex characteristics such as integrity and dynamics, the fact that different diseases may produce the same or similar symptoms, or the same disease may present with different symptoms, it is not possible to define a syndrome qualitatively, quantitatively, and site-specifically using a single index. Furthermore, in the case where there is a lack of appropriate guidance in CM theory, or limitations to the study methods, it is difficult to establish the entire essence of a syndrome and thus to make a breakthrough.

**Metabonomics—A Good Tool to Grasp the Essence of Syndrome in Its Entirety**

The field of "metabonomics" was pioneered by Professor Nicholson and his colleagues in the UK in 1999.\(^{(1)}\) It is a subject which has developed following genomics, transcriptomics, and proteomics, and is an important component of system biology. Metabonomics investigates the final metabolic products of gene and protein expressions. Many changes not seen by genome and proteome analysis can be observed within the metabonom, while minute changes in gene and protein expressions can be enlarged or amplified in the metabolic by product of this expression. Thus, the metabonom of an organism at a given time most directly reflects the physiological and pathological state of the organism at that time.\(^{(2,3)}\)

Modern research on syndromes in CM needs to identify appropriate methods by which underlying mechanisms can be characterized; metabonomics at this time is undoubtedly a favorable option and a technique which can support the CM approach. Metabonomics combines many aspects such as the dynamic state, synthesis with analysis, and emphasizes the study of the human body as a complete system. Its use enables measurement of changes in metabolic networks within the human body produced by disease, or by medical treatment, by measuring changes of a wide variety of metabolites in, for example, body fluids; this has a distinct advantage over other techniques in revealing the mechanism of complicated diseases. CM emphasizes entirety, system, and the determination of treatment based on pathogenesis diagnosed via differentiation of symptoms and signs. It places a great importance on interactions between human beings and nature, between human beings and society, general contact and dynamic changes in the human body, and uses this knowledge to establish an objective "rule" by which a disease can be analyzed or identified over the course of its development. All of these approaches are coincident with metabonomics.\(^{(4)}\)

The research of metabonomics places particular emphasis on looking for common patterns or correlated components. This not only assists with better understanding of changes occurring during a pathological process, or alterations to metabolic pathways and the impact of these changes on our bodies, but also enables the identification of biomarkers, which can be crucial for the diagnosis and treatment of disease on an individual basis.\(^{(5,6)}\) Metabonomics techniques enable effective combination of pattern recognition techniques by identifying, analyzing and assessing defined changes in metabolic composition related with a certain syndrome, and it will make the differentiation of symptoms and signs more objective. Furthermore, it can provide an objective assessment of the functional state of an organism, not only by appropriate modeling of a great quantity of data from individual samples to establish objective criteria or patterns which identify the same syndrome in different individuals; but also interpret the essence of the syndrome according to its development in the same individual by measurements at different times during the course of disease. Combining the study of
a syndrome and its metabonomic profile together will help push the study of syndromes into the forefront of science development, which may be of great importance for modernizing the study of CM.

**Phlegm and Blood Stasis Syndrome of CHD—Thinking Shaped by Clinical Puzzles**

Before the 1970s, differentiation of symptoms and signs of CHD laid particular emphasis on blockage of phlegm, and treated this with Gualou Xiebai Banxia Decoction (瓜蒌薤白半夏汤). After the 1970s, stagnation of blood was considered more important, and Xuefu Zhuyu Decoction (血府逐瘀汤) was commonly used in CHD treatment, by which the curative effects were enhanced. In recent years, following an increase in the standard of living, fundamental changes in diet, increasingly violent competition, and increased air and environment pollution, a great change has happened in CM with respect to the syndromes associated with CHD. Obesity, improper diet, and smoking and drinking addictions increase the ratio of phlegm syndrome in CHD, thus phlegm and blood stasis syndrome has become the most important syndrome associated with CHD.

Phlegm and blood stasis are both pathological products of abnormal metabolism of body fluid and blood. Both phlegm and blood stasis belong to Yin, and fluid and blood share the same origin, therefore phlegm and blood stasis also share the same origin and relationship; one can be transformed into another and vice versa, which makes the determination of treatment based on pathogenesis obtained through differentiation of symptoms and signs increasingly difficult. At present, advances have been made in the study of phlegm and blood stasis in CHD, particularly in blood stasis syndrome which has been shown to be related to dysaemia, platelet aggregation, thrombogenesis and microcirculation dysfunction; this provides important reference information for treatment. However, progress has been relatively weak in the study of phlegm syndrome, which focuses on only some indices, and it is therefore difficult to satisfy clinical need. Following further study, we have found many questions, for example, if phlegm and blood stasis in CHD have the same origin, how do the two affect each other? As we know both phlegm and blood stasis can lead to lipid metabolism dysfunction, is the basis of the two the same or not? Is there a more microcosmic sensitive index by which they can be assessed? All these questions require answers, while explaining the essence of syndromes associated with CHD objectively has great significance to establish appropriate diagnostic criteria for CM and thereby enhance the curative effect.

**Study of the Correspondence between Syndrome and Prescription—A Powerful Supplement to the Essence of A Syndrome Study**

The difficulties of diagnosis and treatment in CM are overall observation of disease and syndrome and how to grasp the entirety and dynamic state of disease and/or syndrome in a curative context, i.e., determining the treatment based on differentiation of symptoms and signs. Combining a disease and syndrome together, and developing a prescription which corresponds with the syndrome, are the foundation for determination of treatment based on differentiation of symptoms and signs. Only by discussing the disease based on its associated syndrome, or by combining disease and syndrome together, can the key points to differentiate the syndrome correctly be determined. Only by discussing a prescription based on the syndrome, and thus corresponding the prescription with the syndrome, can the best clinical curative effect be obtained. (7)

The theory of corresponding a prescription with a syndrome emphasizes the correspondence between the two; there is a syndrome, there is a prescription, and the prescription changes with its syndrome. This formula is a complicated, non-linear system, which regulates the net metabolism of the human body. Using the premise of exact differentiation of symptoms and signs, this formula can normalize the defective part of net metabolism, while at the same time not disturb the normal regulation of metabolic pathways which are responsible for the maintenance of health. Unreasonable or incorrect differentiation of symptoms and signs, and consequent non-correspondence of prescription and syndrome, may produce the opposite effect. Previously in the study of prescription and syndrome, the question of whether the formula, like the human body, is a non-linear, complicated system was neglected. (8) Using metabonomics technology can measure the effects of the prescription on the syndrome, which means validating whether the differentiation of symptoms and signs is exact by observing the effect produced by the prescription. It enables observation of the prescription's mechanisms and means that analysis of correlation between
prescription and syndrome can be undertaken; it provides a scientific basis for drawing conclusions on the correspondence of prescription and syndrome. Chen, et al.(9) using gas doromatography mass spectrum (GC/MS) technique, found that the net metabolism of an animal model of Kidney (Shen) yang asthenia obviously deviated from that of normal or control animals; when an intervention using CM warming yang was applied, the metabolic spectra of the animal model returned to the normal range and showed effects of network restoration. The Sijunzi Decoction (四君子汤) is for treating deficiency of Spleen (Pi)-qi and Stomach (Wei)-qi, and is often used to treat diarrhea and constipation; this is an example of correspondence between prescription and syndrome. It is highly unlikely that in Western medicine the same formula would be used to treat two different, and possibly contradictory diseases. Pharmacologists using various models have found that this formula has multiple actions (adding mucus proteins to the surface of stomach and intestinal cells, antagonizing acetylcholine, promoting hepatic glycogen synthesis, antioxidant activity), demonstrating that this formula had indeed restored activity at many points in the relevant metabolic networks.(10,11)

In summary, metabonomics brings the opportunity to study the essence of a syndrome in the context of CM. In recent years, studies undertaken in this field show favorable prospects, but there has still been no report of a clinical study on patients with CHD in this field using the method of combining disease and syndrome together. Specifically, there is no report on the essence of phlegm and blood stasis syndromes and their treatment by methods in which the prescription corresponds with the syndrome, and comparing this with treatment where prescription and syndrome do not correspond. We propose to use the method of combining disease with syndrome, and thus select patients with phlegm and blood stasis syndromes of CHD, and utilize metabonomics technology to explore the essence of the syndrome by difference analysis of metabolite spectra. Meanwhile, we can draw in the knowledge obtained by measuring the syndrome using CM, and observe changes in the metabolic spectra after treatment in which the prescription corresponds with the syndrome, and compare this with non-corresponding prescription and syndrome. This will enable us to validate fundamental factors in the progress of syndrome formation and to observe changes in these factors, which will not only have significance in enhancing the ability to identify phlegm and blood stasis syndromes in CHD and monitor clinical curative effect of any treatments, but also offer new insights into studying the essence of a syndrome using metabonomics.

REFERENCES


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