

FATIGUE IN PATIENTS WITH SJÖGREN'S SYNDROME AND INTERVENTION OF TRADITIONAL
HERBAL MEDICINE

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Abstract

Background: Fatigue is the main complaint existing in patients with primary Sjögren's Syndrome (pSS) but rarely addressed. Patients described it as an uncontrollable symptom of lack of energy, which has negative impacts on health related quality of life. To date, many studies have demonstrated that cytokines, depression, sleep and endocrine disturbance interrelated with pSS-related fatigue. However, the pathogenesis remains unclear. With a long history, Traditional Chinese Medicine (TCM) as alternative therapy has become increasingly popular among patients with various kinds of disease, especially in pSS. Based on the unique principle of therapy, practitioners have achieved a satisfactory effect on relieving disease-related symptoms with Chinese Herbal Medicine (CHM).

Materials and Methods: In this article, we succinctly reviewed the highly correlated factors to pSS-related fatigue from the standpoint of western medicine. Then, from TCM perspective, we illustrated that theoretic mechanisms lead to fatigue in patients with pSS.

Results: According to the theory of TCM, we concluded that CHM as complementary and alternative medicines are attractive options to alleviate pSS-related fatigue.

Conclusion: In clinic, physicians should remember to inquire whether their patients are worn out easily. Combination of *Yin*-tonifying and *Qi*-tonifying CHM may be the optimal options to pSS-related fatigue.

Key words: Sjögren's Syndrome, fatigue, Traditional Chinese Medicine, Chinese Herbal Medicine, rheumatic diseases

Abbreviations: Sjögren's Syndrome: SS., primary Sjögren's Syndrome: pSS, Traditional Chinese Medicine: TCM, Chinese Herbal Medicine: CHM, Rheumatoid Arthritis: RA, Interleukin-1:IL-1, Interleukin-6:IL-6, Tumor Necrosis Factor- α :TNF- α , Erythrocyte Sedimentation Rate:ESR, C-reactive Protein:CRP, Immunoglobulins:Ig, Rheumatoid Factor:RF, Visual Analog Scale:VAS, antinuclear antibody:ANA, hypothalamic-pituitary-adrenal:HPA, dehydroepiandrosterone:DHEA, Syndrome Differentiation and Treatment:SDAT, Disease Modifying Antirheumatic Drugs: DMARDs, Radix Rehmanniae Preparata:RRP, Radix Rehmanniae Preparata polysaccharides:RRPP, Total Glucosides Peony:TGP, Hydroxychloroquine:HCQ, Aquaporin-5:AQP-5, Ophiopogon japonicus polysaccharides:OJP.

Introduction

Fatigue is one of common symptoms in series of diseases, such as the various cancers (Stone et al., 2008), rheumatic diseases (Overman et al., 2015) and neurological diseases (Brola et al., 2007). Among patients with rheumatic diseases, including Rheumatoid Arthritis (RA), scleroderma, fibromyalgia, and Sjögren's Syndrome etc., prevalence of fatigue has been reported about 65% (Overman et al., 2015), compared with about 20% to 30% of general population (Loge et al., 1998; van't et al., 2010). Approximately, it ranges from 60% to 70% of patients with pSS suffering from fatigue (Segal et al., 2008; Haldorsen et al., 2011).

It is known that SS, an autoimmune disease, may be alone as primary SS or secondary to other connective tissue diseases. The basis of pathologies is attributed to lymphocytic infiltration leading to exocrine glands dysfunction, especially lachrymal and salivary glands, and severe systemic symptoms involvement.

The main symptoms were showed persistent dryness of mouth and eyes, and extra-glandular symptoms such as arthritis, vasculitis, and pain etc. Previous studies indicated that fatigue was more common and serious in patients with pSS than healthy controls (Barendregt et al.1998; van Leeuwen et al., 2015; Godaert et al., 2002), but as a clinical outcome of pSS, it is often ignored (Chaudhuri et al., 2004; Dupond, 2011).

Some investigators suggest fatigue in pSS is not same as normal notion of tiredness, it is accurately described as fluctuant and ever-present lack of vitality, beyond individual's own control (Mengshoel et al., 2014), reducing health-related quality of life and work ability (Segal et al., 2009; Westhoff et al., 2011). Some patients with pSS usually complained that "little interest or pleasure" or "feeling tired or little energy" when to see their doctor (Westhoff et al., 2011).

Generally speaking, fatigue includes physical and mental aspect. Physical fatigue means the exhaustion of body in failure to sustain the force of muscle and limit activities of daily living. Mental fatigue is a highly subjective feeling (Norheim et al., 2011), and patients obscurely describe it reduces motivation (Chalder et al., 1993).

It is difficult for patients to subdivide different aspects of fatigue, but physical fatigue is more frequent and severe in most patients (Segal et al., 2008; Priori et al., 2010). Therefore, there are variously validated questionnaires to measure it (Norheim et al., 2011).

Some are specially designed for SS, even established based on patients' own description (Bowman et al., 2004; Bowman et al., 2009), and some as non-special measurements for all diseases (Fisk et al.,1994; Smets et al.,1995; Chalder et al.,1993; Bowman et al., 2003). It is worth stressing that, in clinical, single instrument was rarely used to assess fatigue in patients with pSS because that some are more adaptive for physical aspect and some are better for mental aspect. Apparently, prevalence and related factors of fatigue are influenced by tools (Ng et al., 2010; Norheim et al., 2011).

In previous studies, cytokines, pain, depression, endocrine disturbance and susceptibility genes were demonstrated as contributors to fatigue in patients with pSS (Norheim et al., 2014; van Hoogmoed et al., 2010; Pollard et al., 2006; Karageorgas et al., 2015). In addition, side-effect of drugs (Meijer et al.,2010; Norheim et al., 2012), sleep disturbance (Theander et al., 2010) and social circumstance (Ibn Yacoub et al., 2012) also have impact on it. Correlated factors of pSS-related fatigue are multiple; however, pathogenesis is as yet unknown. Thus, available treatment is limited.

TCM as a complementary therapy has obvious effects on relieving symptoms of pSS (Chang et al., 2015; Hu et al., 2014).

On the basis of unique system of diagnosis and principle of therapy, CHM became more and more popular among patients. In TCM, fatigue as a secondary symptom reflects special situations of *Yin-Yang* and *Qi* in body. In this review, we summarized correlated factors in standpoint of western medicine; moreover, we elaborate mechanism of fatigue in pSS based on theory of TCM and identified appropriate treatment with CHM.

Correlation Factors in Western Medicine

Biomarkers

Some biomarkers, such as interleukin-1 (IL-1), Tumor Necrosis Factor- α (TNF- α), interleukin-6 (IL-6), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), immunoglobulins (Ig), anti-SSA/B, antinuclear antibody(ANA), platelets and rheumatoid factor(RF) were proposed interrelationships with fatigue in pSS (Norheim et al., 2012; Bax et al., 2002; Hartkamp et al., 2004; Natasari et al., 2013), although outcomes in different studies measured by different instruments sometimes are conflicting and controversial. In fact, some pro-inflammatory cytokines and immunologic markers are deemed as important in assessing pSS, but it is failure to be identified as high correlation factors of fatigue (Priori et al., 2010; Westhoff et al., 2011; Segal et al., 2008; Barendregt et al., 1998; Tensing et al., 2001).

Roberta's study showed that there was no association between fatigue assessed by Visual Analog Scale (VAS) and anti-SSA/B

Neuroendocrine

In recent years, neuroendocrine system as emerging pathogenesis hypothesis of fatigue has been taken into account (Tensing et al., 2001; Straub et al., 2013). Compared to age-matched health controls, more lower activity of hypothalamic–pituitary–adrenal (HPA) axis and serum concentration of dehydroepiandrosterone sulfate (DHEA-S) in patients with pSS (Johnson et al., 1998; Valtysdottir et al., 2001). André Hartkamp suggests dehydroepiandrosterone (DHEA) may be a potential mediator of fatigue, but their study did not support a superior effect of DHEA on improvement of pSS-related fatigue than placebo (Hartkamp et al., 2008).

Depression

Most studies consistently indicated that depression is the best predictor of pSS-related fatigue (van Leeuwen et al., 2015; Priori et al. 2010), not only mental fatigue but also physical (Segal et al., 2008; Bax et al., 2002).

Studies have shown that patients with pSS have a prevalence of depressive symptoms, and depression was regarded as a dominant factor of emotional well-being (Segal et al.,2009), which has a high correlation with fatigue (Valtysdottir et al., 2000; Kotsis et al., 2014; Segal et al., 2012). In addition, poor cognition of illness as one psychological factor is associated with fatigue (van Leeuwen et al., 2015).

pSS with a strong female propensity is most common in the fourth and fifth decade of life (Patel et al., 2014), and the female patients were reported little understanding of their illness (Kotsis et al., 2014).

Hence, customizing cognitive-behavioral interventions of disease may be a possibility of therapeutic option of fatigue (Hartkamp et al., 2008; van Leeuwen et al., 2015). In fact, fatigue is not attributed to depression because that it is common in patients with severe fatigue but no depression (Segal et al., 2008).

Namely, depression only partly accounts for it. Wan-Fai Ng and colleagues supposed that the concurrence of depression and fatigue does not signify a causal link. There may be a potentially similar pathogenesis of them (Ng et al., 2010), although this hypothesis remains unsubstantiated.

Depression is an independent contributor to fatigue, and the strong relevance suggests that psychological intervention may be a possibility in clinical practice (Westhoff et al., 2011; Karageorgas et al., 2015; Segal et al., 2012; Bax et al., 2002).

Mechanism in TCM

TCM as an empirical medicine abide by cumulative experiences recorded in historical textbooks by predecessors. It focused on the individualized plan of therapy, which is different from Western medicine coming from evidence-based medicine. Theory of TCM represents one conception of philosophy in ancient China. It is based on principle of Syndrome Differentiation and Treatment (SDAT) across the process of diagnosing and therapy (Johnson et al., 1998).

TCM pays attention to diagnoses adhering to clinical symptoms of patients, which is a mirror of disease and physical condition. From the perspective of TCM, normal activities of human body are result of balance of *Yin* and *Yang*, by contrary, imbalance of *Yin* and *Yang* is the fundamental element leading to diseases. *Qi* is defined as the most basic substance constituting body and maintaining the activities and metabolism of human body (World Health Organization Pacific region, 2007)

Oppositely, deficiency of healthy *Qi* certainly causes diseases (World Health Organization Pacific region, 2007). According to theory of TCM, fatigue as a symptom in pSS represents condition of *Yin-Yang* and *Qi* of internal body. In this review, we ascribed fatigue to *Qi* deficiency and imbalance between *Yin* and *Yang*.

***Qi* Deficiency**

Qi refers to the abilities of self-regulation, adaptation to environment, resistance against pathogens and self-recovery from illness to maintain healthy body (World Health Organization Pacific region, 2007).

Qi deficiency is marked by a series of symptoms of weakness, lassitude, listlessness and debilitation which aggravates after activities (World Health Organization Pacific region, 2007). It often emerges in the late stage of the course of a disease or in the chronic diseases because of weak constitution and decreased body resistance (Hsu et al., 2012).

According to this definition, fatigue is one of the external manifestations that come from *Qi* deficiency. This interpretation with TCM is similar to explanation of fatigue in Western medicine. Owing to long-term immune-inflammatory impairment, patients with fatigue in pSS always complained difficulty in sustaining voluntary activity or hardly to initiate activities (Chaudhuri et al., 2004). Fatigue is described as ever-present uncontrollable lack of energy or that spirit is willing but the body is not (Chaudhuri et al., 2004; Mengshoel et al., 2014).

As Jean-Louis said, the feeling in patients is that “I don’t feel like doing anything” or “I want to but I can’t” (Dupond, 2011). Therefore, *Qi* deficiency is one of fundamental factors, which cause fatigue appearing in patients with pSS.

Imbalance between *Yin* and *Yang*

Yin and *Yang* are the general descriptive terms for the two opposite, complementary and interrelated cosmic forces in everything on the basis of Chinese philosophy (World Health Organization Pacific region, 2007). *Yin* is characterized by cold, dark and wetness and *Yang* is characterized by warmth, light and dryness (World Health Organization Pacific region, 2007).

The body fluid such as sweat, tears, saliva, snivel, belongs to *Yin*. *Yin* deficiency is a pathological change marked by diminished moistening in the body (World Health Organization Pacific region, 2007).

Patients with pSS expressed excessive dryness not only in mouth and eyes but also in the skin as xeroderma, and most women have experienced vaginal dryness which is not specifically addressed (Catanzaro et al., 2014).

All of the dryness symptoms are attributed to insufficiency of body fluid. Lack of tears, saliva and other secretions are signs of exocrine gland dysfunction due to lymphocytic infiltration in Western medicine, while it symbolizes *Yin* deficiency based on theory of TCM. In many studies, *Yin* deficiency has been supported as the main pathogenesis of pSS (Zhang, 2011).

Therefore, *Qi* deficiency and *Yin* deficiency coexist in patients with pSS accompanied by fatigue. The deficient state causes imbalance between *Yin* and *Yang* that is defined as the origin of diseases. Obviously, imbalance of *Yin* and *Yang* in body is the source of pSS and subsequent symptoms of extra-glands such as fatigue.

Intervention with CHM

In Western medicine practices, improvement of pSS-related fatigue was rarely addressed in therapy. Some biologic therapies or Disease Modifying Anti-rheumatic Drugs (DMARDs) for pSS were proven to have potential benefit on alleviating fatigue (Meijer et al., 2010; Carubbi et al., 2013; Dass et al., 2008). For instance, Rituximab, anti-CD20 monoclonal antibody targets to malignant B cells in patients with Non-Hodgkin lymphomas (Zappasodi et al., 2015), has been demonstrated more effective than placebo on alleviation pSS-related fatigue. However, the utilizations of B-cell blockade for pSS and related symptoms in patients remain generally controversial (van Woerkom et al., 2007; Dass et al., 2008). Additionally, non-pharmacological therapeutic approaches such as saliva and tear substitute, acupuncture and punctum plugs were without adequate evidences to pSS-related fatigue (Hackett et al., 2015). Therefore, intervention of CHM was required in clinic. TCM is widely used in conjunction with Western medicine for patients with pSS in many Asian countries (Yu et al., 2014; Luo et al., 2012). CHM is provided as an alternative approach for patients to alleviate symptoms, improve function of exocrine glands and reduce adverse effects of DMARDs (Chang et al., 2015; Hu et al., 2014). According to TCM theory, intervention with CHM in prescriptions aimed at tonification of *Yin* and *Qi* (Chang et al., 2015; Hu et al., 2014; Wu et al., 2013; Wang et al., 2010). *Yin* deficiency and *Qi* deficiency are the basal mechanisms of fatigue, and

tonifying CHM cope with. Some tonifying CHM have been confirmed effect on anti-inflammatory and immune modulation (Wu et al., 2013; Tan et al., 2012; Wang et al., 2007). Because of the percentage of compositions in each formula based on the symptoms of individual and dosage adjusted frequently, is hardly to be identified accurately active compounds purified from CHM (Seger et al., 2007, Kim et al., 2010), therefore, well-designed randomized controlled trials remain required (Luo et al., 2012). We focus on recent advances of *Yin*-tonifying CHM and *Qi*-tonifying CHM applied to relieve pSS-related fatigue in standpoint of TCM.

Yin-tonifying CHM

Radix Rehmanniae Preparata (RRP) is derived from root of *Rehmannia glutinosa*. It is widely accepted as health food, also used as one of *Yin*-nourishing CHM in conjunction with others in formulas, such as “*Qi Ju Di Huang Wan*” and “*Liu Wei Di Huang Wan*”. They can be used for improving *Yin* deficiency not only in patients with pSS but also in other diseases (Hartkamp et al., 2008, Zheng et al., 2011). Some studies have demonstrated that polysaccharides extracted from RRP may be the active compounds responsible for the effect of anti-anxiety and anti-fatigue (Cui et al., 2013; Tan et al., 2012). Anti-fatigue activity of Radix Rehmanniae Preparata polysaccharides (RRPP) has been demonstrated by Wei Tan and colleagues with animals, that RRPP cannot only accelerate the elimination of fatigue but also improve athletic abilities (Tan et al., 2012). RRPP with effect on excessive exercise consumption, a physical fatigue, represents tonifying function of CHM. These evidences may provide potential fundamentals of RRP to be utilized for pSS-related fatigue through regulating *Yin* deficiency. RRPP has also been demonstrated effect on resisting anxiety in rats, which may be related to inhibiting down-regulation of synuclein and peroxiredoxins in hippocampus (Cui et al., 2013). It may provide a novel intervention of fatigue with RRP through influencing psychological factor to alleviate pSS-related fatigue.

Paeonia Lactiflora

Pallas is a nourishing *Yin* Chinese herb frequently used in prescriptions. It is used either alone or combined with other herbs to treat patients with pSS (Zheng et al., 2011; Chang et al., 2015). Total Glucosides Peony (TGP) is the major active component extracted from Radix Paeoniae, and it is the most common extractive of CHM without evident side-effect for rheumatic disorders (Zhang et al., 2012; Chen et al., 2013). Some pharmacological studies have shown that TGP play an important role in anti-inflammatory, analgesic and immune-modulatory (Zhang et al., 2012). Both *in vitro* and *in vivo* studies support that TGP significantly inhibits productions of pro-inflammatory cytokines or inflammatory cell infiltration. It might also be a similar effectiveness as Hydroxychloroquine (HCQ) to delay the onset of pSS (Li et al., 2013). In addition, TGP protecting exocrine gland cells may be through up-regulating expression of Aquaporin-5(AQP-5), a water transport protein in cell membrane of glands (Wu et al., 2015). This evidence may suggest TGP balance the relationship between *Yin* and *Yang*.

Ophiopogon Japonicas

It is one kind of nourishing *Yin* Chinese herb has been widely used in pSS with a great satisfaction. *Ophiopogon japonicus* Polysaccharides (OJP) is the herbal extract isolated from the root of *Ophiopogon Japonicas* has been shown to possess remarkable effect on anti-inflammatory (Wu et al., 2014).

Yue Wang and colleagues have showed that OJP can increase salivary flow (Wang et al., 2007). Just as the theory of TCM, *Yin*-nourishing herbs are with function of promoting production of fluid in body and improving *Yin* deficiency. Famous Chinese herbal formula, “*Zeng Ye* decoction” has the ability of increasing fluid in body, in which *Ophiopogon japonicas* is the most significant composition. Study by Yong Yang have indicated that “*Zeng Ye* decoction” can up-regulate the expression levels of AQP-5 and AQP-1 and prevent pSS (Wu et al., 2014).

Obviously, *Yin*-nourishing herbs can “moisturize dryness” via increasing grand fluid (Wang et al., 2007).

Qi-tonifying CHM

Astragalus

Astragalus as a popular *Qi*-tonifying herb is derived from the root of Leguminosae plant astragalus membranaceus. It contains more than 60 components, and its effect of anti-inflammatory has been reported in many conditions (Nalbantsoy et al., 2012). Additionally, astragalus can work for fatigue and increase exercise performance (Yeh et al., 2014). Some investigators deemed astragalus as a specific nutrition for alleviating fatigue, because that energy source depletion can cause fatigue and exogenous nutrition supplement can ease it (Yeh et al., 2014). The effect of astragalus on anti-fatigue resembles part of function of *Qi*-tonifying herbs in TCM. Astragalus plays a critical role in traditional formulas used to treat diseases caused by *Qi* deficiency (Seki et al., 2005). “*Bu Zhong Yi Qi* pill” as a *Qi*-tonifying formula, in which astragalus polysaccharides account for 27.8 percent of all components, have been demonstrated improving chemotherapy-induced fatigue through reducing the serum levels of TNF- α potentially (Ouyang et al., 2014). Hence, astragalus may be an optimal option to alleviate fatigue in patients with pSS.

Conclusion

Fatigue in patients with pSS was deemed as unexplained symptom in Western medicine, and often ignored. The correlated factors are multi-factorial, and pathogenesis is unclear. Therefore, there is a necessity to develop a more appropriate method. TCM draws increasing attention worldwide, and it has been playing a significant role in alleviating pSS-related symptoms such as fatigue. It balances the *Yin* and *Yang* in body and relieves symptoms by CHM, but the accurate evidences remain a challenge to convey by modern medicine. So more powered randomized controlled trials to prove the efficacy of TCM are required. Combination of *Yin*-tonifying and *Qi*-tonifying CHM may be the optimal options to fatigue. At last, physicians in clinic practice should remember to inquire whether their patients are worn out easily.

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