NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ

Journal of Education, Health and Sport. eISSN 2450-3118

Journal Home Page
https://apcz.umk.pl/JEHS/index

SZAFRANIEC, Artur, KRĘŻEL, Olga, KRĘŻEL, Maciej, KALINOWSKA, Zuzanna, ALEKSANDROWICZ, Hanna and RYBIŃSKA, Marcelina. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): Post-Exertional Malaise and the Biology of Energy Failure. Journal of Education, Health and Sport. 2026;88:69423. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2026.88.69423

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 01.03.2026. Revised: 08.03.2026. Accepted: 08.03.2026. Published: 15.03.2026.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): Post-Exertional Malaise and the Biology of Energy Failure

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Abstract

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a severe, heterogeneous multisystem disorder defined by persistent fatigue lasting ≥6 months that is disproportionate to exertion, not relieved by rest, and associated with substantial functional decline. Its hallmark feature is post-exertional malaise (PEM), a delayed and prolonged worsening of symptoms after minimal physical or cognitive effort. Common symptoms include unrefreshing sleep, cognitive impairment, pain, flu-like complaints, sensory hypersensitivity, and autonomic dysfunction such as orthostatic intolerance. Diagnosis is clinical and requires exclusion of alternative medical and psychiatric conditions, with commonly used frameworks including the CDC/Fukuda and International Consensus Criteria. Evidence supports a multifactorial pathophysiology involving immune dysregulation, metabolic and mitochondrial abnormalities, neuroendocrine disturbance, gut dysbiosis, and autonomic dysfunction - collectively suggesting impaired energy homeostasis. No validated biomarker exists, though multi-omic immune and metabolic signatures remain under investigation. Management is supportive, emphasizing individualized pacing and treatment of comorbidities.

Keywords: chronic fatigue, immune dysregulation, chronic infections, APT, post-exertional malaise, neuroendocrine system

Aim of the work:

The aim of this work is to provide a comprehensive, evidence-based review of the pathophysiology, diagnosis, clinical features, and management strategies of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Materials and Methods:

The article presents an attempt to provide a comprehensive, evidence-based review of the pathophysiology, diagnosis, clinical features, and management strategies of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). For this purpose, scientific articles were searched for in databases, including PubMed, Google Scholar, and information on publicly available websites dedicated to the dissemination of reliable medical knowledge. Literature in Polish, English, and German was used. The review of articles and scientific papers was carried out in February 2026.

Introduction

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME/CSF), is a severe, systemic illness characterized by persistent and/or recurrent, medically unexplained fatigue that lasts for at least 6 months. This fatigue does not improve with rest, is not the result of overexertion, and leads to a noticeable reduction in social, personal, professional, or educational functioning. [Prins et al., 2006; Yancey et al., 2012; Natelson et al., 2021] The diagnosis of this disease requires the exclusion of other somatic and psychiatric conditions that could explain these symptoms. The most commonly used diagnostic tool was presented by the Centers for Disease Control and Prevention (CDC) and indicates the coexistence of chronic fatigue and a specific set of coexisting symptoms. [Prins et al., 2006; Yancey et al., 2012] A particularly characteristic symptom of ME/CFS is the worsening of symptoms even after minimal physical or intellectual effort. The deterioration in health may occur with a delay and last for many days or weeks. In addition, patients often experience neurocognitive symptoms (slowed thinking, confusion), hypersensitivity to stimuli (sounds, light), sleep disturbances, flu-like symptoms, and symptoms of autonomic dysfunction such as weakness, dizziness, and tremors. In some cases, immune system dysfunction is also observed. [Prins et al., 2006; Yancey et al., 2012; Graves et al., 2024] This disease can be serious and lead to significant disability. Some patients experience a significant reduction in independence and sometimes become housebound or bedridden. Caring for these patients often requires a multidisciplinary approach involving physicians of various specialties, physical therapists, mental health experts, home caregivers, and family members. Hospitalization may be necessary during periods of exacerbation, and chronic treatment includes symptomatic treatment, rehabilitation, and psychosocial support. [Graves et al., 2024] Terminology remains a contentious issue - the term ME/CFS reflects the current controversy over the pathophysiology and overall definition of the disease. Regardless of the nomenclature, it is a serious disease with a significant decline in quality of life, requiring thorough differential diagnosis and a holistic therapeutic approach. [Natelson et al. 2021; Unger et al. 2016]

Diagnostic criteria

Currently, there are no clear guidelines or diagnostic tests for CFS. The diagnosis can be made based on criteria stated below:

1. Center for Disease Control (CDC) criteria for chronic fatigue syndrome:

- Primary (mandatory) symptom – Clinically evaluated, unexplained, persistent or relapsing chronic fatigue that:
  - Has a new or clearly defined onset (not lifelong),
  - Is not a result of ongoing exertion,
  - Is not substantially relieved by rest,
  - Persists for at least 6 months,
  - Results in a significant reduction in previous levels of occupational, educational, social or personal activities.

- Additional symptoms – at least 4 of the following symptoms must be present simultaneously for > 6 months:
  - Impaired memory or concentration,
  - Sore throat,
  - Tender lymph notes,
  - Muscle pain,
  - Multi-joint pain without swelling or redness,
  - Headaches of new type, pattern or severity,
  - Unrefreshing (restless) sleep,
  - Post-exertional malaise (PEM) lasting more than 24 hours.

  Diagnostic requirement: Chronic fatigue (primary symptom) + at least four additional symptoms, with other medical and psychiatric causes exluded. [Lim et al., 2020]

2. International Consensus Criteria (ICC) for the diagnosis of CFS/ME

- Post-Exertional Neuroimmune Exhaustion (PENE) – compulsory criterium. Symptoms:
  - Marked and rapid physical and/or cognitive fatigability in response to exertion,
  - Exacerbation of symptoms such as flu-like feelings, pain, and worsening of other existing symptoms,
  - Exhaustion may occur immidiately or after a delay,
  - Symptoms may last for days, weeks, or longer.
- Neurological Impairments – at least 1 symptom from 3 of the 4 categories below:
  - Neurocognitive Impairments:
    - Impaired concentration,
    - Slowed thinking,
    - Memory problems,
    - Slowed speech,
    - Exertional dyslexia.
  - Pain:
    - Chronic headaches,
    - Muscle tension.
  - Sleep Disturbance:
    - Insomnia,
    - Unrefreshing sleep.
  - Motor issues:
    - Weakness.
- Immune, Gastrointesinal and Genitourinary Impairments – at least 1 symptom from 3 of the 5 categories below:
  - Flu-like symptoms,
  - Increased susceptibility to viral infection,
  - Gastrointestinal symptoms:
    - Nausea,
    - Bloating,
    - Irritable bowel syndrome.
  - Genitourinary symptoms:
    - Urinary urgency,
    - Nocturia.
  - Sensitivities:
    - Sensitivity to food,
    - Sensitivity to odors,
    - Sensitivity to chemicals.
- Energy Production/Transportation Impairments – at least 1 symptom:

- o Cardiovascular:
- • Orthostatic intolerance,
- • Palpitations,
- • Vertigo.
- o Respiratory:
- • Labored breathing,
- • Air hunger,
- • Chest wall muscle fatigue.
- o Thermoregulatory dysfunction:
- • Loss of thermostatic stability,
- • Intolerance to temperature extremes. [Yamano et al., 2021]

3. Fukuda Criteria for CFS/ME
   The patient must exhibit at least 4 of the following 8 symptoms for a minimum of 6 consecutive months.

- Impaired memory or concentration,
- Sore throat without evidence of active infection,
- Tender lymph nodes, particularly in the neck or armpits,
- Widespread muscle pain,
- Multi-joint pain without swelling or redness,
- New-onset, severe headaches,
- Unrefreshing sleep,
- Post-exertional malaise lasting more than 24 hours, characterized by worsening symptoms after physical or menatl exertion. [Brown et al., 2013]

The Fukuda Criteria, though historically central to CFS/ME diagnosis, is limited because it doesn't mandate post-exertional malaise, overlooks multisystem dysfunctions, relies on subjective symptom reporting, and fails to capture the fluctuating nature of the illness, yet it remains widely used in research while newer guidelines aim to provide a more precise and comprehensive framework. [Graves et al., 2024]

Diagnostic biomarkers

There is currently no universally accepted, clinically validated diagnostic biomarker for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) that reliably distinguishes it from other causes of chronic fatigue. However, several promising candidates have emerged in recent literature:

Elevated plasma autoantibodies against β2-adrenergic receptors and muscarinic acetylcholine receptor M4 have been shown to differentiate ME/CFS patients from healthy controls, independent of disease severity. [Gravelsina et al., 2022] Circulating extracellular vesicle (EV) proteins, specifically talin-1 and filamin-A, are increased in ME/CFS and demonstrate high diagnostic accuracy compared to healthy controls and other fatigue-related conditions. [Eguchi et al., 2020; Giloteaux et al., 2023] Distinct expression profiles of circulating microRNAs (miR-127-3p, miR-142-5p, miR-143-3p, miR-150-5p, miR-448, and miR-140-5p) have been identified in ME/CFS patients, correlating with disease severity and offering potential for differentiation from healthy individuals. [Soffritti et al., 2023] Cell-based assays measuring lymphocyte death rate, mitochondrial respiratory function, and TORC1 activity in peripheral blood mononuclear cells can distinguish ME/CFS from healthy controls with high sensitivity and specificity. [Missailidis et al., 2020; Xu et al., 2023] Blood-based Raman spectroscopy profiles of immune cells and cell-free RNA signatures (including plateletderived and immune cell-derived cfRNA) have demonstrated high accuracy in differentiating ME/CFS from healthy and disease controls. [Xu et al., 2023; Clarke et al., 2025; Gardella et al., 2025] Multi-omic proteomic panels and cytokine profiles (e.g., elevated IL-1β, IL-4, IL-6, IL-10, IP-10, leptin, TNF-α, and specific endothelial markers such as ET-1, VCAM-1, serpin E1, E-selectin) can distinguish ME/CFS from healthy controls and from post-COVID-19 conditions, though overlap exists with other inflammatory syndromes. [Giloteaux et al., 2023; Domingo et al., 2024]

While these biomarkers show promise, none are yet recommended for routine clinical diagnosis, and their specificity for ME/CFS versus other chronic fatigue etiologies remains under investigation. [Maksoud et al., 2023; Clarke et al., 2025] Diagnosis continues to rely on clinical criteria and exclusion of other causes.

Epidemiology

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME), has a worldwide prevalence that varies significantly depending on diagnostic criteria and study methodology. The most robust meta-analysis estimates a global prevalence of 0.68% (95% CI 0.48–0.97), with higher rates in women (1.36%) than men (0.86%), and a slight predominance in adults compared to children and adolescents. [Lim et al., 2020] Prevalence estimates range from 0.3% to 2.2% in the United States, with most patients undiagnosed or misdiagnosed. Women are affected three to four times more often than men, and the age at diagnosis is bimodal, peaking in adolescence and again in the thirties. [Latimer et al., 2023; Natelson et al. 2021] The American Academy of Family Physicians notes that the COVID-19 pandemic may increase prevalence due to overlap with post-COVID-19 condition. [Latimer et al., 2023]

In Poland, the only published community-based study using the Fukuda criteria found a prevalence of CFS/ME of approximately 0.05% among individuals self-presenting with fatigue (69 out of 1400 screened), though this likely underestimates true population prevalence due to study design. [Słomko et al., 2019] Polish patients with CFS/ME are predominantly female, with a mean age of 38 years, and most have experienced symptoms for over two years. Comorbidities such as orthostatic intolerance, excessive daytime sleepiness, anxiety, and depression are common, and quality of life is significantly impaired. [Słomko et al., 2019; Kujawski et al., 2021]

Across Europe, prevalence estimates are heterogeneous, but generally align with global figures, with most studies reporting rates between 0.2% and 1% depending on criteria used. [Éstevez-Lopez et al., 2018; Strand et al., 2019] The majority of patients are female, and the illness is characterized by prolonged duration and substantial morbidity. [Prins et al., 2006; Shafran et al., 1991]

Pathogenesis

The pathogenesis of chronic fatigue syndrome is multifactorial and involves the complex interaction of immune, metabolic, neuroendocrine, and autonomic dysfunctions. Current research points to the following mechanisms.

Immune dysregulation involving reduced NK cell cytotoxicity, T cell depletion, B cell dysfunction, and autoantibody production suggests an autoimmune basis for CFS. Chronic inflammation is maintained by the action of pro-inflammatory cytokines, dysfunction of glycolysis processes, and mitochondrial disorders in immune cells, which can cause chronic fatigue and exhaustion of the body. [Dudova et al., 2025; Mandarano et al., 2020; Maya, 2023] One of the most well-documented pathomechanisms of CFS is reduced cytotoxic activity of NK cells. This includes: decreased perforin and granzyme A/B levels, reduced CD107a degranulation, impaired MAPK phosphorylation, defective Ca2+ mobilization, TRPM3 ion channel dysfunction. These mechanisms may lead to increased susceptibility to chronic infections and inflammation. Recent studies also point to clonal exhaustion of CD8+ T cells, which is characterized by: increased inhibitory receptors (PD-1, CTLA-4, TIGIT, Lag-3), reduced proliferation, decreased IL-2, IFN, and TNF production, loss of mitochondrial membrane potential, and metabolic reprogramming. This exhaustion pattern promotes chronic infections and antigen stimulation. Research on B cells is unclear. Some studies indicate an increase in the level of naive B cells and CD20+CD5+ cells, which are responsible for the production of natural antibodies (NAbs) that are important for the functioning of the immune system. Studies using rituximab, an anti-CD20 drug, initially showed a 67% improvement in patients, suggesting an autoimmune component. Studies have shown numerous autoantibodies in CFS patients, including against ANA, dsDNA, phospholipids, gangliosides, adrenergic receptors, endothelial cells, and muscarine receptors. These result in orthostatic intolerance, muscle weakness, hypoxia, vascular dysregulation, and thrombotic risk. Patients with CFS/MS most likely present a complex interaction of immune mechanisms. Although there is no clear evidence for the autoimmune nature of the disease, it certainly plays a major role in some patients. [Dudova et al., 2025]

Metabolic impairments are prominent, particularly mitochondrial dysfunction leading to reduced ATP generation and redox imbalance. This metabolic insufficiency is compounded by shifts toward alternative energy pathways and increased oxidative and nitrosative stress, which further drive symptoms. [Dudova et al., 2025; Hatziagelaki et al., 2018; Morris et al., 2019; Anderson et al., 2020] The hallmark symptoms of CFS/ME, such as post-exertional malaise and fatigue that does not diminish with rest, have led researchers to investigate mitochondrial function and cellular energy mechanisms as a potential cause of this disease. Mitochondrial dysfunction involves increased oxidative stress, impaired calcium homeostasis, impaired mitochondrial membrane potential, and reduced ATP production. In particular, ATP production disorders can lead to symptoms such as fatigue, muscle pain, arthralgia, headaches, sleep disorders, and cognitive disorders. Metabolomic studies comparing ME/CFS patients with healthy controls have identified several biochemical abnormalities: decreased acylcholines (reduced levels may contribute to orthostatic intolerance and gastrointestinal symptoms), reduced dipeptides (reduced levels may contribute to reduced energy levels and hormone imbalance), reduced steroid classes (may reflect dysregulation of the HPA axis), altered sphingolipids concentration (altered cellular signaling and inflammatory processes). [Dudova et al., 2025]

Neuroendocrine disturbances, in particular disturbances of the hypothalamic-pituitary-adrenal (HPA) axis and disturbances of thyroid hormone metabolism, exacerbate immune and metabolic abnormalities. Focal neuroinflammation, possibly triggered by environmental, infectious, or stress-related factors, may disturb central homeostasis and contribute to cognitive and autonomic symptoms. [Dudova et al., 2025; Hatziagelaki et al., 2018; Prins et al., 2006; Glassford et al., 2017] The bidirectional interaction between the immune and endocrine systems plays a central role in the complex pathophysiology of CFS/ME. Cytokine imbalance can disrupt the HPA axis, a key mechanism regulating the stress response. Such disturbances can lead to hormone production disorders and impaired immune regulation, which can lead to symptoms such as fatigue, cognitive dysfunction, sleep disorders, and emotional instability. Thyroid hormones play a central role in metabolic regulation, thermoregulation, and cognitive function. In some patients with CFS, thyroid dysfunction is observed, including subclinical hypothyroidism and impaired conversion of T4 to T3. This can lead to fatigue, weight gain, and cold intolerance. Studies focusing on the HPA axis point to reduced cortisol levels, which cause profound fatigue. Diseases such as Addison's disease and adrenalectomy also have symptoms similar to CFS, leading to the hypothesis that hypocortisolism may be one of the factors causing CFS. Patients with CFS have been found to have low cortisol levels in the morning, impaired cortisol secretion rhythm, and reduced stress response. Interactions between impaired HPA axis, thyroid dysfunction, and autonomic nervous system dysfunction may combine to cause chronic inflammation in CFS. [Dudova et al., 2025]

Gut dysbiosis and increased intestinal permeability promote systemic inflammation via the gut-brain axis, linking gastrointestinal abnormalities to neurocognitive symptoms. [Dudova et al., 2025; Morris et al., 2019; Anderson et al., 2020] Many patients with CFS complain of gastroenterological symptoms such as diarrhea, constipation, nausea, and vomiting. In patients with CFS, gut dysbiosis, i.e., reduced microbial diversity and an imbalance between beneficial and harmful bacteria, is often observed. Studies indicate a decrease in the level of anti-inflammatory bacterial species such as *Bifidobacterium* and an increase in the level of pro-inflammatory species such as *Bacteroidetes* and *Enterobacteriaceae*. Dysbiosis can lead to disturbances in intestinal barrier integrity, leading to so-called "leaky gut," bacterial translocation, and systemic inflammation through the action of bacterial toxins. The gut-brain axis mediates communication between the gut and the CNS through hormonal, neural, and metabolic pathways. Dysbiosis can cause disturbances in neurochemical transmission, immune responses, and neuronal health. [Dudova et al., 2025]

Endothelial dysfunction driven by oxidative stress and autoantibody-mediated receptor interference, may explain orthostatic intolerance and impaired tissue perfusion. [Dudova et al., 2025; Morris et al., 2019] Oxidative and nitrosative stress are key contributors to endothelial dysfunction in CFS and may play an important role in disease pathophysiology. Oxidative stress results from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses. In CFS this imbalance may be amplified by mitochondrial dysfunction, immune dystegulation and chronic inflammation. Excess ROŚ can directly damage endothelial cells through lipid per oxidation, protein oxidation, and DNA damage, leading to impaired vascular function. Nitrosative stress involves excessive production of reactive nitrogen species. These reactive molecules can course nitration and nitrolysation of cellular components, further disrupting endothelial cells through function. It can promote to impaired vasodilation, platelet aggregation and leukocyte adhesion. Both oxidative and nitrosative stress stimulate inflammatory signaling within blood vessels. This leads to upregulation of endothelial cell adhesion molecules. These molecules facilitate adhesion and transmigration of immune cells into the vascular wall, perpetuating inflammation and endothelial damage. Endothelial dysfunction in CFS may manifest as persistent fatigue, cognitive impairment, orthostatic intolerance, exercise intolerance, muscle pain and headaches. [Dudova et al., 2025] Collectively, CFS arises from a self-sustaining cycle of chronic inflammation, metabolic insufficiency, neuroimmune imbalance, and multisystem dysfunction, with genetic and environmental factors acting as predisposing and precipitating elements. [Dudova et al., 2025; Prins et al., 2006; Arron et al., 2024]

Chronic fatigue can result from a wide range of medical, psychiatric, infectious, endocrine, hematologic, autoimmune, and oncologic causes. Below is a detailed discussion of the main etiologies.

Psychiatric causes

Depression and anxiety disorders are among the most common causes of chronic fatigue in clinical practice. [Prins et al., 2006] Key differences between depression and ME/CFS include: in depression, low mood, anhedonia, and feelings of guilt dominate, whereas in ME/CFS, post-exertional malaise and unrefreshing sleep are characteristic. [Prins et al., 2006; Natelson et al., 2021; Maes, 2011] Studies show that ME/CFS and depression can be distinguished with 100% accuracy based on the clinical picture, although they co-occur in approximately 30–40% of cases. [Prins et al., 2006; Maes, 2011]

Endocrine causes

Hypothyroidism is a common and reversible cause of fatigue. Symptoms include weight gain, cold intolerance, dry skin, constipation, and psychomotor slowing. Diagnosis requires measurement of TSH and free T4. Adrenal insufficiency (Addison's disease) is a rare but potentially life-threatening cause. Alarm symptoms include skin hyperpigmentation, orthostatic hypotension, hyponatremia, and hyperkalemia. Diagnosis requires morning cortisol measurement and ACTH stimulation testing.

Hematologic causes

Anemia (due to iron, vitamin B12, folate deficiency, or chronic disease) causes fatigue by reducing oxygen delivery to tissues. Basic diagnostics include complete blood count with smear, ferritin, iron, TIBC, vitamin B12, and folate.

Infectious causes

One hypothesis for ME/CFS etiology is chronic infection or reactivation of latent viruses. Viral agents implicated include Epstein–Barr virus (EBV), human herpesviruses (HHV-6A, 6B, 7, 8), cytomegalovirus (CMV), human parvovirus B19, enteroviruses, retroviruses, Ross River virus, and coronaviruses (including SARS-CoV-2). These viruses may contribute to ME/CFS via latent infection, reactivation, chronic inflammation, immune dysregulation, or triggering autoimmunity. Mechanisms linking infections to autoimmunity include: molecular mimicry: Pathogen antigens resemble self-molecules, potentially inducing autoreactivity; tissue damage: Pathogens or excessive immune responses damage host cells, releasing self-antigens that activate adaptive immune responses. These pathways suggest that post-viral immune dysregulation and autoimmunity may underlie ME/CFS in some patients. [Dudova et al., 2025] Chronic infections with herpesviruses are particularly relevant in the context of ME/CFS: Epstein-Barr virus (EBV) shows the strongest association with ME/CFS. Studies document active EBV infection in a significantly higher proportion of ME/CFS patients compared to controls (24.1% vs 4% EBV DNA in plasma, p=0.0027). [Shikova et al., 2020] The latest studies from 2026 found that 72.5% of ME/CFS patients have elevated IgG antibodies against dUTPase of multiple herpesviruses simultaneously, including EBV, HHV-6, and VZV, correlating with fatigue severity.[Palomo et al., 2026] ME/CFS patients release EBV at significantly higher levels than healthy individuals. [Hannestad et al., 2025] Cytomegalovirus (CMV) and HHV-6 are also studied, though the association is weaker than with EBV. [Shikova et al., 2020; Blomberg et al., 2019] Serological studies show no significant differences in IgG or IgM prevalence between patients and controls. [Shikova et al., 2020; Blomberg et al., 2019] Lyme disease can lead to post-treatment Lyme disease syndrome (PTLDS), which has a symptom profile similar to ME/CFS. Genetic studies suggest that weak binding of Borrelia burgdorferi antigens by specific HLA alleles may predispose to chronic symptoms.[James et al., 2025]

Autoimmune and inflammatory causes

Rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and other autoimmune diseases often present with chronic fatigue. Diagnostics include ESR, CRP, ANA, RF, and anti-CCP Polymyalgia rheumatica in individuals >50 years presents with pain and stiffness in the shoulder and hip girdles with elevated ESR (>40 mm/h) and CRP (>0.5 mg/dL in 99% of cases). [Espigol-Frigole et al., 2023]

Cardiologic causes

Heart failure causes fatigue due to reduced cardiac output and tissue hypoxia. Accompanying symptoms include dyspnea, edema, and orthopnea. ME/CFS is associated with an increased risk of early cardiovascular mortality (mean age 59 vs 78 years in the general population). [Natelson et al., 2021]

Oncologic causes

Lymphomas, leukemias, and other systemic cancers may manifest as chronic fatigue, fever, night sweats, and weight loss. Diagnostics include CBC with smear, LDH, and lymph node evaluation.

Other causes

Sleep apnea and sleep disorders lead to unrefreshing sleep and daytime fatigue. Diagnosis requires polysomnography. Celiac disease, food intolerances, and irritable bowel syndrome may coexist with chronic fatigue. Medications (beta-blockers, benzodiazepines, opioids, antihistamines) can cause fatigue as a side effect.

Psychological vs. Biological Causes

One of the most important controversies concerns whether CFS is primarily a biological or psychological disease. Some researchers cite psychological factors such as chronic stress or somatization as playing a major role in the development of symptoms. This view of the disease has led to the introduction of treatments focused on the patient's psyche. However, there is also much evidence to suggest that biological dysfunctions underlie CFS. These include dysfunctions of the immune, endocrine, mitochondrial, and autonomic systems. Currently, both options are believed to influence the disease. [Dudova et al., 2025]

Symptoms

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME), is characterized by persistent, unexplained, and disabling fatigue lasting at least six months, which is not substantially alleviated by rest and results in a marked reduction in occupational, educational, social, or personal activities. [Latimer et al., 2023; Stave et al., 2024; Prins et al., 2006] The American Academy of Family Physicians and the American College of Occupational and Environmental Medicine both endorse the National Academy of Medicine (formerly Institute of Medicine) diagnostic criteria, which require the following core symptoms:

- Postexertional malaise: A worsening of symptoms after physical, cognitive, or emotional exertion, often described as a "crash".[Latimer et al., 2023; Stave et al., 2024; Stussman et al. 2020]
- Unrefreshing sleep: Sleep that does not restore energy or relieve fatigue. [Latimer et al., 2023; Stave et al., 2024; Prins et al., 2006; Kujawski et al., 2021]
- Cognitive impairment: Often referred to as "brain fog," including difficulties with memory, concentration, and information processing. [Latimer et al., 2023; Stave et al., 2024; Prins et al., 2006; Kujawski et al., 2021]
- Orthostatic intolerance: Symptoms such as lightheadedness, palpitations, nausea, or syncope upon standing, sometimes associated with postural orthostatic tachycardia syndrome (POTS). [Latimer et al., 2023; Stave et al., 2024; Natelson et al., 2021]

Additional symptoms frequently reported include muscle and joint pain, headaches, sore throat, tender lymph nodes, gastrointestinal or genitourinary complaints, hypersensitivity to external stimuli (light, noise, chemicals), impaired immune function, influenza-like symptoms (chills, fever), thermoregulatory issues, visual disturbances, night sweats, and respiratory complaints (air hunger). [Latimer et al., 2023; Stave et al., 2024; Prins et al., 2006; Lorusso et al., 2009; Craig et al., 2002] Onset may follow an infectious episode, such as mononucleosis or COVID-19. [Latimer et al., 2023; Stave et al., 2024; Prins et al., 2006]

Symptoms are heterogeneous and may fluctuate over time, with patients often reporting an average of eight concurrent complaints. [Prins et al., 2006; Kujawski et al., 2021] Psychiatric comorbidities, especially depression and anxiety, are common but not universal. [Prins et al., 2006; Natelson et al., 2021] No physical examination findings or laboratory tests are specific for CFS; diagnosis is clinical and requires exclusion of other medical and psychiatric causes. [Latimer et al., 2023; Prins et al., 2006; Yancey et al., 2012]

Table 1. Common symptoms of CFS/ME

Common symptoms of Chronic Fatigue Syndrome (CFS/ME)	
Neurology	Cognitive dysfunction Sleep dysfunction Hipersensitivity to stimuli Brain Fog
Gastrointestinal System	Vomiting Diarrhea Nausea
Immune System	Flu-like symptoms Tender lymph notes Increased susceptibility to infection
Autonomic System	Tachycardia Orthostatic intolerance Dizziness Fainting
Respiratory System	Dyspnoe Persistent cough Shortness of breath
Other	Myalgia Headache Post-Exertional Malaise

Source: Dudova, D., Bozhkova, M., Petrov, S., Nikolova, R., Kalfova, T., Ivanovska, M., Vaseva, K., Nikolova, M., & Ivanov, I. N. (2025). Insights into the Complex Biological Network Underlying Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *International journal of molecular sciences*, *27*(1), 268. https://doi.org/10.3390/ijms27010268

Comorbidities

The most typical comorbidities seen in patients with chronic fatigue syndrome are: Psychiatric disorders, especially major depressive disorder and generalized anxiety disorder, are highly prevalent, with rates ranging from 45% to 68% in clinical cohorts. Insomnia and other sleep disorders, such as obstructive sleep apnea and periodic limb movement disorder, are also frequently comorbid and can further exacerbate fatigue and cognitive symptoms. [Leong et al., 2022; Marinam et al., 2013; Natelson et al., 2021, 2019; Prins et al., 2006] Medically unexplained syndromes are common, including fibromyalgia, irritable bowel syndrome, and multiple chemical sensitivities. These conditions often co-occur, and the presence of multiple syndromes is associated with greater symptom burden and disability. [Natelson et al., 2019; Craig et al., 2002; Sharif et al., 2018] Autoimmune and rheumatologic conditions such as rheumatoid arthritis and Sjögren's syndrome have been reported at higher rates in CFS populations, suggesting possible overlap or shared pathophysiology. [Leong et al., 2022; Sharif et al., 2018] Cardiovascular disease is increasingly recognized as a comorbidity, with CFS patients demonstrating a higher risk of early cardiovascular mortality and increased prevalence of traditional cardiovascular risk factors, independent of other comorbidities.[Natelson et al., 2021; Denu et al., 2025] Gastrointestinal disorders, including Crohn's disease and ulcerative colitis, as well as metabolic conditions like type 2 diabetes, dyslipidemia, and gout, are also observed more frequently in CFS cohorts compared to controls. [Leong et al., 2022] Clinicians should systematically assess for these comorbidities, as their presence can significantly impact management and prognosis in chronic fatigue syndrome. [Leong et al., 2022; Marinam et al., 2013; Natelson et al., 2019; Aaron et al., 2001; Craig et al., 2002]

Differential diagnosis

The differential diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is extensive, as chronic fatigue is a nonspecific symptom common to many medical and psychiatric conditions. The key to distinguishing ME/CFS from other causes of chronic fatigue is identifying postexertional malaise (PEM) - a prolonged worsening of symptoms following minimal physical, cognitive, or emotional exertion that was previously tolerated. [Natelson et al., 2021; Bateman et al., 2021] Most likely diagnoses:

- Primary sleep disorders (obstructive sleep apnea, insomnia, circadian rhythm disorders) - Sleep-disordered breathing is found in approximately 22-30% of patients evaluated for ME/CFS, and primary sleep disorders are detected in up to 50% of patients referred with presumed CFS. [Bileviciute-Ljungar et al., 2020; Marinam et al., 2013; Gotts et al., 2013] However, these may be comorbid rather than exclusionary conditions, as polysomnographic findings in ME/CFS patients often show sleep architecture abnormalities despite normal total sleep time. [Mohamed et al., 2023; Jackson et al., 2012]
- Major depressive disorder with somatic symptoms - Depression frequently co-occurs with ME/CFS, but can be distinguished by the absence of PEM and different inflammatory profiles. ME/CFS patients have higher plasma proinflammatory cytokines (IL-1, TNF-α) than depressed patients, and the correlation between neopterin and cytokines differs between the two conditions. [Maes et al., 2011; 2012] Importantly, fatigue in depression typically improves with exercise, whereas ME/CFS patients experience symptom exacerbation. [Bateman et al., 2021]
- Generalized anxiety disorder - Similar to depression, anxiety can present with fatigue and somatic symptoms but lacks the characteristic PEM and orthostatic intolerance seen in ME/CFS. [Natelson et al., 2021]
- Hypothyroidism - A subset of ME/CFS patients (approximately 16%) exhibit "low T3 syndrome" with reduced free T3 and total T3 despite normal TSH, resembling a mild form of non-thyroidal illness syndrome. [Ruiz-Nuñez et al., 2018] However, primary hypothyroidism presents with elevated TSH and responds to thyroid replacement, whereas the thyroid abnormalities in ME/CFS may reflect metabolic inflammation rather than primary thyroid disease.
- Anemia (iron deficiency or other) - While anemia causes fatigue that improves with treatment, ME/CFS patients paradoxically show higher ferritin levels compared to controls, though some may have functional iron deficiency. [Baklund et al., 2021]

- Lyme Disease - Lyme disease can mimic CFS symptoms such as fatigue, cognitive impairment and arthralgia
- Multiple Sclerosis - similar symptoms like fatigue, muscle weakness, cognitive dysfunction. Unlike CFS/ME, MS often presents with additional neurological signs, such as visual disturbances, coordination problems, and sensory deficits.
- Rheumatological disorders - similar symptoms like joint pain, weakness, dizziness. Unlike CFS/ME, these conditions may show positive laboratory findings, such as elevated inflammatory markers (ESR, CRP) or autoantibodies, which aid in their diagnosis. [Dudova et al., 2025]

Cannot-Miss Diagnoses:

- Malignancy (especially hematologic) - Weight loss, fever, night sweats, progressive lymphadenopathy, or abnormal blood counts should prompt evaluation for lymphoma, leukemia, or other cancers. [Bateman et al., 2021]
- Heart failure or cardiomyopathy - ME/CFS is associated with increased cardiovascular mortality (mean age 59 vs 78 years in general population), and cardiovascular disease can present with fatigue and exercise intolerance. [Natelson et al., 2021]
- Chronic pulmonary disease (COPD, interstitial lung disease) - Hypoxia from lung disease causes fatigue but is distinguished by abnormal pulmonary function tests and imaging. [Bateman et al., 2021]

Diagnostic approach

The diagnosis of ME/CFS requires: (1) profound fatigue lasting ≥6 months with substantial reduction in pre-illness activity levels; (2) postexertional malaise; (3) unrefreshing sleep; and at least one of (4) cognitive impairment or (5) orthostatic intolerance. [Natelson et al., 2021; Bateman et al., 2021; Latimer et al., 2023] Laboratory evaluation should include a focused panel to exclude alternative diagnoses: complete blood count, comprehensive metabolic panel, TSH, ESR/CRP, creatine kinase, and urinalysis. [Bateman et al., 2021; Sandler et al., 2020] Additional testing based on clinical suspicion may include ferritin, vitamin B12, vitamin D, celiac serology, and rheumatologic markers. [Bateman et al., 2021] Notably, routine blood tests in ME/CFS patients often show subtle abnormalities including elevated inflammatory markers (ESR, leukocytes), lower creatine kinase and creatinine (suggesting muscle metabolic dysfunction), and immunoglobulin deficiencies (particularly IgG3 and IgG4 subclasses in 17.6% of patients). [Baklund et al., 2021; Lutz et al., 2021] Polysomnography should be considered when sleep-disordered breathing is suspected, as it is found in a substantial minority of ME/CFS patients and may be a comorbid treatable condition. [Marinam et al., 2013, 2013]

Assuming basic history, physical examination, and review of systems have been completed, the following targeted approach is recommended:

- Complete blood count with differential
- Comprehensive metabolic panel
- TSH (consider free T3 if TSH normal but clinical suspicion high)
- ESR or CRP
- Creatine kinase
- Urinalysis
- Consider: ferritin, vitamin B12, vitamin D, celiac antibodies based on clinical context

- Characterize the fatigue pattern: Does minimal exertion cause symptom worsening lasting >24 hours (PEM)?
- Sleep quality and witnessed apneas
- Orthostatic symptoms (lightheadedness, palpitations with standing)
- Cognitive symptoms ("brain fog")
- Infectious trigger (flu-like illness, mononucleosis, COVID-19)

Red flags requiring urgent evaluation:

- Unexplained weight loss, fever, or night sweats (malignancy)
- Progressive dyspnea or chest pain (cardiopulmonary disease)
- Focal neurologic deficits (CNS pathology)
- Abnormal blood counts (hematologic malignancy) [Graves et al., 2024]

Treatment

Treatment for chronic fatigue syndrome (CFS) is primarily focused on symptom management and functional improvement, as there is no FDA-approved pharmacologic therapy or disease-modifying intervention. The American Academy of Family Physicians recommends that treatment be individualized and symptom-based, with prioritization according to patient needs. Multidisciplinary care is often required, including regular follow-up and telemedicine for severely affected or homebound patients. [Latimer et al., 2023] The most evidence-supported interventions are cognitive behavioral therapy (CBT) and graded exercise therapy (GET), both of which have demonstrated moderate improvements in fatigue, physical functioning, and social adjustment in randomized controlled trials and real-world clinical settings. [Larun et al., 2024; Sharpe et al., 2022; Prins et al., 2006] CBT is delivered by trained therapists and targets maladaptive cognitions and behaviors related to fatigue, while GET involves a gradual, supervised increase in physical activity. Both should be tailored to the patient’s tolerance and delivered by specialists familiar with CFS/ME. Pharmacologic treatments are not routinely recommended, as trials of agents such as antivirals, immunomodulators, and antidepressants have shown inconclusive or insufficient evidence of benefit. [Smith et al., 2015; Castro-Marrero et al., 2017; Richman et al., 2019] Medications may be used for comorbid symptoms (e.g., pain, sleep disturbance, depression), starting at low doses and titrating cautiously due to increased sensitivity to adverse effects. [Latimer et al., 2023]

Lifestyle management strategies, such as pacing (balancing activity and rest), are advocated by patient groups and may help some individuals, though evidence is limited and mixed. [Prins et al., 2006; astro-Marrero et al., 2017] Nutritional supplements should only be considered in cases of documented deficiency. [Castro-Marrero et al., 2017]

Pharmacological Management

Medications are used to alleviate key symptoms such as pain, sleep disturbances, mood disorders, and immune-related issues. Treatment is individualized based on the patient’s predominant symptoms. Main medication groups include:

- NSAIDs (e.g., ibuprofen, naproxen) - Used to relieve joint and muscle pain, headaches, fever, and inflammation.
- Anticonvulsants (gabapentin, pregabalin) - Often prescribed for neuropathic pain and sleep disturbances.
- Antidepressants (SSRIs and tricyclic antidepressants) - Used for comorbid depression, anxiety, insomnia, and chronic pain. Therapeutic effects typically appear after 3-4 weeks.

- Opioids (tramadol, codeine, morphine) - Reserved for severe pain unresponsive to other treatments; generally used short-term due to addiction risk.
- Antiviral and immunomodulatory agents (e.g., rintatolimod/Ampligen, acyclovir, valganciclovir) - Investigated as potential treatments, but evidence remains limited and adverse effects may occur.
- Interferons - Insufficient high-quality evidence supports their routine use.
- Steroids (hydrocortisone, fludrocortisone) - Studied in several trials, but results are inconclusive.

Overall, pharmacological therapy is supportive and symptom-based rather than disease-modifying. [Graves et al., 2024]

Non-Pharmacological Management

Non-pharmacological approaches include:

- Cognitive Behavioral Therapy (CBT) and Graded Exercise Therapy (GET) - Graded exercise therapy (GET) is a structured intervention for chronic fatigue syndrome (CFS) in which patients are guided to establish a baseline of physical activity and then incrementally increase activity levels, typically starting with low-intensity aerobic exercise such as walking. The approach is based on the theory that deconditioning and avoidance perpetuate symptoms, and the goal is to reverse these processes through gradual, negotiated increases in activity, with careful monitoring to avoid overexertion and exacerbation of symptoms. GET is usually delivered by physiotherapists and may involve setting target heart rates and aiming for 30 minutes of light exercise five times per week, with intensity increased as tolerated. [White et al., 2011]
- Adaptive Pacing Therapy (APT) - Adaptive pacing therapy (APT), in contrast, is based on the "energy envelope" theory, which posits that CFS is an organic disease with a finite energy limit. APT aims to help patients optimize adaptation by planning and pacing activities to avoid symptom exacerbation, prioritizing essential tasks, and alternating activity with rest. Patients are encouraged to avoid exceeding 70% of their perceived energy envelope, and increases in activity are only recommended if tolerated without worsening symptoms. APT is typically delivered by occupational therapists and emphasizes self-management and symptom awareness. [White et al., 2011]

In the PACE trial, a large randomized controlled study, GET and cognitive behavioral therapy (CBT) were found to be moderately more effective than APT or specialist medical care alone in reducing fatigue and improving physical function, with no significant differences in safety outcomes between interventions. [White et al., 2011; 2013] However, patient surveys report variable responses, with some patients experiencing negative effects from GET and favoring pacing strategies. [Geraghty et al., 2019; Casson et al., 2023] Recent systematic reviews confirm that activity pacing interventions can reduce fatigue and psychological distress and improve physical function, especially when gradual escalation of activity is encouraged. [Casson et al., 2023; Thornton et al., 2025] The UK National Institute for Health and Care Excellence (NICE) has recommended GET and CBT, but ongoing debate and evolving patient perspectives highlight the need for individualized, collaborative management. [White et al., 2011; Thornton et al., 2025; Clark et al., 2017]

Future of CFS/ME

CFS/ME is a complex, heterogeneous disorder with variable progression, symptom fluctuations, and limited understanding of its biological basis. Key research priorities and technological approaches include:

- Genetics and Genomics: Identifying genetic variants through GWAS and transcriptomics to understand susceptibility, disease severity, and molecular mechanisms.
- Biomarkers: Developing reliable biomarkers from immune, neuroendocrine, metabolic, and proteomic profiles to improve diagnosis, subtyping, and monitoring of disease progression.

- Metabolomics and Proteomics: Studying metabolic and protein expression patterns to identify disease-specific abnormalities.
- Neuroimaging: Advanced MRI techniques (fMRI, DTI) can reveal brain structure and function changes linked to neurological symptoms.
- Data Integration and AI: Combining omics, neuroimaging, and clinical data with machine learning can enable predictive modeling, better disease subtyping, and personalized treatment strategies.
- Digital Health and Wearables: Real-time monitoring of activity, sleep, and physiological parameters helps track symptom fluctuations and optimize management.
- Gut Microbiome and Environmental Factors: Investigating microbiota, infections, toxins, and stress as contributors to disease pathogenesis.
- Machine Learning for Detection: MRI-based morphological analysis combined with AI can aid early detection, classification, and prediction of CFS/ME, potentially guiding early interventions.

In summary, integrating advanced omics, neuroimaging, digital technologies, and AI holds promise for understanding CFS/ME biology, improving diagnosis, subtyping, and enabling personalized, targeted interventions. [Graves et al., 2024]

Summary

Chronic fatigue syndrome (ME/CFS) is a complex, multisystem disorder marked by persistent fatigue, post-exertional malaise, cognitive impairment, and unrefreshing sleep. Its pathogenesis involves immune, metabolic, neuroendocrine, and autonomic dysfunctions, with potential contributions from infections, autoimmunity, and gut dysbiosis. Diagnosis relies on clinical criteria and exclusion of other conditions, as no definitive biomarker exists. Management is symptomatic and multidisciplinary, incorporating pacing, cognitive behavioral therapy, graded exercise, and targeted pharmacotherapy for comorbidities. Research into biomarkers, genomics, metabolomics, and digital health tools offers promise for improved diagnosis and personalized treatment.

AI

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

DISCLOSURES

Authors contribution:

Conceptualization: A.S
Methodology: A.S, Z.K
Formal analysis: O.K, M.K
Investigation: M.R., A.S

Writing - rough preparation: A.S, O.K
Writing - review and editing: A.S., M.K
Visualization: Z.K
Supervision: M.R

All authors have read and agreed with the published version of the manuscript.

Funding Statement: This Research received no external funding.
Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Not applicable.
Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article's bibliography.
Conflicts of Interests: The authors declare no conflict of interest.

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