

Chronic Fatigue Syndrome: Wrong Name, Real Illness

Miriam E. Tucker | January 08, 2015

Introduction

Sufferers of what has been called chronic fatigue syndrome (CFS) are challenging patients, presenting with complaints of postexertional malaise, persistent flulike symptoms, unrefreshing sleep, "brain fog," and often a long list of other symptoms that don't seem to fit any recognizable pattern. Some appear ill, but many don't. And the routine laboratory tests often come back negative.

For that reason, those with CFS are often labelled as malingerers, depressed, or at least partially psychosomatic. But for the scientists and clinicians in the field, the phenomenon is as real as diabetes or atherosclerosis. Despite the stigma and a severe dearth of research funding, new efforts from the federal government and the private sector could move the field forward.

The name itself is one of the many [controversies](#) surrounding the condition. The CFS moniker has been used in the United States since 1988; in the United Kingdom, Canada, and elsewhere it is called myalgic encephalomyelitis (ME).

Many patients abhor the term "chronic fatigue syndrome" because they feel that it trivializes the condition, which can render individuals severely debilitated, housebound, or bedridden.

Moreover, an [emerging consensus](#) in the field is that "chronic fatigue syndrome" as defined in 1994 by the Centers for Disease Control and Prevention (CDC) represents a more heterogeneous and less severely affected population than does "myalgic encephalomyelitis," captured by the 2003 [Canadian Clinical Case Definition](#). Both definitions require multiple symptoms in addition to 6 months of unexplained fatigue to make the diagnosis, but the ME criteria also require the hallmark symptom of postexertional malaise.^[1]

For now, the compromise term "ME/CFS" has been adopted by the research community and officially by the various agencies within the US Department of Health and Human Services (HHS). In early 2015, the Institute of Medicine, commissioned by HHS, [will release](#) recommendations for new clinical diagnostic criteria and possibly will propose a name change as well.

A Real Condition

For clinicians, the first step is to recognize that the condition is real.

"I think the most important thing for physicians to know is that while we don't have a diagnostic test or a proven treatment, there is now abundant evidence that in these patients there is an underlying biological process. Their symptoms are linked to problems of their biology and not imagined," said Harvard Health Publications editor-in-chief Anthony L. Komaroff, MD, to *Medscape Medical News*. Dr Komaroff is also professor of medicine at Harvard Medical School and senior physician at Brigham and Women's Hospital (Boston). He has been studying the condition since the 1980s.

Jose G. Montoya, MD, professor of medicine, infectious diseases, and geographic medicine, Stanford University Medical Center, who heads Stanford's ME/CFS Initiative, told *Medscape Medical News*, "Obviously, the first thing you have to do is to see that it's real. That's not even a question for me anymore. Once you see that it's real, it's a matter of having the right technology...and a multidisciplinary approach."

The condition is [tragically real](#) for Ronald W. Davis, PhD, professor of biochemistry and genetics at Stanford University and director of the Stanford Genome Technology Center, whose work with genetic linkage mapping enabled the Human Genome Project. His 31-year-old son developed ME/CFS 3 years ago and is now completely bedridden and unable to speak.

"I don't think people understand how horrible this disease is. They don't look that sick. Even my son, who is incredibly debilitated, doesn't look sick," Dr Davis told *Medscape Medical News*.

In his new position as ME/CFS scientific advisory board director of the [Open Medicine Institute](#), Dr Davis has recruited

Nobel laureates James D. Watson, PhD, and Mario R. Capecchi, PhD, and other esteemed scientists as advisors to create what he envisions as a collaborative ME/CFS research effort akin to the Human Genome Project.

"I think it will yield if we get sufficient funding, quite frankly. It may be a tough nut to crack...I'm looking at this long-term. I don't like the long-term because my son is ill, but I'm realizing this won't be temporary," Dr Davis told *Medscape Medical News*.

What Is ME/CFS?

Experts in the field conceptualize ME/CFS as an abnormal immune system response to any of a number of infectious or environmental triggers, resulting in a chronic state of inflammation, autonomic dysfunction, impaired hypothalamic-pituitary-adrenal axis functioning, and neuroendocrine dysregulation.

"People do think it's a spectrum of disease. We've settled on that it's an immune-related disorder, and there is potentially a subset that's autoimmune, a subset that's virally triggered, a chronic viral infection, and perhaps other triggers or stressors...People are still kicking around whether it's autoimmune or chronic low-grade infection," Open Medicine Institute founder and director Andreas M. Kogelnik, MD, told *Medscape Medical News*.

Affecting about 1 million adults and children in the United States (by the CDC definition), the hallmarks of ME/CFS include severe fatigue for 6 months or longer (3 months in children), malaise—some patients describe it as a "crash"—lasting days to weeks following even modest physical or mental exertion, unrefreshing sleep, and cognitive dysfunction. Chronic pain is common and many patients also meet criteria for fibromyalgia.

Other frequent symptoms include orthostatic intolerance—particularly a postural orthostatic tachycardia syndrome that can be elicited by a tilt-table test—gastrointestinal dysfunction including irritable bowel syndrome, heat or cold intolerance, and persistent flulike symptoms. In addition to fibromyalgia, other common comorbid conditions include irritable bowel syndrome, joint hypermobility, interstitial cystitis, and migraines.

Women outnumber men in ME/CFS diagnosis, although about a quarter are male. The condition can appear at any age. Contrary to the "yuppie flu" characterization, ME/CFS appears to be more common among ethnic and racial minority groups and in those of lower socioeconomic status.^[2]

Physical Findings and Biomarkers

Numerous physical abnormalities have been identified in ME/CFS patients, with stronger biological signals seen in studies measuring response to exercise^[3] that differentiate patients from controls and far exceed the effects of mere deconditioning, experts say.

Such evidence includes significantly reduced oxygen consumption and workload for ME/CFS patients after treadmill tests,^[4] and altered gene expression compared with controls following moderate exercise.^[5]

Other biological evidence includes a recent finding of bilateral white matter atrophy in ME/CFS patients compared with controls,^[6] several studies documenting significant decreases in natural killer cell cytotoxic activity, and increased levels of multiple proinflammatory cytokines.^[7]

A highly significant elevation in non-Hodgkin lymphoma—which, like ME/CFS, has been linked to Epstein-Barr virus^[8]—was found among ME/CFS patients aged 66-99 years in a National Cancer Institute study of data from the Surveillance, Epidemiology, and the End Results (SEER) and Medicare registries of approximately 1.2 million cancer cases and 100,000 controls, with an odds ratio of 1.29 and *P* value of .000017.^[9]

In a novel study of 165 consecutive patients with ME/CFS who underwent upper gastrointestinal endoscopies and antrum biopsies, 135/165 (82%) stained positive for enterovirus viral capsid protein 1 compared with just 7/34 (20%) of controls (*P* ≤ .001).^[10]

And in another novel finding that speaks to the phenomenon's heterogeneity, approximately 2% of ME/CFS cases were found to have chromosomally integrated human herpesvirus-6 (HHV-6) as compared to just 0.2%-0.85% of the general population,^[11] suggesting a specific etiology for a small proportion of cases.^[12]

Responses to treatment in randomized, blinded, placebo-controlled trials also point to biological causation, including improvements with valganciclovir in a study of ME/CFS patients with elevated antibody titers to HHV-6 and Epstein-Barr virus,^[13] and a preliminary trial (now being repeated in a larger patient group) in which ME/CFS patients responded to rituximab, a monoclonal antibody that destroys immune system B cells and is approved in the United States for the treatment of non-Hodgkin lymphoma and other B-cell-mediated conditions.^[14]

The investigational immunomodulatory double-stranded RNA drug rintatolimod (Ampligen®; Hemispherx Biopharma, Inc.) produced objective improvement in exercise tolerance and other endpoints in a phase 3 prospective, double-blind, randomized, placebo-controlled trial of 234 subjects with long-standing, debilitating ME/CFS.^[15]

The US Food and Drug Administration (FDA) rejected rintatolimod for treatment of ME/CFS in February 2013 due to insufficient efficacy and safety data, but Hemispherx continues to investigate it open-label among ME/CFS patients with low natural killer cell function, a company consultant told *Medscape Medical News*. (The company is also investigating the drug for treating Ebola and as an adjuvant for intranasal influenza vaccine.^[16])

Dr Montoya's team at Stanford has identified several proinflammatory cytokines that are significantly elevated in samples from 200 ME/CFS patients compared with 400 age- and gender-matched controls, and that correlate with illness severity. "A dose-response effect is very powerful in biology. It's an indicator that what you are seeing is real," he told *Medscape Medical News*.

He believes that in ME/CFS "there is a genetic predisposition for an overwhelming inflammatory response to an infectious agent that was supposed to help the patient but is overwhelming, triggering a tremendous inflammatory cascade."

This model suggests a possible role for anti-inflammatory medications as treatment, he said, noting that both the valganciclovir and rituximab studies suggest proof of concept for that approach.

At a [Stanford meeting](#) held earlier this year, Dr Komaroff pointed out that many of the infectious agents that have been linked to ME/CFS—including Epstein-Barr virus,^[17] HHV-6,^[18] *Coxiella burnetii* (aka "Q fever"),^[19] Ross River virus in Australia,^[20] and various enteroviruses^[21]—are ones that can't be fully eradicated by the immune system even in healthy people and/or are capable of infecting the central nervous system. This suggests the possibility that some ME/CFS patients may have a chronic, low-level encephalitis, he postulated.

Caveats and Subsets

Still, the large volume of biomarker data doesn't add up to an easy diagnostic test just yet. In the article "Chronic Fatigue Syndrome: The Current Status and Future Potentials of Emerging Biomarkers,"^[22] published in June 2014, a team led by Jordan D. Dimitrakoff, PhD, MD, of Harvard School of Public Health provides an overview of published literature on selected potential biomarkers related to neurologic and immunologic components of ME/CFS, summarizing the strengths and weaknesses of each and proposing research approaches that could further their development.

Among the problems with the biomarker studies, the authors note, are small study sample sizes, the wide heterogeneity of the criteria used for patient selection leading to inconsistent findings, and the overlap of abnormalities found in ME/CFS patients with those of other conditions. Moreover, technologies used in some of the studies, such as functional MRI and cytometry, are too expensive and impractical to be employed routinely in clinical settings.

Nonetheless, they conclude, "Based on the current state of research on the topic, biomarkers offer a strong potential for characterizing [ME/CFS] subgroups in terms of clinical phenotypes, endophenotypes, prognosis, and response to therapy."

Clinical Approaches

Even without a definitive laboratory test, physicians can help patients a great deal just by making the diagnosis based on history and symptoms.

In a survey of 256 patients, conducted by the Chronic Fatigue and Immune Dysfunction Syndrome Association of America (now called the Solve ME/CFS Initiative), 88% reported that they had been diagnosed by a physician. However, the majority saw more than four doctors before they received the diagnosis, with delays of 1-5 years for 36%, 5-10 years for 21%, and more than 10 years for 12%.

"This is a desperately long time to live with pain and impairment without validation," Carol Head, the association's president and CEO, said at an Institute of Medicine meeting in January 2014, the first of two open meetings held to discuss the forthcoming new diagnostic criteria.

Many ME/CFS patients—78%, in Dr Komaroff's referral population—are able to pinpoint the condition's onset to a flulike illness from which they never recovered. This differentiates ME/CFS patients from others who seek medical care for other fatiguing illnesses, including depression, whose responses are typically vague when asked when the condition started.

The distinction can also be elicited by asking the patient, "What would you be doing if you weren't ill?" Depressed patients typically won't have an answer, whereas ME/CFS patients will often respond with a laundry list of dreams deferred. "With depression, there is an apathy...[People with ME/CFS] are more angry and frustrated. They want to get better," Dr Komaroff told *Medscape Medical News*.

Of course, depression can develop as a result of living with ME/CFS, but even that appears to occur only in a minority, he noted.

Although there is no treatment as yet for the illness itself, there are numerous modalities for easing some of the common ME/CFS symptoms such as pain, disordered sleep, and gastrointestinal discomfort. Physicians can also help patients to pace themselves to prevent crashes.^[23]

Such management approaches are covered in two Medscape videos for clinicians, "A Case-Based Approach to Chronic Fatigue Syndrome" and "Chronic Fatigue Syndrome: The Challenges in Primary Care." There is also a newly revised "primer" from the International Association for CFS/ME (IACFSME) designed to assist clinicians in managing patients.

A caveat about ME/CFS treatment: use of both cognitive-behavioral therapy and graded exercise is highly controversial. The widely publicized 2011 PACE trial suggested that both modalities were beneficial,^[24] but those findings are rejected by most in the ME/CFS community, who cite numerous study flaws, including the patient selection criteria. The PACE trial was partly funded by the UK government agency that distributes disability benefits, and several of the investigators had ties to the insurance industry.

Some ME/CFS experts do recommend very gentle exercise, if the patient is able to do it, to prevent deconditioning, and may suggest counseling to help patients cope with the illness, but not with the expectation that either modality will improve the illness itself. Also, patients often reject counseling because of the implication that their illness is psychological.

Federal Efforts, Funding, and Future Directions

The US federal government is currently addressing ME/CFS on several fronts. A two-day "Pathways to Prevention" (P2P) workshop aimed at identifying research gaps in the field was held at the National Institutes of Health (NIH) on December 9 and 10, 2014. A [draft report](#) from that meeting was posted online on December 18 for a 30-day comment period.

The FDA has been sponsoring a series of activities addressing drug development for ME/CFS, and the CDC is currently conducting a clinical assessment to better characterize patients with ME/CFS in seven US speciality practices.

Despite these federal initiatives, [research funding](#) from NIH for ME/CFS hovers at just \$5 million. This contrasts with the \$115 million for multiple sclerosis, which affects approximately 400,000 people in the United States, and over \$3000 million for HIV/AIDS, with roughly the same number of affected people, 1 million, as ME/CFS.

Much of the ME/CFS research conducted in recent years has been funded from private sources such as Solve ME/CFS, the Hutchins Family Foundation, and the Edward P. Evans Foundation.

At the P2P meeting, speakers pleaded with NIH to increase the ME/CFS research funding level.

Dr Kogelnik, whose work at the Open Medicine Institute focuses on "Big Data" approaches to unravelling several complex diseases, including ME/CFS, expressed frustration at the lack of funding for applying state-of-the-art genomic, proteomic, and gene expression analyses to larger numbers of ME/CFS patient samples. "We have a lot of interesting pilot data. The challenge for us has been, frankly, a funding issue...We're raising private monies to do these studies...That is not quite right given the nature of data that exist today. NIH really needs to step up with the funding."

Dr Davis told *Medscape Medical News*, "NIH funds researchers...There are very few [ME/CFS] researchers, so NIH's

budget is proportional to that. Of course, the number of researchers is proportional to the NIH funding. So it's a catch-22."

Dr Davis is just beginning to seek funding for the research consortium he envisions. "You have to do something different...When we started the Human Genome Project, they couldn't just fund it proportional to the genome sequencing community, which is very small, so they set up a [new] whole program," he told *Medscape Medical News*.

Dr Davis is among several investigators who hope to begin studies that will entail making home visits to conduct sophisticated testing on the most severely affected bedridden ME/CFS patients, such as his son. Nearly all of the data that have been collected so far have come from patients who were at least well enough to go to a laboratory and perform on a treadmill or undergo other testing.

"The signals that are in those [severely affected] patients for what's wrong are probably much more pronounced...It's true of many diseases—that if you really want to see what's going on, the severe cases give much more information," Dr Davis noted.

Dr Kogelnik told *Medscape Medical News*, "In medicine, we tend to like the one-answer solutions. We're great at diagnosing things that have one problem, like a clogged artery. What we're really bad at are complex diseases that have a systemic issue going wrong. With ME/CFS it's the whole system that's broken down, so there may not be one pill to cure everybody. It's more a matter of figuring out the imbalance in the system. We're not good at thinking that way in medicine. I think that's something that we need to change, particularly around this disease."

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