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Section 4 Syndromes Associated with Chronic Fatigue

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

TABLE 461-1 2015 Institute of Medicine Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Substantial reduction or impairment in the ability to engage in pre-illness levels of activity (occupational, educational, social, or personal life) that: • lasts for >6 months • is accompanied by fatigue that is often profound, of new or definite onset (not lifelong), not the result of ongoing excessive exertion, and is not substantially alleviated by rest Postexertional malaise (PEM)a—worsening of symptoms after physical, mental, or emotional exertion that would not have caused a problem before the illness Unrefreshing sleepa Cognitive impairment or orthostatic intolerancea aFrequency and severity of symptoms should be assessed; should be present at least half of the time and with at least moderate intensity. thinking and concentrating (often referred to by patients as "brain fog") or orthostatic intolerance should be present. PART 13 Neurologic Disorders Patients with ME/CFS may experience a wide range of other symptoms not specified in the IOM diagnostic criteria (Table 461-2). As a result, patients meeting ME/CFS criteria could have very dif ferent clinical features based on the type, frequency, and severity of their symptoms. Patients may describe a precipitating cause for their illness, such as a known or presumed infection, but frequently no initiating factor is recognized. The symptoms may occur sud denly within a day or week or may occur gradually. While the diagnostic criteria specifies that illness must be pres ent at least 6 months, the possibility of ME/CFS should be consid ered for patients with consistent symptoms persisting >1 month, and evaluation and supportive care can begin as early as 4–6 weeks after onset. Listening to patients' descriptions of what they are expe riencing is important. Asking questions can help patients accurately describe their experience with fatigue and PEM. These include ask ing about current activity levels compared with before they became ill, what happens when they are as active as they were pre-illness, and how long it takes to recover after exertion. Whereas patients recognize relapses, the relation of relapse to activity level may not be apparent, and as a result, PEM may not be recognized. Patients may also appear well during an office visit, only to relapse afterward from exertion surrounding the consultation. Although the 2015 IOM ME/CFS criteria do not list medical or psychological conditions that exclude the diagnosis of ME/ CFS, a careful clinical evaluation is required to identify and treat other illnesses that could explain or contribute to the patient's symptoms. The initial evaluation also requires reviewing family his tory, medical history (including infections, traumas/surgeries, and occupational exposure to environmental toxins), and medications and supplements; performing a physical examination, including lean test for postural orthostatic tachycardia syndrome (POTS; Chap. 451); a mental health assessment (screen for depression and anxiety); and routine screening laboratory tests (if recent results are not on record). As routine laboratory tests are usually within nor mal limits, their role is in identifying other illnesses, and the specific TABLE 461-2 Additional Symptoms Experienced by Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Joint pain without swelling or redness Muscle aches New headaches Tender lymph nodes Sensitivity to sensory stimuli (e.g., light, noise, smells) Sore throat Shortness of breath Irregular heartbeat Alcohol intolerance Difficulties with temperature regulation (feeling feverish or chilled)

panel of tests should be adjusted based on the patient’s presenta tion. Typically the tests include complete blood count, erythrocyte sedimentation rate, electrolytes, fasting glucose, renal function tests (blood urea nitrogen, glomerular filtration rate), calcium, phosphate, liver function (bilirubin, alanine aminotransferase, alkaline phospha tase, aspartate aminotransferase, gamma-glutamyl transferase, total protein, albumin/globulin ratio), C-reactive protein, thyroid func tion (thyroid-stimulating hormone, free thyroxine), iron studies to assess both iron overload and iron deficiency (serum iron, transfer rin saturation, ferritin), celiac disease screening tests, and urinalysis. DIFFERENTIAL DIAGNOSIS AND COMORBID CONDITIONS While the differential diagnosis for fatigue is quite broad (Chap. 25), further workups and referrals should be chosen carefully based on the patient’s history, symptoms (particularly those that are new, worsening, or unusual), and results of initial laboratory tests. Con ditions reported to occur in association with ME/CFS (Table 461-3) should be kept in mind during the evaluation and follow-up, as management and treatment modalities for these comorbidities could contribute to an improved quality of life. MANAGEMENT While there are no approved drugs to treat or cure ME/CFS, patients benefit from receiving a diagnosis and an individualized plan that addresses the symptoms that are most problematic for the patient. Some symptoms, in particular, disturbed sleep (Chap. 33) and pain (Chap. 14), may improve with nonpharmacologic thera pies (e.g., sleep hygiene, massage, acupuncture, hot or cold packs) or medications. Any medications should be started at lower doses than usual and only slowly increased. Patients with ME/CFS have been reported to be more sensitive to medications than the general population, and benefits with fewer toxicities may be achieved at lower doses. Narcotics should be avoided, and referral to sleep cen ters or other specialists may be required. Controlled therapeutic trials have not established significant benefit for patients with ME/CFS from acyclovir, fludrocortisone, galantamine, modafinil, and IV immunoglobulin, among other agents. These studies have been limited by small numbers and lack power to investigate benefit in patient subgroups. Preliminary small studies reported the possible effectiveness of the B-celltargeting anti-CD20 monoclonal antibody rituximab in ME/CFS, but a subsequent large, well-designed, prospective, double-blind study found no benefit. Numerous anecdotes circulate regarding other traditional and nontraditional therapies. It is important to guide patients away from therapeutic modalities that are toxic, expensive, or unreasonable. Educating the patient and family about PEM can be helpful in avoiding the harmful cycle of overexertion during “good days” followed by relapse that can negate any functional gains. This is often referred to as “push and crash.” Recognizing limits and using activity management (pacing) can help limit PEM. It is important to maintain tolerated activity levels to minimize deconditioning. Activity may be advanced very gradually as tolerated. TABLE 461-3 Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Comorbid Conditions Chronic overlapping pain conditions: fibromyalgia (FM), chronic migraine, temporomandibular joint disease (TMJ), irritable bowel syndrome (IBS), endometriosis, vulvodynia, urologic chronic pelvic pain syndromes (UCPPS) Postural orthostatic tachycardia syndrome (POTS) Allergies Sjögren’s syndrome Ehlers-Danlos syndrome Mast cell activation syndrome (MCAS) Dysautonomia Multiple chemical sensitivities

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