Myalgic Encephalomyelitis/Chronic Fatigue Syndrome – Etiology, Pathophysiology, Diagnosis and Treatment

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Abstract:
Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex condition characterized by a broad spectrum of overlapping symptoms and manifesting in multiple systems of the body. Patients experience symptoms such as profound fatigue, post-exertional malaise (PEM), unrefreshing sleep, and cognitive impairments. It affects millions worldwide, yet much is still unknown about its etiology and pathophysiology. The condition's onset is frequently linked to infectious triggers, including viral infections, suggesting a dysregulated immune response as a central component. Diagnosing ME/CFS poses significant challenges due to many unspecific symptoms that overlap with various other conditions. Current treatment strategies focus primarily on symptomatic relief and lifestyle modifications to manage disease impact. The COVID-19 pandemic has further spotlighted ME/CFS, drawing parallels between long COVID and ME/CFS symptomatology and underscoring the urgent need for comprehensive research.

Keywords: Myalgic Encephalomyelitis, Chronic Fatigue Syndrome, Infectious trigger, Post-Exertional Malaise, COVID-19, Post-COVID syndrome

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1. Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex and disabling, multi-systemic chronic disease affecting millions of people around the world. Despite its increasing prevalence and debilitating nature, it is still largely unknown to both the public and many medical professionals. Understanding of its etiology and pathophysiology is limited, diagnostic criteria inconsistent, and diagnostic and treatment guidelines inadequate and outdated (Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, 2015). The disease was initially defined only as a "persistent or relapsing, debilitating fatigue of new onset and unknown origin" (Holmes et al., 1988). In recent years it has been established that it is a disease characterized by a broad spectrum of overlapping symptoms manifesting in multiple systems of the body. These symptoms are often widespread, and shared by many other conditions, making ME/CFS difficult to diagnose. Marked variability in presentation, severity, course, and duration of disease in patients as well as lack of a definitive diagnostic test or biomarker, has resulted in controversy and lack of consensus around its diagnosis, with over a dozen different clinical definitions being used. The inconsistency in diagnostic criteria, along with lack of interest and funding, made it difficult to conduct conclusive research and studies that would help us better understand this disease (Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, 2015; Bested and Marshall, 2015).

2. Etiology and pathophysiology

The onset of disease appears to be precipitated by both genetic and environmental factors (Bested and Marshall, 2015). Very often there is a triggering event present at the start of the illness, usually a prolonged infection. Infectious triggers connected to ME/CFS include: Epstein-Barr virus (EBV), Cytomegalovirus, Varicella-Zoster virus, Borrelia burgdorferi (Lyme disease), Coxiella burnetii (Q fever), parvovirus B19, Coxsackie B virus, Chlamydia pneumoniae, mycoplasma, and SARS-CoV-2. Patients may also experience reactivation of previously latent infections (eg. Herpes viruses) (Frémont et al., 2009). Several studies found high titers of specific EBV antibodies in ME/CFS patients as well as the presence of a specific IgG that was not detected in healthy individuals with previous EBV infection (Loebel et al., 2017). The onset of ME/CFS could be explained as an EBV infection-triggered immune system dysregulation. One of the most consistent findings in ME/CFS patients is poor cytotoxic activity of natural killer (NK) cells (Bateman et al., 2021). NK cells are the body's first line of defense and play a crucial role in surveillance against tumor cells and infections, preventing latent viruses from reactivating. A study of cytokine networks has found significant alterations in the cytokine profiles of ME/CFS patients, which showed differences in the relationships between the cytokines when compared to healthy controls (Broderick et al., 2010). A common hypothesis states that an abnormal antiviral immune response to the original state of microbial inflammation triggers a state of low-grade systemic inflammation. There is decreased ability to fight active or latent infections due to decreased NK cell function as well as chronic immune activation even in the absence of microbial infection, characterized by consistently elevated levels of proinflammatory cytokines and oxidative stress. This constant proinflammatory state of the body may bring about changes in different systems of the body, explaining the wide range of symptoms of ME/CFS. Another mechanism heavily contributing to the severe lack of energy seen in patients is the impairment of aerobic respiration. Mitochondria are a major producer of reactive oxygen species (ROS) in the cell which also makes them extremely susceptible to damage by oxidative stress. Increased levels of proinflammatory cytokines and increased oxidative stress damage mitochondrial DNA and membrane and interfere with the process of oxidative phosphorylation, resulting in decreased ATP production by mitochondria (Bested and Marshall, 2015).

3. Symptoms and manifestations

ME/CFS manifests itself in multiple systems of the body. Patients usually exhibit a cluster of signs and symptoms. Some develop all symptoms shortly after the onset, while others develop additional symptoms over time (Committee on the Diagnostic Criteria for Myalgic

Encephalomyelitis/Chronic Fatigue Syndrome, 2015). Fatigue is a broad and common symptom that presents in many different diseases. However, the fatigue experienced by ME/CFS patients is more profound, intense, debilitating and longer-lasting than in other diseases. It is also not a consequence of ongoing exertion and is not alleviated by rest (Bateman et al., 2021). Post-exertional malaise (PEM) refers to the worsening or exacerbation of disease symptoms following physical or mental exertion that was normally tolerated before disease onset. It is the hallmark symptom of ME/CFS, distinct from symptoms of other chronic diseases (Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, 2015). PEM differs from normal exercise intolerance in that it has a delayed onset, an abnormally prolonged recovery period. It usually sets in 12-48 hours after activity and may last anywhere from a few days to many weeks (Jason et al., 2021). Most patients with ME/CFS experience sleep dysfunction. The most common sleep-related symptom that patients report is unrefreshing or non-restorative sleep, often describing it as "feeling as tired upon waking as before going to bed" (Bateman et al., 2021). Patients also suffer from symptoms of neurocognitive dysfunction. When asked to summarize their problems, they usually characterize them as so-called "brain fog" (Bested and Marshall, 2015). This includes symptoms such as confusion, absent-mindedness, difficulty concentrating, disorientation, inability to multitask, and problems with short-term memory (FDA, 2013). In ME/CFS both the sympathetic and parasympathetic parts of the autonomic nervous system (ANS) and the equilibrium between them may be disturbed, manifesting in dysautonomia (Van Cauwenbergh et al., 2014). The most prevalent manifestation of dysautonomia, present in up to 97% of patients is orthostatic intolerance (OI) (Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, 2015). OI is a group of clinical syndromes in which symptoms worsen upon assuming and maintaining a standing position and are alleviated by lying down. This includes symptoms such as fatigue, lightheadedness, dizziness, syncope, nausea, headaches, heart palpitations, and visual disturbances. Specific subtypes of OI found in ME/CFS are: postural orthostatic tachycardia syndrome (POTS), neurally mediated hypotension (NMH) and delayed postural hypotension. Other common symptoms include: chronic pain (fibromyalgia), gastrointestinal symptoms, food and chemical hypersensitivities, and psychiatric symptoms (Bested and Marshall, 2015).

4. Prognosis

Prognosis in ME/CFS is generally considered to be fairly poor. Full recovery is rare with only 5% of patients returning to pre-morbid levels of functioning (Cairns and Hotopf, 2005). About 40% report substantial improvement in their condition, allowing them to resume daily activities, but still functioning at a lower level than pre-disease (Cairns and Hotopf, 2005). Degree of functional impairment ranges from mild to severe. Around 25% of patients are mildly impaired, capable of participating in daily activities at a reduced level. About 50% suffer from a moderate form of disease, are severely limited in their daily activities, and usually incapable of work. Severe form of disease is present in 25% of patients, who spend their days mostly bedbound, requiring assistance to perform basic activities (Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, 2015).

5. Diagnosis

The foundation for suspected ME/CFS is a presentation of new-onset fatigue accompanied by a substantial reduction in functional activity that persists for 6 months, along with additional symptoms. A diagnosis of ME/CFS is made if diagnostic criteria are met following an appropriate history, physical examination, and diagnostic testing. Table 1 contains the data on, and comparisons between four of the most used ME/CFS diagnostic criteria in the 21st century (Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, 2015; Fukuda et al., 1994; Carruthers et al., 2003; National Institute for Health and Care Excellence, 2021).

Table 1. Comparison between different diagnostic criteria for ME/CFS.

Criteria	1994 Fukunda	2003 CCC	2015 IOM	2021 NICE
New onset	Required	Required	Required	Required
Functional impairment	50% decrease	Substantial	Substantial	Significant
Minimal duration	6 months	6 months	6 months	3 months
Fatigue	Required	Required	Required	Required
Motor-sensory disturbances	4 symptoms required from any of these 5 categories	2 symptoms from either	CP or OI	Required
Cognitive problems (CP)		Required		
Pain		Required	Required	Required
Sleep disturbances		Required	Required	Required
PEM		1 symptom from these 3 categories		
Flu-like symptoms				
Infection susceptibility				
Food sensitivities		1 symptom from these 3 categories	CP or OI	
Gastrointestinal problems				
Genitourinary problems				
Orthostatic intolerance (OI)		1 symptom from these 4 categories		
Respiratory problems				
Cardiovascular problems				
Temperature intolerance				
Thermostatic instability				

Table 2. Differential diagnoses of ME/CFS.

Neurological disorders: multiple sclerosis, vitamin B12 deficiency, spinal stenosis, craniocervical instability	**Gastrointestinal disorders:** celiac disease, food allergy/intolerances, inflammatory bowel disease, small intestinal bacterial overgrowth	**Infectious diseases:** HIV, tick borne diseases, hepatitis B/C, giardia, West Nile virus, Q-fever, Epstein-Barr virus, parvovirus 19
Endocrine disorders: primary adrenal insufficiency, hyper-cortisolism, hyper- or hypo-thyroidism	**Rheumatological disorders:** systemic lupus erythematosus, rheumatoid arthritis, polymyositis, polymyalgia rheumatica	**Cardiovascular disorders:** cardiomyopathy, coronary disease, valve disease, arrhythmias
Sleep disorders: sleep apnea, narcolepsy	**Psychiatric disorders:** anxiety, depression, bipolar disorder	**Hematological disorders:** anemia (iron deficiency, other forms), iron overload
Other: Gulf War illness, cancer, adverse medication effects, severe obesity, COPD		

Table 3. Comorbidities of ME/CFS.

Neurological disorders: sensory hypersensitivities, migraine headaches, peripheral neuro-pathy, small fiber neuropathy	**Gastrointestinal disorders:** food allergy/intolerances, gut motility issues, celiac disease, irritable bowel syndrome, small intestinal bacterial overgrowth	**Immunological disorders:** new or worsened allergies, mast cell activation syndrome, multiple chemical sensitivities, immunodeficiency
Endocrine disorders: hypothyroidism, HPA axis dysregulation, metabolic syndrome	**Rheumatological disorders:** fibromyalgia, Ehlers-Danlos syndrome, temporomandibular joint dysfunction, Sic casyndrome (dry eyes/mouth)	**Autonomic dysfunction:** postural orthostatic tachycardia syndrome (POTS), neurally mediated hypotension (NMH), orthostatic hypotension
Sleep disorders: sleep apnea, restless leg syndrome	**Psychiatric disorders:** secondary anxiety, secondary depression	**Gynecological disorders:** endometriosis, premenstrual syndrome
Other: nutritional deficiencies, vitamin B12 and D deficiencies, obesity		

ME/CFS is often a diagnosis of exclusion. Patients present with a wide array of symptoms, many of which are nonspecific and can be commonly observed in other chronic or acute conditions. When making a diagnosis of ME/CFS these diseases need to be excluded as the primary cause of the patient's problems. Many diseases can also co-exist with ME/CFS and precipitate or potentiate some of its symptoms (Bested and Marshall, 2015). Diagnosis of these comorbid conditions does not exclude diagnosis of ME/CFS but can help guide

treatment and improve the patient's health, function, and quality of life. **Tables 2** and **Table 3** detail many of the potential differential diagnoses and comorbidities of ME/CFS as outlined in the 2020 US ME/CFS Clinician Coalition Recommendations (US ME/CFS Clinician Coalition, 2020).

6. Treatment

Currently, there is no treatment that would entirely cure ME/CFS. The disease can be managed and controlled through symptomatic treatment, non-pharmacological therapy, nutritional supplementation as well as alternative approaches (ME/CFS treatment recommendations, US ME/CFS Clinician Coalition, 2021). The goals of ME/CFS treatment are the improvement of current symptoms, functioning, and quality of life, prevention of symptom worsening, and helping patients understand and cope with the impact of the disease (International Association of CFS/ME, 2014). A drug that would interfere with the pathophysiological processes of ME/CFS has not been identified and approved for use in ME/CFS. In 2021 the first official recommendations for pharmacological therapy of ME/CFS, which focus on symptomatic treatment were outlined and released by the US ME/CFS Clinician Coalition (ME/CFS treatment recommendations, US ME/CFS Clinician Coalition, 2021). Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed to manage muscle pain and headaches. Tricyclic antidepressants are usually given to improve sleep quality. Fludrocortisone and fluid expansion therapy have proven to be effective in managing orthostatic intolerance. One of the most effective non-pharmacological methods for the management of disease is to teach patients about physical and cognitive "pacing". Pacing is an individualized approach centered around the adaptation of the patient's lifestyle based on their functional capabilities by balancing rest and activity, with the goal of conserving energy and avoiding flare-ups of post-exertional malaise. Once the patient establishes a baseline level of functioning through pacing, gradual increases in activity can be applied. The use of alternative approaches such as meditation, massage therapy, acupuncture, and chiropractic treatments is not well documented in literature, but may improve the general well-being of patients (International Association of CFS/ME, 2014).

7. COVID-19 and future

Over the last two years, the COVID-19 pandemic has resulted in 530 million cases and 6 million deaths worldwide (Worldometer, 2021). While the devastating acute effects of COVID-19 have been well documented, recently the research community's interest has turned towards the chronic sequelae of the disease (Wong and Weitzer, 2021). Around 87% of patients affected by COVID-19 continue to experience at least one symptom two months after disease onset and up to 30% of people continue to experience at least one symptom, six months after onset (Carfì et al., 2020). This chronic phase of COVID-19 has been given names such as "long COVID" or "post-COVID syndrome. The most frequently reported symptoms six months after onset were fatigue, post-exertional malaise, and cognitive dysfunction ("brain fog") (Wong and Weitzer, 2021). Considering the characteristic pattern of symptoms along with the post-viral onset, parallels can be drawn to ME/CFS and suggest that post-COVID syndrome could be a very similar disease.

8. Conclusion

In conclusion, ME/CFS represents a a growing global issue for patients, healthcare professionals and economies. The advent of the COVID-19 pandemic has not only amplified the global burden of chronic, post-viral syndromes but also highlighted the similarities between long COVID and ME/CFS and the need for new research into the etiology, pathophysiology, diagnosis, and treatment strategies of these diseases. Embracing a multidisciplinary approach to research and patient care will be key in finding a path towards identifying disease triggers, understanding its mechanism refining diagnostic criteria and exploring effective treatments.

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