

VIEWPOINT

Advances in Understanding the Pathophysiology of Chronic Fatigue Syndrome

Anthony L. Komaroff, MD
Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts.

When does an illness become a disease? When the underlying biological abnormalities that cause the symptoms and signs of the illness are clarified.

The illness now called myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) was first described in the mid-1980s. At that time, nothing was known about its underlying biology. Indeed, because many standard laboratory test results were normal, some clinicians explained to patients that “there is nothing wrong.” There was, of course, an alternative explanation: the standard laboratory tests might not have been the right tests to identify the underlying abnormalities.

Over the past 35 years, thousands of studies from laboratories in many countries have documented underlying biological abnormalities involving many organ systems in patients with ME/CFS, compared with healthy controls: in short, there *is* something wrong. Moreover, most of the abnormalities are not detected by standard laboratory tests. In 2015, the Institute of Medicine of the National Academy of Sciences concluded that ME/CFS “is a serious, chronic, complex systemic disease that often can profoundly affect the lives of patients,” affects up to an estimated 2.5 million people in the United States, and generates direct and indirect expenses of approximately \$17 billion to \$24 billion annually.¹

Over the past several years, the National Institutes of Health (NIH) has expanded its research efforts directed toward this disease. It has initiated an unusually comprehensive multisystem study at the NIH Clinical Center, funded 3 extramural ME/CFS research centers and 1 data coordinating center, awarded supplemental support to 7 existing grants, and held regular telebriefings on the illness (as has the Centers for Disease Control and Prevention).²

A 2-day conference at the NIH in April 2019 highlighted recent progress. New research was presented that both reinforced and expanded on previous reports. Equally important, several plausible models were proposed that could explain many of the abnormalities that have been described.

The Central and Autonomic Nervous System

Since the early 1990s, multiple studies have compared patients with ME/CFS with healthy age- and sex-matched controls and found abnormalities of the central and autonomic nervous system.³

- Neuroendocrine abnormalities were among the first evidence reported and involve impairment of several limbic-hypothalamic-pituitary axes (involving cortisol, prolactin, and growth hormone end products). A general downregulation of the hypothalamic-pituitary-adrenal axis is seen in patients with ME/CFS, in contrast to the upregulation of the hypothalamic-pituitary-adrenal axis seen in major depression.

- Impaired cognition has been found by many investigators, including slowed information processing speed and impaired memory and attention that are not explained by concomitant psychiatric disorders.
- Magnetic resonance imaging has revealed increased numbers of punctate areas of high signal in white matter. Functional magnetic resonance imaging has demonstrated different responses to auditory and visual challenges and to tests of working memory, as well as altered connectivity between different brain regions.
- Positron emission tomography and magnetic resonance spectroscopy recently have demonstrated that patients with ME/CFS have a widespread state of neuroinflammation (particularly activation of microglial cells) as well as increased ratios of choline-creatinine and increased levels of lactate that correlate with levels of fatigue.⁴ Spinal fluid contains increased levels of proteins involved in tissue injury and repair.
- Autonomic nervous system abnormalities have been repeatedly demonstrated in ME/CFS, particularly altered systemic and cerebral hemodynamics that correlate with symptoms.⁵ At the NIH conference, it was reported that with prolonged upright posture, abnormal increases in heart rate and decreases in blood pressure are common; even when heart rate and blood pressure responses are normal, substantial cerebral blood flow reductions are noted.

Metabolic Changes

Recently, it has become possible to measure simultaneously thousands of metabolites in a sample of blood or other fluid. Several such metabolomic studies have revealed that in patients with ME/CFS, levels of many metabolites are lower than normal, as occurs in hibernation.⁶ Cellular energy generation from all sources is impaired, including energy from oxygen, sugars, lipids, and amino acids. In other words, the human organism may feel that it lacks “energy” because its cells have a problem generating (and possibly using) energy. In addition, many studies have reported markers of both oxidative stress and nitrosative stress (eg, increased levels of inducible nitric oxide synthase).

Immunologic Changes

Many phenotypic and functional abnormalities have been reported in lymphocytes. The most consistently reported are increased numbers of activated cytotoxic CD8⁺ T cells and poorly functioning natural killer cells. Blood levels of many cytokines are significantly higher in patients with ME/CFS, especially in the first 3 years of illness. Moreover, the levels of many of the circulating cytokines correlate positively with the severity of symptoms. Abnormal levels of several cytokines in spinal fluid also have been reported.

Corresponding Author: Anthony L. Komaroff, MD, Brigham and Women's Hospital, 1620 Tremont St, Boston, MA 02120 (komaroff@hms.harvard.edu).

jama.com

JAMA Published online July 5, 2019

E1

© 2019 American Medical Association. All rights reserved.

At the NIH conference, new HLA associations with both presence and severity of ME/CFS were reported. In addition, investigators performing single T-cell receptor sequencing reported expansion of CD8⁺ T-cell clones; characterization of the antigenic targets is under way.

Provocation Studies

In patients with ME/CFS, physical, postural (orthostatic), and cognitive challenges often produce a flare of symptoms, typically after a 12- to 48-hour delay, a condition called postexertional malaise. Provocation studies seek to clarify whether challenges that make people with ME/CFS feel worse also make a biological abnormality worse. If so, it becomes more likely that the abnormality may be causally connected to the symptoms of the illness.

The NIH conference summarized evidence from multiple studies demonstrating that during exercise, the tissues of patients with ME/CFS have difficulty extracting oxygen, leading to a lower anaerobic threshold; with exercise, patients also have lower heart rate, blood pressure, and preload, several of which become much more prominent during a second exercise test repeated 24 hours after the first.^{7,8}

Potential Unifying Models

What if ME/CFS reflects the activation of biologically ancient, evolutionarily conserved responses to injury or potential injury, a pathological inability to turn these responses off, or both? Several presentations at the NIH conference, citing work in animal models, indicated that low-grade neuroinflammation triggers protective behavioral changes, including reduced activity and appetite and increased sleep; this helps to focus the available energy on preventing or healing the injury. This stereotyped behavior change is likely triggered by a "fatigue nucleus" (a group of neurons); the nucleus is triggered, in turn, by the cytokines produced by neuroinflammation.

The neuroinflammation could have different triggers in different individuals. In some, it could be induced by brain infection (such as by chronic herpesvirus infection), autoantibodies, neurotoxins, or chronic stress. In others, inflammation *outside* the brain may be activating the innate immune system *inside* the brain, both through humoral signals that breach a porous blood-brain barrier and by

retrograde signals sent up the vagus nerve. Several conference presentations included evidence that gut inflammation may be one peripheral trigger of neuroinflammation: the gut microbiota of patients with ME/CFS often include high numbers of proinflammatory species and low numbers of anti-inflammatory species.

The relatively hypometabolic state seen in patients with ME/CFS might also reflect a second and possibly related biologically ancient response to injury. Such hypometabolism is seen during the state of dauer (ie, a developmental larval stage) in the worm *Caenorhabditis elegans* and during hibernation in more complex animals. Dauer and hibernation allow animals that perceive a vital threat (such as crowding in worms or winter in bears) to throttle down non-essential, energy-consuming metabolic processes to preserve the energy needed for vital functions; ie, the animal is temporarily sacrificing its ability to function in order to remain alive. Signals that initiate (and end) dauer and hibernation are known; investigators are pursuing whether they have been activated (or not deactivated) in patients with ME/CFS.

Conclusions

A great deal more is known today than 35 years ago about the underlying biology of ME/CFS. It is clear that many biological measurements clearly distinguish patients with ME/CFS from healthy control individuals.

At the same time, some areas of ME/CFS research remain a challenge, and research has not yet given practicing physicians 2 important tools. First, there are as yet no US Food and Drug Administration-approved treatments. Second, although various biological measurements distinguish patients with ME/CFS from healthy controls, none yet have demonstrated the high sensitivity and specificity required for a good diagnostic test. However, 1 small study (20 cases and 20 controls) described at the NIH conference (and recently published⁹) reported perfect sensitivity; the specificity of the test in individuals with other fatiguing illnesses remains to be shown.

With growing international interest in the illness, and increased research support from the NIH, the day is coming when physicians will be able to explain to patients not only that there is something wrong but also that advances in understanding the pathophysiology have led to effective therapy.

ARTICLE INFORMATION

Published Online: July 5, 2019.
doi:10.1001/jama.2019.8312

Conflict of Interest Disclosures: Dr Komaroff reported receiving personal fees from Ono Pharma and Serimmune Inc and grants from the NIH.

Additional Contributions: Peter C. Rowe, MD, Department of Pediatrics, Johns Hopkins University, provided valuable comments for which he received no compensation.

REFERENCES

1. Institute of Medicine. *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness*. Washington, DC: National Academies Press; 2015.
2. Koroshetz W, Collins F. Moving toward answers in ME/CFS. NIH Director's Blog. March 21, 2017. [https://directorsblog.nih.gov/2017/03/21/moving-](https://directorsblog.nih.gov/2017/03/21/moving-toward-answers-in-mecfs/#more-7931)

[toward-answers-in-mecfs/#more-7931](https://directorsblog.nih.gov/2017/03/21/moving-toward-answers-in-mecfs/#more-7931). Accessed June 22, 2019.

3. Komaroff AL, Cho TA. Role of infection and neurologic dysfunction in chronic fatigue syndrome. *Semin Neurol*. 2011;31(3):325-337. doi:10.1055/s-0031-1287654
4. Mueller C, Lin JC, Sheriff S, Maudsley AA, Younger JW. Evidence of widespread metabolite abnormalities in myalgic encephalomyelitis/chronic fatigue syndrome: assessment with whole-brain magnetic resonance spectroscopy. *Brain Imaging Behav*. 2019. doi:10.1007/s11682-018-0029-4
5. van Campen CLMC, Rowe PC, Visser FC. Blood volume status in ME/CFS correlates with the presence or absence of orthostatic symptoms: preliminary results. *Front Pediatr*. 2018;6:352. doi:10.3389/fped.2018.00352
6. Naviaux RK, Naviaux JC, Li K, et al. Metabolic features of chronic fatigue syndrome. *Proc Natl Acad Sci U S A*. 2016;113(37):E5472-E5480. doi:10.1073/pnas.1607571113
7. Stevens S, Snell C, Stevens J, Keller B, VanNess JM. Cardiopulmonary exercise test methodology for assessing exertion intolerance in myalgic encephalomyelitis/chronic fatigue syndrome. *Front Pediatr*. 2018;6:242. doi:10.3389/fped.2018.00242
8. Nelson MJ, Buckley JD, Thomson RL, Clark D, Kwiatek R, Davison K. Diagnostic sensitivity of 2-day cardiopulmonary exercise testing in myalgic encephalomyelitis/chronic fatigue syndrome. *J Transl Med*. 2019;17(1):80. doi:10.1186/s12967-019-1836-0
9. Esfandyarpour R, Kashi A, Nemat-Gorgani M, Wilhelmy J, Davis RW. A nanoelectronics-blood-based diagnostic biomarker for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *Proc Natl Acad Sci U S A*. 2019;116(21):10250-10257. doi:10.1073/pnas.1901274116

Acad Sci U S A. 2016;113(37):E5472-E5480. doi:10.1073/pnas.1607571113