Chronic Fatigue System: An Overview

August 11, 2023 | Emilee Friedman Fechter, MS, MWC

Introduction

The US Centers for Disease Control and Prevention (CDC) estimates that as many as 2.5 million Americans suffer from chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME).[1] Despite this, the vast majority of patients with CFS remain undiagnosed, and those diagnosed may struggle to receive proper treatment.[2] This is largely due to (1) outdated guidance for clinicians and insufficient coverage by medical educators[2], and (2) the heterogeneity of its presentation.[3] Furthermore, there is no biomarker or other laboratory test for CFS; as a result, some clinicians do not recognize CFS as a true pathological disorder.[4]

Diagnosis

To address the difficulty in describing CFS, the US Institute of Medicine (IOM) was commissioned in 2015 by the Department of Health and Human Services to define the disorder more clearly. As of 2015, the IOM requires the following criteria for a diagnosis of CFS: significant impairment of activities, fatigue persisting for at least six months, post-exertional malaise, unrefreshing sleep, and either cognitive impairment or orthostatic intolerance.[5] It is important to note the difference between CFS and idiopathic chronic fatigue (ICF); patients with ICF may experience unexplained chronic fatigue, but they do not meet the criteria for a diagnosis of CFS.[5] Of note, the 2015 report on CFS also included a proposed name change to systemic exertion intolerance disease (SEID), which IOM believed to better describe CFS.[4]

Heterogeneity of Presentation

In 2021, Murga et al. assessed 91 patients with CFS to characterize their clinical presentation. Various assessments were conducted, quantifying the patients' experiences of pain, fatigue, immune and neuroendocrine pathology, quality of sleep, attention and cognition, autonomic nervous system function, and comorbidities including anxiety and depression. Except for cognitive function, all variables assessed were significantly different compared to healthy controls. Most patients reported poor sleep quality, at least some degree of pain, dysautonomia (e.g., orthostatic intolerance), and progressively worsening fatigue. Around one third of patients evaluated experienced anxiety and depression.[6] Murga et al. also report a higher incidence of CFS in women than men; this is consistent with numerous previous findings.[6–8]

Etiology

Per the CDC, CFS is a complex systemic disease. It has been linked to autonomic, neurological, metabolic, infectious, muscular, and immunological dysfunction.[7,8]

Immunological Pathophysiology

Some sources describe two main groups of patients with CFS; the first comprises patients with early Parkinson's diseases, and the second is characterized by chronic infection and/or inflammation.[9] There is a considerable body of evidence pointing to immune dysregulation, citing components such as dysfunctional T-cells, reduced activity of natural killer (NK) cells, and even hyperreactivity of the entire immune system.[8] A 2019 study at the Stanford University School of Medicine found that immune cells

from patients with CFS respond differently to induced stressors than those from healthy patients.[8] Another study in 2016 found that nearly one third of CFS patients studied had elevated levels of antibodies against their own neurotransmitter receptors.[8]

Neurological Pathophysiology

CFS is often classified as a neurological disorder, based on its features of poor sleep quality, impaired attention and cognition, autonomic dysregulation, and otherwise unexplained pain. Additional dysfunction reported by patients with CFS include decreased reaction time and worsening memory.[2] Potentially secondary to increased systemic inflammation, CFS patients have been found to exhibit brain hypoperfusion, hypometabolism, and impaired intracellular signaling.[9] Unfortunately, little is currently known about the cause of these abnormalities, but various research has indicated potential genetic predisposition.[3,8,9]

Treatment

While there is no single treatment for CFS, various options exist for targeting symptoms of the disease. For example, comorbidities such as depression may be treated with antidepressants, and gastrointestinal symptoms have been shown to improve with probiotic use.[3] Methods to improve immune dysfunction may include B-cell clonal depletion. A high percentage of biological females with CFS report worsening of symptoms during menopause and menstruation; thus, treatments such as hormone replacement therapy (HRT) or hormonal contraceptives may be effective.[8]

Given the prevalence of gastrointestinal and inflammatory illness in patients with CFS, diet and nutrition may play a key role in modulating symptoms of CFS. Diets low in processed foods may help regulate gastrointestinal symptoms. Avoiding components such as sugar, dairy, and gluten has also been suggested.[2] Similarly, diets with sufficient selenium and moderate *omega-6* polyunsaturated fatty acids may improve immune cell function.[2] Antioxidants found in foods such as broccoli, blueberries, cranberries, and dark, leafy greens may also be helpful in counteracting harmful metabolic products of oxidative stress in patients with CFS.[10]

Summary

There is a clear need for more research to improve our understanding of Chronic Fatigue Syndrome. A deeply complex disease, CFS is much more than chronic fatigue or myalgia. Genome-wide assessments from patients with CFS could provide valuable insight into the underlying genetic causes of CFS, and potentially identify targets for improved therapy. In the meantime, improved education of clinicians is crucial to ensure improved diagnosis and symptom management.

References

1. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Centers for Disease Control and Prevention. Published May 18, 2023. Accessed August 10, 2023. https://www.cdc.gov/me-cfs/

2. Bateman L, Bested AC, Bonilla HF, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Essentials of Diagnosis and Management. *Mayo Clin Proc*. 2021;96(11):2861-2878. doi:10.1016/j.mayocp.2021.07.004

3. Anderson G, Maes M. Mitochondria and immunity in chronic fatigue syndrome. *Prog Neuropsychopharmacol Biol Psychiatry*. 2020;103:109976. doi:10.1016/j.pnpbp.2020.109976

4. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. *Mil Med*. 2015;180(7):721-723. doi:10.7205/MILMED-D-15-00085

5. Son CG. Differential diagnosis between “chronic fatigue” and “chronic fatigue syndrome.” *Integr Med Res*. 2019;8(2):89-91. doi:10.1016/j.imr.2019.04.005

6. Murga I, Aranburu L, Gargiulo PA, Gómez Esteban JC, Lafuente JV. Clinical Heterogeneity in ME/CFS. A Way to Understand Long-COVID19 Fatigue. *Front Psychiatry*. 2021;12. doi:10.3389/fpsyt.2021.735784

7. About ME/CFS. National Institutes of Health (NIH): Advancing ME/CFS Research. Published August 12, 2022. Accessed August 10, 2023. https://www.nih.gov/mecfs/about-mecfs#:~:text=According%20to%20the%20CDC%20%2C%20836%2C000,pre%2Ddisease%20level%20of%20functioning.

8. König RS, Albrich WC, Kahlert CR, et al. The Gut Microbiome in Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS). *Front Immunol*. 2022;12. doi:10.3389/fimmu.2021.628741

9. Bjørklund G, Dadar M, Pen JJ, Chirumbolo S, Aaseth J. Chronic fatigue syndrome (CFS): Suggestions for a nutritional treatment in the therapeutic approach. *Biomedicine & Pharmacotherapy*. 2019;109:1000-1007. doi:10.1016/j.biopha.2018.10.076

10. Reilly CT. Top 20 Foods High In Antioxidants. St. John’s Health. Accessed August 10, 2023. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.stjohns.health/documents/content/top-20-foods-high-in-antioxidants.pdf