Chronic fatigue syndrome – challenge in diagnosis and management: a literature review

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Introduction

Chronic fatigue syndrome (CFS) manifests itself as a severe, long-term, disabling fatigue, associated with other symptoms, such as sleep and concentration disorders, musculoskeletal pain, headaches, frequent sore throat and lymph node tenderness [1, 2]. Fatigue persists for at least 6 months and is not relieved by rest. It is accompanied by post-exercise malaise (PEM) as well as restless sleep [3]. It is a clinical diagnosis that can be made after excluding other disease processes, taking into account the characteristics of the ailments, e.g. the duration of fatigue, the relationship between the severity of symptoms and physical activity or rest, triggering factors [4].

The most commonly used diagnostic criteria for CFS include the Oxford criteria and the criteria created by the US Centers for Disease Control and Prevention (CDC) [5]. They differ mainly in the number and intensity of symptoms that are necessary for the diagnosis in addition to fatigue [1]. The Oxford criteria place more emphasis on mental fatigue, while the CDC criteria focus mainly on physical symptoms [5].

According to the CDC criteria, a diagnosis of chronic fatigue syndrome can be made when there is clinical evidence of a new onset fatigue lasting ≥6 months and present for more than half of the time. It affects physical as well as mental state and can be accompanied by muscle pain, sleep or mood disorders. Other diagnoses that may cause chronic fatigue should be excluded, as well as schizophrenia, bipolar disorder, substance abuse, organic brain syndrome and eating disorders [1, 5].

In the past, the Fukuda criteria, which consist of major and minor criteria, were also important in the diagnosis of chronic fatigue syndrome. The diagnosis of CFS was possible after meeting all major criteria and ≥4 minor criteria. Major criteria include fatigue that is present continuously or intermittently for ≥6 months, was not previously present, is not significantly relieved by rest, and is interfering with the patient’s daily activities. It is also necessary to exclude other causes of fatigue. Minor criteria include: impaired short-term memory and concentration, sore throat, muscle pain, headache, tender axillary lymph nodes, post-exercise fatigue, joint pain that is not accompanied by swelling or redness, increased drowsiness or insomnia [6].

The updated criteria have been published by the US National Academy of Medicine (NAM). The diagnosis of chronic fatigue syndrome requires the presence of functional impairment of the patient for at least 6 months, accompanied by new-onset fatigue, malaise after physical exertion as well as unrefreshing sleep. It is also necessary to have ≥1 of the following conditions: orthostatic intolerance or cognitive dysfunction [7].

The Canadian Consensus Criteria (CCC) are also used. According to them all of the following must be met: fatigue, malaise after exercise, sleep disorders, cognitive dysfunction, muscle pain, joint pain, headache. In addition, at least one symptom from two of the following categories must be present: autonomic dysfunction,
neuroendocrine disorders or immune disorders. The duration of symptoms is at least 3 months in children and 6 months in adults [8].

The DePaul Symptom Questionnaire (DSQ) includes 99 items associated with CFS symptoms, disease onset and its duration, energy expenditure and patient’s medical history including psychiatric history [9]. The Institute of Medicine (IOM) proposed a new name for chronic fatigue syndrome, Systemic Exertion Intolerance Disease (SEID), and criteria for the diagnosis that became less specific. The criteria included patients with mental disorders, including serious mental illnesses. For this reason, these criteria resemble the Fukuda criteria and the Oxford criteria. The SEID criteria exclude patients with pain symptoms as well as immune system impairment [8].

The terms myalgic encephalomyelitis (ME) and chronic fatigue syndrome are often used interchangeably. In 2011, it was proposed to use the International Consensus Criteria (ICC) to define ME and distinguish it from CFS patients. To meet the ICC criteria, the patient must have post-exercise neuroimmune exhaustion and ≥3 symptoms associated with neurological disorders, ≥3 symptoms associated with impaired immune function, gastrointestinal or genitourinary system, and ≥1 symptom associated with disorders of energy production or transport [10].

Diagnosis of a patient with chronic fatigue should begin with taking the medical history as well as physical examination, taking into account the mental state [4]. Additional tests allow us to exclude other diagnoses. According to the CDC, a urinalysis, CRP, complete blood count, TSH, phosphorus level, and a metabolic panel are recommended. According to NICE, the level of endomysial antibodies in the IgA class for celiac disease should also be assessed. Other tests should be considered depending on the patient’s history and physical examination. It is important to assess the presence of alarm symptoms that may indicate other serious diseases. Those symptoms include e.g. chest pain, lymphadenopathy, weight loss or neurological deficits [5].

Material and methods

The aim of this review is to discuss the phenomenon of chronic fatigue syndrome, taking into account its epidemiology, pathophysiology, diagnostic criteria, symptoms and strategies for pharmacological and non-pharmacological management. The following keywords were used alone or in combination: "chronic fatigue syndrome", "CFS", "mtRNA", "fatigue", "treatment", "diagnosis", "criteria", "pathophysiology", "prevalence", "risk factors". 45 articles were reviewed and placed in the PubMed and Google Scholar databases. Recent publications were preferred, but older references were also analyzed if they brought valuable information.

Results

Epidemiology

Unfortunately, it is very difficult to estimate the true prevalence of chronic fatigue syndrome. Statistical data show high heterogeneity, which results from differences in the used criteria for diagnosis and diagnostic methods, as well as the random sample of communities and age groups are taken into account in the studies [11, 12]. It has also been suggested that the underestimation may be due to differences in awareness among physicians and in the selection of patients in whom CFS may be suspected [13]. In addition, it should be noted that fatigue itself is a very common symptom, but patients meeting all the criteria of CFS are already a relatively small group [12].

Since chronic fatigue syndrome was first described in 1934 in Los Angeles, many case definitions have been developed because the pathophysiology of this syndrome remains unclear [11, 14]. In a systematic review and meta-analysis of 45 articles and studies published between 1990 and 2018 in 13 countries around the world, a total of 8 case definitions were considered. It has been shown that, depending on the criteria, the incidence of CFS/ME ranges from 0.01 to 7.62%. According to data using one of the most common definitions developed by the CDC in 1988, the average prevalence was 1.46%. It has been proven that the statistics also differ depending on the diagnostic methods. The highest frequency occurred in studies based on a questionnaire (2.03%) and the lowest in medical diagnosis (0.10%). Interestingly, some studies obtained similar prevalence results regardless of
the country in which the statistical data was analyzed. In the synthesized data of this meta-analysis, the average prevalence is estimated at 0.89%. Although these discrepancies indicate the need for a rigorous diagnostic procedure, it can be roughly assumed that approximately 1% of the world’s population, or 17 to 24 million people, suffer from CFS, which gives a similar prevalence to, for example, rheumatoid arthritis [11].

The analysis of statistical data also helps to isolate risk factors for developing CFS. According to research, people between 40 and 70 years old most often struggle with it, and about 1.5 to 2 times more often it affects women [11, 14]. This may suggest the role of hormonal factors, although some researchers explain this by the fact that tests are conducted based on medical history, and women report their ailments much more often [11, 12]. Social risk factors such as lower income and education as well as all kinds of stressors, limited access to health care, or lack of proper nutrition are also important [11, 13].

Occupational groups identified in some studies as more likely to develop CFS include healthcare workers, shift workers, airline pilots, and war veterans. Among the risk factors, viral infections are also distinguished, as they are also one of the possible pathophysiological factors of the syndrome [12]. The relationship between CFS and psychiatric disorders is also interesting. Systematic reviews suggest that about half of CFS patients also have anxiety and/or depression. According to the criteria, to diagnose CFS, some psychiatric diagnoses, including major depression, should be excluded, however, it is suggested that depressive disorders may be defined as diseases co-occurring with CFS [15]. Studies also report personality disorders as a risk factor for CFS [16].

Theories of chronic fatigue syndrome development

Despite many studies and scientific reports, it is not possible to identify a specific mechanism responsible for the CFS development. Various theories on the etiology of the disease are being considered, with the multifactorial nature of the disease seeming to be the most probable (Figure 1).

Infection theory

The occurrence of CFS symptoms is often preceded by a history of an infectious disease, which raises the suspicion of an infectious etiology. Studies have shown that 11% of patients with severe Epstein Barr Virus (EBV), Ross River Virus, Parvovirus B19, Coxiella burnetii, or Giardia lamblia infection will develop CFS [8]. In addition to the pathogens listed above, causative factors may also include: cytomegalovirus, SARS-CoV-1, Ebola virus, enteroviruses, Borrelia burgdorferi, Mycoplasma pneumoniae, as well as fungi of the genus Candida [17]. A trigger for the disease...
may also be reactivation of latent infection with Human Herpes Virus (HHV-6), as evidenced by the presence of anti-HHV-6 antibodies in the IgM class and the HHV-6 antigen in peripheral blood mononuclear cells of patients [18]. Infectious agents activate the nuclear transcription factor NF-κB, which stimulates the immune system response [19].

**Immune theory**

Concomitant systemic inflammation and excessive activation of the immune system are observed in patients with CFS. As a consequence, there is an increased concentration of pro-inflammatory cytokines such as: IL-1, IL-4, IL-5, IL-6, IL-12, IL-17a, tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ). High levels of pro-inflammatory cytokines are responsible for the intensification of chronic fatigue, muscle and joint pain, and flu-like symptoms [17–19]. In the patients, disturbed function of the immune system cells, including chronic activation of CD26 T-lymphocytes, increased number of cytotoxic CD8 T-lymphocytes, and weakened response of T-lymphocytes to mitogens, have been demonstrated [17, 19, 20]. Decreased concentration and cytotoxicity of natural killer (NK) cells are also observed. In addition, their impaired functioning correlates with the severity of the disease and impaired cognitive functions in these patients [8].

In the course of CFS, humoral immunity prevails over cellular immunity [8]. Total IgG concentrations, especially IgG1 and IgG3, are reduced. On the other hand, serum levels of IgA and IgM against lipopolysaccharides of Gram-negative enterobacteria increase due to increased intestinal permeability, bacterial translocation, and increased serum endotoxin levels [19]. In addition, the presence of antibodies is described, mainly against nuclear and membrane structures, as well as against neurotransmitters and their receptors [18].

The pathological mechanism observed in the course of CFS is the dysfunction of one of the main antiviral pathways, which leads to the formation of an abnormal form of ribonuclease L (RNase L) with too low molecular weight. The purpose of a properly functioning RNase L is to hydrolyze the RNA of viruses present in cells. The erroneously produced form of RNase does not respond to negative feedback, as a result of which it constantly destroys cell membranes, including mitochondrial membranes, which leads to damage and impairment of cell functions [8, 19].

Many studies have investigated the potential use of cytokines as diagnostic biomarkers for CFS. Cytokines such as IL-1, IL-6, TNF-α, IFN-γ have been shown to be closely related to CFS. However, the level of cytokines may be different in the CNS compared to their concentration in peripheral blood vessels due to the blood-brain barrier which turns out to be the limitation of this method. In addition, many other factors may affect the level of cytokines at a given moment, so it was concluded that they should not be used as independent diagnostic markers, but only play an auxiliary role in the diagnosis of CFS [22].

**Neuroendocrine theory**

A common abnormality seen in CFS, especially in women, is dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis. The consequence of this is low cortisol concentration, which is responsible for increasing weakness and the feeling of chronic fatigue [22]. Apart from low levels of adrenal hormones, in affected patients, attenuated circadian variability of cortisol and reduced response of the HPA axis to physical factors and stress, are also observed. Adrenal hormones have a negative feedback on the immune system and thus reduce inflammatory reactions in the body. Similarly, reduced levels of these hormones, including cortisol, weaken the negative feedback on the immune system. Consequently, lead to excessive activation of the immune system and increased production of pro-inflammatory cytokines [19]. The cause of HPA axis dysfunction in patients with CFS has not been fully elucidated. It is suggested that this dysfunction may be caused by chronic stress, reduced production of adrenocorticotropic hormone (ACTH), smaller size of the adrenal glands or increased negative feedback within the HPA axis [19, 23].

**Bioenergetic theory**

Reduced level of antioxidants, e.g. glutathione and α-tocopherol, increased oxidative and nitrosative stress resulting in increased levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS), as well as induced nitric oxide synthase (iNOS) is observed in the course of CFS.
Free radicals damage DNA, membrane fatty acids and proteins, and they cause mitochondrial dysfunction \[14, 17\].

Damage to the mitochondria leads to impaired oxidative phosphorylation, resulting in reduced ATP production and thus less energy produced in the aerobic process. The reason for this phenomenon may be the lack of necessary substrates for this process or mitochondria functioning impairment caused by inflammatory cells and free radicals \[8\]. Anaerobic metabolic pathways enable less energy production (18 times less ATP molecules than in aerobic conditions), cause the accumulation of lactic acid and contribute to acidosis development \[7\]. This mechanism favors the occurrence of the so-called PEM syndrome, i.e., malaise and exacerbation of symptoms, even after minor physical and mental effort \[8\].

**Neurological theory**

Studies of the brain of CFS patients have shown a decrease in white matter volume and possibly also gray matter, metabolic dysfunction of glial cells. Inflammatory processes in the brain characterized by generalized activation of astrocytes and microglia is also observed. These changes are the cause of pain symptoms, impairment of cognitive functions and a decrease in the speed of information processing \[7, 14, 17\].

**Autonomus theory**

Autoantibodies directed against β2-adrenergic receptors have been detected in patients with CFS. Dysfunction of these receptors leads to endothelial dysfunction and excessive vasoconstriction in skeletal muscles. Muscle hypoperfusion triggers a compensatory mechanism leading to increased production of endogenous vasodilating substances that enter the systemic circulation. As a consequence, patients develop hypovolemia, reduced cerebral perfusion, reduced left ventricular preload, and decreased cardiac output. Ultimately, this leads to excessive sympathetic activation and decreased vagal tone \[24\]. The predominance of the sympathtetic nervous system also occurs at night, which disturbs physiology and makes sleep less effective \[7\].

**Genetic theory**

Genetic studies of CFS patients have shown changes in the DNA sequences and expression of many genes responsible for the course of the immune response and the bioenergetic and metabolic pathways regulation. In a study conducted by Billing-Ross et al. in 2016, abnormalities in the mitochondrial genome in the form of mtDNA single nucleotide polymorphisms (SNPs) were described in CFS patients. Eight SNPs located at mtDNA positions 150, 930, 1719, 3010, 5147, 16093, 16223, and 16519 have been shown to correlate with symptom severity. Increased incidence of inflammation, gastrointestinal disorders including bloating and abdominal pain, neurological symptoms such as increased sensitivity to bright light, and insomnia at night and excessive sleepiness during the day were observed in patients. Patients also more often reported difficulties in performing work and limited physical activity \[25, 26\].

**Clinical presentation**

CFS is also known as debilitating fatigue that does not subside despite rest and recovery time sufficient for a healthy person. Symptoms of chronic fatigue syndrome include malaise after exertion, non-restorative sleep, memory disturbances, muscle soreness, multi-joint pain, sore throat, lymph node tenderness, and frequent headaches. The most important element of diagnosis is exclusion of organic processes \[8, 27\].

Chronic fatigue syndrome may manifest differently in each patient, therefore the diagnosis is based on a group of symptoms. One of the most common patients' complaints, especially those undergoing cancer or chronic disease treatment, is fatigue \[1, 8\]. This ailment is the most frequently recognized symptom. It also noticeably disrupts daily functioning.

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-COV2) has contributed to an increase in CFS incidence \[28\]. It is likely that post-coronavirus disease 2019 (COVID-19) fatigue syndrome may result from damage to olfactory sensory neurons. This leads to reduced cerebrospinal fluid (CSF) outflow through cribriform plate and accumulation of toxins within the central nervous system.

The etiology of CFS is different in each disease. There are no specific symptoms that occur in every patient \[29, 30\]. CFS leads to reduced physical,
mental and social activity. The fatigue is sometimes so severe that it prevents the patient from dressing, washing himself or climbing stairs [8].

The symptoms are so ambiguous that patients tend to associate them with a systemic disease in the first place. As a result, they seek medical advice, usually from a general practitioner [9, 10]. In cases, when the symptoms are intractable, patients ask for help from a psychiatrist. That is especially when severe CFS causes perceptual and sleep disturbances and difficulties in understanding complex sentences. In addition, CFS symptoms may occur or be more visible as a result of depression, hypotension or disorders that affect the quality and depth of sleep. The onset of chronic fatigue syndrome symptoms is recognizable, so the patient is able to determine up to what point their functioning was normal [1, 8, 27].

The most characteristic CFS symptoms have been mentioned above. However, it should be noted that the clinical course varies. Other symptoms include allergies and food hypersensitivity, diarrhea, bloating, dry eyes, dizziness, earache, night sweats, jaw pain and numbness or tingling in the face, hands and feet [1, 31].

What’s more, CFS often coexists with other autoimmune diseases, which is why the blood may contain, among others, antithyroid antibodies, rheumatoid factor or anti-smooth muscle antibodies [21]. Fatigue, depending on its duration, can be classified as acute (lasting less than 1 month), prolonged (between 1 and 6 months) and chronic (at least 6 months). Acute fatigue resolves with rest, while chronic fatigue may indicate idiopathic chronic fatigue or chronic fatigue syndrome. Chronic fatigue syndrome differs from chronic fatigue of other causes as it is a systemic neuroimmune disease with a different pathophysiology. Idiopathic chronic fatigue is also characterized by chronic fatigue of unknown cause, but the CFS criteria are not met [32].

CFS should be differentiated from other abnormalities causing fatigue. However, CFS also often coexists with other diseases, such as connective tissue diseases. Fibromyalgia was once considered a CFS spectrum disease. However, differences in sleep architecture patterns have been shown between patients with chronic fatigue syndrome and fibromyalgia and those with only CFS. It is important to differentiate fatigue resulting from CFS from fatigue found in other disorders [33]. A diagnosis of CFS is a diagnosis of exclusion and requires the presence of fatigue lasting at least 6 months and concomitant symptoms, such as cognitive impairment, unrefreshing sleep, body pain as well as post-exertional malaise – PEM [33, 34]. Those symptoms are exacerbated by exertion and other stressors. PEM is characterized by the occurrence of malaise after minimal physical or cognitive exertion [34]. PEM is the most indicative of CFS and is described as a hallmark symptom [34, 35].

Pharmacological and non-pharmacological strategies in treatment

An effective causative CFS treatment remains unknown due to its complex and inexplicable etiology. Treatment focuses on symptom alleviation through both pharmacological and non-pharmacological methods (Figure 1) [7]. Multidisciplinary approach in care of patients is required. The management strategies include patient’s education, symptomatic treatment, appropriately adjusted physical activity, body’s energy management and in some cases cognitive-behavioral therapy (CBT) [36–38].

Education about the condition plays a significant role in the therapeutic process. Information provided to the patient and family should be understandable and tailored to the patient’s situation. It is important to explain that CFS is characterized by symptom variability, heterogeneous course and may affect different aspects of a patient’s life [36, 37]. Knowledge of the body’s energy reserves among CFS patients is an important element. The patients need to acknowledge their limitations and learn to manage energy appropriately. Energy self-control allows to reduce the probability of PEM and exacerbation of other symptoms [36].

Decision to incorporate physical activity into the treatment process is determined by the clinical course and the patient’s willingness to exercise. Training plan ought to be tailored and supervised by a physiotherapist with adjustment to the patient’s energy levels. The patient must be aware of the risk of symptom exacerbation during activity. National Institute for Health and Clinical Excellence (NICE) guidelines currently do not recommend graded exercise therapy (GET) [36].

Cognitive-behavioral therapy is not presently approved as a CFS treatment method. It plays
only a supportive role. It is recommended to improve the patient's functioning, psychological state and quality of life [36].

Patients with multimorbidity and comorbid CFS require particular care. Treatment of concomitant diseases should follow guidelines. The possibility of overlapping symptoms of CFS and other diseases needs to be taken into consideration, as it may create a diagnostic challenge [36, 37].

Non-pharmacological strategies include: proper nutrition, dysautonomia's symptoms alleviation, sleep disorder, cognitive dysfunction and pain relief therapy. Balanced diet and appropriate hydration provides the basis of nutritional treatment. Additionally, low-carbohydrate, high-protein, rich in omega-3 fatty acids and anti-inflammatory diet may be considered [37]. Patients having difficulties with maintaining normal body weight should be supervised by a dietician. At risk of vitamin D deficiency are patients whose severe CFS symptoms force them to limit activity or cause immobilization. Therefore, vitamin D supplementation is recommended in accordance with the guidelines [36].

Providing proper quality and quantity of sleep, as well as rest between activities during the day, is an important element of CFS management. The patient should be informed that sleep disturbances may exacerbate fatigue [36, 37]. Helpful tools for regulating patients' sleep include phototherapy, relaxation techniques and use of blue light filters [7].

Symptoms resulting from autonomic system dysfunction can be alleviated by increasing fluid and electrolyte intake, using compression stockings, sleeping with legs elevated, and avoiding prolonged verticalization [7, 37].

Pain management includes physiotherapy, acupuncture, acupressure and use of warm and cold compresses [7, 37].

Patients affected by CFS require help in daily activities. In severe cases, there is a particular risk of physical functioning deterioration due to immobilization. Methods that improve muscle flexibility and joint mobility, balance and positively affect the cardiovascular system are recommended [36].

Adjusting the intensity of mental activity to the patient's capabilities, for example, focusing on doing one activity at a time, as well as using memory aids such as notes or a calendar, can be helpful in improving cognitive function [7].

The initiation of treatment should be preceded by a conversation with the patient. The patient should determine which symptoms are most burdensome and disruptive to daily functioning. The treatment plan and decision to include pharmacotherapy should be individualized and tailored to the type of current symptoms and their severity [8,39]. Due to the fact that there is no pharmacotherapy directed specifically against CFS, drugs are an auxiliary intervention to alleviate symptoms. There are no specific indications for pharmacotherapy. The outcome of pharmacological treatment may be different in each patient. Drugs used to relieve symptoms may be beneficial for one patient but not be effective for another. It is advisable to start pharmacotherapy with over the counter drugs before including prescription drugs while managing the symptoms. This is the reason why medical professionals should support and supervise the patient's condition during the treatment [40, 41].

Pharmacological treatment is used to reduce pain, dysautonomia symptoms, sleep and cognitive dysfunction. In some cases, anti-inflammatory and anti-allergic drugs may also be administered [37]. Due to higher risk of developing drug intolerance, CFS patients should start therapy with a lower dose and increase it gradually [36]. Pain management includes paracetamol, non-steroidal anti-inflammatory drugs, low-dose naltrexone, antiepileptic drugs, serotonin and noradrenaline reuptake inhibitors. Reducing orthostatic intolerance can be achieved by including fludrocortisone, low doses of beta-sympatholytics, alpha-receptor agonists and intravenous saline. For sleep disturbances, trazodone, antiepileptic drugs and low-dose antidepressants are recommended. Cognitive impairment occurring in CFS patients may be treated with methylphenidate or dextroamphetamine, but their addictive potential should be kept in mind. The literature mentions modafinil as well [7, 37].

Hitherto the effectiveness of vitamin and mineral supplementation in treating CFS symptoms has not been confirmed [31]. According to an analysis by Bjørklund et al., vitamin A and E deficiency may play a role in the pathophysiology of CFS. However, further research is needed to confirm this thesis [42]. Due to increasing knowl-
edge about the etiology and pathophysiology of CFS, the research on potential drugs is possible. Experimental therapies targeting immune and mitochondrial dysfunctions are currently being developed [43].

Promising results were obtained during a study conducted by Kujawski et al. It focused on the effect of stretching exercises combined with systemic cryotherapy. The research proved that this method could reduce the sleepiness and fatigue experienced by CFS patients. Improvements in some cognitive functions were mentioned as well [44].

According to the EUROMENE consensus, in the absence of targeted treatment for CFS, the most important thing to do is to manage by avoiding overexertion and mental stress, activities that can lead to symptoms. It is assumed that physical activity should be kept to two-thirds of the duration and intensity that usually causes symptoms. Thus, patients with CFS should first and foremost be properly educated in appropriate energy and physical activity management [37]. Also in a review of national recommendations in European countries, the most commonly recommended treatment procedures are appropriate exercise management and CBT [45]. Hence, patients with CFS without comorbidities should first be given appropriate education about CFS, how to manage energy, adjust exercise and avoid mental stress, which CBT can help with. Thereafter, pharmacological and non-pharmacological treatment of symptoms should only be considered.

Discussion

In our review, we wish to emphasize the care with which CFS should be diagnosed and treated. Simply matching the diagnostic tools used can be problematic. A number of uncharacteristic symptoms, often difficult to assess objectively, and often the need to base the diagnosis on the patient’s subjective feelings, mean that the diagnosis may be delayed [1,31]. One of the most important elements of management is the exclusion of organic processes that may cause such a condition of the patient [8]. The progression of this syndrome, characterized by severe and prolonged fatigue, can lead to disability, so it is important to develop, refine and implement new diagnostic methods for CFS [1].

As we wrote above, it is difficult to estimate the real incidence of CFS, due to the multiplicity
and imperfection of diagnostic criteria or insufficient education of medical staff [11–13]. According to our literature review, the estimated prevalence of CFS can be compared to that of rheumatoid arthritis, which, however, is a disease with a simpler diagnosis and awareness among patients and physicians of the symptoms of this disease is wider than that of CFS [11].

Despite many years of research and attempts to discover the pathomechanism of CFS, the etiology of this syndrome remains unclear and is suspected to be of multifactorial origin. As we indicated above, there are various theories of the pathophysiology of CFS, but none of them fully explains the occurrence of all symptoms. Further research on this topic is needed to develop targeted therapies.

So far, CFS therapy is based on symptomatic treatment. Due to, as we mentioned, the multiplicity and uncharacteristic symptoms, this treatment requires a multidisciplinary approach [7]. Research emphasizes the importance of educating the patient about their own disease and cooperatively developing appropriate management of the body’s energy resources, including the inclusion of adapted quantity and quality of physical activity [33, 34].

In the care of patients with CFS, it is also necessary to treat comorbidities that may worsen the course of CFS, and to provide patients with ongoing and long-term care so that the symptoms of CFS do not mask any possible development of other conditions [33, 34].

Our study shows that CFS is a complex problem with imperfect diagnosis, requiring careful research into its pathophysiology and possible causal therapies. It is also important to raise public awareness of the syndrome and to adequately educate medical professionals.

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