

ME/CFS (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome)

Many clinicians are not aware of the recent advances in the understanding of CFS/ME in the past few years. It is a biological, not psychological condition and must be treated as such.

The CDC and NIH recognize CFS/ME as a real, biological (not psychological) condition:

CDC Symptom list: <https://www.cdc.gov/me-cfs/index.html>

NIH <https://www.nih.gov/mecfs/about-mecfs>

International Consensus Symptoms List (more comprehensive) is below

Stanford, Brigham and Women's Hospital, Columbia University and Harvard have all have CFS/ME research centers and clinics.

Diagnosing and Treating ME/CFS from the US ME/CFS Clinician Coalition

<https://y9ukb3xpraw1vtswp2e7ia6u-wpengine.netdna-ssl.com/wp-content/uploads/2015/05/Diagnosing-and-Treating-MECFS- V1-Final.pdf>

Clinician Coalition Website:

https://mecfscliniciancoalition.org/?fbclid=IwAR0JQ53Kj48c3ZlvOCaw_wZFSfPTieSOj4oWVRV-S3jOM50twXFUK78L8Jw

About Graded Exercise Therapy, Cognitive Behavioral Therapy and the PACE study

There was a deeply flawed study (PACE), that was once the gold standard for “curing” CFS that informed physician education on this disease for decades. Previous “graded exercise and cognitive behavioral therapy” treatments and psychosomatic diagnosis were a result of this now debunked study.

"A review on cognitive behavioral therapy (CBT) and graded exercise therapy (GET) in myalgic encephalomyelitis (ME) / chronic fatigue syndrome (CFS): CBT/GET is not only ineffective and not evidence-based, but also potentially harmful for many patients with ME/CFS"

<https://pubmed.ncbi.nlm.nih.gov/19855350/>

The ‘cognitive behavioral model’ of chronic fatigue syndrome: Critique of a flawed model

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6482658/>

Bad science misled millions with chronic fatigue syndrome. Here's how we fought back
<https://www.statnews.com/2016/09/21/chronic-fatigue-syndrome-pace-trial/>

For People With Chronic Fatigue Syndrome, More Exercise Isn't Better
<https://www.npr.org/sections/health-shots/2017/10/02/554369327/for-people-with-chronic-fatigue-syndrome-more-exercise-isnt-better>

Chronic Fatigue Syndrome Research Gains Funding, And Controversy
<https://www.npr.org/sections/health-shots/2015/11/04/454335755/chronic-fatigue-syndrome-research-gains-funding-and-controversy>

NIH Study Aims To Unravel The Illness Known As 'Chronic Fatigue Syndrome'
<https://www.npr.org/sections/health-shots/2017/05/01/526372209/nih-study-aims-to-unravel-the-illness-known-as-chronic-fatigue-syndrome>

NIH, Stanford, Harvard, Columbia and others are now working on the *biological* causes and effects of CFS, which have been proven in the lab. There are now pharmaceutical treatments, but the biggest treatment is careful pacing and rests to avoid PEM (Post Exertional Malaise)

There are BIOMARKERS for CFS

Stanford's new blood test (made 4/23/2019, as of 7/2020 still not available to public)

<https://med.stanford.edu/news/all-news/2019/04/biomarker-for-chronic-fatigue-syndrome-identified.html>

Working (not static) MRI

https://press.rsna.org/timssnet/media/pressreleases/14_pr_target.cfm?ID=772

SPECT scan <https://www.ncbi.nlm.nih.gov/pubmed/8141022>.

gastrointestinal imbalance

<https://www.webmd.com/chronic-fatigue-syndrome/news/20160715/gut-bacteria-may-hold-clues-to-chronic-fatigue-syndrome>

Non-Standard Inflammation Markers (c4a)

This is Stanford's standard intake tests for CFS patients. Other inflammation tests show nothing.

Orthostatic Intolerance <https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-019-1935-y>

Pharmaceutical Drugs in use

****This is a list for doctors. Never take a prescription drug not prescribed by a medical professional****

Stanford ME/CFS Clinic:

Aripiprazole (Abilify) (2mg) before bed. Started at 1mg for two weeks, then up to 2. *this is supposed to be the most helpful with the least side effects according to Dr. Bonilla at Stanford.

Off label use of Aripiprazole shows promise as a treatment for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): a retrospective study of 101 patients treated with a low dose of Aripiprazole

https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-021-02721-9?fbclid=IwAR1N_R0vx5slmCkPVaUWCaEQxNUPSbHEkuQaH35itelmRnCsp_PO SG7IO6s

Ketotifen (.5 ramping to 1mg) It apparently helps stabilize mast cells and recent research is finding that “individuals diagnosed with moderate to severe ME/CFS have been noted to have higher amounts of or dysfunctional mast cells in circulation” https://medpedia.org/wiki/Mast_cell_activation_syndrome

Celecoxib 100mg 2 times a day. This is a new treatment at Stanford, not of the PDF treatment sheet. Can be used with Abilify

Valacyclovir 1000-3000 mg a day (lowest effective dose). Can be hard on liver, not effective in all patients.
Brigham and Women's in Boston is using Pyridostigmine, seen in this video. <https://youtu.be/FMakVopeww> (mentioned at 23 min in) Stanford finds this has too many side effects to recommend.

Doctor's Guide to Treatment (one perspective)

<https://www.frontiersin.org/articles/10.3389/fped.2018.00415/full>

NOTE: I would add that this condition is very different person to person. Symptoms wax and wane in unpredictable ways (especially since PEM- Post Exertional Malaise can happen 1-48 hours later). As a rule, symptoms get worse when a patient overextends physically, mentally or emotionally or is exposed to stress or over-stimulated.

Some patients never experience a large subset of symptoms (sore throat etc.). Some patients have more cognitive issues and few physical ones, other have more physical issues and minor cognitive ones, some have both. Dr. Chia (infectious disease specialist in LA) has noted that patients are often worst effected in the area they were most active (accountants can't add, runners can't walk, the most active people are the hardest hit). Onset is often following a viral illness, often with a less bad period followed by a worse one after a period of stress, a second viral infection and/or significant exertion.

For more information see cfs-me-navigator.com

Myalgic encephalomyelitis: International Consensus Criteria

■ B. M. Carruthers¹, M. I. van de Sande², K. L. De Meirleir³, N. G. Klimas⁴, G. Broderick⁵, T. Mitchell⁶, D. Staines^{7,8}, A. C. P. Powles⁹, N. Speight¹⁰, R. Vallings¹¹, L. Bateman^{12,13}, B. Baumgarten-Austrheim¹⁴, D. S. Bell¹⁵, N. Carlo-Stella¹⁶, J. Chia^{17,18}, A. Darragh¹⁹, D. Jo²⁰, D. Lewis²¹, A. R. Light²², S. Marshall-Gradisbik⁸, I. Mena²³, J. A. Mikovits²⁴, K. Miwa²⁵, M. Murovska²⁶, M. L. Pall²⁷ & S. Stevens²⁸

From the ¹Independent, Vancouver, BC, Canada; ²Independent, Calgary, AB, Canada; ³Department of Physiology and Medicine, Vrije University of Brussels, Himmunitas Foundation, Brussels, Belgium; ⁴Department of Medicine, University of Miami Miller School of Medicine and Miami Veterans Affairs Medical Center, Miami, FL, USA; ⁵Department of Medicine, University of Alberta, Edmonton, AB, Canada; ⁶Honorary Consultant for NHS at Peterborough/Cambridge, Lowestoft, Suffolk, UK; ⁷Gold Coast Public Health Unit, Southport, Queensland; ⁸Health Sciences and Medicine, Bond University, Robina, Queensland, Australia; ⁹Faculty of Health Sciences, McMaster University and St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada; ¹⁰Independent, Durham, UK; ¹¹Howick Health and Medical Centre, Howick, New Zealand; ¹²Fatigue Consultation Clinic, Salt Lake Regional Medical Center; ¹³Internal Medicine, Family Practice, University of Utah, Salt Lake City, UT, USA; ¹⁴ME/CFS Center, Oslo University Hospital HF, Norway; ¹⁵Department of Paediatrics, State University of New York, Buffalo, NY, USA; ¹⁶Independent, Pavia, Italy; ¹⁷Harbor-UCLA Medical Center, University of California, Los Angeles, CA; ¹⁸EV Med Research, Lomita, CA, USA; ¹⁹University of Limerick, Limerick, Ireland; ²⁰Pain Clinic, Konyang University Hospital, Daejeon, Korea; ²¹Donvale Specialist Medical Centre, Donvale, Victoria, Australia; ²²Departments of Anesthesiology, Neurobiology and Anatomy, University of Utah, Salt Lake City, UT, USA; ²³Department of Medicina Nuclear, Clinica Las Condes, Santiago, Chile; ²⁴Whittemore Peterson Institute, University of Nevada, Reno, NV, USA; ²⁵Miwa Naika Clinic, Toyama, Japan; ²⁶A. Kirchenstein Institute of Microbiology and Virology, Riga Stradins University, Riga, Latvia; ²⁷Department of Biochemistry & Basic Medical Sciences, Washington State University, Portland, OR; and ²⁸Department of Sports Sciences, University of the Pacific, Stockton, CA USA

Abstract. Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Baumgarten-Austrheim B, Bell DS, Carlo-Stella N, Chia J, Darragh A, Jo D, Lewis D, Light AR, Marshall-Gradisbik S, Mena I, Mikovits JA, Murovska M, Pall ML, Stevens S (Independent, Vancouver, BC, Canada; Independent, Calgary, AB, Canada; Department of Physiology and Medicine, Vrije University of Brussels, Himmunitas Foundation, Brussels, Belgium; Department of Medicine, University of Miami Miller School of Medicine and Miami Veterans Affairs Medical Center, Miami, FL, USA; Department of Medicine, University of Alberta, Edmonton, AB, Canada; Honorary Consultant for NHS at Peterborough/Cambridge, Lowestoft, Suffolk, UK; Gold Coast Public Health Unit, Southport, Queensland; Health Sciences and Medicine, Bond University, Robina, Queensland, Australia; Faculty of Health Sciences, McMaster University and St Joseph's Healthcare Hamilton, Hamilton, ON, Canada; Independent, Durham, UK; Howick Health and Medical Centre, Howick, New Zealand; Fatigue Consultation Clinic, Salt Lake Regional Medical Center; Internal Medicine, Family Practice, University of Utah, Salt Lake City, UT, USA; ME/CFS Center, Oslo University Hospital HF, Norway; Department of Paediatrics, State University of New York, Buffalo, NY; Independent, Pavia, Italy; Harbor-UCLA Medical Center, University of California, Los Angeles, CA; EV Med Research,

Lomita, CA, USA; University of Limerick, Limerick, Ireland; Pain Clinic, Konyang University Hospital, Daejeon, Korea; Donvale Specialist Medical Centre, Donvale, Victoria, Australia; Departments or Anesthesiology, Neurobiology and Anatomy, University of Utah, Salt Lake City, Utah, USA; Health Sciences and Medicine, Bond University, Robina, Queensland, Australia; Department of Medicina Nuclear, Clinica Las Condes, Santiago, Chile; Whittemore Peterson Institute, University of Nevada, Reno, NV, USA; Miwa Naika Clinic, Toyama, Japan; A. Kirchenstein Institute of Microbiology and Virology, Riga Stradins University, Riga, Latvia; Department of Biochemistry & Basic Medical Sciences, Washington State University, Portland, OR; Department of Sports Sciences, University of the Pacific, Stockton, CA USA). Myalgic encephalomyelitis: International Consensus Criteria (Review). *J Intern Med* 2011; **270**: 327–338.

The label 'chronic fatigue syndrome' (CFS) has persisted for many years because of the lack of knowledge of the aetiological agents and the disease process. In view of more recent research and clinical experience that strongly point to widespread inflammation and multisystemic neuropathology, it is more appropriate and correct to use the term 'myalgic encephalomyelitis' (ME) because it indicates an underlying pathophysiology. It is also consistent with the neurological classification of ME in the World Health Organization's International Classification of Diseases (ICD G93.3). Consequently, an International Consensus Panel consisting of clinicians, researchers, teaching faculty and an independent

Re-use of this article is permitted in accordance with the Terms and Conditions set out at http://wileyonlinelibrary.com/onlineopen/OnlineOpen_Terms

patient advocate was formed with the purpose of developing criteria based on current knowledge. Thirteen countries and a wide range of specialties were represented. Collectively, members have approximately 400 years of both clinical and teaching experience, authored hundreds of peer-reviewed publications, diagnosed or treated approximately 50 000 patients with ME, and several members coauthored previous criteria. The expertise and experience of the panel members as well as PubMed and other medical sources were utilized in a progression of suggestions/drafts/reviews/revisions. The authors, free of any sponsoring organization, achieved 100% consensus through a Delphi-type process. The scope of this

paper is limited to criteria of ME and their application. Accordingly, the criteria reflect the complex symptomatology. Operational notes enhance clarity and specificity by providing guidance in the expression and interpretation of symptoms. Clinical and research application guidelines promote optimal recognition of ME by primary physicians and other healthcare providers, improve the consistency of diagnoses in adult and paediatric patients internationally and facilitate clearer identification of patients for research studies.

Keywords: chronic fatigue syndrome, criteria, definition, diagnosis, myalgic encephalomyelitis.

Introduction

Myalgic encephalomyelitis (ME), also referred to in the literature as chronic fatigue syndrome (CFS), is a complex disease involving profound dysregulation of the central nervous system (CNS) [1–3] and immune system [4–8], dysfunction of cellular energy metabolism and ion transport [9–11] and cardiovascular abnormalities [12–14]. The underlying pathophysiology produces measurable abnormalities in physical and cognitive function and provides a basis for understanding the symptomatology. Thus, the development of International Consensus Criteria that incorporate current knowledge should advance the understanding of ME by health practitioners and benefit both the physician and patient in the clinical setting as well as clinical researchers.

The problem with broadly inclusive criteria [15, 16] is that they do not select homogeneous sets of patients. The Centers for Disease Control prevalence estimates increased tenfold from 0.24% using the Fukuda criteria [17] to 2.54% using the Reeves empirical criteria [16]. Jason *et al.* [18] suggest that there are flaws in Reeves' methodology because it is possible to meet the empirical criteria for ME without having any physical symptoms and it does not discriminate patients with ME/CFS from those with major depressive disorder. Patient sets that include people who do not have the disease lead to biased research findings, inappropriate treatments and waste scarce research funds [19].

Some symptoms of the Fukuda criteria overlap with depression, whereas the Canadian Consensus Criteria [20] differentiate patients with ME from those who are depressed and identify patients who are more physically debilitated and have greater physical and cognitive functional impairments [21].

International Consensus Criteria

The Canadian Consensus Criteria were used as a starting point, but significant changes were made. The 6-month waiting period before diagnosis is no longer required. No other disease criteria require that diagnoses be withheld until after the patient has **suffered with the affliction for 6 months**. Notwithstanding periods of clinical investigation will vary and may be prolonged, diagnosis should be made when the clinician is satisfied that the patient has ME rather than having the diagnosis restricted by a specified time factor. Early diagnoses may elicit new insights into the early stages of pathogenesis; prompt treatment may lessen the severity and impact.

Using 'fatigue' as a name of a disease gives it exclusive emphasis and has been the most confusing and misused criterion. No other fatiguing disease has 'chronic fatigue' attached to its name – e.g. cancer/chronic fatigue, multiple sclerosis/chronic fatigue – except ME/CFS. Fatigue in other conditions is usually proportional to effort or duration with a quick recovery and will recur to the same extent with the same effort or duration that same or next day. The pathological low threshold of fatigability of ME described in the following criteria often occurs with minimal physical or mental exertion and with reduced ability to undertake the same activity within the same or several days.

The International Consensus Criteria (Table 1) identify the unique and distinctive characteristic patterns of symptom clusters of ME. The broad spectrum of symptoms alerts medical practitioners to areas of pathology and may identify critical symptoms more accurately [18–20]. Operational notes following each criterion provide guidance in symptom expression

Table 1 *Myalgic encephalomyelitis: international consensus criteria*

Adult and paediatric • clinical and research

Myalgic encephalomyelitis is an acquired neurological disease with complex global dysfunctions. Pathological dysregulation of the nervous, immune and endocrine systems, with impaired cellular energy metabolism and ion transport are prominent features. Although signs and symptoms are dynamically interactive and causally connected, the criteria are grouped by regions of pathophysiology to provide general focus.

A patient will meet the criteria for postexertional neuroimmune exhaustion (A), at least one symptom from three neurological impairment categories (B), at least one symptom from three immune/gastro-intestinal/genitourinary impairment categories (C), and at least one symptom from energy metabolism/transport impairments (D).

A. Postexertional neuroimmune exhaustion (PENE pen'-e): Compulsory

This cardinal feature is a pathological inability to produce sufficient energy on demand with prominent symptoms primarily in the neuroimmune regions. Characteristics are as follows:

1. **Marked, rapid physical and/or cognitive fatigability in response to exertion**, which may be minimal such as activities of daily living or simple mental tasks, can be debilitating and cause a relapse.
2. **Postexertional symptom exacerbation**: *e.g. acute flu-like symptoms, pain and worsening of other symptoms.*
3. **Postexertional exhaustion** may occur immediately after activity or be delayed by hours or days.
4. **Recovery period is prolonged**, usually taking 24 h or longer. A relapse can last days, weeks or longer.
5. **Low threshold of physical and mental fatigability (lack of stamina) results in a substantial reduction in pre-illness activity level.**

Operational notes: For a diagnosis of ME, symptom severity must result in a significant reduction of a patient's premorbid activity level. **Mild** (an approximate 50% reduction in pre-illness activity level), **moderate** (mostly housebound), **severe** (mostly bedridden) or **very severe** (totally bedridden and need help with basic functions). There may be marked fluctuation of symptom severity and hierarchy from day to day or hour to hour. Consider activity, context and interactive effects. **Recovery time:** *e.g. Regardless of a patient's recovery time from reading for ½ hour, it will take much longer to recover from grocery shopping for ½ hour and even longer if repeated the next day – if able. Those who rest before an activity or have adjusted their activity level to their limited energy may have shorter recovery periods than those who do not pace their activities adequately.* **Impact:** *e.g. An outstanding athlete could have a 50% reduction in his/her pre-illness activity level and is still more active than a sedentary person.*

B. Neurological impairments

At least one symptom from three of the following four symptom categories

1. Neurocognitive impairments

- a. **Difficulty processing information:** slowed thought, impaired concentration *e.g. confusion, disorientation, cognitive overload, difficulty with making decisions, slowed speech, acquired or exertional dyslexia*
- b. **Short-term memory loss:** *e.g. difficulty remembering what one wanted to say, what one was saying, retrieving words, recalling information, poor working memory*

2. Pain

- a. **Headaches:** *e.g. chronic, generalized headaches often involve aching of the eyes, behind the eyes or back of the head that may be associated with cervical muscle tension; migraine; tension headaches*
- b. **Significant pain** can be experienced **in muscles**, muscle-tendon junctions, joints, abdomen or chest. It is noninflammatory in nature and often migrates. *e.g. generalized hyperalgesia, widespread pain (may meet fibromyalgia criteria), myofascial or radiating pain*

3. Sleep disturbance

- a. **Disturbed sleep patterns:** *e.g. insomnia, prolonged sleep including naps, sleeping most of the day and being awake most of the night, frequent awakenings, awaking much earlier than before illness onset, vivid dreams/nightmares*
- b. **Unrefreshed sleep:** *e.g. awoken feeling exhausted regardless of duration of sleep, day-time sleepiness*

Table 1 *Continued*

Adult and paediatric • clinical and research

4. Neurosensory, perceptual and motor disturbances

- a. **Neurosensory and perceptual:** e.g. inability to focus vision, sensitivity to light, noise, vibration, odour, taste and touch; impaired depth perception
- b. **Motor:** e.g. muscle weakness, twitching, poor coordination, feeling unsteady on feet, ataxia

Notes: Neurocognitive impairments, reported or observed, become more pronounced with fatigue. Overload phenomena may be evident when two tasks are performed simultaneously. Abnormal accommodation responses of the pupils are common. Sleep disturbances are typically expressed by prolonged sleep, sometimes extreme, in the acute phase and often evolve into marked sleep reversal in the chronic stage. Motor disturbances may not be evident in mild or moderate cases but abnormal tandem gait and positive Romberg test may be observed in severe cases.

C. Immune, gastro-intestinal and genitourinary Impairments

At least one symptom from three of the following five symptom categories

1. **Flu-like symptoms may be recurrent or chronic and typically activate or worsen with exertion.** e.g. sore throat, sinusitis, cervical and/or axillary lymph nodes may enlarge or be tender on palpitation
2. **Susceptibility to viral infections with prolonged recovery periods**
3. **Gastro-intestinal tract:** e.g. nausea, abdominal pain, bloating, irritable bowel syndrome
4. **Genitourinary:** e.g. urinary urgency or frequency, nocturia
5. **Sensitivities to food, medications, odours or chemicals**

Notes: Sore throat, tender lymph nodes, and flu-like symptoms obviously are not specific to ME but their activation in reaction to exertion is abnormal. The throat may feel sore, dry and scratchy. Faucial injection and crimson crescents may be seen in the tonsillar fossae, which are an indication of immune activation.

D. Energy production/transportation impairments: At least one symptom

1. **Cardiovascular:** e.g. inability to tolerate an upright position - orthostatic intolerance, neurally mediated hypotension, postural orthostatic tachycardia syndrome, palpitations with or without cardiac arrhythmias, light-headedness/dizziness
2. **Respiratory:** e.g. air hunger, laboured breathing, fatigue of chest wall muscles
3. **Loss of thermostatic stability:** e.g. subnormal body temperature, marked diurnal fluctuations; sweating episodes, recurrent feelings of feverishness with or without low grade fever, cold extremities
4. **Intolerance of extremes of temperature**

Notes: Orthostatic intolerance may be delayed by several minutes. Patients who have orthostatic intolerance may exhibit mottling of extremities, extreme pallor or Raynaud's Phenomenon. In the chronic phase, moons of finger nails may recede.

Paediatric considerations

Symptoms may progress more slowly in children than in teenagers or adults. In addition to postexertional neuroimmune exhaustion, the most prominent symptoms tend to be neurological: headaches, cognitive impairments, and sleep disturbances.

1. **Headaches:** Severe or chronic headaches are often debilitating. Migraine may be accompanied by a rapid drop in temperature, shaking, vomiting, diarrhoea and severe weakness.
2. **Neurocognitive impairments:** Difficulty focusing eyes and reading are common. Children may become dyslexic, which may only be evident when fatigued. Slow processing of information makes it difficult to follow auditory instructions or take notes. All cognitive impairments worsen with physical or mental exertion. Young people will not be able to maintain a full school programme.
3. **Pain may seem erratic and migrate quickly.** Joint hypermobility is common.

Notes: Fluctuation and severity hierarchy of numerous prominent symptoms tend to vary more rapidly and dramatically than in adults.

Table 1 *Continued*

Adult and paediatric • clinical and research

Classification— **Myalgic encephalomyelitis**

— **Atypical myalgic encephalomyelitis:** meets criteria for postexertional neuroimmune exhaustion but has a limit of two less than required of the remaining criterial symptoms. Pain or sleep disturbance may be absent in rare cases.

Exclusions: *As in all diagnoses, exclusion of alternate explanatory diagnoses is achieved by the patient's history, physical examination, and laboratory/biomarker testing as indicated. It is possible to have more than one disease but it is important that each one is identified and treated. Primary psychiatric disorders, somatoform disorder and substance abuse are excluded. Paediatric: 'primary' school phobia.*

Comorbid entities: Fibromyalgia, myofascial pain syndrome, temporomandibular joint syndrome, irritable bowel syndrome, interstitial cystitis, Raynaud's phenomenon, prolapsed mitral valve, migraines, allergies, multiple chemical sensitivities, Hashimoto's thyroiditis, Sicca syndrome, reactive depression. *Migraine and irritable bowel syndrome may precede ME but then become associated with it. Fibromyalgia overlaps.*

and contextual interpretation. This will assist the primary clinician in identifying and treating patients with ME in the primary care setting.

Criteria are supported by research

Criterial symptoms are supported by a study of more than 2500 patients that determined which symptoms had the greatest efficacy to identify patients with ME [22]. Investigations into gene expression [23–27] and structure further support the criteria at a molecular level including anomalies of increased oxidative stress [4, 28], altered immune and adrenergic signaling [29, 30] and altered oestrogen receptor expression [31]. In addition, evidence supporting a genetic predisposition to ME points to modifications in serotonin transporter genes [32, 33], the glucocorticoid receptor gene [34], as well as HLA class II involvement [35]. The potential combinatorial effects of these modifications have received limited attention [33, 36]. Some early broad-based studies show a lack of objective findings such as no association with HLA genotype [37]. A study of patients from a twin registry suggested that environmental factors may outweigh any genetic predisposition in broader patient populations [38].

Underlying problems of inconsistent findings in research studies have been identified [39, 40] and include a need for studies to be based on larger sample sizes with a more clearly defined phenotype, in particular one that recognizes the likely existence of significant subgroups within the patient population. In a study of the Reeves empirical criteria [16], Jason *et al.* [18] reported that 38% of patients diagnosed with

major depressive disorder were misclassified as having CFS and only 10% of patients identified as having CFS actually had ME. Accordingly, the primary goal of this consensus report is to establish a more selective set of clinical criteria that would identify patients who have neuroimmune exhaustion with a pathological low threshold of fatigability and symptom flare in response to exertion. This will enable patients to be diagnosed and enrolled in research studies internationally under a case definition that is acceptable to physicians and researchers around the world.

Postexertional neuroimmune exhaustion (PENE per' -e)

'Malaise' – a vague feeling of discomfort or fatigue [41] – is an inaccurate and inadequate word for the pathological low-threshold fatigability and postexertional symptom flare. Pain and fatigue are crucial bioalarm signals that instruct patients to modify what they are doing in order to protect the body and prevent further damage. Postexertional neuroimmune exhaustion is part of the body's global protection response and is associated with dysfunction in the regulatory balance within and between the nervous, immune and endocrine systems, and cellular metabolism and ion transport [42–46]. The normal activity/rest cycle, which involves performing an activity, becoming fatigued and taking a rest whereby energy is restored, becomes dysfunctional.

Numerous papers document abnormal biological responses to exertion, such as loss of the invigorating effects of exercise [20], decreased pain threshold [47–49], decreased cerebral oxygen and blood volume/flow [50–53], decreased maximum heart rate

[54], impaired oxygen delivery to muscles [55], elevated levels of nitric oxide metabolites [56] and worsening of other symptoms [57]. Patients reach the anaerobic threshold and maximal exercise at a much lower oxygen consumption level [58]. Reported prolonged effects of exertion include elevated sensory signalling to the brain [59] that is interpreted as pain and fatigue [29], elevated cytokine activity [60], delay in symptom activation [61] and a recovery period of at least 48 h [57]. When an exercise test was given on two consecutive days, some patients experienced up to a 50% drop in their ability to produce energy on the second evaluation [62]. Both submaximal and self-paced physiologically limited exercise resulted in postexertional malaise [48].

Neurological impairments

Some viruses and bacteria can infect immune and neural cells and cause chronic inflammation. Structural and functional pathological abnormalities [3] within the brain and spinal cord suggest dysregulation of the CNS control system and communication network [62], which play crucial roles in cognitive impairment and neurological symptoms [20]. Neuroinflammation of the dorsal root ganglia, gatekeepers of peripheral sensory information travelling to the brain, has been observed in spinal autopsies (Chaudhuri A. Royal Society of Medicine Meeting 2009). Identified cerebrospinal fluid proteomes distinguish patients from healthy controls and post-treatment Lyme disease [63]. Neuroimaging studies report irreversible punctuate lesions [64], an approximate 10% reduction in grey matter volume [65, 66], hypoperfusion [50, 67–71] and brain stem hypometabolism [1]. Elevated levels of lateral ventricular lactate are consistent with decreased cortical blood flow, mitochondrial dysfunction and oxidative stress [72]. Research suggests that dysregulation of the CNS and autonomic nervous system alters the processing of pain and sensory input [29, 47, 73, 74]. Patients' perception that simple mental tasks require substantial effort is supported by brain scan studies that indicate greater source activity and more regions of the brain are utilized when processing auditory and spatial cognitive information [75–77]. Poor attentional capacity and working memory are prominent disabling symptoms [20, 75, 78].

Immune impairments

Most patients have an acute infectious onset with flu-like and/or respiratory symptoms. A wide range of

infectious agents have been reported in the subsets of patients, including xenotropic murine leukaemia virus-related virus (XMRV) [79] and other murine leukaemia virus (MLV)-related viruses [80], enterovirus [81–83], Epstein–Barr virus [84], human herpes virus 6 and 7 [85–87], Chlamydia [88], cytomegalovirus [89], parvovirus B19 [90] and *Coxiella burnetii* [84]. Chronic enterovirus infection of the stomach and altered levels of D Lactic acid-producing bacteria in the gastrointestinal tract have been investigated [82, 91]. Possibly, the initial infection damages part of the CNS and immune system causing profound deregulation and abnormal responses to infections [4]. Publications describe decreased natural killer cell signalling and function, abnormal growth factor profiles, decreased neutrophil respiratory bursts and Th1, with a shift towards a Th2 profile [4–8, 92, 93]. Chronic immune activation [27], increases in inflammatory cytokines, pro-inflammatory alleles [4–8, 94–96], chemokines and T lymphocytes and dysregulation of the antiviral ribonuclease L (RNase L) pathway [62, 97–100] may play a role in causing flu-like symptoms, which aberrantly flare in response to exertion [5, 92].

Energy production/transport impairments

The consistent clinical picture of profound energy impairment suggests dysregulation of the mitochondria and cellular energy metabolism and ion transport and channelopathy [9–11, 100, 101]. A biochemical positive feedback cycle called the 'NO/ONOO- cycle' may play a role in maintaining the chronic nature of ME, the presence of oxidative stress [102–104], inflammatory cytokine elevation [94–96] and mitochondrial dysfunction [105–108] and result in reduced blood flow and vasculopathy [106, 107].

Findings of 'small heart' with small left ventricular chamber and poor cardiac performance in patient subsets [109, 110] support previous reports of cardiac and left ventricular dysfunction [13, 111, 112], which predispose to orthostatic intolerance [14, 113]. Low blood pressure and exaggerated diurnal variation may be due to abnormal blood pressure regulation [114]. Altered control and reduced cortisol production during and following exercise may be involved. Orthostatic intolerance is associated with functional impairment and symptom severity [115]. Measurable vascular abnormalities suggest that the brain is not receiving sufficient circulating blood volume in an upright position [12, 113], which is intensified when standing in one place such as a grocery

store check-out line. Significant reduction in heart rate variability during sleep is associated with poor sleep quality and suggests a pervasive state of nocturnal sympathetic hypervigilance [116].

Application of criteria

Diagnostic criteria serve two necessary but divergent functions – the first is diagnosing individuals in a clinical setting and the second is identifying patient sets for research studies.

Clinical application

General considerations

1 Determine whether symptom cluster patterns are congruent with those expected from dysfunction of an underlying causal system.

2 Symptoms interact dynamically within a stable cluster because they share the same deep causal roots. Patients' contextual observations are essential in determining the expression of interaction of symptom patterns and severity of their impact.

3 Symptom severity impact must result in a 50% or greater reduction in a patient's premorbid activity level for a diagnosis of ME. Mild: approximately 50% reduction in activity, moderate: mostly housebound, severe: mostly bedbound and very severe: bedbound and dependent on help for physical functions.

4 Symptom severity hierarchy should be determined periodically to help orient and monitor treatment.

5 Criterial subgroups: Postexertional neuroimmune exhaustion is the hallmark feature. It may be helpful to subgroup according to which of the other diagnostic criterial patterns best represent a patient's cluster of most severe symptoms: neurological, immune, energy metabolism/transport or eclectic (symptoms widely distributed amongst subgroups).

6 Separate primary symptoms from secondary symptoms and aggravators. Distinguish primary symptom complexes formed by a disease process from secondary effects of coping with the disease, such as anxiety about finances. Determine the effects and burden of aggravators and stress enhancers such as fast paced environments and exposure to toxins.

7 Determine total illness burden by assessing symptom severity, interaction and overall impact. Consider all aspects of the patient's life – physical, occupa-

tional, educational, social and personal activities of daily living. Patients who prioritize their activities may be able to do one important activity by eliminating or severely reducing activities in other aspects of their life.

8 The International Symptom Scale should not be part of the initial clinical interview because it may disturb the weighting and significance of results obtained for an individual patient. When used periodically, it can help position the patient within the group, orient the treatment programme and monitor its effectiveness.

Paediatric considerations

1 If possible, interview a young person with both parents because each may remember different symptoms or interactive events that may help determine onset and when the illness began to interfere with daily function.

2 Children cannot be expected to judge pre-illness function with current function. Assess impact by comparing hobbies, educational, social and sport activities the child participated in before illness with present activity level.

3 Children may appear irritable when they are asked to do something when they feel exhausted. On the other hand, they are often able to accommodate fatigue by resting, which may be inappropriately interpreted as being lazy.

4 School Phobia: Young patients spend most of their out-of-school hours resting, whereas children with school phobia will be socializing and participating in activities. However, it is possible that school phobia may become a secondary symptom because of bullying or academic difficulties owing to having ME.

5 Natural Course: Children can be very severely afflicted but those whose symptoms are of mild to moderate severity generally are more likely to have them go into remission than adults. Prognosis cannot be predicted with certainty.

Research application

A clinical diagnosis must be confirmed before a patient can provide useful general knowledge about the disease. The data obtained from patients allow controlled and meaningful observations and suggest hypotheses to be tested and confirmed or refuted.

General considerations

1 *Patients should meet the full criteria* for epidemiological studies. If specific subgroups or atypical ME are included in a research study, that should be clearly indicated.

2 *Specificity*: Because critical symptoms are compulsory, it ensures proper selection of patients. Key operational guidelines enhance clarity and specificity. Ranking the hierarchy of the most troublesome symptoms may be helpful in some studies.

3 *Reliability*: Symptoms must not be viewed as a nominal checklist. The International Consensus Criteria focus on symptom patterns, which increase reliability. The International Symptom Scale ensures consistency in the way questions are asked and further increases the reliability of data collected in different locations. Patients should complete the International Symptom Scale prior to entering a research study.

Optional considerations

Classifying patients by subgroups to enable the comparison of patients within the diagnosis of ME may be helpful in some studies.

1 *Onset*: acute infectious or gradual.

2 *Onset severity* may be a good predictor of severity in the chronic phase.

3 *Symptom severity*: mild, moderate, severe, very severe.

4 *Criterial subgroups*: neurological, immune, energy metabolism/transport or eclectic.

(See clinical application for symptom severity and criterial subgroups.)

Conclusions

The International Consensus Criteria provide a framework for the diagnosis of ME that is consistent with the patterns of pathophysiological dysfunction emerging from published research findings and clinical experience. Symptom patterns interact dynamically because they are causally connected. This has been formally addressed by some investigators who have used well-established multivariate statistical techniques, such as common factor or principal component analyses to identify symptom constructs [117, 118]. Others have extended the use of such methods to guide

the analysis of gene expression profiles [28] and to delineate patient subgroups [119]. Consistent with this approach, the panel is developing an International Consensus Symptom Scale (ICSS) that will build on these underlying interactions. However, a necessary first step in establishing a quantitative score for any diagnostic instrument is the specification of measurable factors that are most relevant to the illness. Establishing such criteria was the primary objective of this work, and we believe the International Consensus Criteria will help clarify the unique signature of ME.

It is important to note that the current emphasis must primarily remain a clinical assessment, with selection of research subjects coming later. For this reason, the panel is developing Physicians' Guidelines, which will include diagnostic protocol based on the International Consensus Criteria and treatment guidelines that reflect current knowledge. Individuals meeting the International Consensus Criteria have myalgic encephalomyelitis and should be removed from the Reeves empirical criteria and the National Institute for Clinical Excellence (NICE) criteria for chronic fatigue syndrome. These guidelines are designed specifically for use by the primary care physician in the hope of improving rapid diagnosis and treatment by first-line medical care providers. This may result in the development of an additional short-form version that would build on the relationships linking symptoms to formulate an abbreviated screening protocol. For the first time, clinical, paediatric and research applications are provided, which will advance the understanding of myalgic encephalomyelitis and enhance the consistency of diagnoses internationally. The compulsory critical criteria allow comparable data to be collected in various locations and may assist in developing consistent biomarkers and further insights into the mechanism and aetiology of myalgic encephalomyelitis.

Funding

This Consensus paper is free of sponsorship. All authors contributed their time and expertise on a volunteer basis and no one received any payments or honorariums.

Conflict of interest statement

All authors have disclosed potential conflicts of interest, and all members declare that they have no competing interests.

Acknowledgements

The panel would like to gratefully acknowledge the participation and support of the patients and their families in the research described herein, and upon which, these guidelines are based.

Author contributions

Coeditors – conception, drafting of paper and revisions: BM Carruthers, MI van de Sande. Initial suggestions and subsequent critical reviews: KL De Meirleir, NG Klimas, G Broderick, T Mitchell, D Staines, ACP Powles, N Speight, R Vallings, L Bateman, B Baumgarten-Austrheim, DS Bell, N Carlo-Stella, J Chia, A Darragh, D Jo, D Lewis, AR Light, S Marshall-Gradisbik, I Mena, JA Mikovits, K Miwa, M Murovska, ML Pall, S Stevens.

Final approval and consensus

There was 100% consensus by the authors on the final consensus paper. BM Carruthers, MI van de Sande, KL De Meirleir, NG Klimas, G Broderick, T Mitchell, D Staines, ACP Powles, N Speight, R Vallings, L Bateman, B Baumgarten-Austrheim, DS Bell, N Carlo-Stella, J Chia, A Darragh, D Jo, D Lewis, AR Light, S Marshall-Gradisbik, I Mena, JA Mikovits, K Miwa, M Murovska, ML Pall, S Stevens.

Consensus coordinator

M van de Sande.

References

- Tirelli U, Chierichetti F, Tavio M *et al.* Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data. *Am J Med* 1998; **105**: 54S–8S.
- Cook DB, Lange G, DeLuca J, Natelson BH. Relationship of brain MRI abnormalities and physical functional status in chronic fatigue syndrome. *Int J Neurosci* 2001; **107**: 1–6.
- Chen R, Liang FX, Moriya J *et al.* Chronic fatigue syndrome and the central nervous system. *J Int Med Res* 2008; **36**: 867–74.
- Broderick G, Fuite J, Kreitz A, Vernon SD, Klimas N, Fletcher MA. A formal analysis of cytokine networks in chronic fatigue syndrome. *Brain Behav Immun* 2010; **24**: 1209–17.
- Lorusso L, Mikhaylova SW, Capelli E, Ferrari D, Ngonga GK, Ricevuti G. Immunological aspects of chronic fatigue syndrome. *Autoimmun Rev* 2009; **8**: 287–91.
- Fletcher MA, Zeng XR, Maher K *et al.* Biomarkers in chronic fatigue syndrome: evaluation of natural killer cell function and dipeptidyl peptidase IV. *PLoS ONE* 2010; **5**: e10817.
- Mihaylova I, DeRuyter M, Rummens JL, Basmans E, Maes M. Decreased expression of CD69 in chronic fatigue syndrome in relation to inflammatory markers: evidence for a severe disorder in the early activation of T lymphocytes and natural killer cells. *Neuro Endocrinol Lett* 2007; **28**: 477–83.
- Klimas NG, Salvato FR, Morgan R, Fletcher MA. Immunologic abnormalities in chronic fatigue syndrome. *J Clin Microbiol* 1990; **28**: 1403–10.
- Myhill S, Booth NE, McLaren-Howard J. Chronic fatigue syndrome and mitochondrial dysfunction. *Int J Clin Exp Med* 2009; **2**: 1–16.
- Piecznik SR, Neustadt J. Mitochondrial dysfunction and molecular pathways of disease. *Exp Mol Pathol* 2007; **83**: 84–92.
- Behan WM, More IA, Behan PO. Mitochondrial abnormalities in the postviral fatigue syndrome. *Acta Neuropathol* 1991; **83**: 61–5.
- Streeten DH, Thomas D, Bell DS. The roles of orthostatic hypotension, orthostatic tachycardia and subnormal erythrocyte volume in the pathogenesis of the chronic fatigue syndrome. *Am J Med* 2000; **320**: 1–8.
- Peckerman A, LaManca JJ, Dahl KA, Chemitiganti R, Qureshi B, Natelson BH. Abnormal impedance cardiography predicts symptom severity in Chronic Fatigue Syndrome. *Am J Med Sci* 2003; **326**: 55–60.
- Hollingsworth KG, Jones DE, Taylor R, Blamire AM, Newton JL. Impaired cardiovascular response to standing in chronic fatigue syndrome. *Eur J Clin Invest* 2010; **40**: 608–15.
- Sharpe MC, Archard LC, Banatvala JE *et al.* A report – chronic fatigue syndrome: guidelines for research. *J R Soc Med* 1991; **84**: 118–21.
- Reeves WC, Wagner D, Nisenbaum R *et al.* Chronic fatigue syndrome – a clinically empirical approach to its definition and study. *BMC Med* 2005; **3**: 19.
- Fukuda K, Straus SE, Hickie I *et al.* Chronic Fatigue Syndrome: a comprehensive approach to its definition and study. *Ann Intern Med* 1994; **121**: 953–9.
- Jason LA, Najjar N, Porter N, Reh C. Evaluating the Centers for Disease Control's empirical chronic fatigue syndrome case definition. *J Disabil Pol Studies* 2009; **20**: 91–100. doi:10.1177/1044207308325995. Accessed on 10 February 2011 at <http://dps.sagepub.com/content/20/2.toc>.
- Jason LA, Choi M. Dimensions and assessment of fatigue. In: Watanabe Y, Evengard B, Natelson BH, Jason LA, Kuratsune H, eds. *Fatigue Science Human Health*. Tokyo: Springer, 2008; 1–16.
- Carruthers BM, Jain AK, De Meirleir KL *et al.* Myalgic encephalomyelitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols. *J Chronic Fatigue Syndr*. 2003; **11**: 7–16. Accessed on 20 March 2011 at <http://www.mefmaction.com/images/stories/Medical/ME-CFS-Consensus-Documents.pdf>.
- Jason LA, Torres-Harding SR, Jurgens A, Helgerson J. Comparing the Fukuda *et al.* Criteria and the Canadian case definition for chronic fatigue syndrome. *J Chronic Fatigue Syndr*. 2004; **12**: 37–52. Accessed on 10 February 2011 at <http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.etal04.pdf>.
- De Becker P, McGregor N, De Meirleir K. A definition-based analysis of symptoms in a large cohort of patients with chronic fatigue syndrome. *J Intern Med* 2001; **250**: 234–40.
- Rowe KS, Rowe KJ. Symptom patterns of children and adolescents with chronic fatigue syndrome. In: Singh NN, Ollendick TH, Singh AN, eds. *Intern Perspective Child Adolescence Mental Health*. Oxford: Elsevier Science Ltd, 2002; 2.

- 24 Kaushik N, Fear D, Richards SC *et al.* Gene expression in peripheral blood mononuclear cells from patients with chronic fatigue syndrome. *J Clin Pathol* 2005; **58**: 826–32.
- 25 Kerr JR, Burke B, Petty R *et al.* Seven genomic subtypes of chronic fatigue syndrome/myalgic encephalomyelitis; a detailed analysis of gene network and clinical phenotypes. *J Clin Pathol* 2008; **61**: 730–9.
- 26 Kerr JR, Petty R, Burke B *et al.* Gene expression subtypes in patients with chronic fatigue syndrome/myalgic encephalomyelitis. *J Infect Dis* 2008; **197**: 1171–84.
- 27 Aspler AL, Bolshin C, Vernon SD, Broderick G. Evidence of inflammatory immune signalling in chronic fatigue syndrome: a pilot study of gene expression in peripheral blood. *Behav Brain Funct* 2008; **4**: 44. doi:10.1186/1744-9081-4-44.
- 28 Broderick G, Craddock RC, Whistler T, Taylor R, Klimas N, Unger ER. Identifying illness parameters in fatiguing syndromes using classical projection methods. *Pharmacogenomics* 2006; **7**: 407–19.
- 29 Light AR, White AT, Huguen RW, Light KC. Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects. *J Pain* 2009; **10**: 1099–112.
- 30 Light AR, Bateman L, Jo D *et al.* Gene expression alterations at baseline and following moderate exercise in patients with Chronic Fatigue Syndrome, and Fibromyalgia Syndrome. *J Intern Med* 2011; **???**: ????. May 26. doi: 10.1111/j.1365-2796.2011.02405.x. [Epub ahead of print].
- 31 Gräns H, Nilsson M, Dahlman-Wright K, Evengård B. Reduced levels of oestrogen receptor beta mRNA in Swedish patients with chronic fatigue syndrome. *J Clin Pathol* 2007; **60**: 195–8.
- 32 Narita M, Nishigami N, Narita N *et al.* Association between serotonin transporter gene polymorphism and chronic fatigue syndrome. *Biochem Biophys Res Commun* 2003; **311**: 264–6.
- 33 Falkenberg VR, Gurbaxani BM, Unger ER, Rajeevan MS. Functional genomics of serotonin receptor 2A (HTR2A): interaction of polymorphism, methylation, expression and disease association. *Neuromolecular Med* 2011; **13**: 66–76.
- 34 Rajeevan MS, Smith AK, Dimulescu I *et al.* Glucocorticoid receptor polymorphisms and haplotypes associated with chronic fatigue syndrome. *Genes Brain Behav* 2007; **6**: 167–76.
- 35 Carlo-Stella N, Bozzini S, De Silvestri A *et al.* Molecular study of receptor for advanced glycation endproduct gene promoter and identification of specific HLA haplotypes possibly involved in chronic fatigue syndrome. *Int J Immunopathol Pharmacol* 2009; **22**: 745–54.
- 36 Goertzel BN, Pennachin C, de SouzaCoelho L, Gurbaxani B, Maloney EM, Jones JF. Combinations of single nucleotide polymorphisms in neuroendocrine effector and receptor genes predict chronic fatigue syndrome. *Pharmacogenomics* 2006; **7**: 475–83.
- 37 Underhill JA, Mahalingam M, Peakman M, Wessely S. Lack of association between HLA genotype and chronic fatigue syndrome. *Eur J Immunogenet* 2001; **28**: 425–8.
- 38 Sullivan PF, Evengård B, Jacks A, Pedersen NL. Twin analyses of chronic fatigue in a Swedish national sample. *Psychol Med* 2005; **35**: 1327–36.
- 39 Landmark-Høyvik H, Reinertsen KV, Loge JH *et al.* The genetics and epigenetics of fatigue. *PMR* 2010; **2**: 456–65.
- 40 Maher K, Klimas NG, Fletcher MA. Immunology. In: Jason LA, Fennell PA, Taylor RR, eds. *Handbook of Chronic Fatigues*. Hoboken, New Jersey & Canada: John Wiley & Sons, 2003; 124–51.
- 41 W.B. Saunders Company. *Dorland's Illustrated Medical Dictionary*, 29th edn. Philadelphia: W.B. Saunders Company; 2000: 1049.
- 42 Jason LA, Helgeson J, Torres-Harding SR, Carrico AW, Taylor RR. Variability in diagnostic criteria for chronic fatigue syndrome may result in substantial differences in patterns of symptoms and disability. *Eval Health Prof* 2003; **26**: 3–22.
- 43 Jason LA, Taylor RR, Kennedy CL *et al.* A factor analysis of chronic fatigue symptoms in a community-based sample. *Soc Psychiatry Psychiatr Epidemiol* 2002; **37**: 183–9.
- 44 Dowsett EG, Ramsay AM, McCartney RA, Bell EJ. Myalgic encephalomyelitis – a persistent enteroviral infection? *Postgrad Med J* 1990; **66**: 526–30.
- 45 Lloyd AR, Hickie I, Boughton CF, Spencer O, Wakefield D. Prevalence of chronic fatigue syndrome in an Australian population. *Med J Aust* 1990; **153**: 522–8.
- 46 Nijs J, Meeus M, McGregor NR *et al.* Chronic fatigue syndrome: exercise performance related to immune dysfunction. *Med Sci Sports Exerc* 2005; **37**: 1647–54.
- 47 Meeus M, Roussel NA, Truijien S, Nijs J. Reduced pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low back pain: an experimental study. *J Rehabil Med* 2010; **42**: 884–90.
- 48 Van Oosterwijck J, Nijs J, Meeus M *et al.* Pain inhibition and postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome; an experimental study. *J Intern Med* 2010; **268**: 265–78.
- 49 Whiteside A, Hansen S, Chaudhuri A. Exercise lowers pain threshold in chronic fatigue syndrome. *Pain* 2004; **109**: 497–9.
- 50 Yoshiuchi K, Farkas I, Natelson BH. Patients with chronic fatigue syndrome have reduced absolute cortical blood flow. *Clin Physiol Funct Imaging* 2006; **26**: 83–6.
- 51 Goldstein JA. *Chronic Fatigue Syndrome: The Limbic Hypothesis*. Binghamton, New York: Haworth Medical Press, 1993: 19, 116.
- 52 Streeten DH. Role of impaired lower-limb venous innervation in the pathogenesis of the chronic fatigue syndrome. *Am J Med Sci* 2001; **321**: 163–7.
- 53 Neary PJ, Roberts AD, Leavins N, Harrison MF, Croll JC, Sexsmith JR. Prefrontal cortex oxygenation during incremental exercise in chronic fatigue syndrome. *Clin Physiol Funct Imaging* 2008; **28**: 364–72.
- 54 VanNess JM, Snell CR, Dempsey WL, Strayer DR, Stevens SR. Subclassifying chronic fatigue syndrome using exercise testing. *Med Sci Sports Exerc* 2003; **35**: 908–13.
- 55 De Becker P, Roeykens J, Reynders M, McGregor N, De Meirleir K. Exercise capacity in chronic fatigue syndrome. *Arch Intern Med* 2000; **170**: 3270–7.
- 56 Suárez A, Guillamó E, Roig T *et al.* Nitric oxide metabolite production during exercise in chronic fatigue syndrome: a case-control study. *J Womens Health (Larchmt)* 2010; **19**: 1073–7.
- 57 VanNess JM, Stevens SR, Bateman L, Stiles TL, Snell CR. Post-exertional malaise in women with chronic fatigue syndrome. *J Womens Health (Larchmt)* 2010; **19**: 239–44.
- 58 Vermeulen RCW, Kurk RM, Visser FC, Sluiter W, Scholte HR. Patients with chronic fatigue syndrome performed worse than controls in a controlled repeated exercise study despite a normal oxidative phosphorylation capacity. *J Transl Med* 2010; **8**: 93. doi:10.1186/1479-5876-8-93.
- 59 Demitrack MA, Crofford LJ. Evidence for and pathophysiologic implication of hypothalamic-pituitary-adrenal axis dysregula-

- tion in fibromyalgia and chronic fatigue syndrome. *Ann NY Acad Sci* 1998; **840**: 684–97.
- 60 White AT, Light AR, Hughen RW *et al.* Severity of symptom flare after moderate exercise is linked to cytokine activity in chronic fatigue syndrome. *Psychophysiol* 2010; **47**: 615–24.
- 61 Yoshiuchi K, Cook DB, Ohashi K *et al.* A real-time assessment of the effect of exercise in chronic fatigue syndrome. *Physiol Behav* 2007; **92**: 963–8.
- 62 Snell CF, VanNess JM, Stayer DF, Stevens SR. Exercise capacity and immune function in male and female patients with chronic fatigue syndrome (CFS). *In Vivo* 2005; **19**: 387–90.
- 63 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.
- 64 Lange G, Wang S, DeLuca J, Natelson BH. Neuroimaging in chronic fatigue syndrome. *Am J Med* 1998; **105**: 50S–3S.
- 65 de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I. Gray matter volume reduction in the chronic fatigue syndrome. *Neuroimage* 2005; **26**: 777–81.
- 66 Okada T, Tanaka M, Kuratsune H, Watanabe Y, Sadato N. Mechanisms underlying fatigue: a voxel-based morphometric study of chronic fatigue syndrome. *BMC Neurol* 2004; **4**: 14.
- 67 Costa DC, Tannock C, Brostoff J. Brainstem perfusion is impaired in chronic fatigue syndrome. *QJM* 1995; **88**: 767–73.
- 68 Mena I, Villanueva-Meyer J. Study of cerebral perfusion by NeuroSPECT in patients with chronic fatigue syndrome. In: Hyde BM, Goldstein J, Levine P, eds. *The Clinical and Scientific Basis of Myalgic Encephalomyelitis, Chronic Fatigue Syndrome*. Ottawa, Ontario & Ogdensburg, New York State: The Nightingale Research Foundation, 1992; 432–8.
- 69 Goldberg MJ, Mena I, Darcourt J. NeuroSPECT findings in children with chronic fatigue syndrome. *J Chronic Fatigue Syndr.* 1997; **3**: 61–6. Accessed on 22 March 2011 at <http://publ.ac.uk/archive/journals/jcfs/v03n0197.htm#5neurospect>.
- 70 Ichise M, Salit I, Abbey S *et al.* Assessment of regional cerebral perfusion by Tc-HMPAO SPECT in Chronic Fatigue Syndrome. *Nucl Med Commun* 1995; **13**: 767–72.
- 71 Biswal B, Kunwar P, Natelson BH. Cerebral blood flow is reduced in chronic fatigue syndrome as assessed by arterial spin labeling. *J Neurosci* 2001; **301**: 9–11.
- 72 Mathew SJ, Mao X, Keegan KA *et al.* Ventricular cerebrospinal fluid lactate is increased in chronic fatigue syndrome compared with generalized anxiety disorder: an in vivo 3.0 T (q)H MRS imaging study. *NMR Biomed* 2009; **22**: 251–8.
- 73 Meeus M, Nijs J, Huybrechts S, Truijzen S. Evidence for generalized hyperalgesia in chronic fatigue syndrome: case control study. *Clin Rheumatol* 2010; **29**: 393–8.
- 74 Siemionow V, Fang Y, Calabrese L, Sahgal V, Yue GH. Altered central nervous system signal during motor performance in chronic fatigue syndrome. *Clin Neurophysiol* 2004; **115**: 2372–81.
- 75 Lange G, Steffner J, Cook DB *et al.* Objective evidence of cognitive complaints in chronic fatigue syndrome: a BOLD fMRI study of verbal working memory. *Neuroimage* 2005; **26**: 513–4.
- 76 Flor-Henry P, Lind JC, Koles ZJ. EEG source analysis of chronic fatigue syndrome. *Psychiatry Res* 2010; **181**: 155–65.
- 77 Cook DB, O'Connor PJ, Lange G, Steffner J. Functional neuroimaging correlates of mental fatigue induced by cognition among fatigue syndrome patients and controls. *Neuroimage* 2007; **36**: 108–22.
- 78 Michiels V, Cluydts R, Fischler B. Attention and verbal learning in patients with chronic fatigue syndrome. *J Int Neuropsychol Soc* 1998; **4**: 456–66.
- 79 Lombardi VC, Ruscetti FW, Das Gupta J *et al.* Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome. *Science* 2009; **326**: 585–9.
- 80 Lo SC, Pripuzova N, Li B *et al.* Detection of MLV-related virus gene sequences in blood of patients with chronic fatigue syndrome and healthy blood donors. *Proc Natl Acad Sci USA* 2010; **107**: 15874–9.
- 81 Chia J, Chia A, Voeller M, Lee T, Chang R. Acute enterovirus infection followed by myalgia encephalomyelitis/chronic fatigue syndrome and viral persistence. *J Clin Pathol* 2010; **63**: 163–8.
- 82 Chia J, Chia A. Chronic fatigue syndrome is associated with chronic enterovirus infection of the stomach. *J Clin Pathol* 2008; **61**: 43–8.
- 83 Chia JK. The role of enterovirus in chronic fatigue syndrome. *J Clin Pathol* 2005; **58**: 1126–32.
- 84 Zang L, Gough J, Christmas D *et al.* Microbial infections in eight genomic subtypes of chronic fatigue syndrome myalgic encephalomyelitis. *J Clin Pathol* 2010; **63**: 156–64.
- 85 Ablashi DV, Eastman HB, Owen CB. Frequent HHV-6 antibody and HHV-6 reactivation in multiple sclerosis (MS) and chronic fatigue syndrome (CFS) patients. *J Clin Virol* 2000; **16**: 179–91.
- 86 Chapenko S, Krumina A, Koziereva S *et al.* Activation of human herpesviruses 6 and 7 in patients with chronic fatigue syndrome. *J Clin Virol* 2006; **37(Suppl 1)**: S47–51.
- 87 Nicolson GL, Gan R, Haiser J. Multiple co-infections (Mycoplasma, Chlamydia, human herpes virus-6) in blood of chronic fatigue syndrome patients: association with signs and symptoms. *APMIS* 2003; **111**: 557–66.
- 88 Chia JK, Chia LY. Chronic Chlamydia pneumonia infection: a treatable cause of chronic fatigue syndrome. *Clin Infect Dis* 1999; **29**: 452–3.
- 89 Beqaj SH, Lerner AM, Fitzgerald JD. Immunoassay with cytomegalovirus early antigens from gene products P52 and CM 2 (UL44 and UL 57) detects active infection in patients with chronic fatigue syndrome. *J Clin Pathol* 2008; **61**: 623–6.
- 90 Kerr JR, Cunniffe VS, Kelleher P, Bernstein RM, Bruce IN. Successful intravenous immunoglobulin therapy in 3 cases of parvovirus B19-associated chronic fatigue syndrome. *Clin Infect Dis* 2003; **36**: e100–6.
- 91 Sheedy JR, Richards EH, Wettenhall REH *et al.* Increased D-lactic acid intestinal bacteria in patients with Chronic Fatigue Syndrome. *In Vivo* 2009; **23**: 621–8.
- 92 Brenu EW, Staines DR, Baskurt OK *et al.* Immune and hemorheological changes in chronic fatigue syndrome. *J Transl Med* 2010; **8**: 1.
- 93 Klimas NG, Koneru AO. Chronic fatigue syndrome: inflammation, immune function, and neuroendocrine interactions. *Curr Rheumatol Rep* 2007; **9**: 483–7.
- 94 Fletcher MA, Zeng XR, Barnes Z, Levis S, Klimas NG. Plasma cytokines in women with chronic fatigue syndrome. *J Transl Med* 2009; **7**: 96.
- 95 Cameron B, Hirschberg DL, Rosenberg-Hassan Y, Ablashi D, Lloyd AR. Serum cytokine levels in postinfective fatigue syndrome. *Clin Infect Dis* 2010; **50**: 278–9.
- 96 Carlo-Stella N, Badulli C, De Sivestri A *et al.* The first study of cytokine genomic polymorphisms in CFS: positive association of TNF-857 and IFN γ 874 rare alleles. *Clin Exp Rheumatol* 2006; **24**: 179–82.

- 97 De Meirleir K, Bisbal C, Campine I *et al.* A 37 kDa 2-5A binding protein as a potential biochemical marker for chronic fatigue syndrome. *Am J Med* 2000; **108**: 99–105.
- 98 Sudolnik RJ, Peterson DL, O'Brien K *et al.* Biochemical evidence for a novel low molecular weight 2-5A-dependent RNase L in chronic fatigue syndrome. *J Interferon Cytokine Res* 1997; **17**: 377–85.
- 99 Nijs J, Frémont M. Intracellular immune dysfunction in myalgic encephalomyelitis/chronic fatigue syndrome: state of the art and therapeutic implications. *Expert Opin Ther Targets* 2008; **12**: 281–9.
- 100 Nijs J, De Meirleir K, Meeus M, McGregor Nr, Englebienne P. Chronic fatigue syndrome: intracellular immune deregulations as a possible etiology for abnormal exercise response. *Med Hypotheses* 2004; **62**: 759–65.
- 101 Wong R, Lopaschuk G, Zhu G *et al.* Skeletal muscle metabolism in the chronic fatigue syndrome. In vivo assessment by ³¹P nuclear magnetic resonance spectroscopy. *Chest* 1992; **102**: 1716–22.
- 102 Jammes Y, Steinberg JG, Mambrini O, Brégeon F, Delliaux S. Chronic fatigue syndrome: assessment of increased oxidative stress and altered muscle excitability in response to incremental exercise. *J Intern Med* 2005; **257**: 299–310.
- 103 Miwa K, Fujita M. Fluctuation of serum vitamin E (alphatocopherol) concentrations during exacerbation and remission phases in patients with chronic fatigue syndrome. *Heart Vessels* 2010; **25**: 319–23.
- 104 Richards RS, Wang L, Jelinek H. Erythrocyte oxidative damage in chronic fatigue syndrome. *Arch Med Res* 2007; **38**: 94–8.
- 105 Pall ML, Satterlee JD. Elevated nitric oxide/peroxynitrite mechanism for the common etiology of multiple chemical sensitivity, chronic fatigue syndrome, and posttraumatic stress disorder. *Ann NY Acad Sci* 2001; **933**: 323–9.
- 106 Kurup RK, Kurup PA. Hypothalamic digoxin, cerebral chemical dominance and myalgic encephalomyelitis. *Int J Neurosci* 2003; **113**: 683–701.
- 107 Pall ML. *Explaining "Unexplained Illnesses": Disease Paradigm for Chronic Fatigue Syndrome, Multiple Chemical Sensitivity, Fibromyalgia, Post-Traumatic Stress Disorder, Gulf War Syndrome and Others.* Binghamton, NY: Harrington Park (Haworth) Press, 2007.
- 108 Chaudhuri A, Watson WS, Pearn J, Behan PO. The symptoms of chronic fatigue syndrome are related to abnormal ion channel function. *Med Hypotheses* 2000; **54**: 59–63.
- 109 Miwa K, Fujita M. Cardiac function fluctuates during exacerbation and remission in young adults with chronic fatigue syndrome and "small heart". *J Cardiol* 2009; **54**: 29–35.
- 110 Miwa K, Fujita M. Small heart syndrome in patients with chronic fatigue syndrome. *Clin Cardiol* 2008; **31**: 328–33.
- 111 Peckerman A, LaManca JJ, Qureishi B *et al.* Baroreceptor reflex and integrative stress responses in chronic fatigue syndrome. *Psychosom Med* 2003; **65**: 889–95.
- 112 Lerner AM, Lawrie C, Dworkin HS. Repetitively negative changing T waves at 24-h electrocardiographic monitors in patients with the chronic fatigue syndrome. Left ventricular dysfunction in a cohort. *Chest* 1993; **104**: 1417–21.
- 113 Rowe PC, Calkins H. Neurally mediated hypotension and chronic fatigue syndrome. *Am J Med* 1998; **105**: 15S–21S.
- 114 Newton JL, Sheth A, Shin J *et al.* Lower ambulatory blood pressure in chronic fatigue syndrome. *Psychosom Med* 2009; **71**: 361–5.
- 115 Costigan A, Elliott C, McDonald C, Newton JL. Orthostatic symptoms predict functional capacity in chronic fatigue syndrome: implications for management. *QJM* 2010; **103**: 589–95.
- 116 Burton AR, Rahman K, Kadota Y, Lloyd A, Vollmer-Conna U. Reduced heart rate variability predicts poor sleep quality in case-control study of chronic fatigue syndrome. *Exp Brain Res* 2010; **204**: 71–8.
- 117 Nisenbaum R, Reyes M, Mawle AC, Reeves WC. Factor analysis of unexplained severe fatigue and interrelated symptoms: overlap with criteria for chronic fatigue syndrome. *Am J Epidemiol* 1998; **148**: 72–7.
- 118 Priebe S, Fakhoury WK, Henningsen P. Functional incapacity and physical and psychological symptoms: how they interconnect in chronic fatigue syndrome. *Psychopathology* 2008; **41**: 339–45.
- 119 Carmel L, Efroni S, White PD, Aslakson E, Vollmer-Conna U, Rajeevan MS. Gene expression profile of empirically delineated classes of unexplained chronic fatigue. *Pharmacogenomics* 2006; **7**: 375–86.

Correspondence: Dr Bruce Carruthers, 4607 Blenheim St., Vancouver, British Columbia V6L 3A3, Canada.
(fax: +1 604 263 9059; e-mail: bcarruth@telus.net); and
Dr. Gordon Broderick, Division of Pulmonary Medicine, Department of Medicine, University of Alberta, WMC 2E4.41 WC Mackenzie Health Sciences Bldg, 8440 – 112 Street, Edmonton AB T6G 2R7, Canada.
(fax: +1 780 407 6384; e-mail: gordon.broderick@ualberta.ca).