REVIEW PAPER

JMS Journal of Medical Science

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

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DOI: https://doi.org/10.20883/medical.e877

Keywords: cellular immunity, cytokines, leishmaniasis, pro-inflammation, HIV co-infection

Received: 2023-06-20
Accepted: 2023-07-23
Published: 2023-09-28

How to Cite: Nieciecka A, Tomys-Składowska J, Lamch M, Jabłońska M, Błasik N, Janiszewska M, Wójcik-Kula A. Chronic fatigue syndrome – challenge in diagnosis and management: a literature review. Journal of Medical Science. 2023;92(4):e877. doi:10.20883/medical.e877

ABSTRACT

Introduction. Chronic fatigue syndrome is a disease that includes a number of various symptoms, among which the most characteristic symptom is fatigue. Diagnostic criteria are not unambiguous and vary depending on the scientific society by which they were developed. The aim of this review is to discuss the phenomenon of chronic fatigue, including its diagnostic criteria, epidemiology, pathophysiology, symptoms, and pharmacological and non-pharmacological strategies.

Material and methods. 45 articles published were reviewed and placed in the PubMed and Google Scholar databases.

Results. Chronic fatigue syndrome is defined as a group of symptoms whose dominant symptom is fatigue that persists after rest for at least 6 months. The Oxford or CDC criteria are most commonly used to make the diagnosis. Statistics on prevalence are inconclusive. There are several theories of origin - infectious, immunological, neuroendocrine, bioenergetic, neurological, autonomic and genetic. Other symptoms of chronic

fatigue syndrome include sleep and memory disorders or muscle and joint pain. Current treatment focuses on symptomatic treatment, including education, diet, and physical activity, as well as pharmacotherapy for pain, sleep, and cognition.
Discussion. Diagnosis and treatment of chronic fatigue syndrome undoubtedly is a medical challenge, due to non-specific symptoms, multifactorial pathogenesis and difficult to estimate prevalence of this disease. Future scientific development should focus especially on exploring the pathomechanism of CFS, which would enable the implementation of causal treatment.

Introduction

Chronic fatigue syndrome (CFS) manifests as 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 six months and is not relieved by rest. Post-exercise malaise (PEM) and restless sleep accompany CFS [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., fatigue duration, the relationship between the severity of symptoms and physical activity or rest, and 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 necessary for the diagnosis, in addition to fatigue [1 Oxford criteria emphasise mainly mental fatigue, while the CDC focuses on physical symptoms [5].

According to the CDC criteria, a diagnosis of chronic fatigue syndrome can be made when there is clinical evidence of new-onset fatigue lasting for at least six months that is not affected by rest or ongoing exertion and results in a significant deterioration in previous activity level. At least four disorders are necessary for the diagnosis: significant memory and concentration impairment, restless sleep, lymph node tenderness, joint or muscle pain, headaches, and post-exercise malaise lasting more than 24 hours. Exclusion criteria include known or suspected diseases that may cause fatigue, severe obesity, depression, psychotic disorders, anorexia nervosa, bulimia, dementia, alcohol or substance abuse [1].

According to the Oxford criteria, the diagnosis of CFS requires the presence of severe fatigue lasting ≥6 months and present for more than half of the time. It affects physical and 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 crucial in diagnosing 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 not accompanied by swelling or redness, increased drowsiness or insomnia [6].

The US National Academy of Medicine (NAM) has published the updated criteria. The diagnosis of chronic fatigue syndrome requires the presence of functional impairment in the patient for at least six months, accompanied by new-onset fatigue, malaise after physical exertion, and 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, and headache. In addition, at least one symptom from two categories must be present: autonomic dysfunction, neuroendocrine disorders or immune disorders. Symptoms are at

least three months in children and six months in adults [8].

The DePaul Symptom Questionnaire (DSQ) includes 99 items associated with CFS symptoms, disease onset and 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 Fakuda criteria and the Oxford criteria. The SEID criteria exclude patients with pain symptoms and immune system impairment [8].

Myalgic encephalomyelitis (ME) and chronic fatigue syndrome are often used interchangeably. In 2011, the International Consensus Criteria (ICC) were proposed to differentiate ME patients from those with CFS. 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 and 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 essential to assess alarm symptoms that may indicate other serious diseases. Those symptoms include chest pain, lymphadenopathy, weight loss or neurological deficits [5].

Materials and methods

This review aims to discuss 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", and "risk factors". Forty-five articles were reviewed and placed in the PubMed and Google Scholar databases. Recent publications were preferred, but older references were also analysed if they brought valuable information.

Results

Epidemiology

Unfortunately, it is challenging 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 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, fatigue is a prevalent 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 where the statistical data was analysed. In the synthesized data of this meta-analysis, the aver-

age 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].

Statistical data analysis also helps isolate risk factors for developing CFS. According to research, people between 40 and 70 years old most often struggle with it, affecting women about 1.5 to 2 times more often [11,14]. Researchers speculate that hormonal factors are involved, but others point out that testing is based on medical history, and women report their ailments more frequently [11,12]. Social risk factors such as lower income and education, 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 appealing. According to systematic reviews, about half of patients with CFS also suffer from anxiety and depression, or either of these. According to the criteria to diagnose CFS, some psychiatric diagnoses, including major depression, should be excluded. However, CFS and depression may co-occur [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 CFS development. Various theories on the aetiology of the disease are being considered, with the multifactorial nature of the disease being the most probable.

Infection theory

An infectious disease often precedes CFS symptoms, which raises the suspicion of an infectious aetiology. 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

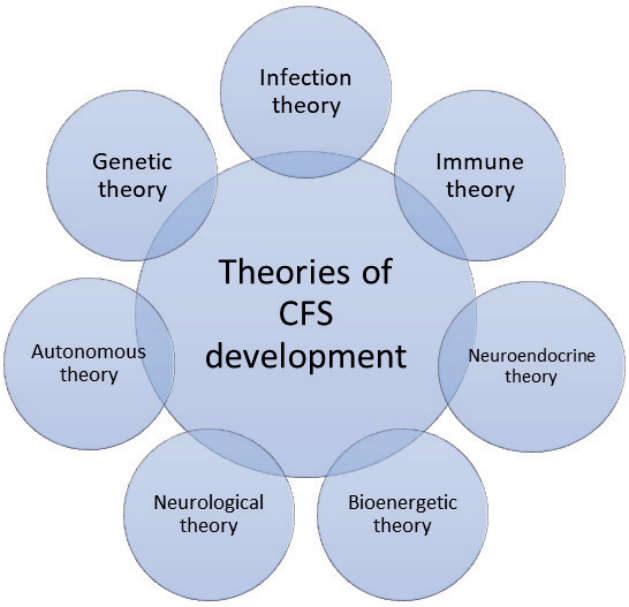

Figure 1. Theories of CFS development.

activate the nuclear transcription factor NF-kB, stimulating the immune system response [19].

Immune theory

Patients with CFS suffer from concurrent systemic inflammation and excessive immune system activation. Consequently, there is an increased concentration of pro-inflammatory cytokines such as IL-1, IL-4, IL-5, IL-6, IL-12, IL-17a, tumour necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ). High levels of pro-inflammatory cytokines are responsible for intensifying chronic fatigue, muscle and joint pain, and flu-like symptoms [17,18,19]. In the patients, disturbed function of the immune system cells, including chronic activation of CD26 T-lymphocytes, an increased number of cytotoxic CD8 T-lymphocytes, and a 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 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, 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, and IFN-γ have proven 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 is 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 diagnosing CFS [22].

Neuroendocrine theory

A common abnormality seen in patients with CFS, especially in women, is hypothalamic-pituitary-adrenal (HPA) axis dysfunction. The consequence is low cortisol concentration, which increases weakness and chronic fatigue [22]. Apart from low levels of adrenal hormones, in affected patients, attenuated circadian variability of cortisol and reduced HPA axis response to physical factors and stress are also observed. Adrenal hormones negatively affect the immune system and thus reduce inflammatory reactions. Similarly, reduced levels of these hormones, including cortisol, weaken the negative feedback on the immune system.

Consequently, it leads to excessive activation of the immune system and increased production of pro-inflammatory cytokines [19]. There is no clear explanation for the dysfunction of the HPA axis in patients with chronic fatigue syndrome. Chronic stress, reduced adrenocorticotropic hormone (ACTH) production, smaller size of the adrenal glands or increased negative feedback within the HPA axis may trigger the dysfunction [19,23].

Bioenergetic theory

Reduced levels 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 phenomenon may be due to 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 fewer ATP molecules than in aerobic conditions), cause the accumulation of lactic acid and contribute to acidosis development [7]. This mechanism favours 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, possibly also grey matter, and metabolic dysfunction of glial cells. An inflammatory process characterised by widespread activation of microglia and astrocytes also occurs in the brain. These changes cause pain symptoms, impairment of cognitive functions and a decrease in the speed of information processing [7,14,17].

Autonomous 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. Consequently, patients develop hypovolemia, reduced cerebral perfusion, left ventricular preload, and decreased cardiac output. Ultimately, this leads to excessive sympathetic activation and decreased vagal tone [24]. The predominance of the sympathetic nervous system also occurs at night, 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 immune response and the regulation of bioenergetic and metabolic pathways. 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, 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 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 crucial diagnosis element is excluding organic processes [8,27].

Chronic fatigue syndrome may manifest differently in each patient. Therefore, the diagnosis is based on a group of symptoms. Fatigue is one of the most common patient complaints, especially those undergoing cancer or chronic disease treatment [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 increased CFS incidence [28]. Post-coronavirus disease 2019 (COVID-19) fatigue syndrome may result from damage to olfactory sensory neurons, thus leading to reduced cerebrospinal fluid (CSF) outflow through the cribriform plate and accumulation of toxins within the central nervous system.

The aetiology of CFS is different in each disease. There are no specific symptoms that occur in every patient [29,30]. CFS leads to a reduced physical, mental and social activity. The fatigue is sometimes so severe that it prevents the patient from dressing, washing themselves 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 true when severe CFS causes percep-

tual and sleep disturbances and difficulties in understanding complex sentences. In addition, CFS symptoms may occur or be more visible due to depression, hypotension or disorders affecting sleep quality and depth. The onset of chronic fatigue syndrome symptoms is recognizable, so the patient can 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, diarrhoea, bloating, dry eyes, dizziness, earache, night sweats, jaw pain and numbness or tingling in the face, hands and feet [1,31].

What is 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 one month), prolonged (between one and six 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. Chronic fatigue of unknown causes also characterises idiopathic chronic fatigue, 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 like 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 essential to differentiate fatigue resulting from CFS from fatigue found in other disorders [33]. A diagnosis of CFS is a diagnosis of exclusion. It requires the presence of fatigue lasting at least six months and concomitant symptoms, such as cognitive impairment, unrefreshing sleep, body pain, and post-exertional malaise – PEM [33,34]. Exertion and other stressors exacerbate those symptoms. Malaise after minimal physical or cognitive exertion characterises PEM [34]. PEM is the most indicative of CFS and is 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 aetiology. Treatment focuses on symptom alleviation through pharmacological and non-pharmacological methods (**Figure 2**) [7]. Patient care based on a multidisciplinary approach is required. The management strategies include patient education, symptomatic treatment, appropriately adjusted physical activity, body's energy management and in some cases cognitive-behavioral therapy (CBT) [36,37,38].

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. CFS symptoms are variabile, represent heterogenous course, and may affect different aspects of a patient's life [36,37]. Knowledge of the body energy reserves among patients with CFS is essential.The patients need to acknowledge their limitations and learn to manage energy appropriately. Energy self-control reduces the probability of PEM and exacerbation of other symptoms [36].

The clinical course and the patient's willingness to exercise determine the decision to incorporate physical activity into the treatment process. A physiotherapist should tailor and supervise the training plan with adjustments 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].

There is no approval for the cognitive-behavioural therapy as a CFS treatment method. It plays only a supportive role. Considering the possibility of overlapping symptoms of CFS and other diseases is necessary, as it may create a diagnostic challenge [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. A balanced diet and

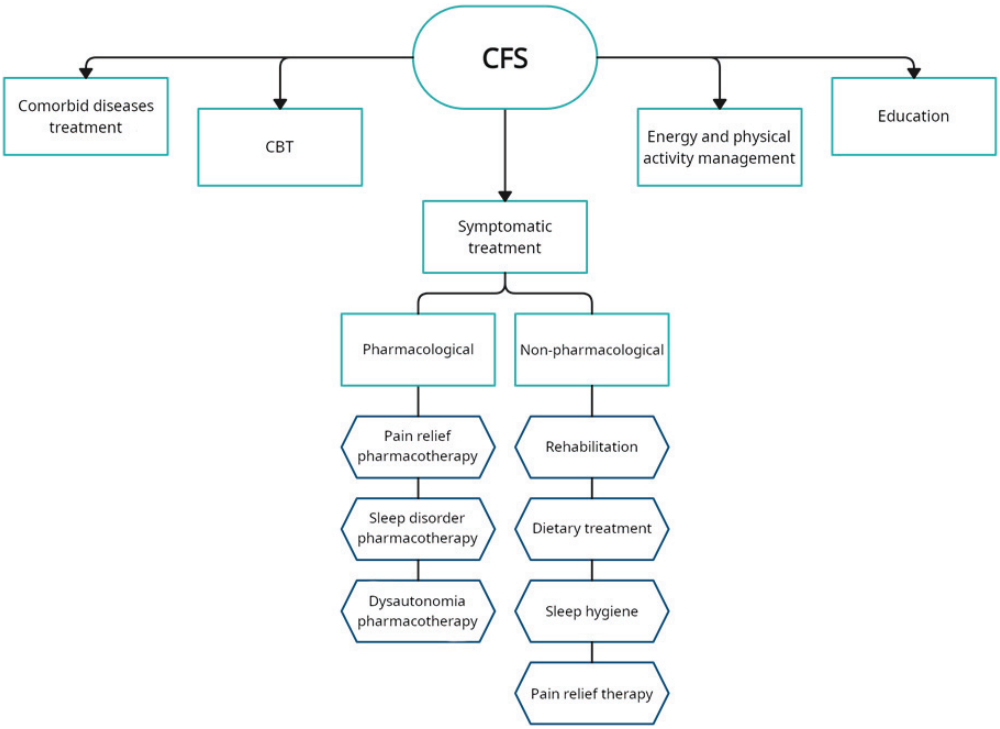

Figure 2. Treatment focused on symptom alleviation through pharmacological and non-pharmacological methods.

appropriate hydration provide the basis of nutritional treatment. Additionally, low-carbohydrate, high-protein, rich in omega-3 fatty acids and anti-inflammatory diet may be considered [37]. A dietician should supervise patients having difficulties with maintaining average body weight. 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 and rest between activities during the day is essential to CFS management. The patient should learn that sleep disturbances exacerbate fatigue [36,37]. Helpful tools for regulating patients' sleep include phototherapy, relaxation techniques and blue light filters [7].

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

Pain management includes physiotherapy, acupuncture, acupressure and 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, joint mobility and 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, and using memory aids such as notes or a calendar, can be helpful in improving cognitive function [7].

A conversation with the patient should precede the initiation of treatment. 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]. Since no pharmacotherapy aims directly 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. One patient may benefit from drugs that relieve symptoms. Howev-

er, these may not be effective for others. When managing the symptoms, it is advisable to start pharmacotherapy with over-the-counter drugs before including prescription drugs. Therefore, medical professionals should support and supervise the patient's condition during the treatment [40,41].

Pharmacological treatment reduces pain, dysautonomia symptoms, sleep and cognitive dysfunction. Some anti-inflammatory and anti-allergic drugs may also be administered [37]. Due to the higher risk of developing drug intolerance, CFS patients should start therapy with a lower dose and increase it gradually [36]. Pain management includes paracetamol, nonsteroidal anti-inflammatory drugs, low-dose naltrexone, antiepileptic drugs, serotonin and norepinephrine 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 in patients with CFS may be treated with methylphenidate or dextroamphetamine, but their addictive potential should be kept in mind. The literature mentions modafinil as well [7,37].

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]. The research on potential drugs is possible because of increasing knowledge of the aetiology and pathophysiology of CFS. Experimental therapies targeting immune and mitochondrial dysfunctions are 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. Physical activity should account for two-thirds of the duration and intensity that usually causes symptoms. Thus, patients with CFS should first and foremost be adequately 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 and without comorbidities should first be adequately educated about CFS, how to manage energy, adjust exercise and avoid mental stress, with which CBT can help. After that, 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. More than simply matching the diagnostic tools used can be problematic. Several uncharacteristic symptoms, often difficult to assess objectively, and often the need to base the diagnosis on the patient's subjective feelings, may delay the diagnosis [1,31]. One of the most essential elements of management is excluding organic processes that may cause such a condition in the patient [8]. The progression of this syndrome, characterized by severe and prolonged fatigue, can lead to disability, so it is crucial to develop, refine and implement new diagnostic methods for CFS [1].

As we wrote above, it is difficult to estimate the actual incidence of CFS due to the multiplicity and imperfection of diagnostic criteria or insufficient medical staff education [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 more straightforward diagnosis and awareness among patients and physicians of the symptoms of this disease is broaderr than that of CFS [11].

Despite many years of research and attempts to discover the pathomechanism of CFS, the aetiology 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 thoroughly 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 disease and cooperatively developing appropriate management of the body's energy resources, including 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 essential to raise public awareness of the syndrome and to adequately educate medical professionals.

Acknowledgements

We sincerely thank Professor Paweł Zalewski for substantive support.

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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