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Myalgic

Encephalomyelitis/

Chronic Fatigue

Syndrome Elizabeth R. Unger, Jin-Mann S. Lin,

Jeanne Bertolli Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic complex illness with multisystem manifestations and longterm impact on functional impairment comparable to multiple sclero sis, rheumatoid arthritis, and congestive heart failure. The hallmark of ME/CFS is persistent and unexplained fatigue resulting in significant impairment in daily functioning, along with worsening symptoms following physical or mental exertion that would have been tolerated before illness (postexertional malaise). Besides intense fatigue, many patients report concomitant symptoms such as pain, cognitive dys function, and unrefreshing sleep. Additional symptoms can include headache, sore throat, tender lymph nodes, muscle aches, joint aches, feverishness, difficulty sleeping, psychiatric problems, allergies, and abdominal cramps. The recognition that ME/CFS is one diagnosable condition in Long COVID has raised clinical awareness about this poorly understood illness, although patients still face stigma and mis understanding among health care providers. The condition has been known by many names, and debate about the name and case definition continues. The composite name ME/CFS was adopted by the U.S. Department of Health and Human Services in rec ognition of the limitations of either ME (absence of definitive inflam mation in brain and spinal cord) or CFS (trivializes an often devastating illness through confusion with fatigue that everyone experiences). EPIDEMIOLOGY Determining how frequently ME/CFS

occurs and characteristics of those affected has been complicated by variability in study design and application of case definitions. In the absence of a simple diagnostic test, evaluation by an experienced clinician is required for case iden tification. Clinic-based studies most accurately identify patients with ME/CFS but overrepresent higher socioeconomic groups with access to ME/CFS clinics. Population-based studies with or without a clinical evaluation estimated that between 836,000 and 3.3 million Americans have ME/CFS. However, studies indicate that ≥80% of those meeting criteria for ME/CFS had not been diagnosed by a health care provider. The illness costs the U.S. economy between $18 and $51 billion annu ally in medical costs and lost income. ME/CFS is three to four times more common in women than men. The highest prevalence is among those 40–50 years of age, but the age range is broad and includes chil dren and adolescents. Persons of all races and ethnicities are affected, and there is some evidence that socioeconomically disadvantaged groups are at increased risk. RISK FACTORS AND PATHOPHYSIOLOGY A wide variety of infectious agents have been reported to be associ ated with a postinfectious fatiguing illness resembling ME/CFS. These include both viral and nonviral pathogens, such as Epstein-Barr virus, Ross River virus, Coxiella burnetti (Q fever), Ebola virus, SARS-CoV-1, and Giardia. While recovery from these infections is the rule, ~10% of those infected remain ill for ≥6 months. Most recently, published reports suggest that SARS-CoV-2 infection is also associated with prolonged fatiguing illness. Host and pathogen factors associated with recovery versus persistent disease remain elusive. In addition to infectious insults,

Fatigue Post-Exertional Malaise Diet/Nutrition Lifestyle Genetics HypothalamicPituitaryAdrenal Axis Cognitive Impairment Sleep Problems Central Nervous System Immune System Metabolism Pain Autonomic Nervous System Infection Stress CHAPTER 461 Orthostatic Intolerance FIGURE 461-1 A multisystem model for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). An example of a unifying model for ME/CFS demonstrating the interactions of multiple organ systems and environmental, genetic, and behavioral factors contributing to symptoms. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
a variety of stressors, including toxins, physical trauma, adverse events, and allostatic load (or “wear and tear” on the body), have been found to be associated with ME/CFS. Twin studies and family histories suggest a role for shared environment as well as genetic factors. Evidence for immunologic dysfunction is inconsistent. Modest ele vations in titers of antinuclear antibodies, reductions in immunoglobu lin subclasses, deficiencies in mitogen-driven lymphocyte proliferation, reductions in natural killer cell activity, disturbances in cytokine pro duction, and altered T-cell metabolism have been described. None of these immune findings has been firmly established and none of these changes appear in most patients. In theory, symptoms of ME/CFS could result from excessive production of a cytokine, such as interleukin 1 or interferon α, which induces fatigue and other flulike symptoms; how ever, compelling data in support of this hypothesis are lacking. Other studies have reported various nonspecific changes in regional brain structures estimated by magnetic resonance imaging; dysfunction of the autonomic nervous system; abnormalities in the hypothalamicpituitary-adrenal (HPA) axis; altered metabolism; and dysbiosis of the intestinal microbiome. Confirmatory studies are needed, and none of the findings are consistent enough to be used for diagnosis. It is clear that ME/CFS represents a complex disorder with alterations in multiple interrelated homeostatic systems. A variety of unifying models for the illness have been proposed, and discoveries about the pathophysiology of ME/CFS hold promise for elucidating novel mechanisms and inter actions important in other illnesses (Fig. 461-1). APPROACH TO THE PATIENT Myalgic Encephalomyelitis/Chronic Fatigue Syndrome DIAGNOSIS A diagnosis of ME/CFS is made based on patient-reported symp toms that fit a characteristic profile. After a careful review of the

literature and symptom-based case definitions for ME, CFS, or ME/ CFS, the Institute of Medicine (IOM) committee recommended in 2015 straightforward diagnostic criteria (Table 461-1). This includes the symptoms consistently noted in prior consensus case definitions: fatigue limiting the patient’s ability to participate in their usual pre-illness activities, sleep problems, and postexertional malaise (PEM). PEM is a relapse in symptoms triggered by physi cal, emotional, or mental exertion that would not have been prob lematic for the patient before onset of ME/CFS. The relapse lasts more than a day and sometimes weeks. In addition, either difficulty

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