Introduction

Chronic fatigue syndrome (CFS) is the most severe condition among fatigue-associated disease, which impairs seriously quality of life (QOL) in aspects of physical, mental, and occupational wellbeing. This disease is characterized by profound fatigue persisting over six months, and other symptoms such as cognitive dysfunction, sleep disturbance and multiple pain. CFS thus often leads social isolation, and is related with high risk of suicide by seven fold.

The prevalence of CFS is reported as approximately 1% in general population worldwide including in Korea. The proposed pathological mechanisms include abnormalities in autonomic nervous system function, immunological response or hypothalamic-pituitary-adrenal (HPA) axis against stress. However, its etiology is not understood yet, and no medications or therapeutics have been approved to date. Although a large-scale clinical study (called the PACE trial) recommended...
cognitive behavioural therapy (CBT) and a graded exercise therapy (GET), they were abandoned or revised due to serious criticism by both scientists and patients\(^\text{10}\).

Meanwhile, there is concerning that many health care providers are not aware of CFS, which may misunderstand the disease or lack knowledge about how to diagnose and treat it\(^\text{11}\). Moreover, patients with CFS are often dealt with a psychological problem or misdiagnosed as depression\(^\text{12}\). Above conflict facts between patients and clinicians have been an important medical issue and then USA government started to drive new policy via a report of Institute of Medicine (IOM)\(^\text{13}\).

Korean medicine (KM) has been traditionally superior to care the fatigue-related disorders. This minireview aims to present the novel information for CFS, especially regarding the recent changes in medical policy on CFS, and new diagnosis criteria.

**Methods**

1. **Data collection**

   In order to collect data on CFS, a literature search was conducted using PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and government-derived reports from Google database in its entirety from January 2011 to February 2019. This search was performed using combinations of the following keywords: “Chronic fatigue syndrome”, “Myalgic encephalomyelitis” and “Fibromyalgia”, respectively. In particular, article type included “Review”, “News”, “Guideline” and “Consensus Development Conference”.

2. **Data analysis**

   150 articles at initial screen, twenty-one papers were finally selected, which contained any important facts in aspect of medical policy, achievements and new diagnosis criteria for CFS. Authors have reviewed carefully the contents, and summarized that information.

**Results and Discussion**

1. **Government-derived new policy for research on CFS**

   In spite of serious medical demands and complains from the patient-side, most of countries and their medical providers had paid little attention to patients suffering from CFS for several decades\(^\text{14}\). Doctors often told that people with CFS were caused by neuroses and depression, but a small fraction of clinicians listened closely to patients and thought it real body’ problem, not from just in their minds. Moreover those facts bring to the issues related to over- or under diagnosis of CFS\(^\text{15}\).

   For many years, patients and scientists have complained the ignorance by the nation's major medical research funder. The remarkably little research funding has been made available to study the etiology, pathophysiology, and effective treatment of this disease. NIH’s new direction on CFS was started by an Institute of Medicine report 2015 in US. In 2016, National Institutes of Health (NIH) of US directed about $7.6 million to research on CFS, and then doubled it as $15 million in 2017\(^\text{16}\). NIH organized a Working Group consisted of 23 NIH institutes, and support four collaborative researches to explore the biological mechanisms underlying CFS, and diagnosis and therapy using microbial agents, genetic analyses and metabolites change, immune system and microbiome, respectively\(^\text{17}\).

   In order to establish the sustainable integrated
network of researchers in Europe, European Network on ME/CFS (EUROMENE) was developed in 2016. This EUROMENE aims to assess current knowledge and deliver information on the burden of CFS in Europe, potential biomarkers, clinical diagnosis and management, and potential treatments to care providers, and patients\(^\text{18}\). Inside EU countries, UK started early to pay medical attention and research on CFS. In 2008 UK developed the CFS/ME Expert Group to enhance the new high-quality research for CFS/ME, and made available up to £1.5 million for new research into the mechanisms of CFS/ME in 2011\(^\text{19}\).

2. Changes of diagnostic criteria

In 1955, 192 hospital staffs had affected an illness complaining muscular and neurological symptoms, including ease of fatigability in the UK, called as Royal Free Hospital outbreak\(^\text{20}\). The characteristic of this disease involving the muscular, brain and CNS symptom made the term ‘myalgic encephalomyelitis (ME)’, which is named with CFS. Although much of the debate about the nature of symptoms, causes and biological processes exist, at present this illness is commonly referred to as CFS, ME or conflated to ME/CFS.

So far, there are many case definitions or diagnostic criteria for CFS according to study groups. Dr Melvin Ramsay had reported the definition criteria for ME in 1986, as form of focusing on the muscular and neurological symptoms, but de-emphasizing fatigue\(^\text{21}\). US Centers for Disease Control and Prevention (CDC) introduced CFS as a clinical entity in 1988 (called as Holmes definition\(^\text{22}\)), and redefined it in 1994 (called as Fukuda definition\(^\text{23}\)). These two definitions emphasized the persistent or relapsing, debilitating fatigue not substantially alleviated by rest. In 2003, the Canadian Consensus Criteria (CCC) for ME/CFS was developed for use in clinical practice, which emphasized the importance of symptoms including post-exertional malaise (PEM), pain, sleep disturbances, and cognitive dysfunction beside fatigue\(^\text{24}\). Based on CCC, an international consensus panel developed the International Consensus Criteria (ICC-ME) in 2011, defining ME as an acquired neurological disease with complex global dysfunctions\(^\text{25}\).

In 2015, US government established a consortium consisting of Department of Health and Human Services (HHS), the National Institutes of Health, the Agency for Healthcare Research and Quality, the Centers for Disease Control and Prevention, the Food and Drug Administration, and the Social Security Administration, and then asked IOM to examine the evidence base for ME/CFS and to redefine this illness\(^\text{26}\). IOM-derived committee published a report titled “Beyond Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome: Redefining an Illness”, which presents new diagnostic criteria for ME/CFS. The diagnostic criteria focused on the central symptoms, which compos is of three mandatory symptoms (a substantial impairment in activities that persists for more than 6 months and is accompanied by fatigue, PEM and unrefreshing sleep) and one optional symptom among cognitive impairment or orthostatic intolerance\(^\text{27}\). The features of diagnostic criteria mentioned above are summarized in Table 1. Based upon these criteria, IOM also provided a diagnostic algorism for ME/CFS (Fig. 1)\(^\text{28}\).

3. New naming and perspectives for CFS

IOM committee recommended a new name, systemic exertion intolerance disease (SEID)
instead of ME/CFS. The word “fatigue” is a common symptom that presented from general patients with any disease or disorders, and moreover experienced by most of populations without any illness\(^{29}\). The term ME indicates the brain inflammation in patients suffering from ME/CFS, which supported by clinical observation\(^{30}\). IOM however thought that the term ME is inappropriate because encephalomyelitis (brain inflammation) has a lack of evidence and myalgia (muscle pain) is not a core symptom in ME/CFS patients. SEID may capture a central characteristic of the disease: any kind of exertion (physical, cognitive, or emotional) can adversely affect patients in many organ systems and in many aspects of their lives\(^{31}\).

Of course, some scientists disagree with that ME and CFS are identical and SEID is appropriate to replace the usage of ME. There are still many uncertainty and arguments regarding the etiology and diagnosis of ME/CFS\(^{32}\). However one consensus is that ME/CFS is a serious, chronic, complex, multisystem disease that dramatically limits the activities of patients, worldwide. CFS is now considered as a not psychiatric or psychological, but central neurological real illness\(^{33}\). Many groups have tried to explore the cause and objective diagnostic biomarkers for CFS as well as to develop therapeutics. These endeavors then will resolve the impasse for CFS in the future.

On the other hand, the fundamental logic of “multiple compounds and multiple targets” of herbal remedies may be a suitable strategy for CFS treatment. Recent studies demonstrated the potentials of the medicinal herbs or other KM-based interventions in management of CFS\(^{34-36}\). In general, symptom differentiation is a key component of KM-based diagnosis and treatment. One group proposed the usefulness of symptom differentiation strategy to treat this illness using herbal drugs, such as *Cistanches Herba* and *Schisandrae Fructus* for CFS patients with *Yang* deficiency\(^{37}\). A systematic review also reported the possibility of acupuncture or moxibustion as a potential treatment for CFS\(^{38}\). Another clinical trial showed a beneficial effect of a combination therapy with herbal formula, called as Lixujieyu recipe, and five elements music therapy for patients with CFS identified as liver stagnation and spleen deficiency (肝鬱脾虛)\(^{39}\). These results may indicate the linkage of KM and CFS, as a common aspect likely systematic strategy of KM and systemic -complex disease of CFS.

Both clinicians and scientists in the field of KM should participate in the strong demands of researches and developments to combat CFS worldwide.
Recently, the changed perception for CFS made the developed countries to drive new medical policy and the new diagnosis criteria. This study presented the changes in CFS-related core information. This review would be helpful for KM-derived researches or therapeutics development for CFS.

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