

Research Progress on Epidemiology, Etiology and Pathogenesis of Chronic Fatigue Syndrome

Weijie Zhang, Mingjia Li

Xuzhou Medical University

Abstract: With the acceleration of life rhythm and the increase of work pressure, the incidence of chronic fatigue syndrome (CFS) is increasing, but its etiology and pathogenesis are not yet clear. In recent years, a large number of studies have shown that this disease may be related to viral infection, biological genetics, social psychology and other factors, and has become a hot topic for researchers at home and abroad. At present, the clinical treatment of CFS mainly emphasizes the elimination of incentives and relief of symptoms. Therefore, it is particularly important to grasp the epidemiological characteristics of the disease and clarify its etiology and pathogenesis. In this paper, the pathogenic factors of CFS are expounded, and the pathogenesis of the disease is discussed around neuroendocrine changes, immune system disorders and protein abnormalities, in order to provide a new direction for the diagnosis, treatment and prevention of CFS.

Keywords: chronic fatigue syndrome; epidemiology; pathogenic factor

The clinical symptoms of chronic fatigue syndrome (CFS) mainly include pathological fatigue, poor sleep, general fatigue and autonomic dysfunction, which belongs to one of the clinical chronic diseases^[1]. With the rapid development of modern society and economy, people's quality of life has been significantly improved, which further enhances people's attention to their own health, and correspondingly promotes the change of the spectrum of diseases. The medical model shows a biological psychological social transformation trend, which leads to the corresponding change in the definition of health. CFS was formally proposed by Centers for Disease Control and Prevention (CDC) in 1988. In August 1994, Fukuda et al. of the CDC formulated the corresponding diagnostic criteria for CFS, which was defined as unexplained fatigue for more than 6 months, combined with four or more symptoms of memory or attention decline, cognitive and sleep disorders, muscle and joint pain, sore throat, and lymph node symptoms. The etiological mechanism of CFS is not completely clear, but it is generally believed that it is related to potential factors such as immune disorders and neuroendocrine. In 2018, CFS reappeared in nature, raising people's attention to this disease and restarting the investigation of the disease. It is also hoped that with the

application of modern analytical biology tools, a comprehensive understanding of all CFS related genes, proteins and their infectious factors can be achieved^[2]. Based on this, this paper analyzes the epidemiology of CFS, and studies its etiology and pathogenesis, which is summarized as follows.

1 Epidemiology of CFS

There are many influencing factors on the incidence of CFS, among which the main influencing factors are the definition, investigation methods and economic development of CFS^[3]. The latest study found that the incidence of CFS is about 0.2% - 2.54%, which is more common in middle-aged women. The incidence of women is significantly higher than that of men, and the ratio of male to female incidence is 1:2. A prospective primary care survey in the UK once showed that the incidence of CFS was only 2.6%, and the incidence was only 0.5% after excluding patients with mental illness. According to the investigation on the incidence of CFS in adolescents, the risk of CFS is higher after the combination of acute influenza like symptoms, mononucleosis like disease and other related diseases, and 0.2%-2.3% of children or adolescents suffer from cfs. According to the survey, Europe



spends about 40 billion pounds on the treatment of CFS every year, and only one state in the United States needs to spend about 452 million dollars in medical expenditure and 1.2 billion dollars in productivity loss. CFS is not only widely prevalent in developed countries, but also in developing countries, where more and more patients with unexplained severe fatigue are hospitalized. Several studies have shown that CFS patients not only have severe fatigue but also have mood disorders. According to the epidemiological survey results in the United States, the incidence of fatigue problems that cannot be alleviated is about 14% in men and 20% in women, and about 1/8 of this population will develop CFS. It can be seen that CFS must be paid attention to.

2 Etiology of CFS

Modern medicine has not yet clarified the cause of CFS, but since the concept was put forward, many scientists have invested a lot of energy to study the cause of the disease. At present, the generally recognized causes of CFS include viral infection factors, biogenetic factors, social and psychological factors and other theories. CFS is similar to cold and is related to viral infection, but the impact of cold on human body lasts for a short time, and CFS virus can be latent in human body for a long time, which is difficult to remove, and will damage the human immune system, nervous system, motor system, digestive system, urinary system, etc. CFS has familial genetic factors. If a family has CFS, the next generation will also be affected by genetic factors to produce CFS. In addition, the incidence of CFS has increased in recent years. Considering that it is related to increased social pressure and accelerated pace of life, patients show depression, anxiety or irritability, so scholars focus on social psychology.

2.1 Virus infection factors

Viral infection is one of the main causes of CFS. Clinical studies have found that a group of comprehensive symptoms presented by CFS patients at the time of onset are very similar to viral infection, such as fever, lymphatic swelling and pain, sore throat, muscle soreness, etc. in some patients at the same time. At present, it is believed that a variety of viruses, including Epstein Barr virus (EBV), human herpesvirus 6 and 7, human T-lymphotropic virus type I, parvovirus B-19, cytomegalovirus, may be associated with the onset of CFS. Lerner et al treated 16 CFS patients with high titers of anti EBV viral capsid antigens (VCA) antibody and / or anti early antigen (EA) antibody in the serum for 6 months with acyclovir in the study in 2002, and obtained obvious curative effect, supporting that EBV is the pathogenesis factor of CFS. In 2002, Kerr et al found a total of 5 CFS patients among 51 patients with acute parvovirus B19 infection. From this point, it can be seen that there is a certain correlation between

parvovirus B19 and CFS, and this virus infection may be secondary to CFS. It should be noted that not all CFS patients are related to viral infection, and some patients may be related to other factors. Therefore, when diagnosing and treating CFS, we need to comprehensively consider a variety of factors, including patient history, signs, laboratory tests, etc.

2.2 Psychosocial factors

In the analysis of clinical data of CFS patients, relevant scholars found that family environment, social status and working environment can also affect CFS. The main clinical symptoms of CFS patients are large mood swings and poor sleep, but they do not have significant laboratory evidence of disease, leading some researchers to regard CFS only as a mental disorder. One of the potential etiologies of CFS is psychosocial factors. Viral infection may lead to evasive behavior in patients and further cause cognitive impairment. Some studies believe that the diagnosis of CFS depends on different somatic and pathopsychological symptoms. According to the literature, 30 patients with CFS underwent clinical combined with laboratory examination, and it was found that some patients with CFS had mild memory impairment. Finally, it was concluded that CFS patients presented multi-dimensional cognitive impairment, and the impairment was closely related to low-level physical fitness. Emotional state not only has a certain correlation with the onset of CFS, but also directly affects the course of CFS and the condition. Some scholars compared the mental health status of CFS patients with Qi deficiency syndrome and non Qi deficiency syndrome in the study. The results showed that the scores of obsessive-compulsive symptoms, interpersonal relationships, depression, hostility, paranoia and psychosis of CFS patients with Qi deficiency syndrome were higher than those of non Qi deficiency syndrome patients. It was concluded that fatigue would have a negative impact on physical feelings and psychological status of patients with Qi deficiency syndrome. A large number of nightlife, unreasonable eating habits and daily routine of modern people promote the symptoms of CFS. Therefore, we can intervene from the perspective of social psychology in combination with the etiology of patients in order to alleviate the symptoms of patients.

2.3 Biological genetic factors

Relevant studies have also proposed that CFS may have familial heritability, and the specific mechanism of action may be affected by genetic factors, which in turn enhances the susceptibility to CFS. Some studies have also proposed that the expression of human leukocyte antigen (HLA) class II antigen (hla-dr/dq) in CFS patients is significantly higher than that in normal people. Therefore, it is proposed that the pathogenesis of CFS may also be affected by genetic factors.

The higher incidence of CFS in families suggests the possibility of genetic factors. In addition, there are differences in gene expression in CFS patients, which may be related to the occurrence and development of CFS. Specifically, CFS patients have abnormal gene expression in the immune system, including cellular immunity and humoral immunity. Some scholars investigated CFS patients in the study, and the results showed that 88 genes had expression differences, of which 85 genes were up-regulated and 3 were down regulated. The functions of these 88 genes were classified as immune diseases, infections, blood diseases, etc.

3 Pathogenesis of CFS

CFS has a significant negative impact on almost all areas of patients' daily life, because in CFS, viral infection, psychosocial and biogenetic factors are only a few triggers that lead to the pathogenesis of the syndrome, and further immune system disorders and neuroendocrine changes may be the pathogenesis that leads to the development and persistence of the syndrome.

3.1 Neuroendocrine changes

According to the research of relevant scholars, the antibody content in the blood of people with CFS is positively correlated with their fatigue and muscle weakness. Therefore, these scholars believe that the occurrence of CFS is inseparable from the neuroendocrine system disorder of the patient, and the hormone level and neurotransmitter in the body interact with each other. If the oxycortisone in the plasma, saliva and urine of the patient is lower than the normal level in the unstressed state, it can be considered that the endocrine function of the patient has been in trouble, and this abnormality is likely to be related to the abnormal function of the human hypothalamic pituitary adrenal axis (HPA). Relevant studies have suggested that the proinflammatory cytokines recombinant human interleukin-1 β (IL-1 β), interleukin-6 (IL-6) and tumor necrosis factor - α (tnf- α) are themselves neuroinflammatory effector mediators, which will directly affect the nervous system damage, as well as the occurrence and progression of the disease. In addition, these factors have also been found to be closely related to the onset and symptoms of CFS. Therefore, in the diagnosis and treatment of CFS, it is necessary to comprehensively consider the functional status of the neuroendocrine system and carry out targeted treatment.

3.2 Immune system disorders

Most studies have found that CFS patients have abnormal immune function, mainly manifested in cytokines. At the initial stage, some researchers called CFS "chronic fatigue immune dysfunction syndrome". In continuous research, it has been proposed that this abnormality will also

be affected by researchers and research individuals. Some scholars have proposed that immunoglobulin A (IGA), immunoglobulin G (IM- munoglobulin G, IgG) 、 Immunoglobulin M (IgM) is relatively low, and in the treatment of patients, the effect of immunoglobulin treatment is significant; Some scholars also proposed that the IgG of CFS rats showed an increasing trend, and recently some scholars confirmed this view through experimental research. Ogawa et al conducted a comparative analysis on the natural killer (NK) cell function of CFS patients and normal people. The results showed that the application of L-arginine could significantly improve the NK cell activity of normal people, but it could not improve the NK cell activity of CFS patients. Further, they detected and analyzed the L-arginine metabolic process of CFS patients, and finally proposed that the activation of NK cells induced by L-arginine in CFS patients may be modulated by nitroxide (no), and this modulation function has some defects. In addition, many studies have proposed that the cytokines of CFS patients are abnormal. The main reason is that the increase of cytokines is an important sign of activating immune function. Cytokines themselves may be the intermediary between infection factors and CFS symptoms. When cytokines are applied to treat the disease, muscle and joint soreness, fatigue and fatigue are prone to occur clinically, which is similar to the manifestations of CFS patients.

3.3 Protein abnormalities

CFS patients suffer from long-term fatigue and fatigue, and also suffer from low-grade fever, muscle soreness and other symptoms. However, the etiology cannot be determined. Some scholars conducted comparative analysis on the blood of 60 CFS patients and 30 healthy people, and finally found that there was a special protein of muscarinic acetylcholine receptor M1 (chrn1) antibody in the blood of patients, but it did not exist in the healthy population; In addition, it was also found that the incidence of muscle weakness in CFS patients with chrn1 protein was higher, which was 1.5 times higher than that in patients without chrn1 protein, and the disease aggravated with the increase of chrn1 protein content. In the human body, the main work of acetylcholine in the brain and heart is to transmit neural information. If the human body is healthy, most of the proteins are mainly for acetylcholine reception. However, in CFS patients, due to the influence of chrn1 protein, they will bind these proteins in advance, which will also have adverse effects on the neural information transmission function of acetylcholine. The protein metabolism of CFS patients may be abnormal, which is manifested in the following aspects. ① Abnormal energy metabolism: CFS patients may have abnormal energy metabolism, including glucose metabolism,

fatty acid metabolism and other aspects, which may be related to abnormal mitochondrial function, abnormal HPA axis function and other factors. ② Abnormal immune system: CFS patients may have abnormal immune system, including cellular immunity and humoral immunity, which may be related to abnormal protein metabolism. ③ Proteomic study: there are abnormal expression levels of some proteins in the plasma of CFS patients, such as serum ferritin, transferrin, α 1-acid glycoprotein, etc. and the abnormal expression of these proteins may be related to the occurrence and development of CFS. It should be noted that the above research results are not completely certain, and further research is needed to determine the protein metabolism abnormalities of CFS.

In conclusion, the pathogenesis of CFS involves a wide range of factors, and its pathogenesis also involves multiple systems. At present, there is still a lack of clear diagnostic basis, so there is also a lack of effective therapeutic drugs. Nevertheless, based on the team's previous clinical research on CFS patients, it is believed that with the continuous development and progress of science and technology and medical treatment, the future research on this disease is bound to be more in-depth and make breakthrough progress.

Author Introduction

Weijie Zhang, master, Research direction: chronic fatigue syndrome

Mingjia Li, master, Research direction: epidemiology

Reference:

- [1] Ghosh P ,Niesen J M ,Pawlowski C , et al.Case-control study on post-COVID-19 conditions reveals severe acute infection and chronic pulmonary disease as potential risk factors[J].iScience,2024,27(8):110406-110406.
- [2] Liu T ,Sun W ,Guo S , et al.Research progress on pathogenesis of chronic fatigue syndrome and treatment of traditional Chinese and Western medicine[J].Autonomic Neuroscience: Basic and Clinical,2024,255103198-103198.
- [3] Bourgonje R A ,Hörstke V N ,Fehringer M , et al.Systemic antibody responses against gut microbiota flagellins implicate shared and divergent immune reactivity in Crohn' s disease and chronic fatigue syndrome[J].Microbiome,2024,12(1):141-141.
- [4] Rugerio Z F M ,Zaragoza C M ,Domingo C J , et al.Sleep and circadian rhythm alterations in myalgic encephalomyelitis/chronic fatigue syndrome and post-COVID fatigue syndrome and its association with cardiovascular risk factors: A prospective cohort study[J].Chronobiology international,2024,11-12.
- [5] Hyland E M ,Antonacci Y ,Bacon M A .Comparison of the symptom networks of long-COVID and chronic fatigue syndrome: From modularity to connectionism.[J].Scandinavian journal of psychology,2024.
- [6] Vroegindewij A ,Eijkelkamp N ,Berg D V A S , et al.Lower hair cortisol concentration in adolescent and young adult patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Q-Fever Fatigue Syndrome compared to controls[J].Psychoneuroendocrinology,2024,168107117-107117.
- [7] Xia W ,Wang Y ,Tao M , et al.Effect of Licorice polysaccharides before and after honey-processing on improving chronic fatigue syndrome and its mechanism.[J].International journal of biological macromolecules,2024,276(P2):133968.
- [8] Ljungström M ,Oltra E ,Pardo M .Stress-Related Chronic Fatigue Syndrome: A Case Report with a Positive Response to Alpha-Methyl-P-Tyrosine (AMPT) Treatment[J].International Journal of Molecular Sciences,2024,25(14):7778-7778.
- [9] Azcue N ,Merino T B ,Acera M , et al.Plasma Neurofilament Light Chain: A Potential Biomarker for Neurological Dysfunction in Myalgic Encephalomyelitis / Chronic Fatigue Syndrome[J].Biomedicines,2024,12(7):1539-1539.
- [10] Kuut T ,Buffart L ,Braamse A , et al.Is the effect of cognitive behaviour therapy for chronic fatigue syndrome (ME/CFS) moderated by the presence of comorbid depressive symptoms? A meta-analysis of three treatment delivery formats[J].Journal of Psychosomatic Research,2024,184111850-111850.
- [11] Coffin M J ,Kearney F M .False Alarm: XMRV, Cancer, and Chronic Fatigue Syndrome.[J].Annual review of virology,2024,
- [12] Betsy K ,N. C R ,J. C F , et al.Cardiopulmonary and metabolic responses during a 2-day CPET in myalgic encephalomyelitis/chronic fatigue syndrome: translating reduced oxygen consumption to impairment status to treatment considerations[J].Journal of Translational Medicine,2024,22(1):627.
- [13] Matthias L ,Josef K W .Potential pathophysiological role of the ion channel TRPM3 in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and the therapeutic effect of low-dose naltrexone[J].Journal of Translational Medicine,2024,22(1):630.
- [14] Weigel B ,Fitch E N ,Thapaliya K , et al.Illness presentation and quality of life in myalgic encephalomyelitis/chronic fatigue syndrome and post COVID-19 condition: a pilot Australian cross-sectional study.[J].Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation,2024.
- [15] R. E U ,S. M J L ,E. L W , et al.Myalgic Encephalomyelitis/Chronic Fatigue Syndrome After SARS-CoV-2 Infection[J].JAMA Network Open,2024,7(7):e2423555-e2423555.
- [16] Xiong R ,Fleming E ,Caldwell R , et al.BioMapAI: Artificial Intelligence Multi-Omics Modeling of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.[J].bioRxiv : the preprint server for biology,2024.
- [17] Yang Y ,Sun R Z ,Li R C , et al.Effect of electroacupuncture on expression of protein phosphorylation in hippocampus tissues of rats

- with chronic fatigue syndrome.[J].Zhen ci yan jiu = Acupuncture research,2024,49(6):594-603.
- [18] Ross M S .Mitochondria Dysfunction and Chronic Fatigue Syndrome.[J].Holistic nursing practice,2024,38(4):245-247.
- [19] Liles G E ,Irving A S ,Koppolu P , et al.Classification Accuracy and Description of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome in an Integrated Health Care System, 2006-2017.[J].The Permanente journal,2024,11-12.
- [20] Sjogren P ,Bragée B ,Britton S .Successful Subcutaneous Immunoglobulin Therapy in a Case Series of Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome.[J].Clinical therapeutics,2024.