ORIGINAL ARTICLES

Matrix Analysis of Traditional Chinese Medicine Differential Diagnoses in Gulf War Illness

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Abstract

Objective: To qualitatively categorize Traditional Chinese Medicine (TCM) differential diagnoses in a sample of veterans with Gulf War Illness (GWI) pre- and postacupuncture treatment.

Subjects and methods: The authors randomized 104 veterans diagnosed with GWI to a 6-month acupuncture intervention that consisted of either weekly or biweekly individualized acupuncture treatments. TCM differential diagnoses were recorded at baseline and at 6 months. These TCM diagnoses were evaluated using Matrix Analysis to determine co-occurring patterns of excess, deficiency, and channel imbalances. These diagnoses were examined within and between participants to determine patterns of change and to assess stability of TCM diagnoses over time.

Results: Frequencies of diagnoses of excess, deficiency, and channel patterns were tabulated. Diagnoses of excess combined with deficiency decreased from 43% at baseline to 39% of the sample at 6 months. Excess+deficiency+channel imbalances decreased from 26% to 17%, while deficiency+channel imbalances decreased from 11% to 4% over the study duration. The authors observed a trend over time of decreased numbers of individuals presenting with all three types of differential diagnosis combinations. This may suggest that fewer people were diagnosed with concurrent excess, deficiency, and channel imbalances and perhaps a lessening in the complexity of their presentation.

Conclusion: This is the first published article that organizes and defines TCM differential diagnoses using Matrix Analysis; currently, there are no TCM frameworks for GWI. These findings are preliminary given the sample size and the amount of missing data at 6 months. Characterization of the TCM clinical presentation of veterans suffering from GWI may help us better understand the potential role that East Asian medicine may play in managing veterans with GWI and the design of effective acupuncture treatments based on TCM. The development of a TCM manual for treating GWI is merited.

Keywords: Gulf War Illness, acupuncture, matrix analysis, Traditional Chinese Medicine

Introduction

A CCORDING TO CLINICAL and registry programs, 25% of the 700,000 veterans of the first Gulf War are affected by multiple symptoms and comorbid medical diagnoses that include: chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, arthralgia, digestive complaints, and mood-related psychiatric disorders, including depression, post-traumatic stress disorder (PTSD), and other anxiety disorders. Approximately 200,000 Veterans of the Gulf War are experiencing these symptoms even 20 years after the war.^{1,2} First Gulf War veterans have been studied in comparison to

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Gulf Era veterans (those who served elsewhere in the world but at the same time). Gulf War veterans report higher prevalence of physical and mental health conditions and likewise have a significant burden of disease, including multiple comorbidities and higher body mass index.¹ People diagnosed with Gulf War Illness (GWI) have difficult symptom presentations, often with complex comorbid symptoms that consist of fatigue, sleep and mood disturbances, cognitive dysfunction, and musculoskeletal pain. These symptoms are grouped into three symptom clusters by the Centers for Disease Control and Prevention (CDC) as follows: fatigability (fatigue 24 h or more after exertion), mood and cognition (feeling depressed, irritable, anxious, difficulty in concentrating, problems getting to sleep), and musculoskeletal (joint or muscle pain). Veterans must experience symptoms from each of the three clusters to be diagnosed with GWI. Overall, veterans diagnosed with GWI are stable (not improving) at 5- and 10-year follow-ups³ and no standard of care presently exists.⁴ There is a need for innovative and effective care of GWI.

Acupuncture has been shown to be effective in treating some of the symptoms of GWI as evident in published research studies, specifically for pain,⁵ anxiety, and depression.⁶ The parent study to this project demonstrated clinically and statistically significant improvement in SF-36 physical and McGill Pain Index scores in the group randomized to receive individualized Traditional Chinese Medicine (TCM) acupuncture treatments twice per week for 6 months.⁴ Preliminary research indicates that acupuncture may be effective in the management of complex conditions that share a similar cluster of symptoms of pain, sleep, and mood problems such as GWI⁴ and fibromyalgia.' The complex diagnostic and treatment process of TCM, which is tailored to each individual's clinical presentation, may provide an effective framework for evaluating and addressing the complex symptoms presented in GWI. Currently, there are no theoretical TCM frameworks for GWI. Their team set out to evaluate the theoretical TCM framework used by TCM practitioners evaluating participants with GWI through a matrix analysis of TCM differential diagnoses. Their main purpose was to characterize ways in which TCM patterns combine in clinically significant ways in this chronic and complex condition.

Methods

Quantitative parent study

Detailed methods are described elsewhere,⁴ but a brief summary of the parent study is provided in this study for context. The authors randomized 104 veteran participants after affirming that each did meet diagnostic criteria of GWI. The authors provided individualized acupuncture care in private practices by experienced Licensed Acupuncturists. Participants provided informed consent and were randomized either to biweekly acupuncture for 6 months or a 2-month wait-list, after which they received weekly acupuncture for 4 months. This research was approved by New England Institutional Review Board and U.S. Army Human Research Protection Office. All participants continued to receive standard care as needed.

The acupuncture intervention lasted ~ 1 h and consisted of consultation with a Licensed Acupuncturist, assessment of the participant, and the development of an individualized treatment plan. Acupuncture points were chosen according to TCM differential diagnosis; acupuncture needles were inserted and retained for 30–45 min. Acupuncture and additional therapies were allowed, including electroacupuncture, heat therapies (e.g., heat lamp), Chinese massage (*tui na*), cupping, and press balls, tacks, or magnets applied to acupoints after needles were removed. Herbal medicine and supplements were not allowed.

Qualitative substudy

Descriptive statistics were drawn from the parent study, and all participants were included in this study. Frequency counts were tabulated for each differential diagnosis. Matrix analysis was then applied to categorize differential diagnoses according to categorizations of excess, deficient, and channel disorders for baseline and 6-month visits. This allowed the detection of patterns of consistency and patterns of change in TCM differential diagnoses over time.

Matrix analysis

Matrix analysis is a qualitative data analysis that involves "the crossing of two or more main dimensions ... to see how they interact."8 In this study, the authors have two dimensions: individual differential diagnoses and categories of excess, deficiency, and/or channel diagnoses. These categories are not mutually exclusive and commonly co-occur in clinical practice. Matrices can be descriptive (depicting conditions), outcome oriented (depicting results or consequences), or process oriented (depicting dynamics of change).⁹ In this study, the authors develop both descriptive and process-oriented matrices. Each author examined 10 participants' data to develop the coding scheme. Once this was agreed upon by the team, two licensed experienced acupuncturists (L.T.-S. and J.C.) acted as coders. They first developed fidelity of the coding scheme by categorizing a sample of veteran participants' data (n=20) to find consensus. After this training, all participants' data were coded first according to all differential diagnoses and then according to excess, deficiency, and/ or channel imbalances. Cohen's kappa was calculated, and the two coders compared any differences and discussed their interpretations of the coding scheme until agreement was obtained.

Results

Demographics

The study participants' demographics were as follows: the mean age was 48.2, 14% were female, and 81% were self-reported as white. Please refer to Table 1.

Reliability

Data were double coded by two Licensed Acupuncturists (J.C. and L.T.-S.) with master's degrees in TCM and a combined 23 years' clinical experience. Reliability was calculated with Cohen's kappa. The reliability coefficient obtained after coders were trained was 0.93.

Matrix analysis

Participants' differential diagnoses were noted at the baseline and 6-month visit. Participants' differential diagnosis consisted of one to six diagnoses (e.g., concurrent

TRADITIONAL CHINESE MEDICINE DIFFERENTIAL DIAGNOSES IN GWI

Table 1.	BASELINE CHARACTERISTICS OF THE STUDY
	POPULATION

Characteristics	
Age-year \pm SD (N=103)	48.2 ± 7.5
Female sex, N (%) ($N=104$)	14 (13.5)
Self-reported race, N (% of total) ($N=1$	104)
White	84 (80.8)
Black or African American	10 (9.6)
Asian	1 (1.0)
American Indian/Alaskan Native	1 (1.0)
More than one race	2 (1.9)
Unknown	$\frac{1}{5}$ (1.0)
Other	5 (4.8)
Self-reported Hispanic, N (% of total) ((N=104)
Yes	6 (5.8)
No	94 (90.4)
No answer	4 (3.8)
Baseline pain, N (group mean) \pm SD	92 (29.0)±9.7
Baseline SF-36 Physical N (group mean) \pm SD	87 (67.7)±23.5

SDs are offered for age, baseline pain, and baseline SF-36 Physical. SD, standard deviation.

spleen (SP) qi deficiency and LV qi constraint and stagnation in the channels). Frequencies of each differential diagnosis component at baseline are displayed below in Table 2. Next, each diagnosis was organized according to TCM theory into one of three categories. These categories are general or overarching theoretical constructs and encompass deficiency (e.g., insufficient qi), excess (e.g., overabundance of qi, which then may become stagnant), and imbalance of the acupuncture channels or meridians (e.g., qi is stagnant in a channel, causing local pain). The categories and the associated differential diagnoses are as follows: Deficiency (of qi, Blood, yin, or yang); Excess (of Damp, Heat, Cold, Phlegm, Fire, Yang rising, Wind,

 TABLE 2. DIFFERENTIAL DIAGNOSIS CATEGORIES

 AT BASELINE

Category	Ν
Deficiency	
Qi	67
B lood	24
Yin	33
Yang	7
Excess	
Damp	25
Heat	23
Cold	2
Phlegm	11
Fire	1
Yang rising	13
Wind	8
<i>Qi</i> stagnation	51
Blood stagnation	10
Channel	
<i>Qi</i> and blood stagnation	30
Deficiency	2
Eight extraordinary meridians	4
Damp Bi syndrome	13
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qi stagnation, or Blood stagnation); and Channel pathology (*qi* and Blood stagnation in the channels, Deficiency of Blood or *yin* in the channels, eight Extraordinary Meridian imbalance or Damp *Bi* Syndrome).

The authors further analyzed 10 of 17 most frequent categories with Matrix Analysis, according to frequency. The 10 highest frequency (cutoff is 11 out of a maximum possible of 104) categories were as follows: qi deficiency, Blood deficiency, yin deficiency, qi stagnation excess, Dampness excess, Heat excess, Yang rising excess, Phlegm excess, qi and Blood Stagnation channel imbalance, and Damp Bi syndrome channel imbalance. Please refer to Appendix Table 1 for descriptions and Table 2 for frequencies. Total number of subjects exceeds N=104 due to the possibility of multiple TCM diagnoses per person: these categories are not mutually exclusive.

Each participant's differential diagnosis was then categorized as to whether there was a single type of pathology (e.g., only deficiency, or only excess, or only channel imbalance no combination of the categories) or two co-occurring differential diagnoses categories (e.g., combination of excess and deficiency, or excess and channel issues, or deficiency and channel issues; or all three, with excess and deficiency and channel issues all co-occurring). These co-occurrences of diagnosis categories at baseline are noted in Table 3.

Matrix Analysis at Baseline

Single TCM differential diagnosis

Twelve individuals had a single category of differential diagnosis. Of the participants with a single category of diagnosis, *qi* deficiency was the most common (five instances), followed by *yin* deficiency, Yang rising, Damp *Bi* syndrome, *yang* deficiency, Blood deficiency, *qi* stagnation, and channel *qi* stagnation (one instance each).

Dual TCM differential diagnoses

Forty participants presented with a combined diagnosis of excess and deficiency differential diagnosis. The most frequent differential diagnosis combination was qi deficiency and qi stagnation (n=12 cases), followed by qi and yin deficiency with qi stagnation (n=3 cases), qi deficiency with Dampness and Heat (2 cases), Dampness and Cold (2 cases), Dampness and Heat (2 cases), qi and Blood deficiency with qi stagnation, Dampness and Heat (2 cases), qi, Blood, and yin deficiency with qi stagnation and Yang rising (2 cases).

TABLE 3. CO-OCCURRENCE OF DIFFERENTIAL DIAGNOSES AT BASELINE

Category	Ν
Only one category (e.g., excess or deficiency or channel)	12
Two categories: excess+deficiency	40
Three categories: excess+deficiency+channel	24
Two categories: deficiency+channel	16
or excess+channel (not excess and deficiency)	
Data missing	12
Total	104

Fourteen (14) other combinations were each seen in one case only. One case could not be summarized in the table.

Sixteen participants presented with mixed excess and channel imbalances or deficiency concurrent with channel imbalances. Of these, six were diagnosed with excess and channel imbalances and each person's were unique (e.g., phlegm/dampness obstructing the lungs and stagnation in the channels and LV *qi* stagnation). Ten participants were diagnosed with deficiency concurrent with channel imbalances, and each person's differential diagnosis combination was unique as well (e.g., SP *qi* deficiency, *Bi* syndrome).

Triple TCM differential diagnoses

Twenty-four participants presented with differential diagnoses at baseline categorized by co-occurring excess and deficiency and channel imbalance. These participants were the most complex in their differential diagnoses, with multiple co-occurring categories of disharmony.

Matrix Analysis at 6 Months

Differential diagnoses were evaluated at 6 months and classified according to excess, deficiency, and channel problems. Baseline and 6 months' differential diagnoses were compared (please refer to Table 4). A within-person analysis was also performed, 25 participants' diagnoses changed from one category to another (e.g., two co-occurring categories of excess and deficiency at baseline and one category only at 6 months), 51 participants' category was the same at baseline and at 6 months, and 28 participants could not be categorized due to missing data.

Discussion

The results of the matrix analyses indicate that the clinical presentation of people GWI can be characterized by a broad constellation of TCM differential diagnoses or Chinese Medicine patterns. GWI presents in participants of this study with a combination of excess and deficiency patterns both at baseline (38% of the sample) and at 6 months (35% of the sample). The next most frequent category was that of three co-occurring differential diagnoses (excess, deficiency, and channel imbalances all co-occurring), which was the next most frequent category both at baseline (23%) and 6 months (15%).

Regarding the single category of diagnosis

Qi deficiency was the most frequent type of deficiency, and this can progress to include concurrent *yin* or Blood

deficiency. Chronic stress and/or environmental exposures may lead to Yang rising, Dampness, or qi stagnation. These are plausible differential diagnoses in fatigue, cognitive, and mood disorders and musculoskeletal pain.

Regarding two categories of diagnosis

Qi deficiency and qi stagnation co-occur frequently, and this is commonly seen in clinic. Qi deficiency can lead to qistagnation and the formation of Dampness and generation of internal Heat and Phlegm. *Yang* can become unrooted without the *yin* and Blood to anchor it, and this leads to Yang rising (the authors see that it co-occurs with qi and Blood deficiency and *yin* deficiency).

Regarding three categories of diagnosis with co-occurring excess, deficiency, and channel imbalances, the authors observed TCM patterns described by TCM theory that are also common in practice. Clinically, the authors would interpret long-standing qi deficiency and qi stagnation to engender Dampness, Phlegm, internal Heat, and eventually qi/Blood stagnation in the channels and Damp Bi syndrome. In this study, participants exhibited a superficial excess condition, with underlying deficient symptoms, which leads to symptoms within the channels of pain (qi and blood stagnation and damp-Bi syndrome).

It is interesting to note that participants in the biweekly acupuncture treatment group demonstrated clinically and statistically significant improvement in SF-36 Physical and McGill Pain scores,⁴ and yet the overall trend seen in the present study is stability in differential diagnoses. While this finding may be counterintuitive from a biomedical point of view, it may be understood from the view of TCM theory. TCM diagnostic strategy allows for the description of the state of health of multiple systems in the body simultaneously. This holism can be described with the metaphor of root (constitutional disharmony) and branch (acute or emergent disharmony). The concept of a constitutional disharmony is not a concept shared with biomedicine. Yet, it is certainly intuitive in a biomedical context to consider that some people have weak digestion from a young age or a susceptibility to colds and asthma. It is plausible in this sample that the differential diagnoses were reflecting root presentations, meaning very stable individual constitutions. This root can be compared to branch diagnoses, which are reflective of emergent or acute conditions. For this reason, it is plausible that while participants' symptoms improved, their differential diagnoses were rather stable, as these reflected root constitutions and not acute or emergent branch symptoms. This same finding, of clinical improvement tracking with

TABLE 4. BASELINE AND 6-MONTH DIFFERENTIAL DIAGNOSES

Category	Baseline frequency, N (%)	6-Month frequency, N (%)	Descriptive changes
Only one category (e.g., excess or deficiency or channel)	12 (12)	15 (14)	Slight increase
Excess+deficiency	40 (38)	36 (35)	Slight decrease
Excess+deficiency+channel	24 (23)	16 (15)	Decrease
Deficiency+channel	10 (10)	4 (4)	Decrease
Excess+channel	6 (6)	5 (5)	Slight decrease
Data missing	12 (11)	28 (27)	Increase
Total	104	104	

branch, but not root diagnosis, has been found in other studies of Asian Medicine treatments.¹⁰

Limitations of this study include the small sample size, particularly given that there are 28 cases of missing data at 6 months. It is important to note that not all participants with missing data dropped out of the study. Missing data made it impossible to categorize 28 participants' differential diagnoses at 6 months. In addition, while the parent study was adequately powered to detect clinically and statistically significant change in primary and secondary outcomes, the analyses in this study demonstrated very small N in several classification categories. Due to the sample size, the matrix analysis needs to be replicated with a larger GWI acupuncture study to further validate the differential diagnosis co-occurrences for GWI. Another potential limitation of this study is that the authors have not organized their sample according to more detail regarding symptoms, pulse, and tongue characteristics. This would lend additional levels of detail that might help us better discover who best responded to acupuncture in the trial and who might be more likely to transition from, say, three or two to one type of differential diagnosis (possibly indicating a lessening in complexity of clinical presentation with fewer differential diagnoses). Finally, an important limitation to this work is that stability of TCM differential diagnoses cannot be verified across TCM practitioners. Meaning that if a patient was seen by two TCM practitioners, they may receive differential diagnoses that do not align. The present work aims to characterize patterns of excess, deficiency, and channel imbalances and does not aim to confirm or refute validity of differential diagnoses across TCM practitioners.

Since GWI is a recently defined illness and treatment with acupuncture has only initially been evaluated (their parent study), the development of a TCM treatment manual is warranted. The treatment manual could utilize the differential diagnosis framework developed in this study (deficiency, excess, channel concerns) as a basis for symptom presentations that are most likely to occur in patients with GWI. A theoretical TCM pathologic foundation could also be explored as to the causes of *qi*, *yin*, *yang*, and blood deficiency or excess in GWI patients.

Future research with this matrix analysis technique could help explain common symptom clusters seen across different complex medical illnesses. For example, patients with GWI and fibromyalgia often present similar symptom clusters (chronic fatigue, pain, anxiety, and depression). The rich diagnostic framework of TCM theory—and all of traditional East Asian medicine theory and the myriad of approaches that encompasses—presents novel patient classification into subgroups, which may respond differentially to variations in treatment. The present analysis aims to support a beginning discussion with TCM and biomedical scientists toward a fully integrated science of Integrative Evidence Based Practice, one that theoretically supports the participating disciplines to harness the healing potential available to all patients.

Acknowledgments

This work was supported, in part, by the Office of the Assistant Secretary of Defense for Health Affairs through the GWI Research Program under Award No. W81XWH- 09-2-0064 and W81XWH-14-1-0533. Opinions, interpretations, conclusions, and recommendations are those of the author and are not necessarily endorsed by the Department of Defense. This work was also supported, in part, by NIH National Library of Medicine (NLM) Training Program in Biomedical and Health Informatics at the University of Washington, Grant No. T15LM007442.

Authors' Contributions

Conceptualization of study: L.A.C. and L.T.-S. Data coding: J.C., R.S., K.-Y.H., B.A.S., L.A.C., L.T.-S. Data analysis: L.T.-S. and J.C. Article: L.T.-S., J.C., L.A.C., R.S., K.-Y.H., B.A.S.

Author Disclosure Statement

The authors have nothing to disclose.

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(Appendix follows \rightarrow)

Appendix

	Definition	Symptom examples
Deficiency		
Qi	When <i>qi</i> is deficient, or weak, it will not have the energy to provide some or all the basic functions of lifting, warming, transforming, transporting, holding, and defending.	Low energy, shortness of breath, bloating, catch colds easily
Blood	Blood deficiency occurs when food we eat is not transformed into the energy needed to create Blood. Blood deficiency is also created from too much blood loss.	Pale complexion, dizziness, dry skin/hair, palpitations, anxiety, poor memory, weak limbs
Yin	<i>Yin</i> deficiency occurs when the body is too weak and is unable to cool.	Insomnia, flushing, night sweats, irritable
Yang	<i>Yang</i> deficiency is a weakness where the body is unable to warm itself.	Fatigue, cold hands and feet, water retention, sweating easily
Excess		
Dampness	Improper regulation of fluids within the body, which can become stuck or thickened.	Diarrhea, epigastric fullness, swelling, difficult or painful urination
Heat	Also if <i>qi</i> becomes too blocked it can start to form heat.	Irritability, red face, scanty dark urine, emotional disturbances, yellow mucus, sweating
Cold	An internal pathogen that can affect the organs.	Low temperature, pale, profuse urination, loose bowels
Phlegm	If <i>qi</i> doesn't move, it can cause phlegm. If dampness accumulates it can turn to phlegm.	Cough, asthma, nausea
Fire	Caused by a pathogenic invasion of heat in the body.	High fever, red face, constipation, urinary difficulties with dark urine
Yang rising	The body is too deficient to keep this energy subdued and excess heat signs will surface.	Flash anger, headache on one side, tinnitus
Wind	A pathogenic factor can cause wind in the body. Also deficiency of blood can allow wind to flow in the channels.	Twitching, tics, spasms
Qi stagnation	<i>Qi</i> becomes stagnant when it is unable to flow freely.	Depression, mood swings, sighing, sensation of a lump in the throat, ache in muscles
Blood stagnation	Blood stagnation is when the blood is not moving freely and becomes stuck.	Sharp pain, traumatic injury, menstrual pain
Channel pathology		
<i>Qi</i> and blood stagnation	When the <i>Qi</i> and Blood become stagnated within a specific channel or area of a limb.	Pain that is both sharp and aches. Spasmodic pain
Deficiency	When a channel is deficient, <i>qi</i> cannot continuously flow.	Catch colds easily
Eight extraordinary vessels	The eight extraordinary vessels are deeper energetic reservoirs through which <i>qi</i> flows.	 Yang Qiao/Du Mai: psychosis, insomnia, low back pain Yang Wei/Dai Mai: lethargy, pain at sides/ribs Yin Qiao/Ren Mai: unable to be joyful; Neurosis, gynecologic issues Yin Wei/Chong Mai: sad, anxious, overthink
Damp Bi syndrome	Obstruction of <i>qi</i> and Blood in the channels.	Pain in the joints and muscles, swelling