

Review Article

Minireview for Chronic Fatigue Syndrome and its Medical Attention recently

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Objectives: Chronic fatigue syndrome (CFS) is a debilitating illness impairing seriously quality of life, while CFS would be an optimized target disorder of Korean medicine. This study aims to present the recent information especially in aspect of medical policy and new diagnosis criteria for CFS.

Methods: The literature survey was conducted using the terms of “chronic fatigue syndrome”, “myalgic encephalomyelitis” and “fibromyalgia” in PubMed database and Google database in its entirety from January 2011 to February 2019. The in-depth review was made focusing on the changes in policy and medical perspective for CFS.

Results: Recently large medical attentions and researches for CFS have been existed worldwide. By supporting of USA government, IOM made a report which led to a turning point in clinical practices and research in 2015. This report recommended a new name of CFS to systemic exertion intolerance disease (SEID), and new diagnostic criteria focusing on post-exertional malaise, unrefreshing sleep, cognitive impairment and orthostatic intolerance. The medical perspective also was changed into “a serious, chronic, complex, systemic disease” from a psychological-like disorder, and then UAS and EU governments sharply increased the research grants.

Conclusions: This study provided practitioners in Korean medicine (KM) a core information about the recent changes in CFS-related perspectives. This review would be helpful for KM-derived researches or therapeutics development for CFS.

Key Words : Chronic fatigue syndrome, systemic exertion intolerance disease, myalgic encephalomyelitis

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 wellbeing¹⁾. This disease is characterized by profound fatigue persisting over six months, and other symptoms such as cognitive dysfunction, sleep disturbance and multiple pain²⁾. CFS thus often leads social isolation, and is related with high

risk of suicide by seven fold³⁾.

The prevalence of CFS is reported as approximately 1% in general population worldwide including in Korea^{4,5)}. The proposed pathological mechanisms include abnormalities in autonomic nervous system function, immunological response or hypothalamic-pituitary-adrenal (HPA) axis against stress⁶⁻⁸⁾. However, its etiology is not understood yet, and no medications or therapeutics have been approved to date⁹⁾. Although a large-scale clinical study (called the PACE trial) recommended

• Received : 7 March 2019

• Revised : 14 May 2019

• Accepted : 16 May 2019

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cognitive behavioural therapy (CBT) and a graded exercise therapy (GET), they were abandoned or revised due to serious criticism by both scientists and patients¹⁰.

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 it¹¹. Moreover, patients with CFS are often dealt with a psychological problem or misdiagnosed as depression¹². 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)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 decades¹⁴. 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 CFS¹⁵.

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 2017¹⁶. 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, respectively¹⁷.

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 patients¹⁸. 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 2011¹⁹.

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 outbreak²⁰. 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 fatigue²¹. US Centers for Disease Control and Prevention (CDC) introduced CFS as a clinical entity in 1988 (called as Holmes definition²²), and redefined it in 1994 (called as Fukuda definition²³). 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 fatigue²⁴. 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 dysfunctions²⁵.

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 illness²⁶. 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 composes 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 intolerance²⁷. The features of diagnostic criteria mentioned above are summarized in Table 1. Based upon these criteria, IOM also provided a diagnostic algorithm for ME/CFS (Fig. 1)²⁸.

3. New naming and perspectives for CFS

IOM committee recommended a new name, systemic exertion intolerance disease (SEID)

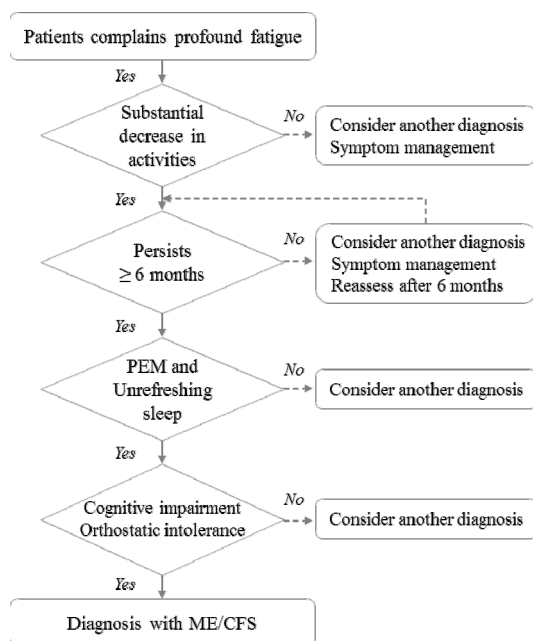


Fig. 1. Diagnostic algorithm for ME/CFS by IOM

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 illness²⁹. The term *ME* indicates the brain inflammation in patients suffering from ME/CFS, which supported by clinical observation³⁰. 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 lives³¹.

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/CFS³². 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 illness³³. 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 CFS³⁴⁻³⁶. 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 CFS³⁸. 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.

Table 1. Summary of changes in diagnostic criteria for CFS

Name (year)	Feature of diagnostic criteria
Ramsay (1986) ²¹⁾	Focusing on the muscular and neurological symptoms, including ease of fatigability and potentially relapsing and remitting course. But fatigue is not a cardinal feature of Ramsay's ME.
Holmes (1988) ²²⁾	To meet criteria for CFS, debilitating fatigue (≥ 6 months) that does not resolve with bed rest. Requiring at least 8 of 11 symptoms (fever or chills, sore throat, lymph node pain, muscle weakness, muscle pain, post-exertional malaise, new headache, migratory arthralgia, neuropsychiatric complaints, sleep disturbance, and a sudden onset of symptoms).
Fukuda (1994) ²³⁾	To meet criteria for CFS, debilitating fatigue (≥ 6 months) that does not resolve with bed rest. Requiring at least 4 of 8 symptoms (prolonged post-exertional malaise, unrefreshing sleep, impaired memory and concentration, muscle pain, joint pain without swelling or redness, headache, sore throat, tender lymph node).
CCC (2003) ²⁴⁾	To meet criteria for ME/CFS, significant degree of physical-mental fatigue, post-exertional malaise, sleep dysfunction, pain in muscles or joints. Two or more neurological/cognitive manifestations and one or more symptoms from two of the categories of autonomic, neuroendocrine, and immune manifestations.
ICC-ME (2011) ²⁵⁾	To meet criteria for ME, post-exertional neuroimmune exhaustion, at least one symptom from three neurological impairment categories (neurocognitive impairments, pain, sleep disturbance), at least one symptom from three immune/gastro-intestinal/genitourinary impairment categories, and at least one symptom from energy metabolism/transport impairments.
IOM (2015) ²⁶⁾	To meet criteria for ME/CFS, debilitating fatigue (≥ 6 months) with a substantial impairment in occupational, educational, social, or personal activities, post-exertional malaise and unrefreshing sleep. One optional symptom among cognitive impairment or orthostatic intolerance.

Conclusion

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.

Acknowledgments

This research was supported by the Ministry of Education, Science and Technology (NRF-2018R1A6A1A03025221).

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