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Current knowledge about Chronic fatigue syndrome / myalgic encephalomyelitis (CFS/ME) causes – summary

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Abstract

Chronic Fatigue Syndrome (CFE) is a severe and disabling disease whose etiology has not yet been elucidated. This implies the lack of a specific biomarker for the diagnosis of PE, and no causal treatment. There are a number of diagnostic criteria that facilitate the diagnosis of PE, but it is still a diagnosis with exclusion. This chapter reviews the scientific literature systematically, summarizing the available knowledge about the probable etiology of Chronic Fatigue Syndrome. The current topic of the influence of SARS-Cov-2 virus infection on the development of symptoms of IPC was also taken into account in particular. A clear explanation of the etiology of PE is necessary for the further development of scientific knowledge about the Chronic Fatigue Syndrome.

Keywords: chronic fatigue syndrome, myalgic encephalomyelitis, CFS/ME causes, post-infection fatigue, post viral fatigue, post-covid fatigue

1. Introduction

The chronic fatigue syndrome (CFS) / myalgic encephalomyelitis (ME) is a severe and overwhelming disease, possibly involving the central nervous system, characterized primarily by constant, chronic fatigue, characteristically aggravating after undertaking physical or mental exertion and accompanying it with various additional symptoms. The topic of chronic fatigue syndrome is currently very topical, due to the ongoing pandemic of COVID-19 disease, caused by the SARS-Cov-2 virus, one of the complications of which is the development of chronic fatigue. The CFS etiology has not been confirmed yet, which implies difficulties in its diagnosis and treatment. In this publication, we would like to summarize the current scientific reports on the considered possible causes of the development of chronic fatigue syndrome.

2. Material and methods

This publication is based on a review of the scientific literature which was carried out by searching the Google Scholar and PubMed scientific databases. The following keywords were searched for: chronic fatigue syndrome, myalgic encephalomyelitis, CFS/ME causes, post-infection fatigue, post viral fatigue, post-covid fatigue. Based on the found publications, the current knowledge on the etiology and risk factors for the development of chronic fatigue syndrome was summarized.

3. Epidemiology of chronic fatigue syndrome

The occurrence of CFS is not precisely defined. Depending on the diagnostic criteria and the degree of their compliance, various sources indicate the frequency from 0.002% to 1% of the population [10]. We know, however, that due to the lack of an unambiguous definition of this disease and the lack of clear criteria for its diagnosis, the actual number of patients with IA is certainly much greater. The stereotypical image of a patient with PE is a white woman, aged 20-50 years, belonging to the white class, most often educated and ambitious ("yuppie flu") [11]. They suffer from severe chronic fatigue that reduces their quality of life (QOL) for months or years due to lack of specific treatment. CFS brings measurable economic losses to the society and health service [12].

4. The etiology of the chronic fatigue syndrome

The etiology and pathogenesis of chronic fatigue syndrome has not been clarified so far. Therefore, there is currently no specific test or marker that would allow a clear diagnosis of this disease [9, 13].

The high frequency of comorbidities with chronic fatigue syndrome suggests that its pathogenesis must involve the entire system, mechanism or multiple systems that influence each other, such as the cerebral-intestinal axis or the autonomic nervous system [12]. The research highlights the role of the immune system in the CFS pathogenesis [14]. Symptoms of CFS are often preceded by a flu-like viral infection, and infectious mononucleosis is a documented risk factor for the development of CFS [15]. Additionally, patients with CFS

have increased levels of pro-inflammatory cytokines, increased expression of T-lymphocyte activation markers - CD26 and CD38, and a decrease in NK cells [16, 17].

The high frequency of digestive system disorders, such as abdominal pain, changes in the rhythm of bowel movements, nausea, diarrhea or flatulence in those patients [5, 13]. Patients with chronic fatigue are significantly more likely to have a previous diagnosis of irritable bowel syndrome (IBS) in their medical history [18]. The frequent coexistence of chronic fatigue syndrome and irritable bowel syndrome may be associated with an increased level of pro-inflammatory cytokines activating the cerebral-intestinal axis [19]. In patients with diagnosed CFS and irritable bowel syndrome, higher levels of IL-6, IL-8, IL-1 β and TNF- α have been proven [19]. Studies suggest that in patients with chronic fatigue there is a diffuse, low-grade chronic inflammation in the intestinal wall [20], which constantly activates the immune system and enhances the production of pro-inflammatory cytokines. An important link between the immune system and the brain is the hypothalamic-pituitary-adrenal axis [21]. Activation of the immune system and increased levels of pro-inflammatory cytokines, through this axis, increase the release of corticotropin-releasing hormone from the hypothalamus, which activates the hypothalamic-pituitary-adrenal axis, increases the level of stress hormones in the body [21, 22] and in response to the systemic stress response causes dysfunction and intestinal inflammation [20].

One of the postulated etiologies of chronic fatigue syndrome is the previously mentioned high level of pro-inflammatory cytokines and chronic diffuse intestinal inflammation [20]. There is a unique intestinal microflora in the human digestive tract, consisting of over 17 types of bacteria, with a total of about 500 different species of intestinal bacteria [13]. In a healthy organism, these bacteria remain in balance with each other and regulate a number of systemic reactions and processes in their host. The composition of the intestinal microflora, however, can be disturbed by a number of factors, including stress [23]. It has been proven that stress can reduce the size of the Bifidobacteria and Lactobacilli populations in the intestinal microflora [24]. Bifidobacteria have been shown to reduce intestinal lipopolysaccharide (LPS) levels in mice [25]. This results in the inhibition of LPS-dependent NK cell activation, which significantly reduces the level of pro-inflammatory cytokines and cyclooxygenase 2 (COX-2) [25]. Interestingly, stress (psychological or caused by physical exhaustion) is a well-proven risk factor for chronic fatigue syndrome [16].

Research shows that in people with IBS there are clear, measurable changes in the composition of the intestinal microflora, namely the level of Bifidobacteria is significantly reduced and the level of aerobic bacteria increases [26]. The determination of the composition of the intestinal microflora from stool samples of patients with chronic fatigue syndrome proved that *Escherichia coli* bacteria accounted for 92.3% of the aerobic microflora composition in the control group, compared to 49% in the group of CFS patients. On the other hand, aerobic bacteria of the genus *Enterococcus* and *Streptococcus* were overrepresented in the microflora of patients with IBS [27, 28]. Moreover, it has been shown that the greater the growth of *Enterococcus* bacteria in patients with PE, the more severe their cognitive impairment and neurological disorders such as anxiety, nervousness, memory impairment, easy forgetfulness and confusion [27]. The altered intestinal microflora may produce greater amounts of bacterial endotoxins, which may contribute to high levels of LPS in CFS patients [29].

The gastrointestinal tract, in order to prevent the development of uncontrolled, chronic inflammation, has developed a tight intestinal barrier, which is designed to limit the excessive growth of the intestinal microflora, inhibit the direct contact of the intestinal wall with bacteria and protect against the spread of bacteria from the intestinal lumen to adjacent tissues. Composed of a single layer of epithelial cells, the mucosal intestinal barrier is one of the most important

5. The influence of SARS-Cov-2 virus infection on the development of the chronic fatigue syndrome

For a long time, researchers have postulated viral infection as a trigger, a specific trigger factor that initiates a cascade of molecular and biochemical processes leading to the development of chronic fatigue syndrome in predisposed individuals, probably due to genetic factors [6]. There is scientific evidence confirming the development of CFS after infection with Epstein-Barr virus, enteroviruses, hepatotropic viruses, Parvovirus B19, Ebola virus, Coxiella burnetii, polio virus [6]. It is postulated that viral infection can initiate a "cytokine storm" and a chain of chronic pro-inflammatory cytokine activation that can stimulate the immune system. The body's natural response to the immune system's fight against infection is "feeling sick", including weakness and fatigue, but also many other symptoms that are characteristic of CFS. Cytokine-activated pro-inflammatory cell initiation of the immune system and low-grade neuroinflammation, with microglia activation, may underlie CFS. [6]

COVID-19 is a viral infection caused by the SARS-CoV-2 virus that primarily affects the respiratory system, with initial symptoms often including shortness of breath and fever. Currently, less than 190 million confirmed cases of infections have been reported in the world so far, and millions of infected people have died. A significant proportion of COVID-19 survivors experience long-term health consequences, including development of chronic fatigue.

In the acute phase of COVID-19 disease, multi-organ damage, especially of the lungs, heart and kidneys, may occur, which may itself lead to the development of chronic complications. Therefore, in some people with persistent, debilitating fatigue after COVID-19, documented damage to these organs may be a sufficient explanation for their fatigue [45]. However, many cases of chronic fatigue develop in convalescents who have not suffered permanent damage to their internal organs. follows acute infections not known to cause permanent damage to the heart, lungs, or kidneys - and in people without PTSD or depression. In a typical case of CFS, in particular, the cause of the "infection-like" disease most often appears to be a transient infection or a primary infection that becomes permanent and usually does not cause chronic multiorgan dysfunction [45]. The pathogenesis of the development of chronic fatigue after COVID-19 may probably be very similar to the previously described cytokine cascade after viral infection. The final etiology of CFS requires further research and a final explanation. Perversely, it can be said that one of the good effects of a pandemic may be the increased awareness of the disease, which is chronic fatigue syndrome. Until now, this disease was present mainly in the scientific world, while among clinicians and people who have daily contact with such patients, the knowledge about CFS was very low.

7. Summary

In conclusion, a review of the currently available studies attempting to elucidate the etiology of chronic fatigue syndrome shows that the etiology may be complex and multifactorial. The most probable theories seem to be the post-infectious cytokine cascade, disturbances in the composition of the intestinal microflora and intestinal barrier dysfunction, disturbances on the cerebral-intestinal and cerebral-adrenal axis, the persistence of a low level of immune system stimulation and chronic oxidative stress in the body. Further research in the field of elucidating the etiology and pathogenesis of CFS is necessary. This will enable in the future the development of a biochemical marker that will make it possible to unequivocally make the diagnosis of CFS, and will also contribute to the development of an effective method of causal treatment of this disease.

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