Commentary

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Fibromyalgia: Definitions, Similarities, and Differences

Benjamin H. Natelson, MD

Department of Neurology, Pain & Fatigue Study Center, Icahn School of Medicine at Mount Sinai, New York, NY, USA

ABSTRACT

This commentary presents a simplified way of making the diagnosis of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) using the 1994 Centers for Disease Control and Prevention case definition. The format used can easily be modified for other case definitions. The commentary then discusses whether ME/CFS is the same or a different illness from fibromyalgia. Because overlap exists between the 2 syndromes, some investigators have posited that they are variants of the same illness. I have viewed this as an empirically testable hypothesis and have summoned considerable amounts of data that suggest that the 2 illnesses differ. Were differences to exist, that would suggest different pathophysiologic processes for each, leading to different treatments. (*Clin Ther*. 2019;41:612–618)

Keywords: unexplained illness, pain, fatigue, overlap.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and fibromyalgia are medically unexplained illnesses, predominantly in women, characterized by disabling fatigue and widespread pain with tenderness, respectively. The term ME/CFS was advanced in the Institute of Medicine's 2015 review of the illness; prior to that, the illness was identified as CFS. Because there are currently no known biomarkers that can be used to diagnose each of these illness processes, diagnosis is based on clinical criteria. One major difference between the 2 diagnoses is that the existence of any medical cause of severe fatigue excludes patients from receiving the diagnosis of CFS; in contrast, there are no medical exclusions in making the diagnosis of fibromyalgia. Instead, patients with no other cause for body-wide pain are diagnosed as having primary fibromyalgia, whereas those with coexisting rheumatologic diagnoses receive the diagnosis of secondary fibromyalgia. This difference in diagnosis is responsible for a 10-fold difference in prevalence, with CFS occurring in approximately 0.3%[1] of the population and fibromyalgia in approximately 4%.[2]

I was a part of the committees that arrived at the 1994 and 2015 case definitions for CFS and ME/CFS, respectively; therefore, these are the definitions described here. The 1994 Centers for Disease Control and Prevention–based case definition defined the illness as new onset of fatigue that lasted at least 6 months and was severe enough to produce a substantial decrease of activity at work, at school, or while doing personal or social activities. We have operationalized the way we assess severity of fatigue by asking patients to score their reduction in activity using a 5-point visual analog scale, ranging from 0 for none to 3 for substantial and 5 for very severe. We then ask patients to provide duration and burden of (using the same 0- to 5-point visual analog scale) the following symptoms: sore throat, tender lymph glands, headache, myalgia, arthralgia, unrefreshing sleep, difficulty with concentration and attention, and the report that even minimal physical or mental exertion produce a flare-up of all these other symptoms.

Accepted for publication December 31, 2018
https://doi.org/10.1016/j.clinthera.2018.12.016
0149-2918/$ - see front matter

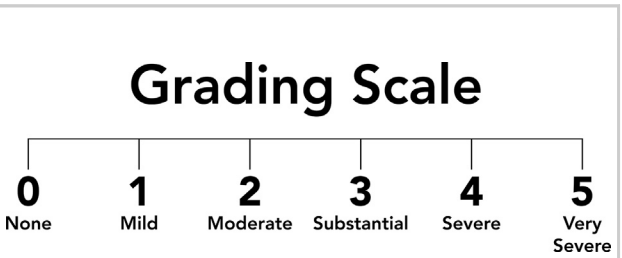

Figure 1. Visual analog scale shown to patients during their evaluation for the possible diagnosis of chronic fatigue syndrome. To use this most efficiently, put this on one side and Figure 2 on the back side of a piece of paper.

Figures 1 and 2 show how to facilitate making this diagnosis. Figure 1 depicts the visual analog scale going from none (rating of 0) to very severe (rating of 5). The physician holds the scale shown in Figure 1 in front of the patient and then reads the text in Figure 2 to the patient. Figure 2 allows the examiner to first assess the effects of the patient's fatigue on his or her life sphere. We define a substantial reduction in activity as endorsement of at least 1 of the life spheres at a rating of $\geq$3. Patients who do not report having fatigue sufficient to produce such a reduction in activity would receive the diagnosis of idiopathic chronic fatigue rather than the more severe diagnosis of CFS. However, if the patient fulfills the life sphere criterion, the examiner than consults the list of 8 symptoms that accompany severe fatigue and makes the diagnosis of CFS; these symptoms are sore throat, tender lymph glands, headache, myalgia, arthralgia, unrefreshing sleep, difficulty with attention and concentration, and postexertional malaise. If the patient rates 4 of these 8 symptoms on the list as a moderate or greater problem, that patient fulfills the symptom severity criterion and then receives the diagnosis of CFS (in our research, we require patients to rate symptoms as substantial or worse to be included in studies).

Next, blood tests are performed to eliminate many of the myriad medical causes of fatigue, including anemia, occult liver dysfunction, hypothyroidism, an underlying inflammatory disorder via sedimentation

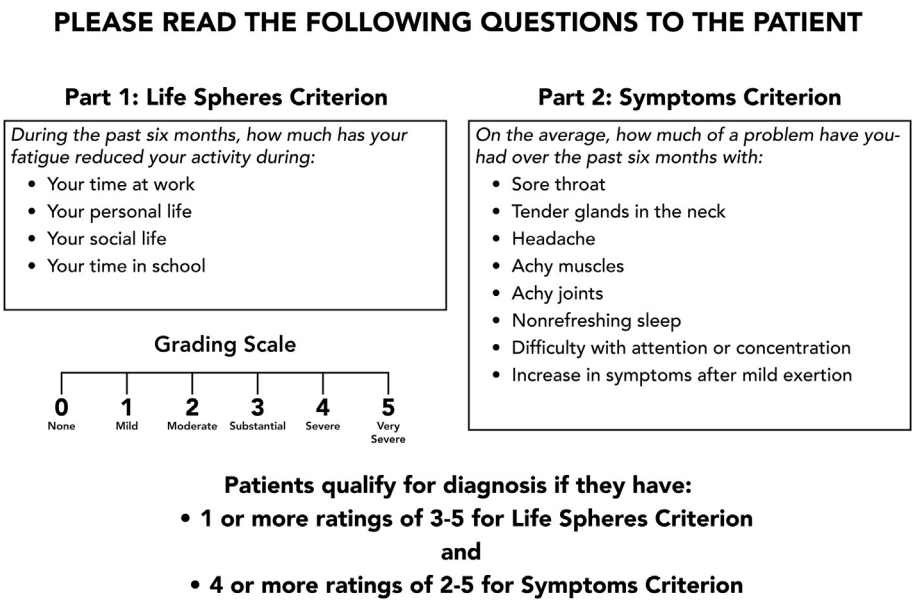

Figure 2. Read this script to the patient. If the patient fulfills the criteria noted herein, that patient will fulfill the 1994 Centers for Disease Control and Prevention case definition for chronic fatigue syndrome. If the patient reports moderate or greater problems with unrefreshing sleep, cognitive problems, and postexertional malaise, the patient would also fulfill criteria for the 2015 clinical case definition developed by an expert committee at the Institute of Medicine for ME/CFS.

rate and C-reactive protein level, Lyme disease via C6 Lyme ELISA, and rheumatologic disease via rheumatoid factor and antinuclear antibody. Because some severe psychiatric illnesses could present with fatigue, those with a history of psychotic or bipolar disorders, recent eating disorder, or problems with alcohol or drug abuse would be excluded from receiving the diagnosis.

In contrast to this research case definition, a committee of experts met at the Institute of Medicine in 2015 and came up with an easier way to make the clinical diagnosis of the illness and changed its name to ME/CFS. The case definition was similar in defining the illness as requiring new onset of 6 months of fatigue that produced a substantial decrease in activity. In addition, patients must have moderate, substantial, or severe problems (scores of 2, 3, or 4, respectively, on our visual analog scale) that occur at least half the time with unrefreshing sleep, postexertional malaise, and either cognitive problems or objective evidence of orthostatic intolerance. To determine whether a patient has physiologic evidence of orthostatic intolerance, we record physiologic data while the patient is supine and then every minute during a 10-minute lean test during which the patient is asked to keep feet together leaning against a wall without talking; a video of this procedure can be found at https://www.facebook.com/painandfatigue/videos/1318728218235453/.

The 2 most common examples of physiologic manifestations of orthostatic intolerance are orthostatic tachycardia with increases in heart rate that exceed 30 beats per minute or orthostatic hyperventilation with decreases in exhaled carbon dioxide of 31 or lower; for clinical practice, we use values of 33 or lower. Earlier work suggested that delayed hypotension was also common, but we were unable to replicate this finding in a controlled study.[3]

The diagnosis of fibromyalgia[4] requires widespread pain that lasts at least 3 months and is accompanied by tenderness on palpation with pressure of 4 kg in at least 11 of 18 locations (see Figure 3 for their location); however, patients usually report pain wherever they are pressed—thus the notion of widespread pain. However, the American College of Rheumatology came up with an operational definition of the term *widespread*: pain on left and right sides of the body, above and below the waist, and accompanied by pain in the cervical spine, anterior chest, thoracic spine, or low back. Patients who fulfilled these criteria often report symptoms also consistent with the diagnosis of temporomandibular joint/muscle disorder.[6]

Despite the difference in prevalence between the 2 syndromes, the core symptoms of fatigue, sleep problems, and cognitive difficulties exist across both syndromes and lead to significant comorbidity between them; we have found that 34% of 313 patients diagnosed with CFS had comorbid fibromyalgia.[7] The fact that these 2 syndromes coexist so often has led some to question whether they are, in fact, distinct diagnostic entities. Barsky and Borus,[8] for example, have suggested that the "similarities between them outweigh the differences"—a position similar to that taken by other researchers. We have termed this the *unitary* hypothesis—a position our own data and those of others do not support, as we will report. A revision of the original 1990 case definition for fibromyalgia published in 2010[5] has blurred the diagnostic differences between the 2 illnesses, nearly doubling the rate at which patients with CFS also receive the diagnosis of fibromyalgia compared with when the 1990 case definition is used.[9] Doing this leaves open the research question of whether the 2 illnesses are variants of one another or are attributable to different pathophysiologic processes. If the former hypothesis were true, discrete case definitions corresponding to distinct illness syndromes would be unnecessary because the pathophysiologic underpinnings of the 2 syndromes would be similar; plans to treat one syndrome would apply to the other as well. Therefore, a critical question at this juncture is to answer the question of CFS and fibromyalgia are the same or different illnesses.

Although overlap between the occurrence of CFS and fibromyalgia exists, there are differences between the illnesses. For example, substance P is increased in the spinal fluid of patients with fibromyalgia but not in the spinal fluid of patients with CFS.[10] This increase in fibromyalgia has recently been replicated in serum and extended to report an increase in corticotrophin-releasing hormone, with both of these leading to further increases in interleukin 6 and tumor necrosis factor via mast cell activation.[11] Of potential importance is the recent suggestion that this inflammatory process can be limited with treatment with interleukin 37.[12] A critical next step will be to move these studies to a side by side comparison of

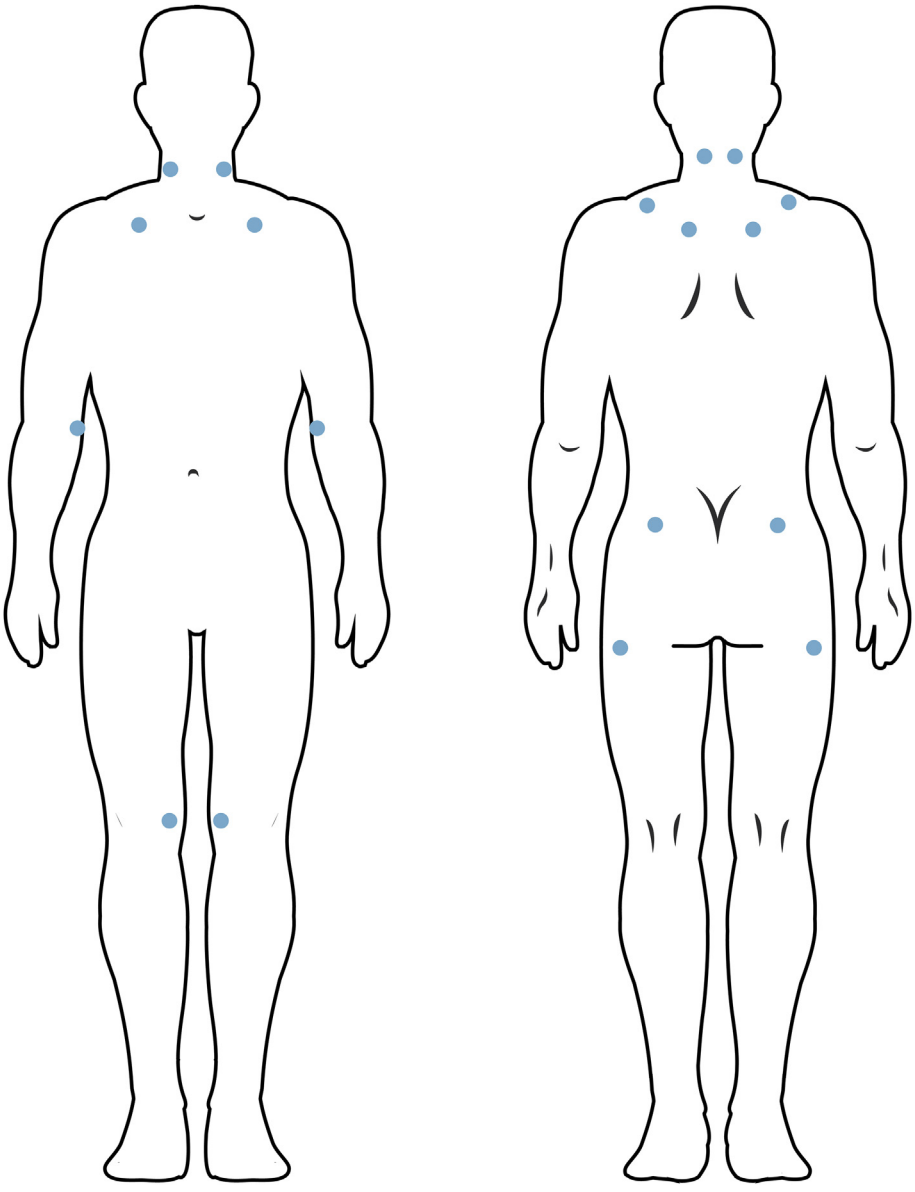

Figure 3. This figure depicts the location of the 18 tender points that should be probed for tenderness at a force of 4 kg. The patient will usually report pain at pressure substantially <4 kg. If the patient reports tenderness at >10 of the 18 locations, that fulfills the tender point requirement for the diagnosis of fibromyalgia.

fibromyalgia with CFS to determine whether differences in this immune regulatory process exist between the illnesses.

We have reviewed the work of others in which biochemical, physiologic, and genetic differences have been reported between the 2 syndromes[13]; moreover, many of our own studies also found differences between the 2 illnesses, supporting the position that the illnesses are different and produced by different pathophysiologic processes.

Because our studies were subsumed under the auspices of an National Institute of Health (NIH)–funded CFS cooperative research center, we studied patients with CFS only or with CFS and fibromyalgia

and did not recruit those with fibromyalgia only for study. Those in the CFS-only group but not the CFS and fibromyalgia group had neuropsychological dysfunction and an elevated brain serotonergic response to tryptophan infusion relative to controls.[14,15] Those with CFS and fibromyalgia did not have these findings, but the patients with CFS only had an altered physiologic response to a standardized submaximal exercise test through reduced blood pressure and an increased stroke index.[16] Concerning posttraumatic stress disorder, patients with CFS only had rates of having this diagnosis on diagnostic psychiatric interview (ie, 1.5%) seen in community samples, whereas those with CFS and fibromyalgia had substantially and significantly higher rates (ie, 8.5%) (Natelson BH, unpublished data). Another group also reported this.[17] Approximately twice as many patients with CFS only developed their illness after a sudden, influenza-like onset compared with those with CFS and fibromyalgia.[7] Finally, our group has identified a series of patients diagnosed with obstructive sleep apnea based on data recorded during overnight polysomnography.[18] Fourteen percent of these patients had CFS only, 4% fulfilled case criteria for the diagnosis of CFS and fibromyalgia; in contrast, none of these patients had fibromyalgia only. These findings indicate discordance in rates of CFS and fibromyalgia; compared with substantially higher rates for CFS (compare 14% to 0.3% in community samples), rates of fibromyalgia only were not different from those found in community samples (approximately 4% in both). This review strongly suggests that CFS only and CFS and fibromyalgia are categorically different and not just the same disorder that differs in severity.

Most recently, we turned our focus on the sleep architecture of patients with CFS only and those with CFS and fibromyalgia and have found these to differ.[19] These differences were not seen using standard Rechtschaffen and Kales criteria but were seen using our newer approach that determined the probability for transitioning among the various sleep phases.[20] The original Rechtschaffen and Kales method of assessing sleep rates the sleep stage status of every sequential 30-second epoch after sleep onset. In general, people fall into light sleep early, with sleep getting deeper later in the night. This process allows sleep researchers to quantify the duration of light and deeper sleep during the entire night as well as periods when the sleeper wakes after sleep onset. However, this method only provides a rather coarse representation of sleep architecture. In contrast, we count every transition from one sleep stage to another. So, for example, as one falls asleep, a transition might occur between wake and light (N1) sleep. Then as the patient falls deeper asleep, transitions may occur from N1 to N2 or even N3 sleep, both of which capture the deeper stages of sleep.

The data from this study are shown in Figure 4. Patients with CFS only had a very different abnormality from patients with CFS and fibromyalgia, in the form of increased transitions from REM to wake. In contrast, patients with CFS and fibromyalgia but not those with CFS only or healthy controls, had data indicative of sleep disruption, namely, higher probabilities of transitioning from slow wave sleep to N1. As a compensation, these patients also had evidence of greater sleep pressure than those with CFS only by having increased transitions from wake to N2.

These differences in sleep architectures indicate that patients with CFS and fibromyalgia exhibit an additional sleep-disrupting component to their disease not found in patients with CFS only, supporting the

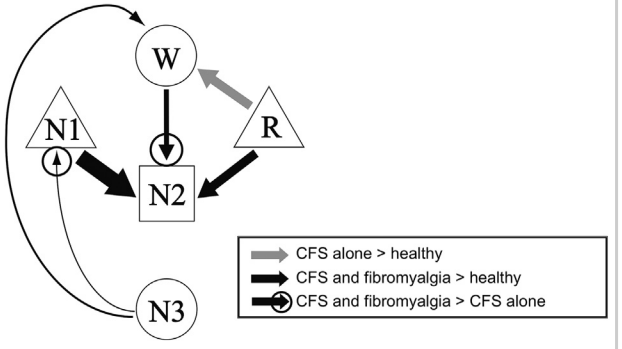

Figure 4. This figure shows a summary of all the transitions among sleep stages (N1, N2, and N3, indicating progressively deeper sleep) for chronic fatigue syndrome (CFS) only, CFS and fibromyalgia, and healthy controls. Note that the sleep architecture of the patients with CFS only differs considerably from those with CFS and fibromyalgia. R = REM sleep; W = wake.

idea that pathophysiologic differences exist between patients with CFS only and those with CFS and fibromyalgia; such differences may mean that CFS with fibromyalgia is a different illness from CFS without FM. We have recently been approved to receive NIH funding to allow us to use a method to make this determination by nonpharmacologically improving some elements of sleep. A report from Swiss researchers studied the sleep architecture of 10 young men during two 45-minute naps: one on a normal bed and the other on a bed that moved back and forth like a cradle[21] (while this is an oscillating movement, the authors called it "rocking"—a term I will continue to use here also). Sleep in the rocking bed condition was better than in the stable bed condition, with shorter periods of light sleep, increases in N2 sleep accompanied by a higher density of sleep spindles, and evidence for improved deep sleep (significantly higher delta power throughout the nap). Because in our data only the patients with CFS and fibromyalgia had disrupted sleep, specifically in the pattern improved by the rocking bed, the hypothesis we will test with the newly available funding is that the rocking bed will improve the sleep disruption of the patients with CFS and fibromyalgia significantly more than it will for the sleep of patients with CFS only.

Going forward, we have also recently learned that the NIH will fund the next step of our proteomics effort using spinal fluid collected from patients who were not using brain-active medications to determine whether CFS alone is a different illness from CFS and fibromyalgia. Our initial study compared spinal fluid from a mixed sample of patients with CFS compared with spinal fluid from patients whose fatigue followed well-treated Lyme disease.[22] Importantly, the proteomic analysis identified >600 proteins that seemed unique to CFS based on limits of detection, thus differentiating it both from the patients with Lyme disease and from healthy controls. However, inferences about these results were limited by the need to pool the spinal fluid from >20 patients with CFS to attain a volume sufficient for analysis. Advances in methods have now obviated the need for so much pooling. With the new NIH support, we can limit pooling to 2 patients per group and are able to assay 5 such groups; thus, we will be able to aliquot spinal fluids from patients with either CFS only or CFS and fibromyalgia in discrete pools. Being able to do this will allow us to eliminate outliers and determine whether the proteome of those with CFS only is similar to or different from those with CFS and fibromyalgia—a major step forward.

ACKNOWLEDGMENTS

NIH grants supporting this review: AI-32247; NS-075653; AI-54478.

REFERENCES

1. Jason LA, Richman JA, Rademaker AW, et al. A community-based study of chronic fatigue syndrome. *Arch Intern Med*. 1999;159:2129–2137.
2. White KP, Speechley M, Harth M, Ostbye T. The London fibromyalgia epidemiology study: the prevalence of fibromyalgia syndrome in London, Ontario. *J Rheumatol*. 1999;26:1570–1576.
3. LaManca JJ, Peckerman A, Walker J, et al. Cardiovascular response during head-up tilt in chronic fatigue syndrome. *Clin Physiol*. 1999;19:111–120.
4. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee. *Arthritis Rheum*. 1990;33:160–172.
5. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res (Hoboken)*. 2010;62:600–610.
6. Fraga BP, Santos EB, Farias Neto JP, et al. Signs and symptoms of temporomandibular dysfunction in fibromyalgic patients. *J Craniofac Surg*. 2012;23:615–618.
7. Ciccone DS, Natelson BH. Comorbid illness in the chronic fatigue syndrome: a test of the single syndrome hypothesis. *Psychosom Med*. 2003;62:268–275.
8. Barsky AJ, Borus JF. Functional somatic syndromes. *Ann Intern Med*. 1999;130:910–921.
9. Kaseeska K, Brown M, Jason LA. Comparing two fibromyalgia diagnostic criteria in a cohort of chronic fatigue syndrome patients. *Bull IACFS/ME*. 2011;19:47–57.
10. Evengård B, Nilsson CG, Lindh G, et al. Chronic fatigue syndrome differs from fibromyalgia: no evidence for elevated substance P levels in cerebrospinal fluid of patients with chronic fatigue syndrome. *Pain*. 1998;78:153–155.
11. Tsilioni I, Russell IJ, Stewart JM, Gleason RM, Theoharides TC. Neuropeptides CRH, SP, HK-1, and inflammatory cytokines IL-6 and TNF are increased in serum of patients with fibromyalgia syndrome, implicating mast cells. *J Pharmacol Exp Ther*. 2016;356:664–672.

12. Mastrangelo F, Frydas I, Ronconi G, et al. Low-grade chronic inflammation mediated by mast cells in fibromyalgia: role of IL-37. *J Biol Regulat Homeost Agents*. 2018;32:195—198.
13. Abbi B, Natelson BH. Is chronic fatigue syndrome the same illness as fibromyalgia: evaluating the 'single syndrome' hypothesis. *Q J Med*. 2013;106:3—9.
14. Cook DB, Nagelkirk PR, Peckerman A, Poluri A, Mores J, Natelson BH. Exercise and cognitive performance in chronic fatigue syndrome. *Med Sci Sports Exerc*. 2005;37:1460—1467.
15. Weaver SA, Janal MN, Aktan N, Ottenweller JE, Natelson BH. Sex differences in plasma prolactin response to tryptophan in Chronic Fatigue Syndrome patients with and without comorbid fibromyalgia. *J Womens Health (Larchmt)*. 2010;3:6—11.
16. Cook DB, Stegner AJ, Nagelkirk PR, Meyer JD, Togo F, Natelson BH. Responses to exercise differ for chronic fatigue syndrome patients with fibromyalgia. *MedSciSports Exerc*. 2012.
17. Roy-Byrne P, Smith WR, Goldberg J, Afari N, Buchwald D. Post-traumatic stress disorder among patients with chronic pain and chronic fatigue. *Psychol Med*. 2004;34:363—368.
18. Pejovic S, Natelson BH, Basta M, Fernandez-Mendoza J, Mahr F, Vgontzas AN. Chronic fatigue syndrome and fibromyalgia in diagnosed sleep disorders: a further test of the 'unitary' hypothesis. *BMC Neurol*. 2015;15:53.
19. Kishi A, Natelson BH, Togo F, Struzik ZR, Rapoport DM, Yamamoto Y. Sleep-stage dynamics in patients with chronic fatigue syndrome with or without fibromyalgia. *Sleep*. 2011;34:1551—1560.
20. Kishi A, Struzik ZR, Natelson BH, Togo F, Yamamoto Y. Dynamics of sleep stage transitions in healthy humans and patients with chronic fatigue syndrome. *Am J Physiol Regul Integr Comp Physiol*. 2008;294:R1980—R1987.
21. Bayer L, Constantinescu I, Perrig S, et al. Rocking synchronizes brain waves during a short nap. *Curr Biol*. 2011;21:R461—R462.
22. Schutzer SE, Angel TE, Liu T, et al. Distinct cerebrospinal fluid proteomes differentiate post-treatment lyme disease from chronic fatigue syndrome. *PLoS One*. 2011;6:e17287.

Address correspondence to: Benjamin H. Natelson, MD, Icahn School of Medicine at Mount Sinai, Department of Neurology, Pain & Fatigue Study Center, 10 Union Square East, New York, NY 10003, USA. E-mail: benjamin.natelson@mountsinai.org