

Myalgic Encephalomyelitis: International Consensus Criteria

From The Journal of Internal Medicine, July 2011 (manuscript accepted 15 July 2011 and published online on 20 July 2011)

enlace: <http://www.meassociation.org.uk/?p=7173>

Bruce M Carruthers, MD, CM, FRCP(C) (coeditor); Independent, Vancouver, B.C., Canada
Marjorie I van de Sande, BEd, GradDip Ed (coeditor); Independent, Calgary, AB, Canada
Kenny L De Meirleir, MD, PhD; Department of Physiology and Medicine, Vrije University of Brussels, Himmunitas Foundation, Brussels, Belgium.

Nancy G Klimas, MD; Department of Medicine, University of Miami Miller School of Medicine and Miami Veterans Affairs Medical Center, Miami, FL, USA

Gordon Broderick, PhD; Department of Medicine, University of Alberta, Edmonton, AB, Canada

Terry Mitchell, MA, MD, FRCPath; Honorary Consultant for NHS at Peterborough/Cambridge, Lowestoft, Suffolk, United Kingdom.

Don Staines, MBBS, MPH, FAFPHM, FAFOEM; Gold Coast Public Health Unit, Southport, Queensland; Health Sciences and Medicine, Bond University, Robina, Queensland, Australia AC

Peter Powles, MRACP, FRACP, FRCP(C), ABSM; Faculty of Health Sciences, McMaster University and St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada.

Nigel Speight, MA, MB, BChir, FRCP, FRCPCH, DCH; Independent, Durham, United Kingdom

Rosamund Vallings, MNZM, MB, BS, MRCS, LRCP; Howick Health and Medical Centre, Howick, New Zealand.

Lucinda Bateman, MS, MD; Fatigue Consultation Clinic, Salt Lake Regional Medical Center: adjunct faculty – Internal Medicine, Family Practice, University of Utah, Salt Lake City, UT, USA.

Barbara Baumgarten-Austrheim, MD; ME/CFS Center, Oslo University Hospital HF, Norway. David S Bell, MD, FAAP; Department of Paediatrics, State University of New York, Buffalo, NY.

Nicoletta Carlo-Stella, MD, PhD; Independent, Pavia, Italy

John Chia, MD; Harbor-UCLA Medical Center, University of California, Los Angeles; EV Med Research, Lomita, CA, USA

Austin Darragh, MA, MD, FFSEM. (RCPI, RCSI), FRSHFI Biol I (Hon); University of Limerick, Limerick, Ireland

Daehyun Jo, MD, PhD; Pain Clinic, Konyang University Hospital, Daejeon, Korea

Don Lewis, MD; Donvale Specialist Medical Centre, Donvale, Victoria, Australia

Alan R Light, PhD; Depts or Anesthesiology, Neurobiology and Anatomy, University of Utah, Salt Lake City, Utah, USA.

Sonya Marshall-Gradisbik, PhD; Health Sciences and Medicine, Bond University, Robina, Queensland, Australia.

Ismael Mena, MD; Depart. Medicina Nuclear, Clinica Las Condes, Santiago, Chile

Judy A Mikovits, PhD; Whittemore Peterson Institute, University of Nevada, Reno, NV USA

Kunihisa Miwa, MD, PhD; Miwa Naika Clinic, Toyama, Japan

Modra Murovska, MD, PhD; A. Kirchenstein Institute of Microbiology and Virology, Riga Stradins University, Riga, Latvia,

Martin L Pall, PhD; Department of Biochemistry & Basic Medical Sciences, Washington State University, Portland, OR, USA

Staci Stevens, MA; Department of Sports Sciences, University of the Pacific, Stockton, CA USA.

This is an Accepted Article that has been peer-reviewed and approved for publication in the Journal of Internal Medicine, but has yet to undergo copy-editing and proof correction. Please cite this article as an “Accepted Article”; doi: 10.1111/j.1365- 2796.2011.02428.x

Running Title: ME: Intl. Consensus Criteria

Abstract

The label “chronic fatigue syndrome” (CFS) has persisted for many years because of lack of knowledge of the etiological agents and of 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 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 ME patients, 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 health care providers, improve consistency of diagnoses in adult and paediatric patients internationally, and facilitate clearer identification of patients for research studies.

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 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 ME/CFS patients 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 ME patients 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 six-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 six 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 and contextual interpretation. This will assist the primary clinician in identifying and treating ME patients in the primary care setting.

Table 1

MYALGIC ENCEPHALOMYELITIS: INTERNATIONAL CONSENSUS CRITERIA
Adult and Pediatric • 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 post-exertional 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. Post-Exertional 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:

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. Post-exertional symptom exacerbation: e.g. acute flu-like symptoms, pain and worsening of other symptoms
3. Post-exertional exhaustion may occur immediately after activity or be delayed by hours or days.
4. Recovery period is prolonged, usually taking 24 hours 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 1/2 hour, it will take much longer to recover from grocery shopping for 1/2 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 non-inflammatory 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. awaken feeling exhausted regardless of duration of sleep, day-time sleepiness

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 reaction to light – fluctuation or reduced accommodation responses of the pupils with retention of reaction. 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 & 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. Facial injection and crimson crescents may be seen in the tonsillar fossae, which are an indication of immuneactivation.

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 post- exertional 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 program.
3. Pain may seem erratic and migrate quickly. Joint hyper-mobility is common.

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

Classification ____ Myalgic Encephalomyelitis ____ Atypical Myalgic Encephalomyelitis: meets criteria for post-exertional neuroimmune exhaustion but has two or 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.

Co-morbid 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.

Criteria Are Supported by Research

Criterial symptoms are supported by a study of more than 2,500 patients that determined which symptoms had the greatest efficacy to identify ME patients [22]. Investigations of 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 signalling [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 [36, 37]. Some early broad based studies show a lack of objective findings such as no association with HLA genotype [38]. A study of patients from a twin registry suggested that environmental factors may outweigh any genetic predisposition in broad based patient populations [39].

Underlying problems of inconsistent findings in research studies have been identified [40, 41] 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 thirty-eight percent (38%) of patients diagnosed with Major Depressive Disorder were misclassified as having CFS and only ten percent (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 like patients to be diagnosed and enrolled in research studies internationally under a case definition that is acceptable to physicians and researchers around the world. A. Post-Exertional Neuroimmune Exhaustion (PENE pen'-e)

“Malaise – a vague feeling of discomfort or fatigue” [42] is an inaccurate and inadequate word for the pathological low-threshold fatigability and post-exertional 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. Post-exertional 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 [43-47]. 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 [48-50], decreased cerebral

oxygen and blood volume/flow [51-54], decreased maximum heart rate [55], impaired oxygen delivery to muscles [56], elevated levels of nitric oxide metabolites [57], and worsening of other symptoms [58]. Patients reach the anaerobic threshold and maximal exercise at a much lower oxygen consumption level [59]. Reported prolonged effects of exertion include elevated sensory signalling to the brain [60] that is interpreted as pain and fatigue [61], elevated cytokine activity [62], delay in symptom activation [63] and a recovery period of at least 48 hours [58]. 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 [64]. Both submaximal and self-paced physiologically limited exercise resulted in post-exertional malaise [49].

B. 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 [64], which play crucial roles in cognitive impairment and neurological symptoms [20]. Neuroinflammation of the dorsal root ganglia, gatekeepers of peripheral sensory information traveling 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 [65].

Neuroimaging studies report irreversible punctuate lesions [66], an approximate 10% reduction in gray matter volume [67, 68], hypoperfusion [69-74] and brain stem hypometabolism [1]. Elevated levels of lateral ventricular lactate are consistent with decreased cortical blood flow, mitochondrial dysfunction and oxidative stress [75]. Research suggests that dysregulation of the CNS and autonomic nervous system alters processing of pain and sensory input [48, 61, 76, 77]. 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 [78-80]. Poor attentional capacity and working memory are prominent disabling symptoms [20, 78, 81].

C. 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 subsets of patients including Xenotropic murine leukemia virus-related virus (XMRV) [82] and other murine leukemia virus (MLV)-related viruses [83], enterovirus [84-86], Epstein Barr virus [87], human herpes virus 6 and 7 [88-90], Chlamydia [91], cytomegalovirus [92], parvovirus B19 [93] and *Coxiella burnetii* [87]. Chronic enterovirus infection of the stomach and altered levels of D Lactic acid producing bacteria in the gastrointestinal tract have been investigated [85, 94]. 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, 95, 96]. Chronic immune activation [27], increases in inflammatory cytokines, pro-inflammatory alleles [4-8, 97-99], chemokines and T lymphocytes, and dysregulation of the

antiviral ribonuclease L (RNase L) pathway [64, 100-103] may play a role in causing flu-like symptoms, which aberrantly flare in response to exertion [5, 95].

D. 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, 103, 104]. 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 [105-107], inflammatory cytokine elevation [97-99] and mitochondrial dysfunction [108-111], and result in reduced blood flow and vasculopathy [109, 110].

Findings of “small heart” with small left ventricular chamber and poor cardiac performance in patient subsets [112, 113] support previous reports of cardiac and left ventricular dysfunction [114-116], which predispose to orthostatic intolerance [14, 117]. Low blood pressure and exaggerated diurnal variation may be due to abnormal blood pressure regulation [118]. Altered control and reduced cortisol production during and following exercise may be involved. Orthostatic intolerance is associated with functional impairment and symptom severity [119]. Measurable vascular abnormalities suggest that the brain is not receiving sufficient circulating blood volume in an upright position [12, 117], 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 [120].

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.

A. Clinical Application

1. General Considerations

- a. Determine whether symptom cluster patterns are congruent with those expected from dysfunction of an underlying causal system.
- b. 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.
- c. Symptom severity impact must result in a 50% or greater reduction of 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.
- d. Symptom severity hierarchy should be determined periodically to help orient and monitor treatment.
- e. Criterial subgroups: Post-exertional 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 among subgroups).
- f. 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.
 - g. Determine total illness burden by assessing symptom severity, interaction and overall impact. Consider all aspects of the patient's life – physical, occupational, 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.
 - h. 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 program and monitor its effectiveness.

2. Paediatric Considerations

- a. 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.
- b. 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.
- c. 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.
- d. 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 due to having ME.
- e. 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.

B. Research Application

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

1. General Considerations

- a. 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.
- b. 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.

c. 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 reliability of data collected in different locations. Patients should complete the International Symptom Scale prior to entering a research study.

2. Optional Considerations

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

a. Onset: acute infectious or gradual

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

c. Symptom severity: mild, moderate, severe, very severe d. 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 [121, 122]. Others have extended the use of such methods to guide the analysis of gene expression profiles [28] and to delineate patient sub-groups [123]. 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 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 etiology of myalgic encephalomyelitis.

KEY WORDS: myalgic encephalomyelitis, chronic fatigue syndrome, criteria, definition, diagnosis. 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: B.M. Carruthers, M.I. van de Sande.

Initial suggestions and subsequent critical reviews: K.L. De Meirleir, N.G. Klimas, G. Broderick, T. Mitchell, D. Staines, A.C.P. Powles, N. Speight, R. Vallings, L. Bateman, B. Baumgarten- Austrheim, D.S. Bell, N. Carlo-Stella, J. Chia, A. Darragh, D. Jo, D. Lewis, A.R. Light, S. Marshall- Gradisbik, I. Mena, J.A. Mikovits, K. Miwa, M. Murovska, M.L. Pall, S. Stevens.

Final approval and consensus: There was 100% consensus by the authors on the final consensus paper. B. M. Carruthers, M. I. van de Sande, K.L. De Meirleir, N.G. Klimas, G. Broderick, T. Mitchell, D. Staines, A.C.P. Powles, N. Speight, R. Vallings, L. Bateman, B. Baumgarten-Austrheim, D.S. Bell, N. Carlo-Stella, J. Chia, A. Darragh, D. Jo, D. Lewis, A.R. Light, S. Marshall-Gradisbik, I. Mena, J.A. Mikovits, K. Miwa, M. Murovska, M.L. Pall, S. Stevens.

Consensus Coordinator: M. van de Sande

References

1. Tirelli U, Chierichetti F, Tavio M, Simonelli C, Bianchin G, Zanco P, Ferlin G. Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data. *Amer J Med* 1998; 105: 54S-8S. [PMID: 9790483]
2. 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. [PMID: 11328679]
3. Chen R, Liang FX, Moriya J, Yamakaw J, Sumino H, Kanda T, Takahashi T. Chronic fatigue syndrome and the central nervous system. *J Int Med Res* 2008; 36: 867-74. [PMID: 18831878]
4. 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. [PMID: 20447453].
5. Lorusso L, Mikhaylova SW, Capelli E, Ferrari D, Ngonga GK, Ricevuti G. Immunological aspects of chronic fatigue syndrome. *Autoimmun Rev* 2009; 8: 287-91. [PMID: 18801465]

6. Fletcher MA, Zeng XR, Maher K, et al. Biomarkers in chronic fatigue syndrome: Evaluation of natural killer cell function and dipeptyl peptidase IV. *PLoS ONE* 2010; 5: e10817. [PMID: 20520837]
7. 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. [PMID:17693977]
8. Klimas NG, Salvato FR, Morgan R, Fletcher MA. Immunologic abnormalities in chronic fatigue syndrome. *J Clin Microbiol* 1990; 28: 1403-10. [PMID: 2166084]
9. Myhill S, Booth NE, McLaren-Howard J. Chronic fatigue syndrome and mitochondrial dysfunction. *Int J Clin Exp Med* 2009; 2: 1-16. [PMID: 19436827]
10. Pieczenik SR, Neustadt J. Mitochondrial dysfunction and molecular pathways of disease. *ExpMolPathol*2007;83:84-92. [PMID:17239370]
11. Behan WM, More IA, Behan PO. Mitochondrial abnormalities in the postviral fatigue syndrome. *Acta Neuropathol* 1991; 83: 61-5. [PMID: 1792865]
12. 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. [PMID: 10910366]
13. Peckerman A, LaManca JJ, Dahl KA, Chemitiganti R, Qureishi B, Natelson BH. Abnormal impedance cardiography predicts symptom severity in Chronic Fatigue Syndrome. *Am J Med Sci* 2003; 326: 55-60. [PMID: 12920435]
14. 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. [PMID: 20497461]
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. [PMID: 1999813]
16. 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. [PMID: 16356178]
17. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A, and the International Chronic Fatigue Syndrome Study Group. Chronic Fatigue Syndrome: a comprehensive approach to its definition and study. *Ann Intern Med* 1994; 121: 953-59. [PMID: 7978722]
18. Jason LA, Najar 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 10/02/2011 at <http://dps.sagepub.com/content/20/2.toc>
19. 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.
20. Carruthers BM, Jain AK, De Meirleir KL, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. *J CFS* 2003; 11(1): 7-116. Accessed on 20/03/2011 at [http://www.mefmaction.com/images/storie ... cument.pdf](http://www.mefmaction.com/images/storie...cument.pdf)
21. 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 CFS* 2004; 12: 37-52. Accessed on 10/02/2011 at <http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.etal04.pdf>

22. 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. [PMID: 11555128]
23. 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; (vol 2): 395 -421.
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: 826-832. [PMID: 16049284]
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: 730-739. [PMID: 18057078]
26. Kerr JR, Petty R, Burke B, Gough J, Fear D, Sinclair LI, et al. Gene expression subtypes in patients with chronic fatigue syndrome/myalgic encephalomyelitis. *J Infect Dis* 2008; 197: 1171-84. [PMID: 18462164]
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. [PMID: 18822143]
28. BroderickG,CraddockRC,WhistlerT,TaylorR,KlimasN,UngerER. Identifying illness parameters in fatiguing syndromes using classical projection methods. *Pharmacogenomics* 2006; 7: 407-19. [PMID: 16610951]
29. Light AR, White AT, Hughen 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. [PMID: 19647494]
30. Light AR, Bateman L, Jo D, Hughen RW, Vanhaisma TA, White AT, Light KC. 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] [PMID: 21615807]
31. GränsH,NilssonM,Dahlman-WrightK,EvangårdB. Reduced levelsof oestrogenreceptor beta mRNA in Swedish patients with chronic fatigue syndrome. *J Clin Pathol* 2007; 60: 195- 8. [PMID: 16731592]
32. NaritaM,NishigamiN,NaritaN,YamagutiK,OkadoN,WatanabeY,KuratsuneH. Association between serotonin transporter gene polymorphism and chronic fatigue syndrome. *Biochem Biophys Res Commun* 2003; 311: 264-6. [PMID: 14592408]
33. FalkenbergVR,GurbaxaniBM,UngerER,RajeevanMS. Functionalgenomicsofserotonin receptor 2A (HTR2A): interaction of polymorphism, methylation, expression and disease association. *Neuromolecular Med* 2011; 13: 66-76. [PMID: 20941551]
34. RajeevanMS,SmithAK,DimulescuI,UngerER,VernonSD,HeimC,ReevesWC. Glucocorticoid receptor polymorphisms and haplotypes associated with chronic fatigue syndrome. *Genes Brain Behav* 2007; 6: 167-76. [PMID: 16740143]
35. Carlo-StellaN,BozziniS,DeSilvestriA,SbarsiI,PizzocheroC,LorussoL, MartinettiM, Cuccia M. 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. [PMID: 19822091]
36. GoertzelBN,PennachinC,deSouzaCoelhoL,GurbaxaniB,MaloneyEM,JonesJF. Combinations of single nucleotide polymorphisms in neuroendocrine effector and receptor genes predict chronic fatigue syndrome. *Pharmacogenomics* 2006; 7: 475-83. [PMID: 16610957]

37. 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. [PMID: 20941551]
38. 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. [PMID: 11422420]
39. Sullivan PF, Evengård B, Jaks A, Pedersen NL. Twin analyses of chronic fatigue in a Swedish national sample. *Psychol Med* 2005; 35: 1327-36. [PMID: 16168155]
40. Landmark-Høyvik H, Reinertsen KV, Loge JH, Kristensen VN, Dumeaux V, Fosså SD, Børresen-Dale AL, Edvardsen H. The genetics and epigenetics of fatigue. *PM R* 2010; 2: 456-65. [PMID: 20656628]
41. 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: 124-151.
42. Dorland's Illustrated Medical Dictionary. 29th Edition. Philadelphia: W.B. Saunders Company; 2000: 1049.
43. 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. [PMID: 12629919]
44. 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: 183-89. [PMID: 12027245]
45. Dowsett EG, Ramsay AM, McCartney RA, Bell EJ. Myalgic Encephalomyelitis – A persistent enteroviral infection? *Postgrad Med J* 1990; 66: 526-30. [PMID: 2170962]
46. Lloyd AR, Hickie I, Boughton CF, Spencer O, Wakefield D. Prevalence of chronic fatigue syndrome in an Australian population. *Med J Aust* 1990; 153: 522-28. [PMID: 2233474]
47. Nijs J, Meeus M, McGregor NR, Meeusen R, de Schutter G, van Hoof E, De Meirleir K. Chronic Fatigue Syndrome: Exercise Performance Related to Immune Dysfunction. *Med Sci Sports Exerc* 2005; 37: 1647-54. [PMID: 16260962]
48. Meeus M, Roussel NA, Truijzen 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. [PMID: 20878051]
49. Van Oosterwijk J, Nijs J, Meeus M, Lefever I, Huybrechts L, Lambrecht L, Paul L. Pain inhibition and postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome; an experimental study. *J Intern Med* 2010; 268: 265-78. [PMID: 20412374]
50. Whiteside A, Hansen S, Chaudhuri A. Exercise lowers pain threshold in chronic fatigue syndrome. *Pain* 2004; 109: 497-99. [PMID: 15157711]
51. 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. [PMID: 16494597]
52. Goldstein JA. *Chronic Fatigue Syndrome: The Limbic Hypothesis*. Binghampton, New York: Haworth Medical Press; 1993:19, 116.
53. Streeten DH. Role of impaired lower-limb venous innervation in the pathogenesis of the chronic fatigue syndrome. *Am J Med Sci* 2001; 321: 163-67. [PMID: 11269790]
54. 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 Imag* 2008; 28: 364-72. [PMID: 18671793]

55. 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. [PMID: 12783037]
56. 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. [PMID: 11088089]
57. Suárez A, Guíllamó 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. [PMID: 20469961]
58. VanNess JM, Stevens SR, Bateman L, Stiles TL, Snell CR. Postexertional malaise in women with chronic fatigue syndrome. *J Women's Health (Larchmt)* 2010; 19: 239-244. [PMID: 20095909]
59. 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. [PMID: 20937116]
60. Demitrack MA, Crofford LJ. Evidence for and pathophysiologic implication of hypothalamic-pituitary-adrenal axis dysregulation in fibromyalgia and chronic fatigue syndrome. *Ann NY Acad Sci* 1998; 840: 684-97. [PMID: 9629295]
61. Light AR, White AT, Hughen 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. [PMID: 19647494]
62. White AT, Light AR, Hughen RW, Bateman L, Martins TB, Hill HR, Light KC. Severity of symptom flare after moderate exercise is linked to cytokine activity in chronic fatigue syndrome. *Psychophysiol* 2010; 47: 615-24. [PMID: 20230500]
63. Yoshiuchi K, Cook DB, Ohashi K, Kumano H, Kuboki T, Yamamoto Y, Natelson BH. A real-time assessment of the effect of exercise in chronic fatigue syndrome. *Physiol Behav* 2007; 92: 963-8. [PMID: 17655887]
64. 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. [PMID: 15796202]
65. 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. [PMID: 21383843]
66. Lange G, Wang S, DeLuca J, Natelson BH. Neuroimaging in chronic fatigue syndrome. *Am J Med* 1998; 105: 50S-53S. [PMID: 9790482]
67. deLange FP, Kalkman JS, Bleijenberg G, Hagoort P, vanderMeer JW, Toni I. Gray matter volume reduction in the chronic fatigue syndrome. *Neuroimage* 2005; 26: 777-81. [PMID: 15955487]
68. 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. [PMID: 15461817]
69. Yoshiuchi K, Frakas J, Natelson B. Patients with chronic fatigue syndrome have reduced absolute blood flow. *Clin Physiol Funct Imag* 2006; 26: 83-6. [PMID: 16494597]
70. Costa DC, Tannock C, Brostoff J. Brainstem perfusion is impaired in chronic fatigue syndrome. *QJM* 1995; 88: 767-73. [PMID: 8542261]
71. 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.

72. Goldberg MJ, Mena I, Darcourt J. NeuroSPECT findings in children with chronic fatigue syndrome. *J CFS* 1997; 3: 61-6. Accessed on 22/03/2011 at [http://bubl.ac.uk/archive/journals/jcfs ... neurospect](http://bubl.ac.uk/archive/journals/jcfs...neurospect)
73. Ichise M, Salit I, Abbey S, Chung DG, Gray B, Kirsh JC, Freedman M. Assessment of regional cerebral perfusion by Tc-HMPAO SPECT in Chronic Fatigue Syndrome. *Nucl Med Commun* 1995; 13: 767-72. [PMID: 1491843]
74. Biswal B, Kunwar P, Natelson BH. Cerebral blood flow is reduced in chronic fatigue syndrome as assessed by arterial spin labeling. *J Neurol Sci* 2001; 301: 9-11. [PMID: 21167506]
75. 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. [PMID: 18942064]
76. Meeus M, Nijs J, Huybrechts S, Truijten S. Evidence for generalized hyperalgesia in chronic fatigue syndrome: case control study. *Clin Rheumatol* 2010; 29: 393-398. [PMID: 20077123]
77. 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. [PMID: 15351380]
78. 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. [PMID: 15907308]
79. Flor-Henry P, Lind JC, Koles ZJ. EEG source analysis of chronic fatigue syndrome. *Psychiatry Res* 2010; 181: 155-65. [PMID: 20006474]
80. Cook DB, O'Connor PJ, Lange G, Steffener J. Functional neuroimaging correlates of mental fatigue induced by cognition among fatigue syndrome patients and controls. *Neuroimage* 2007; 36: 108-22. [PMID: 17408973]
81. Michiels V, Cluydts R, Fischler B. Attention and verbal learning in patients with chronic fatigue syndrome. *J Int Neuropsychol Soc* 1998; 4: 456-66. [PMID: 9745235]
82. 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. [PMID: 19815723]
83. Lo SC, Pripuzova N, Li B, Komaroff AL, Hung GC, Wang R, Alter HJ. 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. [PMID: 20798047]
84. 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. [PMID: 19828908]
85. Chia J, Chia A. Chronic fatigue syndrome is associated with chronic enterovirus infection of the stomach. *J Clin Pathol* 2008; 61: 43-8. [PMID: 17872383]
86. Chia JK. The role of enterovirus in chronic fatigue syndrome. *J Clin Pathol* 2005; 58: 1126-32. [PMID: 16254097]
87. 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. [PMID: 19955554]

88. 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. [PMID: 10738137]
89. Chapenko S, Krumina A, Koziereva S, Nora Z, Sultanova A, Viksna L, Murovska M. Activation of human herpesviruses 6 and 7 in patients with chronic fatigue syndrome. *J Clin Virol* 2006;37Suppl1:S47-S51. [PMID:17276369]
90. 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. [PMID: 12887507]
91. Chia JK, Chia LY. Chronic Chlamydia pneumonia infection: a treatable cause of chronic fatigue syndrome. *Clin Infect Dis* 1999; 29: 452-3. [PMID: 10476765]
92. 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. [PMID: 18037660]
93. 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. [PMID: 12715326]
94. 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. [PMID: 19567398]
95. BrenuEW, StainesDR, BaskurtOK, AshtonKJ, RamosSB, ChristyRM, Marshall-Gradisnik SM. Immune and hemorheological changes in chronic fatigue syndrome. *J Transl Med* 2010; 8: 1. [PMID: 20064266]
96. Klimas NG, Koneru AO. Chronic fatigue syndrome: inflammation, immune function, and neuroendocrine interactions. *Curr Rheumatol Rep* 2007; 9: 483-7. [PMID: 18177602]
97. Fletcher MA, Zeng XR, Barnes Z, Levis S, Klimas NG. Plasma cytokines in women with chronic fatigue syndrome. *J Transl Med* 2009; 7: 96. [PMID: 19909538]
98. 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. [PMID: 20034348]
99. Carlo-Stella N, Badulli C, De Sivistri 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. [PMID: 16762155]
100. De Meirleir K, Bisbal C, Campine I, De Becker P, Salehzada T, Demettre E, Lebleu B. A 37 kDa 2-5A binding protein as a potential biochemical marker for chronic fatigue syndrome. *Am J Med* 2000; 108 (2): 99-105. [PMID: 11126321]
101. Sudolnik RJ, Lombardia V, Peterson DL, 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. [PMID: 9243369]
102. 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. [PMID: 18269338]
103. 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. [PMID: 15082102]
104. Wong R, Lopaschuk G, Zhu G, et al. Skeletal muscle metabolism in the chronic fatigue syndrome. In vivo assessment by ^{31}P nuclear magnetic resonance spectroscopy. *Chest* 1992; 102: 1716-22. [PMID: 1446478]

105. 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. [PMID: 15715687]
106. 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. [PMID: 20676841]
107. Richards RS, Wang L, Jelinek H. Erythrocyte oxidative damage in chronic fatigue syndrome. *Arch Med Res* 2007; 38(1): 94-8. [PMID: 1717431]
108. 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. [PMID: 12000033]
109. Kurup RK, Kurup PA. Hypothalamic digoxin, cerebral chemical dominance and myalgic encephalomyelitis. *Int J Neurosci* 2003; 113: 683-701. [PMID: 12745627]
110. 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.
111. 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. [PMID: 10790725]
112. 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. [PMID: 19632517]
113. Miwa K, Fujita M. Small heart syndrome in patients with chronic fatigue syndrome. *Clin Cardiol* 2008; 31: 328-33. [PMID: 18636530]
114. Peckerman A, LaManca JJ, Qureishi B, Dahl KA, Golfetti R, Yamamoto Y, Natelson BH. Baroreceptor reflex and integrative stress responses in chronic fatigue syndrome. *Psychosom Med* 2003; 65: 889-95. [PMID: 14508037]
115. Peckerman A, LaManca JJ, Dahl KA, Chemitiganti R, Qureishi B, Natelson BH. Abnormal impedance cardiography predicts symptom severity in chronic fatigue syndrome. *Am J Med Sci* 2003; 326: 55-60. [PMID: 12920435]
116. 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. [PMID: 8222798]
117. Rowe PC, Calkins H. Neurally mediated hypotension and chronic fatigue syndrome. *Am J Med* 1998; 105: 15S-21S. [PMID: 9790477]
118. Newton JL, Sheth A, Shin J, Pairman J, Wilton K, Burt JA, Jones DE. Lower ambulatory blood pressure in chronic fatigue syndrome. *Psychosom Med* 2009; 71: 361-5. [PMID: 19297309]
119. 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. [PMID: 20534655]
120. 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. [PMID: 20502886]
121. 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. [PMID: 9663406]

- 122.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. [PMID: 18765959]
- 123.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. [PMID: 16610948]

Correspondence address.

Corresponding author: Dr. Bruce Carruthers, 4607 Blenheim St., Vancouver, British Columbia V6L 3A3, Canada. bcarruth@telus.net

Corresponding author for submission of document: 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. gordon.broderick@ualberta.ca

Requests for Single Reprints: Ms. Marj van de Sande, 151 Arbour Ridge Circle NW, Calgary, Alberta T3G 3V9, Canada. mvandes@shaw.ca

Current Author Addresses

Dr. Carruthers: 4607 Blenheim St., Vancouver, BC, V6L 3A3, Canada. bcarruth@telus.net

Ms. van de Sande: 151 Arbour Ridge Circle NW, Calgary, AB T3G 3V9, Canada. mvandes@shaw.ca

Dr. De Meirleir: Department of Physiology, Vrije University of Brussels, Himmunitas Foundation, Brussels, 1120, Belgium. DE.MEIRLEIR@telenet.be

Dr. Klimas: Department of Medicine, University of Miami, 1201 NW 16 St., Miami, FL 33125, USA. nkdoc123@aol.com

Dr. Broderick: Division of Pulmonary Medicine, Department of Medicine, University of Alberta, WMC 2E4.41 WC Mackenzie Health Sciences Bldg, 8440 – 112 Street, Edmonton, Alberta, T6G 2R7, Canada. gordon.broderick@ualberta.ca

Dr. Mitchell: Lowestoft, Suffolk, NR32 5HD, United Kingdom. terry@gerken.org.uk

Dr. Staines: Public Health Medicine and Neuroimmunology, Queensland Health, Gold Coast Public Health Unit, Southport, Queensland 4215; Faculty of Health Sciences and Medicine, Bond University, Robina, Queensland 4229; Australia.

Don_Staines@health.qld.gov.au Dr. Powles: Faculty of Health Sciences, McMaster University and St. Joseph's Healthcare Hamilton, 50 Charlton Ave E., Hamilton, Ontario L0R 1H2, Canada. ppowles@stjosham.on.ca

Dr. Speight: Southlands Gilesgate, Durham, DH1 1QN, United Kingdom. speight@doctors.org.uk

Dr. Vallings: Howick Health and Medical Centre, 108 Ridge Road, Howick, New Zealand. vallings@xtra.co.nz

Dr. Bateman: Fatigue Consultation Clinic , 1002 East South Temple, Suite 408, Salt Lake City, Utah 84102, USA. fcclinic@xmission.com

Dr. Baumgarten-Austrheim: ME/CFS Center, Oslo University Hospital HF, Pb 4956 Nydalen, N- 0424 Oslo, Norway. uxbaba@ous-hf.no

Dr. Bell: 77 South Main Street, Lyndonville NY 14098, NY, USA. dsbellmd@yahoo.com

Dr. Carlo-Stella: Menocchio 10, I-27100, Pavia, Italy. nickics@libero.it

Dr. Chia: Harbor-UCLA Medical Center, University of California, Los Angeles, CA 90024; EV Med

Research, 25332 Narbonne Ave. #170, Lomita, CA 90717, USA. evmed@sbcglobal.net

Dr. Darragh: 'Tarabeag', Hill of Tara, Tara, Co Meath, Ireland ; Chemical & Environmental Science Department, University of Limerick, Limerick, Ireland.
daratara@eircom.net

Dr. Jo: Pain Clinic, Konyang University Hospital, Daejeon, Korea. pandjo@paran.com

Dr. Lewis: CFS Discovery, Donvale Specialist Medical Centre, Suite 8, 90 Mitcham Road, Donvale, Victoria 3111, Australia. dplewis@cfsdiscovery.oc.au

Dr. Light: Depts. of Anesthesiology, Neurobiology and Anatomy, 3C 444 SOM, University of Utah, 30N 1900E, Salt Lake City, Utah 84132, USA. alan.light@hsc.utah.edu

Dr. Marshall-Gradisnik: Faculty of Health Sciences and Medicine, Bond University, Robina, Queensland 4229, Australia. smarshal@bond.edu.au

Dr. Mena: Depart. Medicina Nuclear, Clinica Las Condes, Santiago, Chile.
imenamd@gmail.com

Dr. Mikovits: Whittemore Peterson Institute for Neuro-Immune Disease, Applied Research Facility, Rm. 401/MS199, 1664 North Virginia St., University of Nevada, Reno, NA 89557, USA. judym@wpinstitute.org

Dr. Miwa: Miwa Naika Clinic, Shintomicho 1-4-3, Toyama 930-0002, Japan. k-3wa@pm.ctt.ne.jp

Dr. Murovska: A. Kirchenstein Institute of Microbiology and Virology, Riga Stradins University, Ratsupites St. 5, Riga, Latvia, LV-1067. modra@latnet.lv

Dr. Pall: Dept. of Biochemistry and Basic Medical Sciences, Washington State University, 638 NE 41st Ave., Portland, OR 97232 USA. martin_pall@wsu.edu

Ms. Stevens: Pacific Fatigue Laboratory, Department of Sport Sciences, University of the Pacific, 3601 Pacific Avenue, Stockton, CA 95211, USA. sstevens@pacific.edu