In view of recent research and clinical experience with CFS 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. 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. 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.


The authors review what is known about the immune system in CFS. Slightly increased parameters of inflammation and pro-inflammatory cytokines such as interleukin (IL) 1, IL6 and tumour necrosis factor (TNF) α are likely present. Additionally, impaired natural killer cell function appears evident. Alterations in T cell numbers have been described by some and not others. While the prevalence of positive serology for the common herpes viruses appears no different from healthy controls, there is some evidence of viral persistence and inadequate containment of viral replication. The ability of certain herpes viruses to impair the development of T cell memory may explain this viral persistence and the continuation of symptoms.

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Exploratory factor analysis was performed on symptoms present at assessment in 333 children and young people with CFS/ME. Three phenotypes were identified using factor analysis: Factor 1, musculoskeletal, had loadings on muscle and joint pain and hypersensitivity to touch, and was associated with worse fatigue, physical function and pain. Factor 2, migraine, loaded on noise and light hypersensitivity, headaches, nausea, abdominal pain and dizziness and was most strongly associated with physical function and pain. Factor 3, sore throat, had loadings on sore throat and tender lymph nodes and was not associated with fatigue or pain.


Besides persistent fatigue, a clinical syndrome of CFS with infectious, neurological and rheumatological characteristics is outlined from the data in Italy.


Several mechanisms have been suggested to play a role in CFS, such as excessive oxidative stress following exertion, immune imbalance characterized by decreased natural killer cell and macrophage activity, immunoglobulin G subclass deficiencies (IgG1, IgG3) and decreased serum concentrations of complement component. Autoantibodies were also suggested as a possible factor in the pathogenesis of CFS. Recent studies indicate that anti-serotonin, anti-microtubule-associated protein 2 and anti-muscarinic cholinergic receptor 1 may play a role in the pathogenesis of CFS. It has been demonstrated that impairment in vasoactive neuropeptide metabolism may explain the symptoms of CFS.
Hooper M. Myalgic encephalomyelitis: a review with emphasis on key findings in biomedical research. J Clin Pathol. 2007 May;60(5):466-71. PMID: 16935967

A review of research findings in CFS, termed a “chronic multiple-symptom, multiorgan, multisystem illness.”


Studies of CFS patients show a variety of dysfunctions, including mitochondrial dysfunction and immune dysfunction.


For children and adolescents with CFS, four major symptoms are important: sleep disorders, easy fatigability, disturbed learning and memorization and immunological problems.


Recent studies reveal that CFS can be understood to be a special condition based on the abnormality of neuroendocrine-immunologic system caused by the psycho-social stress and some genetic components. Under these conditions, a reactivation of various kinds of herpes virus infections and/or chronic infections might occur as a result of immune dysfunction, causing the abnormal production of several cytokines. A distinctive feature of CFS is thought to be the secondary brain dysfunction caused by the abnormal production of several cytokines.

The authors did an analysis of a population of CFS patients and came up with musculoskeletal, infectious and neurological subtypes.

Gurbaxani BM, Jones JF, Goertzel BN, Maloney EM. Linear data mining the Wichita clinical matrix suggests sleep and allostatic load involvement in chronic fatigue syndrome. Pharmacogenomics. 2006 Apr;7(3):455-65. PMID: 16610955

The authors provide basic data about a group of CFS sufferers in Wichita, Kansas.


Individuals with chronic fatigue have symptoms that can be differentiated into theoretically distinct factors, including: Lack of Energy, Physical Exertion, Cognitive Functioning, and Fatigue and Rest.

**Cancer Risk**


CFS was associated with an increased risk of non-Hodgkin lymphoma (NHL). Among NHL subtypes, CFS was associated with diffuse large B cell lymphoma, marginal zone lymphoma, and B cell NHL not otherwise specified. CFS was also associated, although not after multiple comparison adjustment, with cancers of the pancreas, kidney, breast, and oral cavity and pharynx.

The authors investigated the possibility that chronic fatigue syndrome (CFS) predisposes to cancer by comparing the cancer pattern in an area in northern Nevada, where an outbreak of a fatiguing illness, which included cases of CFS, was reported, to an area in southern Nevada, where no such illness was reported. Higher incidences of NHL and primary brain tumors were noted in the two northern Nevada counties (Washoe and Lyon) in 1986 and 1987 respectively, compared to the southern Nevada (Clark) county.


The authors consider whether the decreased natural killer cell function in CFS clusters may be related to brain/CNS tumors and non-Hodgkin's lymphoma, finding a trend that merits future research.


The authors examined the prevalence of non-Hodgkins lymphoma in epidemic areas for CFS.

**Cardiac Abnormalities**
Miwa K. Cardiac dysfunction and orthostatic intolerance in patients with myalgic encephalomyelitis and a small left ventricle. Heart Vessels. 2014 Apr 16. PMID: 24736946

A small left ventricle heart size with a low cardiac output was common in ME patients, in whom orthostatic intolerance was extremely common. Cardiac dysfunction with a small heart appears to be related to the symptoms of ME.


CFS and other conditions with an association with neurocardiogenic syncope are discussed.


This research study suggests that a) disability of CFS patients is not only related to fatigue but to other symptoms as well; b) altered cardiovascular autonomic control is associated with certain symptoms; c) The CDC criteria are poorly associated with disability, symptoms, and indices of altered autonomic nervous activity.


At rest, low frequency heart rate variability (sympathetic) was significantly increased in CFS compared to controls, while parasympathetic markers were significantly reduced. Total diastolic blood pressure spectral power was increased across all domains, with a shift towards sympathetic and away from parasympathetic SBPV. On standing, overall
systolic response was significantly reduced with reductions in both sympathetic and parasympathetic components.


A small size of left ventricular with low cardiac output was noted in subjects with orthostatic intolerance, and especially in those patients also suffering from CFS. A small heart appears to be related to both cerebral and systemic hypoperfusion.


Patients with CFS have markedly reduced cardiac mass and blood pool volumes, particularly end-diastolic volume: this results in significant impairments in stroke volume and cardiac output compared to controls. The CFS group appeared to have a delay in the release of torsion.


A shorter-than-usual QT interval has been reported in patients with Chronic Fatigue Syndrome.


Reduced cardiac stroke volume and cardiac output was demonstrated in more severely afflicted patients with CFS, and this is primarily attributable to a measurable reduction in blood volume.

This study indicates that lower cardiac volume levels, displayed primarily by subjects with severe CFS, were not linked to diminished cardiac contractility levels, but were probably a consequence of a co-morbid hypovolaemic condition.

Miwa K, Fujita M. Cardiovascular dysfunction with low cardiac output due to a small heart in patients with chronic fatigue syndrome. Intern Med. 2009;48(21):1849-54. PMID: 19881233

CFS patients have low cardiac output due to a small left ventricular chamber. Frequently reported cardiovascular symptoms (including shortness of breath, dyspnea on effort, rapid heartbeat, chest pain, fainting, orthostatic dizziness, coldness of feet and hypotension) may be results of this.

Miwa K, Fujita M. Cardiac function fluctuates during exacerbation and remission in young adults with chronic fatigue syndrome and "small heart". J Cardiol. 2009 Aug;54 (1):29-35. PMID: 19632517

CFS patients had small left ventricular heart chambers and poor cardiac performance, and this was correlated with the severity of their symptoms.


A high percentage of CFS patients have a small heart, and this leads to orthostatic dizziness, foot coldness, pitting edema and other symptoms.

CFS is associated with a short corrected electrocardiographic QT interval (QTc).


Relative short QTc intervals are features of the CFS-related dysautonomia.


The prevalence of abnormal cardiac wall motion (ACWM) at rest in CFS patients was 10 out of 87 patients (11.5%). With stress exercise, 21 patients (24.1%) demonstrated ACWM. Cardiac biopsies in 3 of these CFS patients with ACWM showed a cardiomyopathy. Among the controls, ACWM at rest was present in 4 out of 191 patients (2%) (p=0.0018).


The patients with severe CFS had significantly lower stroke volume and cardiac output than the controls and less ill patients. Postexertional fatigue and flu-like symptoms of
infection differentiated the patients with severe CFS from those with less severe CFS (88.5% concordance) and were predictive (R² = 0.46, P < 0.0002) of lower cardiac output. In contrast, neuropsychiatric symptoms showed no specific association with cardiac output.

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Eleven patients diagnosed with chronic fatigue syndrome were found to have abnormal left ventricular myocardial dynamics as indicated on MUGA studies. Among the abnormalities noted were abnormal wall motion at rest and stress, dilatation of the left ventricle, and segmental wall motion abnormalities.

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A group of patients with CFS (age 50 or younger, no risk factors for coronary artery disease) all had abnormal Holter readings, while 22.4 percent patients without CFS had abnormal readings (p < 0.01). Mild left ventricular dysfunction was noted in 8 of 60 patients. All 60 showed repetitively flat to inverted T waves alternating with normal T waves. Stress multiple gated acquisitions (MUGAs) (labeled erythrocytes with stannous pyrophosphate) were abnormal in eight patients. Although resting ejection fractions (EFs) were normal, with increasing work loads, gross left ventricular dysfunction occurred.

**Orthostatic Intolerance**

Via a systematic literature review, the authors concluded that there are differences in autonomous response between patients with CFS and healthy controls. The heart rate dynamic response during the head-up tilt test differs between patients with CFS and healthy controls, supporting the increased prevalence of postural orthostatic tachycardia syndrome.


In an Australian sample of CFS patients, 11% also suffered from POTS. CFS-POTS patients were significantly younger, had a shorter length of illness, experienced greater task difficulty and were able to stand for significantly shorter periods compared to the CFS-only patients. CFS-POTS patients experienced significantly lower baseline diastolic blood pressure, significantly higher heart rate and lower pulse pressures at each standing measurement. Early heart rate changes and overall heart rate change were significant predictors of completion status, whereas heart rate variability and female gender were significant predictors of increased perceived task difficulty.


Postural orthostatic tachycardia syndrome and its relationship to CFS is discussed.


CFS patients with POTS (13% of this sample) were younger, less fatigued, less depressed and had reduced daytime hypersomnolence, compared with patients without POTS. In addition, they exhibited greater orthostatic intolerance and autonomic dysfunction.

The authors compared CFS and POTS (postural tachycardia syndrome) patients, concluding that most POTS patients met the criteria for CFS. CFS-POTS patients have higher markers of sympathetic activation, but are part of the spectrum of POTS. Targeting this sympathetic activation should be considered in the treatment of these patients.


This paper provides a literature review on postural tachycardia syndrome (POTS), including its role in CFS.


The researchers explored the clinical value of non-invasive optical multi-site photoplethysmography (PPG) technology to assess cardiovascular responses to standing.

Increasing orthostatic stress combined with a cognitive challenge impairs the neurocognitive abilities of working memory, accuracy, and information processing in CFS/postural orthostatic tachycardia syndrome, but this is not related to changes in cerebral blood flow velocity. Individuals with CFS/POTS should be aware that orthostatic stress may impair their neurocognitive abilities.


In CFS patients, intolerance is correlated with fatigue, and fatigue is worse in mornings than later in the day.


CFS in adolescents is characterized by reduced systolic blood pressure variability and a sympathetic predominance of baroreflex heart rate control during orthostatic stress.


Treatment of orthostatic symptoms in CFS has the potential to improve functional capacity and quality of life.

Heart problems in CFS cause orthostatic intolerance, meaning that symptoms get worse when standing up.


CFS patients have heart problems, emerging during mild orthostatic stress. Possible underlying mechanisms include low blood volume and abnormalities of reflex mechanisms.


Postural orthostatic tachycardia syndrome (POTS), with abnormally high heart rate on standing, is a frequent finding in patients with CFS/ME and results in fatigue.


CFS patients were more susceptible to orthostatic intolerance, with the unique manifestation of postural orthostatic tachycardia syndrome.

Adolescents with CFS have increased sympathetic activity at rest with exaggerated cardiovascular response to orthostatic stress, but attenuated cardiovascular response when performing isometric exercise during orthostatic stress.

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The clinical picture, diagnosis, and management of POTS are discussed.

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Adolescents with CFS have sympathetic predominance of cardiovascular regulation during very mild orthostatic stress.

* 


Autonomic function might be partly involved in CFS such as orthostatic dysfunction, but its priority in causing CFS is unclear.

* 

Natelson BH, Intriligator R, Cherniack NS, Chandler HK, Stewart JM. Hypocapnia is a biological marker for orthostatic intolerance in some patients with chronic fatigue syndrome. Dyn Med. 2007 Jan 30;6:2. PMID: 17263876

A substantial number of CFS patients have orthostatic intolerance in the form of orthostatic hypocapnia.

The authors hypothesize that dysautonomia is pivotal in the pathophysiology CFS and that manipulating the autonomic nervous system may be an effective treatment.


In CFS, deficiencies in orthostatic regulation, but not in centrally mediated stress responses, may involve the baroreceptor reflex.


Prolongation of acetylcholine-induced vasodilatation is suggestive of a disturbance to cholinergic pathways, perhaps within the vascular endothelium of patients with CFS, and might be related to some of the unusual vascular symptoms, such as hypotension and orthostatic intolerance, which are characteristic of the condition.


In a study of CFS patients, orthostatic intolerance determined by cardiovascular responses to standing was observed in 16 of 28 patients: instantaneous orthostatic hypotension in 8, delayed orthostatic hypotension in 2, and postural orthostatic tachycardia in 6. A rapid recovery of oxy-Hb by near infrared spectroscopy at the onset of active standing was not found in 15 of 16 patients with chronic fatigue and orthostatic intolerance and in 6 of 12 patients with chronic fatigue without orthostatic intolerance.
but only in 2 of 20 control subjects. Thirteen of 16 patients with orthostatic intolerance showed prolonged reduction in oxy-Hb during standing.


The hemodynamic instability score, related to cardiovascular response to postural challenge, adds objective criteria confirming the diagnosis of CFS.


Heart rate and blood pressure regulation in POTS and CFS patients are similar and indicate attenuated efferent vagal baroreflex associated with increased vasomotor tone. Loss of beat-to-beat heart rate control may contribute to a destabilized blood pressure resulting in orthostatic intolerance.


Delayed orthostatic hypotension and/or tachycardia caused by excessive gravitational venous pooling, which is correctable with external lower-body compression, together with subnormal circulating erythrocyte volume, are very frequent, although not invariably demonstrable, findings in moderate to severe CFS.

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Among patients with CFS and orthostatic intolerance, a subset also has Ehlers-Danlos syndrome.


Symptoms and patterns of orthostatic heart rate and blood pressure change in orthostatic tachycardia syndrome overlap strongly with those of CFS. Orthostatic intolerance in orthostatic tachycardia syndrome may represent an attenuated form of chronic fatigue pathophysiology.


On average, the duration of disease and patient age were significantly less and the onset of symptoms was more often subacute in CFS patients with OI than in those without OI.


CFS is highly related to orthostatic intolerance in adolescents. The orthostatic intolerance of CFS often has heart rate and BP responses similar to responses in the syndrome of orthostatic tachycardia, suggesting that a partial autonomic defect may contribute to symptomatology in these patients.

Fatigue is a very common symptom in patients with delayed orthostatic hypotension, as well as both primary and secondary hypocortisolism.


Patients with CFS have a high prevalence of neurally mediated hypotension, and open treatment of this autonomic dysfunction has been associated with improvements in CFS symptoms.


This study suggests an overlap in the symptoms of chronic fatigue syndrome and neurally mediated hypotension.

**Tilt Table Test**


Adolescents with CFS have significant abnormalities of cardiovascular regulation in response to mild orthostatic stress.

*

Hyperventilation appears to be the major abnormal response to postural challenge in sustained hypocapnia. Because unrecognized hypocapnia is common in CFS, fibromyalgia, and nonspecific dizziness, capnography should be a part of the evaluation of patients with such conditions.


Orthostatic instability was similar in persons with chronic fatigue syndrome and nonfatigued controls subjects recruited from the general Wichita population. Delayed responses to head-up tilt tests were common and may reflect hydration status.


We studied 18 CFS patients without POTS, eight CFS patients with POTS and 25 sedentary healthy controls during supine rest and during the first 10 min after HUT. Even CFS patients without POTS may have a subtle underlying disturbance in autonomic function.

Patients with CFS did not have abnormal cerebral blood flow velocity (CBFV) compared with controls in response to orthostatic stress. The median time to hypotension did not differ, but the median time to onset of orthostatic symptoms was shorter in those with CFS.

*Yamamoto Y, LaManca JJ, Natelson BH. A measure of heart rate variability is sensitive to orthostatic challenge in women with chronic fatigue syndrome. Exp Biol Med (Maywood). 2003 Feb;228(2):167-74. PMID: 12563023

This study suggests that a decrease in aperiodic fractal component of heart rate variability in response to head up tilt can be used to differentiate patients with CFS from controls.


The authors developed a method that uses a head-up tilt test (HUTT) to estimate blood pressure and heart rate instability during tilt. There is a particular dysautonomia in CFS that differs from dysautonomia in other disorders, characterized by haemodynamic instability score >0.98. This can reinforce the clinician's diagnosis by providing objective criteria for the assessment of CFS.


Head-up tilt evokes postural tachycardia or (pre)syncope in a minority of CFS patients. In this study, head-up tilt-negative CFS patients had a higher heart rate at baseline together with a marked decrease in stroke volume in response to head-up tilt.

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Cardiovascular response during postural challenge were more problematic in CFS patients than in healthy controls or than in fibromyalgia patients.


POTS may occur in adolescents and represents a mild, potentially treatable form of autonomic dysfunction that can be readily identified during head upright tilt table testing.


This study examined the cardiovascular response to orthostatic challenge, noting differences between patients and controls.


In a tilt table test, 81% of CFS patients fainted, compared to 30% of controls. Heart rate variability indices were strikingly decreased in CFS patients. These data may indicate autonomic impairment in patients with CFS.

After a tilt table test, CFS patients had abnormally high heart rates and abnormally low frequency power.


An abnormal response to upright tilt was observed in 22 of 78 patients with CFS. After sodium chloride therapy for 8 weeks, half of patients did not show an abnormal response to the test and reported improvement in CFS symptoms. Patients who did not respond to sodium chloride therapy were found to have low plasma renin activity.

Freeman R, Komaroff AL. Does the chronic fatigue syndrome involve the autonomic nervous system? Am J Med. 1997 Apr;102(4):357-64. PMID: 9217617

CFS subjects had a significant increase in baseline and maximum heart rate (HR) on standing and a tilt table test. Tests of parasympathetic nervous system function were significantly less in the CFS group as were measures of sympathetic nervous system function. Twenty-five percent of CFS subjects had a positive tilt table test. The physical activity index was a significant predictor of autonomic test results; and the blood pressure decrease in phase II of the Valvalsa maneuver, whereas premorbid and coexistent psychiatric conditions were not. The onset of autonomic symptoms occurred within 4 weeks of a viral infection in 46% of patients—a temporal pattern that is consistent with a postviral, idiopathic autonomic neuropathy.

Upright tilt-table testing induced significant hypotension and increased heart rate in a group of five CFS patients.


An abnormal response to upright tilt was observed in 22 of 23 patients with chronic fatigue syndrome vs four of 14 controls (P < .001). Seventy percent of chronic fatigue syndrome patients, but no controls, had an abnormal response during stage 1 (P < .001). Nine patients reported complete or nearly complete resolution of chronic fatigue syndrome symptoms after therapy directed at neurally mediated hypotension.

Other Cardiovascular Issues


Multiscale analyses suggested that there are notable differences in heart rate variability between CFS patients and matched controls before a social stress test, but that these differences seemed to diminish during the test.

Fibromyalgia patients show more heart rate variability aberrances and indices of increased sympathetic activity. Increased sympathetic activity is only present in CFS patients at night.


In adolescent CFS patients at night, heart rate, arterial blood pressure and diastolic blood pressure were higher than normal; during daytime, heart rate was higher than normal but both blood pressure readings were normal.


This study identified significant reductions in vagal modulation of heart rate during sleep in CFS. Low heart rate variance strongly predicted sleep quality-suggesting a pervasive state of nocturnal sympathetic hypervigilance in CFS.


CFS patients have lower blood pressure and abnormal blood pressure regulation.

Symptoms of autonomic dysfunction were associated with CFS and correlated with the severity of the fatigue.


The presence of increased heart rate and reduced heart rate variability in CFS during sleep coupled with higher norepinephrine levels and lower plasma aldosterone suggest a state of sympathetic ANS predominance and neuroendocrine alterations.


Autonomic testing in patients with chronic fatigue syndrome yielded a significantly greater increase in heart rate together with a more pronounced systolic blood pressure fall on standing compared to healthy individuals. Heart rate beat-to-beat variation on deep breathing and responses to the Valsalva manoeuvre were normal. Serum erythropoietin levels were within reference range.


On a graded exercise test, significant differences were found between impairment levels of CFS patients for percentage of predicted [OV0312]O(2) and peak heart rate.


The cardiovascular reactivity in patients with CFS has certain features in common with the reactivity in patients with recurrent syncope or non-CFS chronic fatigue, such as the frequent occurrence of vasodepressor reaction, cardioinhibitory reaction, and postural tachycardia syndrome. Apart from to these shared responses, the large majority of CFS patients exhibit a particular abnormality which is characterized by hemodynamic instability score values >0.98, lending objective criteria to the assessment of CFS.


This study aimed to develop a method to distinguish between the cardiovascular reactivity in chronic fatigue syndrome (CFS) and other patient populations. The authors found that the best cut-off distinguishing CFS patients from others was the Fractal & Recurrence Analysis-based Score, which has potential as a diagnostic.


Individuals with CFS have a significantly lower peak oxygen consumption and an insignificant trend toward lower blood volume compared with controls. These two factors are highly related to one another.

Women with CFS have a diminished cardiovascular response to cognitive stress. Patients with the lowest cardiovascular reactivity had the highest ratings of CFS symptom severity.


CFS patients had higher heart rates and (in supine position) lower spectral indices of blood pressure variability than normal people.


CFS patients have a subtle abnormality in vagal activity to the heart that may explain, in part, their post-exertional symptom exacerbation.


Patients with CFS have normal resting cardiac function but a markedly abbreviated exercise capacity characterized by slow acceleration of heart rate and fatigue of exercising muscles long before peak heart rate is achieved.

Exercise & Activity Intolerance

The study looked at repeat cardiopulmonary exercise tests (CPET) done on two consecutive days. Compared to healthy controls, a group of ME/CFS patients showed significant decreases from Day 1 to Day 2 in oxygen consumption (VO2) peak, heart rate (HR) peak, minute ventilation (Ve) peak, and workload (Work) at peak. Decreases in ventilatory threshold (VT) measures included VO2@VT (15.8%), Ve@VT (7.4%), and Work@VT (21.3%). Peak respiratory exchange ratio was high and did not differ between tests, indicating maximum effort by participants during both CPETs. If data from only a single CPET test is used, a standard classification of functional impairment based on VO2peak or VO2@VT results in over-estimation of functional ability for 50% of ME/CFS participants in this study.

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The authors analysed the cardiopulmonary exercise tests of CFS patients, idiopathic chronic fatigue (CFI) patients and healthy visitors. They concluded that low oxygen uptake by muscle cells causes exercise intolerance in a majority of CFS patients, indicating insufficient metabolic adaptation to incremental exercise. They also stated that the high increase of the cardiac output relative to the increase of oxygen uptake argues against deconditioning as a cause for physical impairment in these patients.

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Compared to controls, CFS patients demonstrated a higher level of sleep abnormalities subsequent to exercise.

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The objective of this study was to determine the discriminative validity of objective measurements obtained during cardiopulmonary exercise testing to distinguish participants with CFS from participants who did not have a disability but were sedentary. The lack of any significant differences between groups for the first exercise test would appear to support a deconditioning hypothesis for CFS symptoms. However, the results from the second test indicated the presence of CFS-related postexertion fatigue.


The researchers found evidence of altered sympathetic-neural and sympathetic adrenomedulla reactivity in CFS. Exercise stress revealed a subtle catecholaminergic hyporeactivity in CFS patients.


The researchers conducted repeat blood sampling for cytokine levels from healthy subjects and CFS patients during both postexercise and total sleep deprivation nights and assayed for protein levels in the blood samples, mRNA activity in peripheral blood lymphocytes (PBLs), and function in resting and stimulated PBLs. They found that these environmental manipulations did not produce clinically significant upregulation of proinflammatory cytokines.

* White AT, Light AR, Hughen RW, Vanhaitsma TA, Light KC. Differences in metabolite-detecting, adrenergic, and immune gene expression after moderate exercise in patients

Postexercise mRNA increases in metabolite-detecting receptors were unique to patients with CFS, whereas both patients with MS and patients with CFS showed abnormal increases in adrenergic receptors. Among patients with MS, greater fatigue was correlated with blunted immune marker expression.

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The purpose of the present study was to examine cardiac and perceptual responses to steady-state submaximal exercise in CFS patients and healthy controls. The CFS + FM group exhibited an exercise response characterized by higher stroke index, ventilatory equivalents for oxygen and carbon dioxide and rating of perceived exertion, lower systolic blood pressure, and similar HR responses compared to controls.

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The presence of stress factors in the history of CFS patients is associated with severe oxidative stress and the suppression of protective HSP27 and HSP70 responses to exercise.

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CFS patients exhibit “profound abnormality in bioenergetic function.” When they exercise at the level of normal people, they demonstrate increased intramuscular acidosis that does not decrease normally with repeated exercise. Compared to normal people, it also takes four times as long for their pH to return to baseline after exercise.


CFS patients suffer from hyperresponsiveness of the central nervous system to various stimuli, including heat, mechanical pressure, electrical stimulation and histamine. Exercise worsens this tendency.


CFS patients exhibited two different abnormal responses to exercise. Some patients demonstrated abnormal increases in mRNA for sensory and adrenergic receptors and a cytokine, resulting in fatigue or pain. A second group demonstrated abnormal decreases in adrenergic α-2A receptor's transcription. None of the normal patients in the study showed these responses, and the authors thus suggest that this finding has the potential of serving as a biomarker for the disease.


Presence of just three measures (fatigue, sleep and pain) was effective in predicting exercise intolerance -- a definitional indicator of CFS status.

CFS patients reached the anaerobic threshold and the maximal exercise at a much lower oxygen consumption than the controls, and this worsened in the second test. This implies an increase of lactate, the product of anaerobic glycolysis, and a decrease of the mitochondrial ATP production in the patients.


The authors administered the antidepressant citalopram to CFS patients and then had them perform a submaximal exercise protocol, preceded and followed by an assessment of endogenous pain inhibition. Significant negative effects were observed in all patients and the authors decided that proceeding with the study would be unethical.


CFS patients show hyperalgesia and abnormal central pain processing during submaximal aerobic exercise.


The more that patients with CFS are sedentary and the better activity is dispersed, the fewer symptoms and variations they experience on the same and next day. Inversely,
more symptoms and variability is experienced when patients were more active that day or the previous day.

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CFS patients had a higher increase in nitric oxide metabolites after exercise than did controls.

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Following exercise, complement C4a levels go up more in CFS patients than in healthy people.

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Maes M, Twisk FN. Chronic fatigue syndrome: Harvey and Wessely's (bio)psychosocial model versus a bio(psychosocial) model based on inflammatory and oxidative and nitrosative stress pathways. BMC Med. 2010 Jun 15;8:35. PMID: 20550693

The authors describe how physiological abnormalities related to inflammatory, immune, oxidative and nitrosative pathways interfere with exercise tolerance in CFS.

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CFS patients displayed abnormalities in recovery of intramuscular pH, related to autonomic dysfunction, following exercise.


CFS patients often display negative responses to exercise, as a result of abnormal inflammatory cytokine activity.


CFS patients have higher levels of F(2)-isoprostanes, an indicator of oxidative stress, after exercise.


Healthy subjects are able to tolerate a higher level of pain following exercise, while CFS patients are able to tolerate a lower level of pain following exercise.

* Brown M, Khorana N, Jason LA. The role of changes in activity as a function of perceived available and expended energy in nonpharmacological treatment outcomes for ME/CFS. J Clin Psychol. 2010 Oct 25. PMID: 20976708
CFS patients who were within their energy envelope before treatment showed more improvement in physical functioning and fatigue compared with those outside of their energy envelope.


Following an exercise test, all the normal sedentary controls recovered quickly (within 24-48 hours) while none of the CFS patients did. Symptoms the patients reported after the test included fatigue, light-headedness, muscular/joint pain, cognitive dysfunction, headache, nausea, physical weakness, trembling/instability, insomnia and sore throat/glands.


After sustained moderate exercise, CFS patients showed greater increases than control subjects in gene expression for metabolite detecting receptors ASIC3, P2X4, and P2X5, for SNS receptors alpha-2A, beta-1, beta-2, and COMT and IS genes for IL10 and TLR4. This correlated with an exacerbation in their symptoms.

* Twisk FN, Maes M. 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. Neuro Endocrinol Lett. 2009;30(3):284-99. PMID: 19855350

The authors discuss how the use of exercise therapy in CFS may be harmful to patients.

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The authors review recent findings on inflammatory and oxidative and nitrosative stress (IO&NS) pathways in CFS and suggest that for these patients, exercise can be a trigger factor causing damage.


Mannan-binding lectin serine protease 2 (MASP2) was higher than normal following exercise in CFS patients, and this seems related to the phenomenon of post-exertional malaise.


CFS patients have more severe and longer oxidative stress following exercise, and this may result from delayed and insufficient heat shock proteins protecting the cells.


Compared to controls walking at the same speed, CFS patients had a lower gross and net oxygen uptake and suffered a higher physiological cost.

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In case reports, the authors show that Belgian patients who received Graded Exercise Therapy in fact suffered from disorders of the inflammatory/oxidative/nitrosative stress pathways, including intracellular inflammation, an increased translocation of gram-negative enterobacteria (leaky gut), autoimmune reactions and damage by O&NS. They suggest that exercise was inappropriate treatment and recommend policy changes.

* 


CFS patients who were able to keep their expended energy close to available energy (i.e. were able to stay within their “energy envelope”) experienced significant improvements in physical functioning and fatigue severity.

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Patients with CFS have significantly decreased aerobic capacity. Self-reports of physical activity predicted VO(2peak), and may be used as an indicator of activity-based aerobic capacity. Self-reports of fatigue, however, did not correlate with VO(2peak) and hence are assessing something other than an index of aerobic capacity.

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Heat shock protein expression following exercise is abnormal in CFS, suggesting an abnormal response to oxidative stress. This has potential of serving as a biomarker.

Decreased cerebral oxygenation and blood flow may make contribute to the reduced exercise abilities in CFS.


Limiting both the intensity and duration of exercise prevents important health status changes following a walking exercise in people with CFS, but was unable to prevent short-term symptom increases.


CFS patients engaging in a stepwise exercise protocol had lower mechanical efficiency (ratio peak workload/peak oxygen uptake) than those engaging in a linear exercise protocol.


This study aimed at examining whether physiological exercise variables at the submaximal level, defined as 75% of the age-predicted target heart rate, are able to predict peak exercise performance in women with chronic fatigue syndrome (CFS).

CFS patients experienced increased physical symptoms after exercise, on average with a five-day delay. Psychological symptoms and cognitive functioning did not change after exercise.


CFS sufferers respond to incremental exercise with a lengthened and accentuated oxidative stress response, explaining muscle pain, postexertional malaise, and the decrease in pain threshold following graded exercise in CFS patients.


In the overall sample, there were no significant differences in cardiorespiratory parameters between the CFS only group and the controls. However, the CFS plus FM group exhibited lower ventilation, lower end-tidal CO2, and higher ventilatory equivalent of carbon dioxide compared with controls, and slower increases in heart rate compared with both patients with CFS only and controls. Peak oxygen consumption, ventilation, and workload were lower in the CFS plus FM group. Subjects in both the CFS only group and the CFS plus FM group rated exercise as more effortful than did controls.

There appears to be an association between intracellular immune deregulation and exercise performance in patients with CFS.

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Following exercise, CFS patients have lengthened and accentuated oxidative stress together with marked alterations of the muscle membrane excitability.

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The 2'-5' oligoadenylate (2-5 A) synthetase/RNase L pathway in CFS patients appears to be both upregulated and deregulated, and this seems to be related to performance during a graded exercise stress test.

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CFS patients who attempt to increase their activity by participating in a daily walking program have a difficult time maintaining that increase over time and usually compensate by reducing other activity.

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After exercise, CFS patients reported fatigue for an additional two days, compared to two hours for matched sedentary controls.


Abnormal immune activity related to oxidative stress, nitric oxide related toxicity and hyperactivation of Rnase-L is related to exercise intolerance in CFS patients.

* Whistler T, Jones JF, Unger ER, Vernon SD. Exercise responsive genes measured in peripheral blood of women with chronic fatigue syndrome and matched control subjects. BMC Physiol. 2005 Mar 24;5(1):5. PMID: 15790422

Following an exercise challenge, CFS patients differed from controls on a variety of genes, including chromatin and nucleosome assembly, cytoplasmic vesicles, membrane transport and G protein-coupled receptor ontologies. Differences in ion transport and ion channel activity were evident at baseline and exaggerated after exercise.


A technique to predict peak oxygen uptake in CFS patients was developed.

During exercise, normal people have higher pain thresholds and CFS patients have lower pain thresholds.


This study shows a lack of correlation between kinesiophobia (fear of movement) and exercise capacity, activity limitations, or participation restrictions, at least in patients with CFS who are experiencing widespread muscle or joint pain.


CFS involves altered central nervous system signals in controlling voluntary muscle activities, especially when the activities induce fatigue.


CFS patients have evidence of hyperemic flow and reduced oxygen delivery, but this does not seem to result in disturbed muscle metabolism.

These results suggest a moderate association between exercise capacity and activity limitations/participation restrictions in patients with CFS. The observed correlations lack strength to predict activity limitations/ participation restriction based on exercise capacity parameters.


Exercise challenge induced significant increases of the complement split product C4a, but not C3a or C5a, at 6 hours after exercise only in the CFS group. This has potential of serving as a biomarker.


Severely affected CFS patients are more impaired during exercise stress tests in terms of peak systolic blood pressure and peak heart rate.


Seventy-three CFS patients performed a graded exercise test to voluntary exhaustion. Forty-six patients had elevated RNase L levels. The elevated RNase L group had a lower peak VO2 and duration than the normal group, but a higher KPS. Both Rnase L and exercise intolerance have potential as biomarkers for CFS.

*Ohashi K, Yamamoto Y, Natelson BH. Activity rhythm degrades after strenuous exercise in chronic fatigue syndrome. Physiol Behav. 2002 Sep;77(1):39-44. PMID: 12213500*
CFS patients had an abnormal lengthening (P < .05) of mean circadian period (MCP) after exercise that was longer than 24 hours.

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CFS patients tend to have low blood volume and low peak oxygen consumption, and this seems to be related to their exercise intolerance.

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CFS patients demonstrated significantly lower cardiovascular as well as ventilatory values at peak exercise, compared with the control group.

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The basic principles of envelope theory are explained. By not overexerting themselves, people with CFS can avoid the setbacks and relapses that commonly occur in response to overexertion while increasing their tolerance to activity.

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Compared to healthy controls, CFS patients suffered abnormally reduced time constant of oxygen delivery and oxidative metabolism following exercise.

Using a simple to administer maximal exercise test on a cycle ergometer, it is possible to predict accurately the VO2peak of a patient with CFS from peak work rate alone. This value can then be used as an aid to setting appropriate exercise intensity for a rehabilitation programme.


Throughout a period of exercise, patients were able to exercise less than controls. Recovery was prolonged in the patient group, however, with a significant difference compared to initial amount of exercise being evident during the recovery phase after exercise (P = 0.001) and also at 24 h (P < 0.001). These findings support the clinical complaint of delayed recovery after exercise in patients with CFS.


After a physically demanding exercise, CFS subjects demonstrated impaired cognitive processing compared with healthy individuals.

After exertion, patients with chronic fatigue syndrome showed a greater decrease than healthy controls on everyday tests of focused and sustained attention, as well as greater deterioration than depressed patients on the focused attention task.


Muscle histometry in patients with chronic fatigue syndrome generally did not show the changes expected as a result of inactivity. However, patients with abnormal lactate responses to exercise had a significantly lower proportion of mitochondria rich type 1 muscle fibres.


The authors present evidence against an association in CFS between avoidance of physically demanding tasks and early anaerobic metabolism during effort.


Voluntary activation of the tibialis was significantly lower in CFS patients during maximal sustained exercise.

CFS patients reach exhaustion much more rapidly than normal subjects, at which point they also have relatively reduced intracellular concentrations of ATP. These data suggest a defect of oxidative metabolism with a resultant acceleration of glycolysis in the working skeletal muscles of CFS patients.

Montague TJ, Marrie TJ, Klassen GA, Bewick DJ, Horacek BM. Cardiac function at rest and with exercise in the chronic fatigue syndrome. Chest. 1989 Apr;95(4):779-84. PMID: 2924607

Patients with chronic fatigue syndrome have normal resting cardiac function but a markedly abbreviated exercise capacity characterized by slow acceleration of heart rate and fatigue of exercising muscles long before peak heart rate is achieved.

Oxidative Stress and Inflammation


Glutathione depletion and concomitant increase in oxidative and nitrosative stress pathways as well as mitochondrial dysfunctions play a role in the pathophysiology of diverse neuroimmune disorders, including depression, myalgic encephalomyelitis/chronic fatigue syndrome and Parkinson's disease, suggesting that depleted GSH is an integral part of these diseases.


Sources of continuous activation of O&NS and immune-inflammatory pathways in ME/CFS are chronic, intermittent and opportunistic infections, bacterial translocation, autoimmune responses, mitochondrial dysfunctions, activation of the Toll-Like Receptor...
Radical Cycle, and decreased antioxidant levels. Consequences of chronically activated O&NS and immune-inflammatory pathways in ME/CFS are brain disorders, including neuroinflammation and brain hypometabolism / hypoperfusion, toxic effects of nitric oxide and peroxynitrite, lipid peroxidation and oxidative damage to DNA, secondary autoimmune responses directed against disrupted lipid membrane components and proteins, mitochondrial dysfunctions with a disruption of energy metabolism (e.g. compromised ATP production) and dysfunctional intracellular signaling pathways.


Abnormalities in ME/CFS include elevated oxidative and nitrosative stress (O&NS), activation of immuno-inflammatory pathways, and mitochondrial dysfunctions with depleted levels of adenosine triphosphate (ATP) synthesis. There is also evidence that many patients with ME/CFS (up to around 60%) may suffer from autoimmune responses. This paper reviews the potential sources of the autoimmunity.


Peripheral blood mononuclear cells (PBMC) showed decreased levels of CoQ10 and ATP from CFS and FM subjects compared to controls. CFS/FM patients had significantly increased levels of lipid peroxidation, indicative of oxidative stress-induced damage. Mitochondrial citrate synthase activity, mitochondrial DNA content (mtDNA/gDNA ratio) and expression levels of PGC-1α and TFAM were significantly lower in FM patients than in controls.

Researchers measured the concentrations of IL-1a, 1b, 2, 4, 5, 6, 8, 10, 12 (p70), 13, 15, 17 and 23, IFN-γ, TNF-α and TNF-β in CFS patients vs. controls. Study results suggest that co-expression patterns in as few as 5 cytokines associated with Th17 function may hold promise as a tool for the diagnosis of post-infectious CFS.


The expression of TGF-β1 in PBMCs is significantly elevated in patients with CFS.


The findings show that ME/CFS is characterized by low-grade inflammation and activation of cell-mediated immunity and suggest that inflammatory mediators such as IL-1 and TNFα are factors in the disease.


Plasma peroxide concentrations were significantly higher in patients with ME/CFS than in normal controls. There was a trend towards significantly higher serum oxLDL antibodies in ME/CFS than in controls. Both biomarkers contributed significantly in discriminating between patients with ME/CFS and normal controls. Plasma peroxide and serum oxLDL antibody levels were both significantly related to one of the FF symptoms. The results show that ME/CFS is characterized by increased oxidative stress.

CFS is associated with lipid peroxidation and oxidative stress. High levels of malondialdehyde, positively correlated with total cholesterol and lower HDL cholesterol levels, might be indicative of proatherogenic events in female CFS patients.


Biomedical anomalies seen in adults with CFS/ME-increased oxidative stress and increased white blood cell apoptosis-can also be observed in children with clinically diagnosed CFS/ME compared with matched controls.


CFS patients have lower levels of Vitamin E (and therefore possible greater oxidative stress) during times of exacerbation than during times of remission.


CFS can affect the immune, neuroendocrine, autonomic, and neurologic systems. Abnormal biological findings among some patients have included aberrant ion transport and ion channel activity, cortisol deficiency, sympathetic nervous system hyperactivity, EEG spike waves, left ventricular dysfunction in the heart, low natural killer cell
cytotoxicity, and a shift from Th1 to Th2 cytokines. We propose that the kindling and oxidative stress theories provide a heuristic template for better understanding of this illness.


Previous reports suggest that CFS patients dying of heart failure do so at a significantly lower age than non-patients (59 years vs. 83 years). A number of abnormalities in CFS may be responsible for this, including: a) chronic low grade inflammation with extended production of nuclear factor kappa B and COX-2 and increased levels of tumour necrosis factor alpha; b) increased O&NS with increased peroxide levels, and phospholipid oxidation including oxidative damage to phosphatidylinositol; c) decreased levels of specific antioxidants, i.e. coenzyme Q10, zinc and dehydroepiandrosterone-sulphate; d) bacterial translocation as a result of leaky gut; e) decreased omega-3 polyunsaturated fatty acids (PUFAs), and increased omega-6 PUFA and saturated fatty acid levels; and f) the presence of viral and bacterial infections and psychological stressors.


Patients with CFS have lower serum alpha-tocopherol concentrations, suggesting the presence of oxidative stress in the illness.


Measures related to oxidative stress were studied in CFS patients.

The role of oxidative stress in CFS is an emerging focus of research due to evidence of its association with some pathological features of this syndrome. New data collectively support the presence of specific critical points in the muscle that are affected by free radicals.

Pall ML, Bedient SA. The NO/ONOO- cycle as the etiological mechanism of tinnitus. Int Tinnitus J. 2007;13(2):99-104. PMID: 18229788

Tinnitus may be related to abnormal levels of such cycle elements as N-methyl-D-aspartate activity; oxidative stress; nitric oxide; peroxynitrite; vanilloid activity; NF-kappaB activity; and intracellular calcium levels.


CFS patients showed oxidative stress evidence in terms of misshapen red blood cells and levels of malondialdehyde (MDA), methemoglobin (metHb) and 2,3-diphosphoglyceric acid (2,3-DPG).

Maes M, Mihaylova I, Leunis JC. Chronic fatigue syndrome is accompanied by an IgM-related immune response directed against neopitopes formed by oxidative or nitrosative damage to lipids and proteins. Neuro Endocrinol Lett. 2006 Oct;27(5):615-21. PMID: 17159817

CFS is characterized by an IgM-related immune response directed against disrupted lipid membrane components, by-products of lipid peroxidation, S-farnesyl-L-cysteine,
and NO-modified amino-acids, which are normally not detected by the immune system but due to oxidative and nitrosative damage have become immunogenic.


CFS is accompanied by a low serum zinc status and that the latter is related to signs of inflammation and defects in early T cell activation pathways. Since zinc is a strong antioxidant, the present results further support the findings that CFS is accompanied by increased oxidative stress.


CFS patients showed elevations in a variety of measures, including isoprostanes, of oxidative stress.


It is hypothesised that a nitric oxide (NO)-dependent reduction in inhibitory activity of the central nervous system and consequent central sensitisation accounts for chronic widespread pain in CFS patients.

Cell membrane oxidative stress may offer a common explanation for the observed MRS changes in the muscles and brain of CFS patients and this may have important therapeutic implications.


Elevated protein carbonyl levels confirm earlier reports suggesting that oxidative stress is associated with CFS and are consistent with a prediction of the elevated nitric oxide/peroxynitrite theory of chronic fatigue syndrome and related conditions.


Increased oxidative stress and decreased antioxidant defenses are related to the extent of symptomatology in CFS.


Patients with CFS have increased susceptibility of LDL and VLDL to copper-induced peroxidation, and this is related both to their lower levels of serum transferrin and to other unidentified pro-oxidising effects of CFS.

Evidence supporting the role of elevated nitric oxide/peroxynitrite in CFS and other disease states is summarized


Free radicals may be a problem in CFS.


The authors detected oxidative damage to DNA and lipids in muscle specimens of CFS patients as compared to age-matched controls, as well as increased activity of the antioxidant enzymes catalase, glutathione peroxidase, and transferase, and increases in total glutathione plasma levels.


CFS patients had increases in malondialdehyde, methaemoglobin, mean erythrocyte volume and 2,3-diphosphoglycerate compared with controls. Methaemoglobin was found to be the major component associated with variation in symptom expression, including fatigue, musculoskeletal symptoms, pain and sleep disturbance. Variation in levels of malondialdehyde and 2,3-diphosphoglycerate were associated with variations in cognitive symptoms and sleep disturbance. These data suggest that oxidative stress
due to excess free radical formation is a contributor to the pathology of CFS and was associated with symptom presentation.


The author proposes a hypothesis of CFS in which either viral or bacterial infection induces one or more cytokines, IL-1beta, IL-6, TNF-alpha and IFN-gamma. These induce nitric oxide synthase (iNOS), leading to increased nitric oxide levels. Nitric oxide, in turn, reacts with superoxide radical to generate the potent oxidant peroxynitrite. Multiple amplification and positive feedback mechanisms are proposed by which once peroxynitrite levels are elevated, they tend to be sustained at a high level.

Cytokines & Complement


The authors conducted repeat blood sampling for cytokine levels from healthy subjects and CFS patients during both postexercise and total sleep deprivation nights and assayed for protein levels in the blood samples, mRNA activity in peripheral blood lymphocytes (PBLs), and function in resting and stimulated PBLs. They found that these environmental manipulations did not produce clinically significant upregulation of proinflammatory cytokines.

Self-reported fatigue severity was significantly correlated with leptin levels in 60% of the participants with CFS and in 10% of healthy controls. A machine learning algorithm distinguished high from low fatigue days in the CFS group with 78.3% accuracy.


Common to both Gulf War Illness and CFS, IL-10 and IL-23 expression contributed in an illness and time-dependent manner, accompanied in male subjects by NK and Th1 markers IL-12, IL-15, IL-2 and IFNγ. In female GWI and CFS subjects IL-10 was again identified as a delineator but this time in the context of IL-17 and Th2 markers IL-4 and IL-5. Exercise response also differed between sexes: male GWI subjects presented characteristic cytokine signatures at rest but not at peak effort whereas the opposite was true for female subjects.


The authors found evidence to support a role for an increase in interleukin-10, an anti-inflammatory cytokine. Although the changes were small, they may contribute to the common complaint in CFS patients of disrupted sleep.


CFS patients have specific immune responses related to the presence of inflammatory processes consistent with the presence of a latent viral infection.

CFS patients display a large number of abnormal cytokines, with increases in some (LTalpha, IL-1alpha, IL-1beta, IL-4, IL-5, IL-6 and IL-12) and decreases in others (IL-8, IL-13 and IL-15). Some of these have the potential of serving as biomarkers for the disease.


This report describes a case of chronic fatigue syndrome (CFS) that followed a well-documented episode of acute Epstein-Barr virus (EBV) mononucleosis. After 2 years of chronic fatigue following the acute illness, measurements of complement split products were positive for complement activation and remained positive for 14 months, after which the patient then recovered from CFS.


The study results suggest an altered diurnal cortisol rhythm and IL-6 concentrations in CFS cases.

* Metzger K, Frémont M, Roelant C, De Meirleir K. Lower frequency of IL-17F sequence variant (His161Arg) in chronic fatigue syndrome patients. Biochem Biophys Res Commun. 2008 Nov 7;376(1):231-3. PMID: 18774769

T helper 17 (Th17) cells belong to a recently identified subset of T helper cells, with crucial regulatory function in inflammatory and autoimmune processes. Th17 cells are implicated in allergic inflammation, intestinal diseases, central nervous system inflammation, disorders that may all contribute to the pathophysiology of CFS. IL-17F is
one of the pro-inflammatory cytokines secreted by Th17 cells. The results suggest a role of Th17 cells in the pathogenesis of CFS.


The authors concluded that ongoing production of cytokines does not play a role in postinfective fatigue syndrome.


Although overlap in symptomatology between the general population and patients with CFS was observed, only CFS patients show a skewing of the cytokine balance towards an anti-inflammatory profile.

* Pall ML. Nitric oxide synthase partial uncoupling as a key switching mechanism for the NO/ONOO- cycle. Med Hypotheses. 2007;69(4):821-5. PMID: 17448611

The author discusses how NF-kappa-beta activity in CFS might be triggered.

There is a highly significant increase of TNF -857 TT and CT genotypes among CFS patients with respect to controls and a significant decrease of IFN gamma low producers (A/A) among patients with respect to controls.


Although cortisol responses to stress were normal, pro-inflammatory cytokine levels in CFS patients were significantly attenuated. TNF-alpha and IL-6 were especially problematic.


CFS patients showed significantly lower mRNA levels and transforming growth factor-beta1 (TGF-beta1) production. Cytokine dysregulation affects CFS pathogenesis. TGF-beta1 may aid treatment because it affects CFS inflammatory characteristics.


It is hypothesized that CFS has chronic inflammation at its basis.

The authors found evidence of a significant bias towards Th2- and Tc2-type immune responses in CFS compared to controls. In contrast, levels of IFN-gamma, IL-2 and IL-10-producing cells were similar in both study groups. There is an effector memory cell bias towards type 2 responsiveness in patients with CFS, as well as ongoing type 0 immune activation in unstimulated cultures of peripheral blood cells.


Prolonged endurance exercise induces a sequenced release of pro- and anti-inflammatory cytokines, and IL-6 plays a dominant role. Although many types of cells are capable of producing cytokines, the main source of the exercise-induced IL-6 production appears to be the exercising muscle.


An IL-6 provocation exacerbated the CFS patients' self-reported symptoms but did not reveal notable cognitive impairments between patients and controls during cytokine-induced acute influenza-like symptoms.


Patients with a parvovirus B19 infection had elevated IL-6, TNF-alpha, IL-1 beta, and IFN-gamma.

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In CFS patients, LPS-induced cytokine secretion in whole blood cultures showed a significant increase in IL-10 and a trend towards a decrease in IL-12 as compared with healthy controls. In general, the data are suggestive for a disturbed glucocorticoid regulation of IL-10 in CFS.

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In patients with CFS there is chronic lymphocyte overactivation with cytokine abnormalities that include perturbations in plasma levels of proinflammatory cytokines and decrease in the ratio of Type 1 to Type 2 cytokines produced by lymphocytes in vitro following mitogen stimulation.

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Neural-network classifiers were used to detect immunological differences in groups of chronic fatigue syndrome (CFS) patients that heretofore had not shown significant differences from controls. Of all the cytokines evaluated, the only one to be in the final model was interleukin-4 (IL-4).

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CFS is associated with increased IL-6 secretion which is manifested by chronically elevated plasma alpha2-macroglobulin concentrations.


CFS patients have a significant increase serum TNF-alpha in patients with CFS (P<0.0001) compared to non-CFS controls.


A significant increase in spontaneous, phytohemagglutinin- and lipopolysaccharide-induced IL-6 secretion by both lymphocytes and monocytes was observed in CFS patients during 'natural fatigue' as compared to during state. However, no such changes in IL-6 production were observed during fatigue experienced after exercise. These data suggest a role of IL-6 in natural symptomatology and perhaps in the pathogenesis of CFS. In addition, the data demonstrate that laboratory-induced fatigue (experimental fatigue) may not be a good model to study immunological changes in CFS; immunological parameters should be studied in a longitudinal manner during the natural course of the disease.


TGF-beta levels were significantly higher in CFS patients compared to patients with various diseases known to be associated with immunologic abnormalities and/or pathologic fatigue.

The levels of spontaneously (unstimulated) produced TNF-alpha by non-adherent lymphocytes and spontaneously produced IL-6 by both adherent monocytes and non-adherent lymphocytes were significantly increased in CFS patients. The abnormality of IL-6 was also observed at mRNA level. In contrast, spontaneously produced IL-10 by both adherent and non-adherent cells and by PHA-activated non-adherent cells were decreased.


At rest, serum transforming growth factor beta (TGF-beta) levels were elevated in CFS patients. Serum TGF-beta and cerebral blood flow abnormalities, detected by single-photon emission-computed tomographic scanning, were accentuated postexercise in the CFS group.


CFS patients had higher circulating levels of TNF-alpha and TNF-beta than controls.

Serum bioactive transforming growth factor beta (TGF-beta) levels were higher in patients with CFS. Lipopolysaccharide-stimulated release of interleukin 1 beta (IL-1 beta), IL-6, and tumor necrosis factor-alpha was increased; enhanced IL-6 release to phytohemagglutinin was also observed.


**Rnase L**


Proteolytic cleavage of the native RNase L enzyme is characteristic of the dysregulation of intracellular immunity in CFS.

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The role of RNase-L, known to be dysfunctional in CFS, is discussed.

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The 2-5A synthetase/RNase L pathway in CFS patients appears to be both up-regulated (i.e. increased levels of bioactive 2-5A synthetase and increased activity of the RNase L enzyme) and deregulated (elastase and calpain initiate 83 kDa RNase L proteolysis, generating two major fragments with molecular masses of 37 and 30 kDa, respectively). The deregulation of the 2-5A synthetase/RNase L pathway in CFS accompanies
decreased NK-function and deregulation of apoptotic pathways. Various components of the pathway appear to be related to performance during a graded exercise stress test.


CFS patients have disruptions in immune activity in the form of a dysregulation in the 2', 5'-oligoadenylate (2-5A)-dependent RNase L antiviral pathway in peripheral blood mononuclear cells (PBMC) of CFS. This is characterized by upregulated 2-5A synthetase and RNase L activities, as well as by the presence of a low molecular weight (LMW) 2-5A-binding protein of 37-kDa related to RNase L.


In the absence of acute infection or chronic inflammation, a high RNase L ratio could distinguish CFS patients from healthy volunteers.


A 37-kDa binding polypeptide accumulates in peripheral blood mononuclear cell (PBMC) extracts from CFS patients and is being considered as a potential diagnostic marker. The authors establish here that this low molecular weight 2-5A-binding polypeptide is a truncated form of the native 2-5A-dependent ribonuclease L (RNase L), generated by an increased proteolytic activity in CFS PBMC extracts.

Amongst a group of CFS patients, a group with elevated Rnase L had a lower peak V02 and duration than the normal group, but a higher performance score. The results suggest that both exercise testing and the RNase L biomarker have potential to aid in the diagnosis of CFS.


A 2',5'-oligoadenylate (2-5A)-dependent 37-kDa form of RNase L has been reported in extracts of peripheral blood mononuclear cells (PBMC) from individuals with chronic fatigue syndrome (CFS). The authors examined the biochemical relationship between the 80-kDa RNase L in healthy control PBMC and the 37-kDa RNase L in PBMC from individuals with CFS.


We investigated the levels of 2-5A synthetase, RNase L and RLI in patients with CFIDS and found a statistically significant decrease in RLI mRNA. The increased activation of RNase L may result in an increased cellular RNA turnover and subsequent inhibition of protein synthesis; thus resulting in general fatigue, myalgia muscle weakness and other symptomatologies shown in CFIDS patients.

The authors present evidence suggesting that the RNase L enzyme dysfunction in CFS is more complex than previously reported.


Mitochondria


ME/CFS is an neuro-immune disorder accompanied by chronic low-grade inflammation, increased levels of oxidative and nitrosative stress (O&NS), O&NS-mediated damage to fatty acids, DNA and proteins, autoimmune reactions directed against neoantigens and brain disorders. Mitochondrial dysfunctions have been found in ME/CFS, e.g. lowered ATP production, impaired oxidative phosphorylation and mitochondrial damage. This paper reviews the pathways that may explain mitochondrial dysfunctions in ME/CFS.

Morris G, Maes M. Myalgic encephalomyelitis/chronic fatigue syndrome and encephalomyelitis disseminata/multiple sclerosis show remarkable levels of similarity in phenomenology and neuroimmune characteristics. BMC Med. 2013 Sep 17;11:205. PMID: 24229326
Mitochondrial dysfunctions, including lowered levels of ATP, decreased phosphocreatine synthesis and impaired oxidative phosphorylation, are heavily involved in the pathophysiology of both MS and ME/CFS. The findings produced by neuroimaging techniques are quite similar in both illnesses and show decreased cerebral blood flow, atrophy, gray matter reduction, white matter hyperintensities, increased cerebral lactate and choline signaling and lowered acetyl-aspartate levels.

Meeus M, Nijs J, Hermans L, Goubert D, Calders P. The role of mitochondrial dysfunctions due to oxidative and nitrosative stress in the chronic pain or chronic fatigue syndromes and fibromyalgia patients: peripheral and central mechanisms as therapeutic targets? Expert Opin Ther Targets. 2013 Sep;17(9):1081-9. PMID: 23834645

The current evidence regarding oxidative and nitrosative stress and mitochondrial dysfunction in CFS and FM is presented in relation to chronic widespread pain.


The researchers looked at the possible association between mitochondrial biogenesis and oxidative stress in patients with CFS vs. patients with fibromyalgia (FM) and healthy controls. Compared to controls, both CFS and FM patients had decreased levels of Coenzyme Q10, decreased ATP levels, and increased levels of lipid peroxidation. Several measures (mitochondrial citrate synthase activity, mitochondrial DNA content and expression levels of peroxisome proliferator-activated receptor gamma-coactivator 1-alpha and transcription factor A, mitochondrial by immunoblotting) were significantly lower in FM patients than either CFS patients or controls.

Researchers found that all CFS patients tested had measurable mitochondrial dysfunction, correlating with the severity of the illness. The patients divide into two main groups differentiated by how cellular metabolism attempts to compensate for the dysfunction. The major immediate causes of the dysfunction are lack of essential substrates and partial blocking of the translocator protein sites in mitochondria.


CFS patients have very low levels of CoQ10, a mitochondrial nutrient that acts as a cofactor for ATP production and has antioxidant effects. This may be related to increased mortality from chronic heart failure in the disease.


The expression of a number of genes in CFS are altered, including ones related to mitochondrial function and oxidative balance, energy production, muscular trophism, and neuromuscular transmission.


Anticardiolipin antibodies (an anti-mitochondrial antibody found in specific other diseases) were detected in an extremely high percentage of CFS patients.

Mitochondrial dysfunction is strongly associated with CFS.


Compared to healthy controls and sufferers of anxiety disorder, CFS patients have significantly raised concentrations of ventricular lactate in their spinal fluid. The is potentially related to decreased cortical blood flow, secondary mitochondrial dysfunction and oxidative stress abnormalities.


Patients with CFS, chronic Ciguatera fish poisoning and Gulf War Illness were all more likely to demonstrate anticardiolipin antibody, associated with mitochondrial dysfunction.

**Natural Killer Cells**

This study’s results confirm decreases in immune function in CFS/ME patients, suggesting an increased susceptibility to viral and other infections. Furthermore, NK cytotoxic activity may be a suitable biomarker for diagnosing CFS/ME as it was consistently decreased during the course of the 12 months study.


CFS patients display abnormal natural killer cell function, and this has potential as a biomarker for CFS.


Relative to CFS patients with normal Natural Killer Cell Activity (NKCA), low-NKCA patients reported less vigor, more daytime dysfunction, and more cognitive impairment. In addition, low-NKCA patients performed less on objective measures of cognitive functioning relative to normal-NKCA patients.


Compared to patients with multiple sclerosis, patients with CFS had greater numbers of CD16(+)CD3(-) NK cells.

In healthy control subjects, NK activity was significantly increased after treatment with L-Arg, an NK function enhancer, for 24 h, whereas the same treatment failed to enhance NK activity in the CFS patients. Further study results demonstrate that the L-Arg-induced activation of NK activity is mediated by NO and that a possible dysfunction exists in the NO-mediated NK cell activation in CFS patients.


Low levels of natural killer cell activity have been reported in a significant percentage of cases in CFS.


Low NK activity some families may be a result of a genetically determined immunologic abnormality predisposing to CFS and cancer.


This data suggest a correlation between low levels of natural killer cell activity and severity of CFS.
Low natural killer cell function is associated with CFS.


Restoration of NK activity was correlated with recovery from CFS in patients.


Authors found increased percentages of CD56+, and especially CD56bright+ NK cells in post-viral fatigue patients patients. They also found significantly increased percentages of CD56+ high affinity interleukin-2 (IL-2) receptor (CD25)+ and CD56+ transferrin receptor (CD71+) subsets of cells, most of which also stained brightly for CD56. They also found an increased percentage of CD56+ CD3+ cells, many of which stained brightly for CD56, although there was no increase in the percentage of CD56- CD3+ T cells in these patients. There also was a very low percentage of CD56- CD25+ cells and a decreased percentage of CD56+ Fc gamma receptor (CD16)+ NK cells.


A majority of patients with CFS have low numbers of NKH1+T3- lymphocytes, a population that represents the great majority of NK cells in normal individuals. Patients with CFS consistently demonstrated low levels of killing. After activation of cytoltyic activity with recombinant interleukin 2, patients were able to display increased killing against K562 but most patients remained unable to lyse Epstein-Barr virus-infected B
cell targets. Additional cytotoxicity experiments were carried out utilizing anti-T3 monoclonal antibody to block killing by NKH1+T3+ cells. These experiments indicated that the NK cell that appears to be responsible for much of the functional activity remaining in patients with CFS belongs to the NKH1+T3+ subset, which under normal circumstances represents only approximately 20% of the NK cell population.

**Immune Abnormalities**


Thirty patients with CFS/ME and 25 non-fatigued controls were recruited for this study. Significant changes were observed in B-cell subsets, Tregs, CD4(+)CD73(+)CD39(+) T cells, cytotoxic activity, granzyme B, neutrophil antigens, TNF-α and IFN-γ in the CFS/ME patients in comparison with the non-fatigued controls. Alterations in B cells, Tregs, NK cells and neutrophils suggest significant impairments in immune regulation in CFS/ME.


CFS patients showed increased levels of T regulatory cells (CD25+/FOXP3+) CD4 T cells, and lower proliferative responses. Moreover, CD8 T cells from the CFS group showed significantly lower activation and frequency of effector memory cells. NK cells from CFS individuals displayed higher expression of NKp46 and CD69 but lower expression of CD25 in all NK subsets defined.

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Compared to healthy controls, CFS patients had greater numbers of naive B cells as a percentage of lymphocytes, greater numbers of naive B cells as a percentage of B cells, greater numbers of transitional B cells and reduced numbers of plasmablasts. The authors speculate whether this may suggest a subtle tendency to autoimmunity.

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There was a significant reduction in the expression levels of microRNA(miR)-21, in both the natural killer and CD8(+)T cells in the CFS/ME sufferers. Additionally, the expression of miR-17-5p, miR-10a, miR-103, miR-152, miR-146a, miR-106, miR-223 and miR-191 was significantly decreased in NK cells of CFS/ME patients in comparison to the non-fatigued controls.

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CFS is a heterogeneous disorder with a common set of symptoms. Slightly increased parameters of inflammation and pro-inflammatory cytokines such as interleukin (IL) 1, IL6 and tumour necrosis factor (TNF) α are likely present. Additionally, impaired natural killer cell function appears evident. Alterations in T cell numbers have been described by some and not others. There is some evidence of viral persistence and inadequate containment of viral replication. The ability of certain herpes viruses to impair the development of T cell memory may explain this viral persistence and the continuation of symptoms.

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CFS patients (n = 10) had significant decreases in neutrophil respiratory burst, NK cytotoxic activity and CD56(bright)CD16(-) NK phenotypes in comparison to healthy controls (n = 10). Hemorheological characteristic, aggregation, deformability, fibrinogen, lymphocyte numbers and CD56(dim)CD16(+) NK cells were similar between the two groups.


CFS patients display a number of immunological abnormalities also seen in cancer, including abnormalities of ribonuclease (RNase) L, hyperactivation of nuclear factor kappa beta (NF-kappa B), high oxidative stress and natural killer cell malfunction.


Immunological problems in CFS include an alteration in cytokine profile, a decreased function of natural killer (NK) cells, a presence of autoantibodies, and a reduced responses of T cells to mitogens and other specific antigens have been reported. The observed high level of pro-inflammatory cytokines may explain some of the manifestations such as fatigue and flu-like symptoms and influence NK activity. Abnormal activation of the T lymphocyte subsets and a decrease in antibody-dependent cell-mediated cytotoxicity have been described. An increased number of CD8+ cytotoxic T lymphocytes and CD38 and HLA-DR activation markers have been reported, and a decrease in CD11b expression associated with an increased expression of CD28+ T subsets has been observed.

This investigation measured the percentage of Th1-like and Th2-like memory cells using cell surface flow cytometry in 114 individuals with CFS. Results indicated that individuals who exhibited a more extreme shift towards a Th2 immune response also exhibited poorer sleep and high levels of basal salivary cortisol. The implications of these findings are discussed.


CFS patients have a variety of immunological abnormalities, including Rnase L-cleavage, protein kinase R and elastase activity.


CFS patients have B cell dysfunction with coordinated immune activation supporting persistent inflammation and antibody-mediated NK cell modulation of T cell activity. The CD19+ genes have potential as a biomarker.

The expression of the CD69 activation marker on T cells (CD3+, CD3+CD4+, and CD3+CD8+) and on NK cells (CD45+CD56+) was significantly lower in CFS patients than in healthy subjects, indicating immune abnormalities.


CFS patients had a significant reduction in the NK cell associated perforin levels and a reduced perforin level within the cytotoxic T cells.


CFS patients had higher numbers of apoptotic neutrophils, lower numbers of viable neutrophils, increased annexin V binding, and increased expression of the death receptor, tumour necrosis factor receptor-I, on their neutrophils than did the 34 healthy controls. Patients with CFS also had raised concentrations of active TGFbeta1.


The objective of this study was to assess the nature and extent of abnormalities in lymphocyte cell surface markers and NK cell activity in patients with CFS while controlling for genetic factors. In a twin study, significantly greater variability was noted in twins discordant for CFS than in the concordant healthy twins for 20 of 48 variables examined.

Chronic fatigue syndrome (CFS) patients show evidence of immune activation, as demonstrated by increased numbers of activated T lymphocytes, including cytotoxic T cells, as well as elevated levels of circulating cytokines. Nevertheless, immune cell function of CFS patients is poor, with low natural killer cell cytotoxicity (NKCC), poor lymphocyte response to mitogens in culture, and frequent immunoglobulin deficiencies, most often IgG1 and IgG3. Immune dysfunction in CFS, with predominance of so-called T-helper type 2 and proinflammatory cytokines, can be episodic and associated with either cause or effect of the physiological and psychological function derangement and/or activation of latent viruses or other pathogens.


CD4 T cells from CFS patients produced less interferon-gamma than did cells from controls. With CD4 T cells from CFS patients (compared with cells from controls), a 10- to 20-fold lower DEX concentration was needed to achieve 50% inhibition of interleukin-4 production and proliferation, indicating an increased sensitivity to DEX in CFS patients. A differential sensitivity of cytokines or CD4 T cell subsets to glucocorticoids might explain an altered immunologic function in CFS patients.


Increased apoptotic cell population in peripheral blood lymphocytes was observed in CFS individuals. This was accompanied by an abnormal cell arrest in the S phase and the G2/M boundary of the cell cycle and by enhanced PKR mRNA and protein levels as compared to healthy controls. Protein kinase RNA-mediated apoptosis in CFS individuals may contribute to the pathogenesis and the fatigue symptomatology associated with CFS.

Immune responses of CFS patients compared to normal people were more pronounced when they were grouped by type of disease onset (gradual or sudden) or by how they were feeling on the day of the test.


The authors examined blood of CFS patients. Whilst no significant differences were found in the absolute numbers of circulating total T cells (CD3+) and of total helper/inducer (CD4+) or suppressor/cytotoxic (CD8+) T cells, an evident reduction in CD3-/CD16+ and CD57+/CD56+ NK lymphocytes along with an expansion of the CD8+/CD56+ and CD16-/CD56+ NK subsets, were found in the CFS group. In addition, CD56+ NK cells from CFS subjects were found to express an increased amount of cell adhesion molecules (CD11b, CD11c, CD54) and activation antigens (CD38). Both the percentage and absolute numbers of CD4+ T cells bearing the CD45RA antigen appeared significantly reduced in CFS patients, and CD4+ T lymphocytes from CFS subjects displayed an increased expression of the intercellular adhesion molecule-1 (ICAM-1/CD54). Finally, the total numbers of circulating (CD19+) B lymphocytes, were significantly higher in CFS cases than in controls, and in 11 out of 30 CFS patients the increase in circulating B cells was sustained by the expansion of the CD5+/CD19+ subset of B lymphocytes.


Immunologic studies have demonstrated activated CD8+ cells and reduced function of natural killer cells suggesting a host response to an infection that has led to persistent immune disorders. Some of the symptoms of CFS may be due to cytokines produced by this hyperactive immune response to a virus that is still present in the host or that has been eliminate but leaves abnormal immunologic sequelae.

Compared with those of healthy individuals, CFS patients' CD8+ T cells expressed reduced levels of CD11b and expressed the activation markers CD38 and HLA-DR at elevated levels. In many of the individuals in whom expression of CD11b was reduced the expression of CD28 was increased. These findings indicate expansion of a population of activated CD8+ cytotoxic T lymphocytes. A marked decrease in NK cell activity was found in almost all patients with CFS.


Compared to controls, in CFS patients the percentage of CD4 T cells and CD4,CD45RA, or naive T cells, was reduced. The CD4,CD45RO, or memory T-cell, subset was numerically normal but expressed increased levels of adhesion markers (CD29, CD54, and CD58). CFS patient lymphocytes showed reduced proliferative responses to phytohemagglutinin, concanavalin A, and staphylococcal enterotoxin B.


Patients with CFS demonstrated impaired lymphocyte responses to phytohaemagglutinin (PHA) stimulation, and reduced or absent delayed-type hypersensitivity (DTH) skin responses.

Reduced CD8 suppressor cell population and increased activation markers (CD38, HLA-DR) on CD8 cells were found in CFS sufferers.


Natural killer cells as defined by CD16, CD56 and CD57 antigens were significantly reduced in a group of CFS patients. A significant increase in the proportions of CD4+ ICAM 1+ T cells was observed in CFS. Monocytes from CFS displayed increased density (as determined by mean fluorescence channel numbers) of intercellular adhesion molecule 1 (ICAM-1) and lymphocyte function associated antigen 1 (LFA-1), but showed decreased enhancing response to recombinant interferon-gamma in vitro. The lymphocyte DNA synthesis in response to phytohaemoglobin (PHA), Concanavalin A (Con A) and pokeweed mitogen (PWM) was normal but the response to soluble antigens was significantly reduced. In vivo specific antibody response to pneumococcus vaccine was depressed in CFS. Forty percent of patients showed titres of anti-human herpes virus 6 (anti-HHV-6) antibody higher than that in the controls (greater than or equal to 1/80).


CFS patients immunological abnormalities are profiled. The most consistent was low natural killer (NK) cell cytotoxicity. The number of NK cells, as defined by reactivity with monoclonal antibody NKH.1 (CD56), was elevated, but the killing of K562 tumor cells per CD56 cell was significantly diminished. Lymphoproliferative responses after stimulation with phytohemagglutinin and pokeweed mitogen were decreased in most patients, as was the production of gamma interferon following mitogen stimulation. Lymphocyte phenotypic marker analysis of peripheral blood lymphocytes showed that there were significant differences between patients with CFS and controls. There was an increase in the percentage of suppressor-cytotoxic T lymphocytes, CD8, and a
proportionally larger increase in the number of CD8 cells expressing the class II activation marker. Most patients had an elevated number of CD2 cells which expressed the activation marker CDw26. The numbers of CD4 cells and the helper subset of CD4+CD29+ cells in patients with CFS were not different from those in controls. There was, however, a significant decrease in the suppressor inducer subset of CD4+CD45RA+ cells. The number of B cells, CD20 and CD21, were elevated, as were the numbers of a subset of B cells which coexpressed CD20 and CD5.


In patients with CFS, a significant reduction was found in the absolute number of peripheral blood lymphocytes in the total T-cell (CD2), the helper/inducer T-cell (CD4) and the suppressor/cytotoxic T-cell (CD8) subsets. A significant reduction also was found in T-cell function. Reduced immunoglobulin (Ig) levels were common (56% of patients), with the levels of serum IgG3- and IgG1-subclasses particularly affected.

Autoimmune Issues


The incidence of positive autoimmune activity against serotonin was significantly higher in ME/CFS than in patients with chronic fatigue or controls. ME/CFS patients with 5-HT autoimmune activity displayed higher TNFα, IL-1 and neopterin and increased IgA responses against LPS of commensal bacteria than those without 5-HT autoimmune activity. Anti-5-HT antibody positivity was significantly associated with increased scores on hyperalgesia, fatigue, neurocognitive and autonomic symptoms, sadness and a flu-like malaise.

Herpesviruses
This study focused on identifying risk factors for the acquisition of CFS in adolescents following Infectious Mononucleosis. A number of variables were predictors of post-infectious CFS at 6 months; however, when autonomic symptoms were used as a control variable, only days spent in bed since mono was a significant predictor.

The authors analyzed the EBV-specific memory B- and T-cell response in patients with CFS. While they observed no difference in viral capsid antigen (VCA)-IgG antibodies, EBV nuclear antigen (EBNA)-IgG titers were low or absent in 10% of CFS patients. When analyzing the EBV-specific memory B-cell reservoir in vitro a diminished or absent number of EBNA-1- and VCA-antibody secreting cells was found in up to 76% of patients. They proposed a deficient EBV-specific B- and T-cell memory response in CFS patients and suggest an impaired ability to control early steps of EBV reactivation.

Researchers in Taiwan identified more than 9,000 patients with herpes zoster (HZ) infection and 36,000 patients without herpes zoster infections. The incidence rate of CFS was higher in the HZ cohort than in the non-HZ cohort.

Oakes B, Hoagland-Henefield M, Komaroff AL, Erickson JL, Huber BT. Human endogenous retrovirus-k18 superantigen expression and human herpesvirus-6 and

The authors fail to demonstrate a difference in HERV-K18 env transcripts, HHV-6 viral copy number, and HHV-7 viral copy number between CFS patients and healthy controls.


No statistically significant differences in antibody levels or frequency of HHV-6A or HHV-6B infection were detected between the controls and CFS patients.


Active viral infection with HHV6, HHV7 and/or parvovirus B19 was found in 64.8% of patients and in 13.3% of practically healthy persons. Increase in peripheral blood leukocyte DNA HHV-6 load as well as in proinflammatory cytokines' levels was detected in patients during active viral infection.


There is prolonged elevated antibody level against the encoded proteins EBV dUTPase and EBV DNA polymerase in a subset of CFS patients.
Shapiro JS. Does varicella-zoster virus infection of the peripheral ganglia cause Chronic Fatigue Syndrome? Med Hypotheses. 2009 Nov;73(5):728-34. PMID: 19520522

This article posits that infection of the peripheral ganglia causes at least some cases of Chronic Fatigue Syndrome (CFS), with a neurotropic herpesvirus, particularly varicella-zoster virus (VZV), as the most likely cause of the infection.


Immunooassays that use early antigen recombinant HCMV CM(2) and p52 are five times more sensitive than HCMV ELISA assay using viral lysate, and are specific in the detection and differentiation of active human cytomegalovirus infection in a subset of patients with CFS.


EBV viremia in CFS is associated with cell-mediated immune activation and increased tryptophan degradation.


The amount of HHV-6 and HHV-7 reactivation has potential as a biomarker for CFS.

HHV-6 enhances the progression of simian immunodeficiency virus in monkeys.


Reactivation of HHV6 and HHV7 in combination is frequent in CFS patients.


HHV6 is common in CFS and may serve to trigger and perpetuate the disease.


HHV-6 established latency in the macrophage, kept a fairly stable intermediate stage between latency and reactivation, and the viral reactivation was induced by two or more factors. HHV-6 is reactivated during work-induced fatigue, and HHV-6 reactivation can be an objective biomarker for fatigue.

* Lerner AM, Beqaj SH, Deeter RG, Fitzgerald JT. IgM serum antibodies to Epstein-Barr virus are uniquely present in a subset of patients with the chronic fatigue syndrome. In Vivo. 2004 Mar-Apr;18(2):101-6. PMID: 15113035

Serum antibody to EBV VCA IgM may be a specific diagnostic test for a subset of CFS patients.
Lerner AM, Beqaj SH, Deeter RG, Fitzgerald JT. IgM serum antibodies to human cytomegalovirus nonstructural gene products p52 and CM2(UL44 and UL57) are uniquely present in a subset of patients with chronic fatigue syndrome. In Vivo. 2002 May-Jun;16(3):153-9. PMID: 12182109

The study suggests a relationship between CFS and human cytomegalovirus.


Identical twins discordant for CFS did not show differences on PCR assays for viral DNA for HHV-6, HHV-7, HHV-8, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, varicella zoster virus, JC virus, BK virus, or parvovirus B19.


Persistent low-dose stimulation by HHV-6 may favor imbalanced immune response rather than overt immune deficiency.


The authors found no evidence that active or latent infection with HHV-6A, HHV-6B, HHV-7, or any combination these 3 HHVs is associated with chronic fatigue syndrome. [PubMed - indexed for MEDLINE]

In both MS and CFS patients, the authors found increased levels of HHV-6 antibody and HHV-6 DNA. A decrease in cellular immune responses was also detected in CFS patients.


Serological analyses of serum anti-EBV and anti-HHV6 antibody titers showed no significant differences between the CFS and control patients. [PubMed - indexed for MEDLINE]


The study showed a high proportion of CFS patients infected with HHV-6 but with low viral load.


Differences in the seroprevalence or GMTs of antibodies to 13 viruses were not consistently found in those with chronic fatigue compared with control subjects, or in any subsets of patients including those with CFS, an acute onset of illness, or a documented fever.

EBV titers were higher among CFS patients and were associated with being more symptomatic.


More CFS patients than controls had elevated levels of HHV-6 EA-specific IgM, perhaps indicating active replication of HHV-6 in CFS.


The authors failed to demonstrate a role for reactivation of EBV in CFS.


HHV-7 was present in over 80% of CFS patients and healthy controls, while the prevalence of HHV-6 variant A increased significantly in CFS cases (22 versus 4%; P = 0.05).

*

The results suggest that CFS patients may have reactivations of EBV, HHV-6 and HHV-7.


In the majority of cases of CFS, elevation of viral antibody titers does not seem to be due to a nonspecific polyclonal immune response.


The results suggest active replication of HHV-6 in patients with CFS.


Antibodies against EBV DNAP may be a useful marker in delineating a subset of patients with severe fatiguing illness.

Epstein-Barr virus-DNA was detected more frequently in male CFS patients, 5/9 (55.6%), than controls, 0/6 (0%), but there was no difference in frequency in female patients, 4/32 (12.5%), than control subjects, 1/29 (3.4%). Cytomegalovirus-DNA was detected infrequently in patients and controls, 13% versus 22% respectively. The presence of EBV-DNA did not correlate with antibody titers nor with the complaint of sore throat.


Herpesvirus can directly target and kill NK cells, a potential strategy to suppress the natural anti-viral immunity of the host.


Results of the study suggest that a relationship exists between CFS and EBV.


CFS patients who displayed elevated titres of antibodies to Early Antigens of EBV did not differ clinically from those displaying titres in the control range. Four of nine patients who had increased antibodies to Early Antigens also had evidence of active enterovirus infection.

In a group of CFS patients, IgG antibody titers to EB virus viral capsid antigen were more elevated in the CFS patient group compared to that of the control, and the mean number of NK cells was lower.


HHV-6 is reported to be reactivated in CFS.


CFS is associated with reactivated HHV-6 and Epstein Barr Virus.


The study analyzed spontaneous transformation rates of peripheral blood lymphocytes, EBV viral genome characteristics as determined by DNA restriction fragment polymorphisms, and antibody production by Western blot analysis. Thirty percent of CFS patients versus 8% of control subjects underwent spontaneous transformation in the two studies. Western blot studies suggested that ill subjects made antibodies to lytic proteins more frequently than did healthy control subjects.

A patient with ME and HHV6 is profiled.


No evidence of ongoing EBV infection with either transforming or nontransforming strains was demonstrated in this population of CFS patients.


Antibodies acting against EBV-specific DNase and DNA polymerase, which are expressed only during virus replication, were assayed. Three of the six patients with elevated anti-EBV enzyme antibody levels developed fatal lymphomas.


Human B-lymphotropic virus (HBLV), also known as human herpesvirus-6 (HHV-6), is elevated in AIDS patients and patients with chronic fatigue syndrome.
Enteroviruses


Three representative patients with different manifestations of acute enterovirus infections progressed to have chronic symptoms of ME/CFS. Persistent viral infection was demonstrated in the antrum years later. Chronic enterovirus infection in an immunocompetent host may be an example of a stalemate between attenuated, intracellular viruses and an ineffective immune response.

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Enterovirus VP1, RNA and non-cytopathic viruses were detected in the stomach biopsy specimens of CFS patients with chronic abdominal complaints.

* 


Enteroviruses may play a role in CFS.

* 


More CFS patients than controls had evidence of enterovirus on a PCR assay.

*

The research results suggest there is persistence of enterovirus infection in some CFS patients and indicate the presence of distinct novel enterovirus sequences.


Enteroviral specific sequences were detected in 36 of 88 serum samples from chronic fatigue patients and 3 of 126 healthy individuals.

Bowles NE, Bayston TA, Zhang HY, Doyle D, Lane RJ, Cunningham L, Archard LC. Persistence of enterovirus RNA in muscle biopsy samples suggests that some cases of chronic fatigue syndrome result from a previous, inflammatory viral myopathy. J Med. 1993;24(2-3):145-60. PMID: 8409778

CFS may be a sequela of a previous inflammatory viral myopathy.


An increase in the number and size of muscle mitochondria was found in 70% of postviral fatigue cases, suggesting an abnormality in metabolic function. Evidence of hypothalamic dysfunction was present, particularly involving 5-hydroxytryptamine metabolism.

A highly significant number of muscle biopsies from CFS patients were positive for enteroviral sequences.


Persistent enteroviral infection of muscle may occur in some patients with postviral fatigue syndrome.

Cunningham L, Bowles NE, Lane RJ, Dubowitz V, Archard LC. Persistence of enteroviral RNA in chronic fatigue syndrome is associated with the abnormal production of equal amounts of positive and negative strands of enteroviral RNA. J Gen Virol. 1990 Jun;71 ( Pt 6):1399-402. PMID: 2161907

This study suggests that enterovirus persistence in muscle is due to a defect in control of viral RNA synthesis.

Gut


These results showed that intestinal microbiota was altered in a group of ME/CFS patients from Belgium and Norway.

CFS patients have a variety of gut problems, including mucosal barrier dysfunction (“leaky gut”), an altered mucosal immune system, and presence of various microorganisms related to disease.


CFS patients have abnormal levels of Gram positive facultative anaerobic D-lactic bacteria in their intestinal systems. This has the potential of explaining some of the symptoms and of serving as a biomarker.


CFS patients tend to have a variety of pathogenic viruses colonizing their gastrointestinal tracts; these include parvovirus B19, HHV6, HHV7 and EBV.


CFS patients have high intestinal permeability, and treatment of this can result in improvements in their condition.
Maes M, Mihaylova I, Leunis JC. Increased serum IgA and IgM against LPS of enterobacteria in chronic fatigue syndrome (CFS): indication for the involvement of gram-negative enterobacteria in the etiology of CFS and for the presence of an increased gut-intestinal permeability. J Affect Disord. 2007 Apr;99(1-3):237-40. PMID: 17007934

Prevalences and median values for serum IgA against the LPS of enterobacteria are significantly greater in patients with CFS than in normal volunteers and patients with partial CFS. Serum IgA levels were significantly correlated to the severity of illness.

* Maes M, Coucke F, Leunis JC. Normalization of the increased translocation of endotoxin from gram negative enterobacteria (leaky gut) is accompanied by a remission of chronic fatigue syndrome. Neuro Endocrinol Lett. 2007 Dec;28(6):739-44. PMID: 18063928

CFS is accompanied by an increased translocation of endotoxins from gram-negative enterobacteria through the gut wall, as demonstrated by increased prevalences and median values for serum IgM and IgA against the endotoxins of gram-negative enterobacteria. This condition can also be described as increased gut permeability or leaky gut. Here, a patient was treated with specific antibiotics and diet to treat gut permeability, as well as intravenous immunoglobins, and went into remissions.

**Candida**

Evengård B, Gräns H, Wahlund E, Nord CE. Increased number of Candida albicans in the faecal microflora of chronic fatigue syndrome patients during the acute phase of illness. Scand J Gastroenterol. 2007 Dec;42(12):1514-5. PMID: 17886123

CFS patients have an overgrowth of candida in the intestines.

It is proposed that chronic intestinal candidiasis may be an agent which leads to immune depression in many CFS patients and therefore that it could be a causal factor in CFS.

**Mycoplasma**

Endresen GK. Mycoplasma blood infection in chronic fatigue and fibromyalgia syndromes. Rheumatol Int. 2003 Sep;23(5):211-5. PMID: 12879275

Mycoplasma blood infection has been detected in about 50% of patients with CFS and/or FMS. Most patients with CFS/FMS who have mycoplasma infection appear to recover and reach their pre-illness state after long-term antibiotic therapy with doxycycline.


Compared to American CFS patients (M. pneumoniae>M. hominis>M. penetrans), a slightly different pattern of mycoplasmal infections was found in European CFS patients (M. hominis>M. pneumoniae, M. fermentansz.Gt;M. penetrans).

* Nasralla M, Haier J, Nicolson GL. Multiple mycoplasmal infections detected in blood of patients with chronic fatigue syndrome and/or fibromyalgia syndrome. Eur J Clin Microbiol Infect Dis. 1999 Dec;18(12):859-65. PMID:10691196

More than 60% of patients with CFS were found to have mycoplasmal blood infections, such as Mycoplasma fermentans infection. More than half the patients had multiple infections.

A polymerase chain reaction (PCR)-based assay was used to detect Mycoplasma genus and M. fermentans genomes in peripheral blood mononuclear cells (PBMC) of CFS patients. Mycoplasma genus and M. ferments were found in 52% and 24% of CFS samples, vs. 14% and 8% of control subjects (P<0.0001).


The percentage of Mycoplasma infection was found to be 52% in CFS patients and 15% in healthy individuals. Mycoplasma fermentans, M. hominis and M. penetrans were detected in 32%, 9% and 6% of the CFS patients, compared to 8%, 3% and 2% of the healthy control subjects, respectively.

Parvovirus B19


Eighty-three CFS patients (41.5 %) as compared with fourteen (7%) normal blood donors tested positive for anti-B19 NS1 IgG. Of these 83 patients, 61 complained of chronic joint pain, while 22 did not. Parvovirus B19 DNA was detected in serum of 11 CFS patients and none of the controls by Taqman real-time PCR. Positivity for anti-B19 NS1 IgG was associated with higher expression levels of the human CFS-associated genes NHLH1 and GABPA.

Some patients who get sick after a parvovirus B19 infection do not show antibodies.


In a study of CFS patients, six genes were found to be differentially expressed with roles in the cytoskeleton (SKIP, MACF1, SPAG7, FLOT1), integrin signalling (FLOT1, RASSF5), HLA class III (c6orf48), and tumour suppression (RASSF5). These results have implications not only for B19 but also for other persistent viruses.


The authors report the case of a young woman with recurrent fever and a syndrome indistinguishable from chronic fatigue syndrome. After extensive investigation, they found persistent parvovirus B19 viremia, which was detectable by polymerase chain reaction (PCR) despite the presence of IgM and IgG antibodies to parvovirus B19. The patient's fever resolved with the administration of intravenous immunoglobulin.

**Coxiella Burnetii**

Although in the researchers’ sample fatigue symptoms were common among Q fever patients, they found no increased prevalence of CFS in contrast to several other studies.

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Coxiella burnetii infection may be involved in the evolution of CFS.

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Four CFS patients (the CFS group) and 54 controls [the post-Q fever fatigue syndrome (QFS) group] positive for C. burnetii were treated mainly with minocycline or doxycycline (100 mg/day) for 3 months. After treatment, all 58 patients tested negative for C. burnetii infection. In the CFS group, health did not improve.

*  


The authors looked at a group of people who were infected with Q fever in 1989, finding CFS in 42.3% of cases and 26% of controls.

**Borna Disease**

In Japanese patients with CFS, the prevalence of Borna disease virus infection was 34% (30/89) and 12% (7/57) by immunoblotting and PCR analysis, respectively. Furthermore, anti-BDV antibodies and BDV RNA were detected in a family cluster with CFS. These results suggested that this virus contributes to or initiates CFS, although the single etiologic role of BDV is unlikely.


Laboratory analysis suggests that there is a prevalence of 32% of Borna disease virus in Japanese CFS patients.

**Stealth Virus**

Martin WJ. Genetic instability and fragmentation of a stealth viral genome. Pathobiology. 1996;64(1):9-17. PMID: 8856790

Partial sequencing was performed on cloned DNA obtained from cultures of a stealth virus isolated from a patient with the chronic fatigue syndrome. The results extend earlier findings showing regions of homology to cytomegalovirus (CMV).


The clinical histories and brain biopsy findings of 3 patients with severe stealth virus encephalopathy are reviewed.

*

The findings implicate an African green monkey as the probable source of the “stealth” virus isolated from this CFS patient.

* 


A simian cytomegalovirus-related stealth virus, isolated from a patient with the chronic fatigue syndrome, induced an acute neurological illness when inoculated into cats.

* 


The authors describe a novel type of CMV-related "stealth" virus that is able to establish a clinically persistent human infection.

Other Infections


A peptide from Chlamydia pneumoniae human heat shock protein was detected in 24% of ME samples compared to less than 1% of non-ME samples (taken from blood donor, multiple sclerosis patients and systemic lupus erythematosus patients).

*

A high prevalence of chronic fatigue has previously been reported following giardiasis after a large waterborne outbreak in Bergen, Norway in 2004. This study shows that Giardia duodenalis may induce CFS persisting as long as five years after the infection.

*  


A Giardia outbreak was associated with development of post-infectious functional gastrointestinal disorders (PI-FGID) and chronic fatigue syndrome (PI-CFS). Five years later, researchers found significantly higher CD8 T-cell levels in PI-FGID, and significantly lower NK-cell levels in PI-CFS patients. Severity of abdominal and fatigue symptoms correlated negatively with NK-cell levels.

*  


After a giardiasis enteritis outbreak, at least 5% of those affected developed clinical characteristics and functional impairment comparable to previously described post-infectious fatigue syndrome.

*  

The authors report seven cases of adrenal histoplasmosis in immunocompetent patients. All patients presented as chronic fatigue syndrome. The onset of symptoms ranged from one to three months. A cure was accomplished in 6 out of 7 cases.


Increased IgA responses to commensal bacteria in ME/CFS are associated with inflammation and cell-mediated immunity activation, which are associated with symptom severity. It is concluded that increased translocation of commensal bacteria may be responsible for the disease activity in some ME/CFS patients.


The authors propose that CFS is caused by a circovirus.


The major hypothesis of the pathogenesis of CFS is that infectious agents such as viruses, may trigger and lead to chronic activation of the immune system with abnormal regulation of cytokine production. The authors summarize the recent progressive literature of virus, rickettsia, and mycoplasma implicated in the pathogenesis of CFS.

* Hickie I, Davenport T, Wakefield D, Vollmer-Conna U, Cameron B, Vernon SD, Reeves WC, Lloyd A; Dubbo Infection Outcomes Study Group. Post-infective and chronic
fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. BMJ. 2006 Sep 16;333(7568):575. PMID: 16950834

A significant minority of people with variety of infections (including Epstein-Barr virus, Coxiella burnetii or Ross River virus) remain ill with a post-infection syndrome qualifying as CFS over the long term.

* Jones JF, Kulkarni PS, Butera ST, Reeves WC. GB virus-C--a virus without a disease: we cannot give it chronic fatigue syndrome. BMC Infect Dis. 2005 Sep 28;5:78. PMID: 16191201

GB virus-C (GBV-C) virus is a flavivirus with cell tropism and host defense induction qualities compatible with a role in producing the syndrome. The authors found no evidence that active or past infection with GBV is associated with CFS.


Some CFS patients may be associated with EBV or C. burnetii infection. The up-regulation of 2-5AS activities suggests immunological dysfunctions with some virus infections in the CFS patients.


A large subset of CFS patients show evidence of bacterial and/or viral infection(s), and these infections may contribute to the severity of signs and symptoms found in these patients.

Chlamydia pneumoniae is discussed as a contributor to CFS.


**Endocrine System**


Pre-treatment salivary cortisol levels were significantly lower in CFS patients than in healthy controls. The hypocortisolism found in CFS patients was significantly correlated to the amount of sleep.

Meta-analyses revealed an attenuation of the cortisol-awakening response increase within CFS compared to controls but no statistically significant differences between groups for other markers.


A dynamic systems model was used to generate parameters describing a phenotype of Hypothalamic-Pituitary-Adrenal (HPA) behavior in a sample of 36 patients with chronic fatigue syndrome (CFS) and/or fibromyalgia (FM) and 36 case-matched healthy controls.


The weight of current evidence supports the presence of the following factors related to hypothalamic-pituitary-adrenal (HPA) axis dysfunction in patients with chronic fatigue syndrome (CFS): mild hypocortisolism; attenuated diurnal variation of cortisol; enhanced negative feedback to the HPA axis; and blunted HPA axis responsiveness.


A review of evidence about a role of hypothalamic-pituitary-adrenal axis in the pathogenesis of CFS.

CFS patients with a disease duration of ≤ 5 years had significantly higher levels of alpha-MSH in their peripheral blood, and this has potential as a biomarker.


Among CFS patients, plasma antidiuretic hormone was significantly decreased and serum osmolality and plasma renin activity were significantly increased (p < or = 0.001). Serum concentration of aldosterone, cortisol, NT-proBNP and sex hormones were not significantly different in the two groups.


In an experimental model, CFS was associated with abnormalities in adrenal function.


Women with CFS alone, but not CFS plus fibromyalgia, showed upregulated plasma prolactin responses compared with controls. There were no differences among groups of men.

CFS patients’ presenting symptoms are not early features of “significant endocrine pathology.”

* Rybakina EG, Shanin SN, Fomicheva EE, Korneva EA. Cellular and molecular mechanisms of interaction between the neuroendocrine and immune systems under chronic fatigue syndrome in experiment. Ross Fiziol Zh Im I M Sechenova. 2009 Dec;95(12):1324-35. PMID: 20141043

In an experimental model, CFS was associated with alterations in HPA axis activity. This likely results in changes in both the activity of immune-competent cells and membranes of brain cells.


CFS patients display disordered HPA axis and adrenal functioning.


The authors hypothesize that that HPA axis hypofunction in CFS, conceptualized within a system-biological perspective, primarily reflects a fundamental and persistent dysregulation of the neurobiological stress system.

A case study of involving membranous dysmenorrhea suggests a hormonal dysfunction as a possible cause of CFS.

* Papadopoulos A, Ebrecht M, Roberts AD, Poon L, Rohleder N, Cleare AJ. Glucocorticoid receptor mediated negative feedback in chronic fatigue syndrome using the low dose (0.5 mg) dexamethasone suppression test. J Affect Disord. 2009 Jan;112 (1-3):289-94. PMID: 18573538

A low-dose dexamethasone (0.5 mg) suppression test in CFS patients showed no differences with controls except in the patients who also were depressed.


This work investigates the significance of changes in association patterns linking indicators of neuroendocrine and immune activity in patients with CFS. Findings align with known mechanisms of chronic inflammation and support possible immune-mediated loss of thyroid function in CFS exacerbated by blunted HPA axis responsiveness.


CFS patients show deviations from expected patterns of cortisol, and this appears to be associated with fatigue and pain.

* Nater UM, Maloney E, Boneva RS, Gurbaxani BM, Lin JM, Jones JF, Reeves WC, Heim C. Attenuated morning salivary cortisol concentrations in a population-based study of

CFS was associated with an attenuated morning cortisol response, but the effect was limited to women.


CFS is globally associated with reduced cortisol responses in the combined low-dose Dex/CRF test, but this effect is only clearly present in CFS patients without a history of early-life stress.


Hypofunction of the hypothalamic-pituitary-adrenal (HPA) axis is a problem in a proportion of the patients with CFS, possibly as a consequence of other factors.


There is enhanced sensitivity of the HPA axis to negative feedback in CFS.

The CFS group showed significantly lower mRNA expression levels of ERbeta wt compared with the healthy control group. This is consistent with an immune-mediated pathogenesis of CFS. A possible connection between oestrogen, oestrogen receptors and CFS should be evaluated further.


The role of the hypothalamo-pituitary-adrenal (HPA) axis in CFS is discussed.

* Maloney EM, Gurbaxani BM, Jones JF, de Souza Coelho L, Pennachin C, Goertzel BN. Chronic fatigue syndrome and high allostatic load. Pharmacogenomics. 2006 Apr;7(3):467-73. PMID: 16610956

CFS was associated with a high level of allostatic load. The three allostatic load components that best discriminated cases from controls were waist:hip ratio, aldosterone and urinary cortisol.


CFS is accompanied by lowered levels of DHEAS, and this may play a role in the immune (defect in the early activation of T cells) and the inflammatory pathophysiology of CFS.

Adolescents with CFS have subtle alterations in adrenal function suggesting a reduction in central stimulation of the adrenal glands


Patients with CFS demonstrated subtle alterations in HPA axis activity characterized by reduced ACTH over a full circadian cycle and reduced levels during the usual morning physiological peak ACTH secretion. This provides evidence of subtle dysregulation of the HPA axis in CFS.


CFS patients, fibromyalgia patients and normal controls all look different in their basal circadian architecture of HPA axis hormones.

* Cevik R, Gur A, Acar S, Nas K, Sarac AJ. Hypothalamic-pituitary-gonadal axis hormones and cortisol in both menstrual phases of women with chronic fatigue syndrome and effect of depressive mood on these hormones. BMC Musculoskelet Disord. 2004 Dec 8;5:47. PMID: 15588275

There were no significant differences in FSH, LH, estradiol and progesterone levels in both of menstrual phases of CFS patients versus controls. Cortisol levels were significantly lower in patients compared to controls.

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CFS patients had a significantly reduced area under the ACTH response curve (AUC) in the ITT. The AUC was significantly associated with the duration of CFS symptoms and the severity of fatigue symptomatology. In addition, duration of CFS was correlated with the severity of fatigue symptoms.


Regarding the adrenal response to ACTH stimulation CFS subjects present heterogeneous group. In some subjects cortisol response is preserved, while in the others it is similar to one found in secondary adrenal insufficiency.

* Murphy BE, Abbott FV, Allison CM, Watts C, Ghadirian AM. Elevated levels of some neuroactive progesterone metabolites, particularly isopregnanolone, in women with chronic fatigue syndrome. Psychoneuroendocrinology. 2004 Feb;29(2):245-68. PMID: 14604604

Increases in ring A-reduced progesterone metabolites, particularly isopregnanolone, are associated with CFS. The pathophysiology of CFS is unlikely to be due to depression.


No response differences for salivary and plasma cortisol were detectable after administration of either low-dose or high-dose ACTH for CFS patients vs. controls,
indicating that primary adrenal insufficiency is unlikely to play a significant role in the etiology of chronic fatigue syndrome.

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CFS patients seem capable of mounting a sufficient cortisol response under different types of stress, but on a central level subtle dysregulations of the HPA axis exist.

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The circadian rhythms of prolactin, thyrotropic hormone, adrenocorticotropic hormone and cortisol were statistically significant in both CFS and control groups.

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CFS patients had significantly increased serum aluminum and decreased iron compared to controls. In the females, serum iron and dehydroepiandrosterone sulphate were significantly decreased and correlated. Total cholesterol was significantly increased, and significantly negatively correlated with dehydroepiandrosterone sulphate. There were no differences in zinc, copper, cortisol, hemoglobin, transferrin and ferritin concentrations, or in transferrin genetic subtypes.

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Chronic fatigue syndrome (CFS) has been associated with increased prolactin (PRL) responses to the serotonin (5-HT) releasing agent fenfluramine. The sensitivity of post-synaptic 5-HT2c receptors was not increased in patients with CFS. This suggests that the increased PRL response to fenfluramine in CFS is due to elevated activity of pre-synaptic 5-HT neurones.

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In conclusion, peripheral blood mononuclear cells of CFS patients display an increased sensitivity to glucocorticoids.

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There is mild hypocortisolism in chronic fatigue syndrome.

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In CFS patients a decreased Th1/Th2 balance may be the result of selective effects of glucocorticoids on the IL-10/IL-12 regulatory circuit.

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The authors looked at endocrine measures in CFS patients before and after an exercise challenge, and conclude that post-exertional malaise is not the result of endocrine problems.


The authors describe a 39-member Italian-Australian family with a novel complete loss of function (null) mutation of the corticosteroid-binding globulin gene. Idiopathic chronic fatigue was present in 12 of 14 adult null heterozygote subjects (86%) and in 2 of 3 null homozygotes. Five cases met the Centers for Disease Control criteria for chronic fatigue syndrome.


Patients with chronic fatigue syndrome had a reduced ACTH response to a vasopressin infusion and a more rapid cortisol response to the infusion.


ACTH significantly elevates DHEA levels, with no difference in output between CFS and healthy subjects. The DHEA/cortisol ratio decreased in response to ACTH stimulation in healthy subjects but not in the CFS cohort. We suggest this divergence of response
between the two groups represents an imbalance in the relative synthetic pathways of the CFS group which, if present chronically and if comparable to daily stressors, may manifest itself as an inappropriate response to stress.


Individuals with CFS do not show the normal fluctuations of motor cortical excitability that accompany and follow non-fatiguing repetitive bimanual finger movements.


Nocturnal saliva melatonin levels were significantly higher in CFS patients, compared with controls, at midnight, 0100 h, and 0200 h (P < 0.001).


CFS patients have a tendency for impaired spontaneous nocturnal GH secretion.


There was a significant impairment of GH response during insulin-induced hypoglycaemia and a low nocturnal GH secretion in CFS patients. These changes did, however, not lead to different concentrations in serum IGF-I. Significantly increased prolactin and TSH levels were found when compared to controls.
Adrenal gland size was reduced by over 50% in CFS patients, indicative of significant adrenal atrophy.

DHEA and DHEA-S levels were significantly lower in the CFS compared to the healthy group. A potential role for DHEA, both therapeutically and as a diagnostic tool, in CFS, is suggested.

Desmopressin was capable of normalizing the pituitary-adrenal response to corticotropin-releasing hormone in CFS patients; this suggests there may be increased vasopressinergic responsivity of the anterior pituitary in CFS and/or that desmopressin may be exerting an effect at an adrenal level.

CFS patients in this study had normal basal DHEA levels, but a blunted serum DHEA response curve to i.v. ACTH injection.

The majority of Japanese patients with CFS had a serum dehydroepiandrosterone sulfate (DHEA-S) deficiency, possibly related to phenomena such as memory, stress, anxiety, sleep and depression.


This study provides evidence for a subtle pituitary-adrenal insufficiency in subjects with chronic fatigue syndrome compared to healthy volunteers.


The results of this study suggest that normal endocrine influences on the circulating neutrophil pool may be disrupted in patients with CFS.


Altered water metabolism resulting from inappropriate release and/or response to arginine vasopressin (AVP) is proposed as a pathophysiological basis of certain chronic fatigue disorders.

The release of ACTH was significantly attenuated in a group of CFS patients (P < 0.005), as was the release of cortisol.

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The authors studied the detailed, pulsatile characteristics of the HPA axis in a group of CFS patients. Results were consistent with the view that patients with CFS have a reduction of HPA axis activity due, in part, to impaired central nervous system drive.

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The release of ACTH (but not cortisol) was significantly blunted in the CFS subjects compared with controls.

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Release of ACTH (but not cortisol) in response to ipsapirone challenge was significantly blunted in patients with CFS. The authors conclude that serotonergic activation of the hypothalamic-pituitary-adrenal axis is defective in CFS.

*

IL-1Ra secretion for CFS patients was twofold higher than controls during the follicular phase, but luteal-phase levels were similar between groups. In both phases of the menstrual cycle, IL-1sRII release was significantly higher for CFS patients compared to controls. These results suggest that an abnormality exists in IL-1 beta secretion in CFS patients that may be related to altered sensitivity to estradiol and progesterone. The increased release of IL-1Ra and sIL-1RII by cells from CFS patients is consistent with the hypothesis that CFS is associated with chronic, low-level activation of the immune system.


In CFS patients, the authors found attenuated basal levels of IGF-I and IGF-II; reduced GH response to hypoglycemia; higher insulin levels; and lower IGFBP-1 levels.


Patients with CFS had significantly higher plasma prolactin concentrations and experienced more nausea in response to buspirone than did controls.

In a group of CFS patients, the researchers found attenuated prolactin responses to hypoglycemia, a greater ACTH response and higher peak ACTH concentrations.


The author hypothesizes that CFS may be related to mild adrenocorticoid deficiency.


Patients with post viral fatigue syndrome had significantly low baseline arginine-vasopressin levels and evidence of increased total body water content, suggesting hypothalmic dysfunction.


CFS patients demonstrated significantly reduced basal evening glucocorticoid levels and low 24-h urinary free cortisol excretion, but elevated basal evening ACTH concentrations. There was increased adrenocortical sensitivity to ACTH, but a reduced maximal response. Patients showed attenuated net integrated ACTH responses to oCRH.

Nervous System

A review of 186 articles suggests that sympathetic nervous system predominance is common in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis.

**Brain Abnormalities**


Testing using 11C-(R)-PK11195 and PET suggested that neuroinflammation is present in widespread brain areas in CFS patients and was associated with the severity of neuropsychologic symptoms.


The researchers demonstrated that metronome sounds can cause mental fatigue sensation as a result of repeated pairings of the sounds with mental fatigue and that the insular cortex is involved in the neural substrates of this phenomenon.

* He J, Hollingsworth KG, Newton JL, Blamire AM. Cerebral vascular control is associated with skeletal muscle pH in chronic fatigue syndrome patients both at rest

Cerebral vascular control is closely related to skeletal muscle pH both at rest and after dynamic stimulation in CFS.


Significant voxels depicting reduced grey matter volume in the CFS group were noted in the occipital lobes (right and left occipital poles; left lateral occipital cortex, superior division; and left supracalcrine cortex), the right angular gyrus and the posterior division of the left parahippocampal gyrus. Significant voxels depicting reduced white matter volume in the CFS group were also noted in the left occipital lobe. These data support the hypothesis that significant neuroanatomical changes occur in CFS.


Cerebral blood flow velocity activation, normally tightly linked to cognitive neuronal activity, is unrelated to cognitive performance in CFS subjects; the increased critical closing pressure and vasomotor tone may indicate an uncoupling of the neurovascular unit during orthostasis.

The study results demonstrate that serum autoantibody against the muscarinic cholinergic receptor (mAChR) can affect the brain mAChR without altering acetylcholinesterase activity and cognitive functions in CFS patients.


Data from high-resolution structural 3-T cerebral MRI scanning support the hypothesis that significant neuroanatomical changes occur in CFS, and are consistent with the complaint of impaired memory that is common in this illness. They also suggest that subtle abnormalities in visual processing, and discrepancies between intended actions and consequent movements, may occur in CFS.


Most CFS patients have decreases in cerebral blood flow.


No abnormal patterns in rate and extent of brain atrophy, ventricle volume, white matter lesions, cerebral blood flow or aqueductal CSF flow were detected in the CFS population.

During active cognitive conditions, a CFS group showed significantly greater source-current activity than the controls in the left frontal-temporal-parietal regions of the cortex.


Neuroimaging evidence supports the hypothesis that chronic fatigue syndrome patients have structural or functional abnormalities within the brain.

* Sherlin L, Budzynski T, Kogan Budzynski H, Congedo M, Fischer ME, Buchwald D. Low-resolution electromagnetic brain tomography (LORETA) of monozygotic twins discordant for chronic fatigue syndrome. Neuroimage. 2007 Feb 15;34(4):1438-42. PMID: 17169580

Neurophysiological activity in specific areas of the brain may differentiate individuals with CFS from those in good health. The study corroborates that slowing of the deeper structures of the limbic system is associated with affect. It also supports the neurobiological model that the right forebrain is associated with sympathetic activity and the left forebrain with the effective management of energy.


These data indicate that patients with CFS have reduced absolute cortical blood flow in rather broad areas when compared with data from healthy controls and that those devoid of psychopathology had the most reductions in cortical flow.


There were significant reductions in global gray matter volume in CFS patients, and the decline in gray matter volume was linked to the reduction in physical activity.


Patients with CFS had reduced gray-matter volume in the bilateral prefrontal cortex. Within these areas, the volume reduction in the right prefrontal cortex paralleled the severity of the fatigue of the subjects.


No group differences were found for performance on single-photon emission computerized tomography scans despite CFS subjects' perceptions of exerting more mental effort to perform the task than healthy subjects. Inspection of the aggregate scans by group and task suggested a pattern of diffuse regional cerebral blood flow among subjects with CFS in comparison with the more focal pattern of regional cerebral blood flow seen among healthy subjects. Although CFS subjects showed less perfusion in the anterior cingulate region, the change in CFS subjects' activation of the left anterior cingulate region during the PASAT was greater than that observed for healthy subjects.

CFS has a dysfunction in the basal ganglia function, with an increase in the spectra from choline-containing compounds. This may be an indicator of higher cell membrane turnover due to gliosis or altered intramembrane signalling.

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The mean ratio of choline to creatine in the occipital cortex in CFS was significantly higher than in the controls; thus, there may be an abnormality of phospholipid metabolism in the brain in CFS.

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Proton magnetic resonance spectroscopy showed a significantly reduced concentration of N-acetylaspartate in the right hippocampus of CFS patients (p = 0.005).

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Both CFS and depressive patients had increased perfusion in the right thalamus, pallidum and putamen. CFS patients also had increased perfusion in the left thalamus. Depressed patients differed from those with CFS in having relatively less perfusion of the left prefrontal cortex.
MR spectroscopy (MRS) study revealed remarkable elevation of the choline/creatine ratio in the three children with CFS. The authors suggest that the various clinical symptoms in CFS patients may be closely related to an abnormal brain function.

On an MRI, cerebral changes in the CFS-No Psych group consisted mostly of small, punctate, subcortical white matter hyperintensities, found predominantly in the frontal lobes. This frontal lobe pathology could explain the more severe cognitive impairment previously reported in this subset of CFS patients.

In CFS, there is discordance between SPET brain perfusion and 18F-FDG brain uptake.

Positron emission tomography PET images of CFS patients showed a significant hypometabolism in the brainstem (having potential as a biomarker) and right mediofrontal cortex.

Some patients with chronic fatigue syndrome show an abnormal increase in plasma lactate following a short period of moderate exercise, in the sub-anaerobic threshold exercise test (SATET), and this cannot be explained satisfactorily by the effects of deconditioning.

Costa DC, Tannock C, Brostoff J. Brainstem perfusion is impaired in chronic fatigue syndrome. QJM. 1995 Nov;88(11):767-73. PMID: 8542261

Patients with ME/CFS were found to have a generalized reduction of brain perfusion, with a particular pattern of hypoperfusion of the brainstem.


SPECT abnormalities occur more frequently and in greater numbers than MR abnormalities do in patients with CFS.


Abnormalities in brain scans indicates that some CFS patients have some organic problem manifesting itself on neuroimaging.

CFS patients had a higher mean CD4/CD8 T-cell ratio than matched healthy controls. Magnetic resonance scans of the brain showed punctate, subcortical areas of high signal intensity consistent with edema or demyelination in 78% of patients.


Study of brain blood flow or metabolism by PET or SPECT is a possible tool for establishment of the CFS identity.


CFS patients showed abnormally low cortical/cerebellar rCBF ratios, throughout multiple brain regions. 80% showed at least one or more rCBF ratios significantly less than normal values. The major cerebral regions involved were frontal (63%), temporal (35%), parietal (53%) and occipital lobes (38%). The rCBF ratios of basal ganglia were also reduced.

**Cognitive Impairment**

Compared to controls, a group of CFS patients showed impaired information processing speed (reaction time) but comparable performance on tests of attention, memory, motor functioning, verbal ability, and visuospatial ability. Moreover, information processing speed was not related to psychiatric status, depression, anxiety, the number or severity of CFS symptoms, fatigue, sleep quality, or everyday functioning.


Comparison of data from two groups of CFS patients (those with and without comorbid major depressive disorder) to controls consistently showed that error rates did not differ among groups across conditions, but speed of information processing did. Processing time was prolonged in both CFS groups and most significantly affected in response to the most complex task conditions. For simpler tasks, processing time was only prolonged in CFS participants with depression.

* Hutchinson CV, Badham SP. Patterns of Abnormal Visual Attention in Myalgic Encephalomyelitis. Optom Vis Sci. 2013 May 17. PMID: 23689679

In a study of visual attention difficulties, CFS patients exhibited marginally worse performance compared with controls on the divided attention subtest and significantly worse performance on the selective attention subtest. In the spatial cueing task, they were slower than controls to respond to the presence of the target, particularly when cues were invalid. They were also impaired, relative to controls, on visual search tasks.


Neurocognitive impairment (including reduced attention control in switching and divided-attention tasks) is a feature of childhood chronic fatigue syndrome.

In a cognitive task study, patients with CFS showed no deficits in performance accuracy, but were significantly slower than healthy controls. CFS was further characterized by low and unresponsive heart rate variability; greater heart rate (HR) reactivity and prolonged HR-recovery after cognitive challenge.

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This study’s findings suggest that poor effort is unlikely to contribute to cognitive test performance of persons with CFS.

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CFS patients have objective impairments in attention and memory, but with good motivation and without exaggerated suggestibility.

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Ocon AJ. Caught in the thickness of brain fog: exploring the cognitive symptoms of Chronic Fatigue Syndrome. Front Physiol. 2013;4:63. PMID: 23576989

The cognitive symptoms of CFS may be due to altered cerebral blood flow activation and regulation that are exacerbated by a stressor, such as orthostasis or a difficult mental task, resulting in the decreased ability to readily process information.

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Higher-order level cognitive dysfunction affects childhood CFS pathogenesis. Alternative attention performance evaluated by the mATMT may be used to monitor improvement in patients with CCFS. Combined treatment with CBT and medication may be effective to improve poor attention characteristics associated with CCFS.

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Post-infective fatigue syndrome (PIFS) is associated with a disturbance in bidirectional autonomic signalling resulting in heightened perception of symptoms and sensations from the body in conjunction with autonomic hyper-reactivity to perceived challenges.

*  


CFS patients demonstrate specific cognitive impairments.

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Dickson A, Toft A, O'Carroll RE. Neuropsychological functioning, illness perception, mood and quality of life in chronic fatigue syndrome, autoimmune thyroid disease and healthy participants. Psychol Med. 2009 Sep;39(9):1567-76. PMID: 19144216

The results of this study suggest that the primary cognitive impairment in CFS is attention and that this is not secondary to affective status. The lower treatment control perceptions and greater illness concerns that CFS patients report may be causally related to their affective status.

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Patients with CFS or depression demonstrated overall fine motor slowing and similar cognitive impairments.


Children with CFS/ME appear to experience problems with attention, which may have adverse implications for verbal memory.


CFS patients have alterations in motor speed and working memory independent of comorbid psychiatric disease and medication usage.


In a study of CFS patients and healthy identical twins, patients exhibited decreases in motor functions, speed of information processing, verbal memory, and executive functioning.

CFS patients often have memory and cognitive complaints. Neuroimaging studies demonstrate cerebral abnormalities and a pattern of increased neural recruitment during cognitive tasks.


This study shows strong concordance between subjective complaints of mental fatigue and objective measurement of cognitive impairment in CFS patients and suggests that mental fatigue is an important component of CFS-related cognitive dysfunction.


CFS may be characterised by attenuation of the responsiveness to stimuli not directly related to the fatigue-inducing task.


Patients with CFS show both quantitative and qualitative differences in activation of the working memory network compared with healthy control subjects.*

CFS patients without comorbid FM exhibit subtle cognitive deficits in terms of speed, consistency, and efficiency that are not improved or exacerbated by light exercise.


Central activation is diminished in CFS patients. Possible causes include changed perception, impaired concentration, reduced effort and physiologically defined changes, e.g. in the corticospinal excitability or the concentration of neurotransmitters. As a consequence, demands on the muscle are lower, resulting in less peripheral fatigue.


Compared to healthy controls (HC) and a group of participants with rheumatoid arthritis (RA), the CFS-noPsych group displayed significantly reduced performance on tests of information processing speed, but not on tests of working memory.

This study provides evidence that changing motor deficits in CFS have a neurophysiological basis. The slowness of simple reaction times supports the notion of a deficit in motor preparatory areas of the brain.


The current research shows that slowed processing speed, impaired working memory and poor learning of information are the most prominent features of cognitive dysfunctioning in patients with CFS.


People with long-duration CFS reported a large number of specific cognitive difficulties that were greater in severity than those reported by participants with short-duration CFS. The pattern of comorbid disorders in the CFS groups was consistent with hypersensitivity and viral reactivation hypotheses.


CFS patients were poorer than controls on recall of verbal information.


The learning rate of verbal and visual material for patients with CFS was slower, and delayed recall of verbal and visual information was impaired, compared to normals.
There was a high variability in cognitive impairment within the CFS group. The neuropsychological variables of psychomotor performance and verbal memory were found to discriminate best between patients and controls.


A subset of CFS patients may experience significant impairments in learning and memory.


CFS patients are more impaired on auditory than on visual processing tasks.


Patients with chronic fatigue syndrome have reduced attentional capacity resulting in impaired performance on effortful tasks requiring planned or self ordered generation of responses from memory.


Impaired information processing, rather than primary memory dysfunction, may be at the root of the cognitive problems that afflict so many patients with CFS.

A study of CFS patients revealed significant memory deficits consistent with temporal-limbic dysfunction.


Subjects with CFS showed significant impairment on a test of complex concentration.


Cognitive impairment in CFS involves response-related processes.

Gait Abnormalities


Gait velocity or pattern can be used to monitor patients’ progress in CFS.

CFS patients were different in gait parameter than normal people. Heart rate responses demonstrated that both groups were exercising at similar loads, although this was perceived to be higher by the CFS group.


The gait of CFS patients revealed significant abnormalities in the symmetry indices of the bilateral parameters and in the linear relationships among parameters, and between these parameters and the physical characteristics of the patients. The abnormalities were present as from the beginning of the gait, which indicates that they are unlikely to be caused by the rapid increasing fatigue. This strengthens the hypothesis of a direct involvement of the central nervous system (CNS) in the onset of the disease.


The researchers evaluated their clinical impression that patients with CFS did not walk normally, finding that they did indeed have objective gait abnormalities.

**Sleep Abnormalities**


Of 343 patients with CFS, 30.3% were identified with a Primary Sleep Disorder explaining their diagnosis. Of the remaining patients, 89.1% met quantitative criteria for at least one objective sleep problem.

Results of this study suggest that beat-to-beat RR interval dynamics or autonomic nervous system activity during non-REM sleep might be associated with disrupted sleep in patients with CFS.


There is currently insufficient evidence to indicate that treatment of primary sleep disorders sufficiently improves the fatigue associated with CFS. Therefore, primary sleep disorders may be a comorbid rather than an exclusionary condition with respect to CFS.


CFS is associated with lower ultra-slow (0.5-0.8Hz) delta power, underscoring the importance of looking beyond conventional EEG frequency bands.


A distinct subgroup of CFS patients with clinical features of insomnia and specific sleep problems was identified.

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This review provides a comprehensive overview of the literature examining sleep in CFS/ME and the issues surrounding the current research findings.


Sleep disturbances in CFS were evaluated according to the Pittsburgh Sleep Quality Index (PSQI) scale.


The strong and potentially reciprocal relationship between cancer-related fatigue (CRF) and disrupted sleep-wake patterns suggests a possible shared physiologic pathway.

* Kishi A, Natelson BH, Togo F, Struzik ZR, Rapoport DM, Yamamoto Y. Sleep-Stage Dynamics in Patients with Chronic Fatigue Syndrome with or without Fibromyalgia. Sleep. 2011 Nov 1;34(11):1551-60. PMID: 22043126

The probability of transition from REM sleep to waking was significantly greater in subjects with CFS alone than in control subjects. Probabilities of (a) transitions from waking, REM sleep, and S1 to S2 and (b) those from SWS to waking and S1 were significantly greater in subjects with CFS+FM than in control subjects; in addition, rates of these transitions were also significantly increased in subjects with CFS+FM. These results suggest that CFS and FM may be different illnesses associated with different problems of sleep regulation.

Abnormal findings on sleep studies and associated human leukocyte antigen markers, and a clinical pattern suggestive of narcolepsy, are present in a high proportion of CFS and fibromyalgia patients. Sixty percent of patients treated with oxybate experienced significant relief of pain, while 75% experienced significant relief of fatigue. The authors postulate that the response to oxybate in CFS and FM suggests a disturbance of sleep similar to narcolepsy.


CFS includes specific sleep problems, including difficulties in transitioning from REM sleep to wakening.


CFS patients have sleep disorders that prompt cognitive and behavioural motor performance.

In CFS: (a) objectively measured nocturnal sleep time effectively approximated subjective experience although nocturnal wakefulness did not; (b) total sleep time and sleep efficiency differentiated individuals with and without insomnia complaints; (c) daytime sleepiness, fatigue, and non-refreshing sleep were not reflected by the objective sleep-related measures (polysomnography and actigraphy).

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Sleep is disturbed in CFS patients as a group, but exercise does not exacerbate this sleep disturbance.

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In persons with CFS, delta power was diminished during slow wave sleep, but elevated during both stage 1 and REM. Alpha power was reduced during stage 2, slow wave, and REM sleep. Those with CFS also had significantly lower theta, sigma, and beta spectral power during stage 2, Slow Wave Sleep, and REM.

*  

CFS participants with and without sleep apnea/hypopnea syndrome did not differ on various measures. The authors conclude that SAHS should not be an exclusion criterion for CFS.

Sleep efficiency was lower in both CFS than controls. CFS patients showed a higher microarousal index than controls. Anxiety, but not depression symptoms were more intense in the CFS group. The distribution of nonrapid eye movement sleep in CFS differs sizeably from what can be observed in a primary sleep disorder.


No significant differences in spectral power in any frequency band in a sleep study were found between those with CFS and their nonfatigued cotwins.


The “fatigue” in CFS is not exactly the same as normal sleepiness.


CFS patients had significant differences in polysomnographic findings from healthy controls and felt sleepier and more fatigued than controls after a night's sleep. This difference was due primarily to a decrease in the length of periods of uninterrupted sleep in the patients with more sleepiness in the morning than on the night before.

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Specific sleep problems in CFS are examined.


People with CFS reported sleep problems significantly more often than control subjects. Yet, when measured these parameters and sleep architecture did not differ between the two subject groups.


Compared to the control group, total sleep time was longer and physical activity was lower in CFS.


CFS patients reported poor quality sleep, but objective sleep quality parameters, like the Sleep Efficiency Index (SEI) or the amount of slow-wave sleep did not differ significantly.

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Actigraphy analysis showed that mean awake activity was decreased and duration of sleep was prolonged in patients with CFS.

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CFS patients display a variety of sleep disorders.

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CFS is associated with a blunted slow wave analysis response to sleep challenge, suggesting that the basic sleep drive and homeostatic response are impaired.

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CFS patients experienced a prolonged sleep latency, showed a low sleep efficiency index, and had a low percentage of slow wave sleep.

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Although disordered breathing during sleep may be associated with CFS, this study generally did not provide evidence that altered sleep architecture is a critical factor in CFS.


The complaints of chronic fatigue and unrefreshing sleep were associated with an abnormal cyclic alternating pattern rate, with increase in slow delta power spectrum, affirming the presence of an abnormal sleep progression and non-rapid eye movement sleep instability. These specific patterns were related to subtle, undiagnosed sleep-disordered breathing.


Sleep issues were examined for a population of CFS patients in Wichita, Kansas. 81.4% of subjects had an abnormality in at least one SAQ sleep factor. Subjects with sleep factor abnormalities had significantly lower wellness scores but statistically unchanged fatigue severity scores compared to those without SAQ abnormality.


In ambulatory conditions, the circadian rhythm of CBT in CFS is nearly indistinguishable from that of normal control subjects although there was a tendency for greater variability in the rhythm. Hence, it is unlikely that the symptoms of CFS are because of disturbance in the circadian rhythm of CBT.

Compared with controls, teenagers with CFS showed significantly higher levels of sleep disruption by both brief and longer awakenings.


CFS patients reported significantly more naps and waking by pain, a similar prevalence of difficulties in maintaining sleep, and significantly less difficulty getting off to sleep compared to depressed patients. Sleep continuity complaints preceded fatigue in only 20% of CFS patients, but there was a strong association between relapse and sleep disturbance. Disrupted sleep appears to complicate the course of CFS. Sleep complaints in CFS do not seem related to depression.


In contrast to patients with fibromyalgia, in whom levels of somatomedin C have been found to be reduced, levels in patients with CFS were found to be elevated. Thus, despite the clinical similarities between these two conditions, they may be associated with different abnormalities of sleep and/or of the somatotropic neuroendocrine axis.

CFS sufferers were different than controls on variables of sleep-onset latency and the number of stage shifts/hour.


CFS patients showed no significant correlation between the timing of the temperature acrophase and the melatonin onset, whereas the normal significant correlation was observed in the controls. Dissociation of circadian rhythms could be due to the sleep deprivation and social disruption, and/or the reduction in physical activity which typically accompany CFS.


Women with CFS encounter problems with quality as well as amount of sleep.


Alpha-delta sleep is not a marker of CFS, but may contribute to the illness of nondepressed patients with these conditions.


Study results suggest that patients who qualify for CFS diagnoses may have sleep disorders that, while they don’t cause the disease, may improve with treatment.

Subjective sleep disturbance is common in CFS and some CFS patients may have objective sleep disorders.


Most people in a group of CFS patients had sleep disorders, which are likely to contribute to daytime fatigue.

Pain


There is an association between “pain catastrophizing,” bodily pain, exercise performance, and self-reported disability in female patients with CFS who experience widespread pain.


Delayed pain inhibition may play a role in chronic widespread pain in CFS.

Although cold pain threshold and tolerance levels were slightly lower in twins with CFS than their cotwins without CFS, these differences failed to reach statistical significance. Subjective ratings of pain and fatigue at multiple time points during the experimental protocol among twins with CFS were significantly higher than ratings of pain (P = 0.003) and fatigue (P < 0.001) by their cotwins without CFS.


Chronic pain is important in CFS and needs to be studied more.


CFS patients’ responses to painful experimental stimuli were measured.

**Muscles


Patients have less peak isometric muscle strength compared to healthy sedentary control subjects.

The authors suggest that there is a simpler sensation of fatigue that is triggered by inputs from specific receptors that are sensitive to metabolites produced by muscle contraction. They propose that this elementary sensation is transduced, conducted, and perceived within a unique sensory system with properties analogous to other sensory modalities such as pain, and call it the “sensation of muscle fatigue.”


This study supports the view that muscle tissue is directly involved in the pathogenesis of CSF and it might contribute to the early onset of fatigue typical of the skeletal muscles of CFS patients.


Oxidative metabolism is reduced in CFS patients compared to sedentary controls.

Patients with acute onset post viral fatigue syndrome lose muscle protein synthetic potential, but not muscle bulk.


Muscle fibre density estimation may be a useful way of identifying a subgroup of CFS sufferers with a possible primary muscle disorder.


Muscle biopsies of patients with postviral fatigue syndrome showed mild to severe atrophy of type II fibres in 39 biopsies, with a mild to moderate excess of lipid. On ultrastructural examination, 35 of these specimens showed branching and fusion of mitochondrial cristae. Mitochondrial degeneration was obvious in 40 of the biopsies with swelling, vacuolation, myelin figures and secondary lysosomes.

**Physical Symptoms**


People diagnosed with CFS/ME consistently report that they experience vision-related symptoms associated with their illness.

The high prevalence of migraine in CFS was confirmed and extended to GWI subjects.


This study showed that a much higher percentage of CFS patients than healthy controls significant dyspnea (shortness of breath).


CFS patients have a higher prevalence of migraine headaches (with and without aura) than healthy controls.


A greater proportion of women with CFS than controls reported pelvic pain unrelated to menstruation, endometriosis, and periods of amenorrhea. Compared to controls, women in the CFS group had a higher mean number of pregnancies and gynecological surgeries. Among menopausal women, 76% of the CFS group reported hysterectomy vs. 54.6% of controls, and 56% of women with CFS reported oophorectomy vs. 34.3% of controls.


CFS and interstitial cystitis/painful bladder syndrome are related.

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There is a high prevalence of idiopathic nonallergic rhinopathy in CFS. CFS also has significant overlap with systemic hyperalgesia (fibromyalgia), autonomic dysfunction (irritable bowel syndrome and migraine headaches), sensory hypersensitivity (dyspnea; congestion; rhinorrhea; and appreciation of visceral nociception in the esophagus, gastrointestinal tract, bladder, and other organs), and central nervous system maladaptations (central sensitization) recorded by functional magnetic resonance imaging (fMRI). Neurological dysfunction may account for the overlap of CFS with idiopathic nonallergic rhinopathy.

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Maloney EM, Boneva RS, Lin JM, Reeves WC. Chronic fatigue syndrome is associated with metabolic syndrome: results from a case-control study in Georgia. Metabolism. 2010 Sep;59(9):1351-7. PMID: 20102774

CFS was associated with metabolic syndrome, which further exacerbated fatigue.

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CFS patients exhibited more generalized hyperalgesia than controls.

*

Sexual dysfunction is a problem experienced by patients with chronic fatigue syndrome (CFS).


Contact lens-related Acanthamoeba keratitis was diagnosed in a 58-year-old man with a history of CFS. After medical management failed to prevail, a penetrating keratoplasty was performed in the affected eye.


Anaesthesia is likely to be associated with adverse effects in CFS patients but the effects are not likely to be severe.


Adolescent patients with chronic fatigue syndrome have abnormal catecholaminergic-dependent thermoregulatory responses, suggesting sympathetic dysfunction and possibly.

Qualitatively, cancer related fatigue appears closely related to CFS.


CFS patients were more likely than controls to have joint hypermobility.


Patients with CFS had lower blood pressure, stiffer arteries and more extensible skin, but did not have joint hypermobility.


Atopy was not more prevalent in patients with CFS than in healthy controls, although the CFS group tended to report more respiratory symptoms and drug allergies.


Phantom lymphadenopathy may be a symptom in some people with CFS.

Headaches, lymph node pain, sore throat, joint pain, muscle pain, muscle weakness at multiple sites differentiate CFS patients from controls. The disease includes many cardiopulmonary, neurological, and other symptoms not included in the CDC case definition.


Joint hypermobility is more common in patients with CFS than in otherwise healthy children with common skin disorders.


In a CFS population, 24% had no significant rhinitis complaints, 30% had positive skin tests suggesting the potential for allergic rhinitis complaints, and 46% had nonallergic rhinitis.


Women with CFS reported increased gynecologic complications, a lower incidence of premenstrual symptomatology. Issues included self-reported irregular cycles, periods of amenorrhea, sporadic bleeding between menstrual periods, and factors suggestive of abnormal ovarian function (such as a history of polycystic ovarian syndrome, hirsutism, and ovarian cysts).

63% of people belonging to a group for chronic fatigue sufferers fulfilled a diagnosis of irritable bowel syndrome (recurrent abdominal pain and at least three Manning criteria). This greatly exceeds estimates of irritable bowel syndrome prevalence of up to 22% in the general population.


People with CFS had more frequent cervical and axillary adenopathy, poorer functional status, and greater psychological distress than controls.


Vagal power was significantly lower in a CFS group versus healthy controls.


Significant ocular symptoms were present in all 25 of a group of CFS patients. The most common clinical findings were abnormalities of the preocular tear film and ocular surface and reduced accommodation for age.

The authors found a weak association between hyperventilation and chronic fatigue syndrome.


CFS patients are especially likely to report a wide variety of eye problems.


A particular pattern of redness in the throat may be related to CFS.

**Physical Abnormalities**

Chen CS, Lin WM, Yang TY, Chen HJ, Kuo CN, Kao CH. Chronic fatigue syndrome is associated with the risk of fracture: a nationwide cohort study. QJM. 2014 Mar 13. PMID: 24619129

Researchers used the National Health Insurance Research Database in Taiwan to conduct a prospective cohort study, identifying 3744 patients with a CFS diagnosis and 14,976 patients without CFS. The incidence rate of fracture was higher in the CFS cohort than in the non-CFS cohort.

ME/CFS patients showed relatively intact ability to accurately fixate the target (prosaccades), but were impaired when required to focus accurately in a specific position opposite the target (antisaccades). Patients were most markedly impaired when required to direct their gaze as closely as possible to a smoothly moving target (smooth pursuit).


Patients and controls performed similarly on the processing speed subtest of the Useful Field of View. However, patients exhibited marginally worse performance compared with controls on the divided attention subtest and significantly worse performance on the selective attention subtest. In the spatial cueing task, they were slower than controls to respond to the presence of the target, particularly when cues were invalid. They were also impaired, relative to controls, on visual search tasks.

He J, Hollingsworth KG, Newton JL, Blamire AM. Cerebral vascular control is associated with skeletal muscle pH in chronic fatigue syndrome patients both at rest and during dynamic stimulation. Neuroimage Clin. 2013 Jan 5;2:168-73. PMID: 24179772

The researchers found that cerebral vascular control is closely related to skeletal muscle pH both at rest and after dynamic stimulation in CFS.

Visible and near-infrared spectroscopy of the thumb combined with chemometrics analysis may provide a valuable tool for diagnosing CFS.


Endothelial dysfunction is present in CFS.


CFS patients had more abrupt interruptions of voluntary physical activity during diurnal periods in normal daily life, probed by the decreased correlation in the negative modulus maxima of the wavelet-transformed activity data, possibly due to their exaggerated fatigue.


CFS patients have slowed reaction times reduced premovement-related potentials, suggesting that central motor mechanisms accompanying motor response preparation were impaired in CFS for some tasks.

CFS patients displayed impaired acquisition of the eyeblink response using a delayed-type conditioning paradigm. This suggests organic brain dysfunction within a defined neural substrate in CFS patients.


Researchers performed vestibular function testing performed on 11 CFS patients and concluded that results are more suggestive of central nervous system deficits than of peripheral vestibular disfunction.

**Laboratory Abnormalities**


Urine specimens from 104 of 112 CFS patients (93%) were positive for at least one mycotoxin. Ochratoxin A was detected in 83% of samples and macrocyclic trichothecenes were detected in 44%.


This study shows the presence of differentially expressed proteins in the saliva of the couple of monozygotic twins discordant for CFS, probably related to the disease.

This review is focused on the recent literature related to biomarkers for fatigue associated with CFS/ME and, for comparison, those associated with other diseases.


The response to local cutaneous heating may be altered by local levels of ROS, particularly H(2)O(2) in CFS subjects, and may be related to their hyperesthesia/hyperalgesia.


Self-reported fatigue severity was significantly correlated with leptin levels in six out of 10 CFS patients and one out of 10 healthy control.


The study results suggest that the biosynthetic pathways of the monoamine neurotransmitters that are mediated by tyrosine hydroxylase and GTP cyclohydrolase I might be associated with the CFS clinical findings.

The study’s results show that, in ME/CFS, increased serotonin (5-HT) autoimmune activity is associated with activation of immuno-inflammatory pathways and increased bacterial translocation, factors which are known to play a role in the onset of autoimmune reactions.

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A group of CFS patients had higher levels of triglycerides, malondialdehyde and protein oxidation protein carbonyl and lower levels of HDL cholesterol than the control group. This suggests an unfavorable lipid profile and signs of oxidative stress induced damage to lipids and proteins.

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This study’s results showed a significant reduction of glutamine and ornithine in the blood of the CFS samples. Correlation analysis of glutamine and ornithine with other metabolites in the CFS sera showed relationships with glucogenic amino acids and metabolites that participate in the urea cycle. This indicates a possible disturbance to amino acid and nitrogen metabolism.

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In two previous reports, the researchers found significantly higher levels of ventricular cerebrospinal fluid (CSF) lactate in patients with CFS relative to those with generalized anxiety disorder and healthy volunteers (HV), but not relative to those with major depressive disorder (MDD). In this new study, they found elevated ventricular lactate and decreased GSH in patients with CFS and MDD relative to HVs. Collectively, the results of this third independent study support a pathophysiological model of CFS in which increased oxidative stress may play a key role in CFS etiopathophysiology.


Ventricular CSF lactate was significantly elevated in CFS compared to healthy volunteers. There was a significant correlation between ventricular CSF lactate and severity of mental fatigue that was specific to the CFS group.


Analysis of cerebral spinal fluids accurately distinguished CFS, Chronic Lyme and healthy subjects, and thus has potential as a biomarker.


Plasma Neuropeptide Y is elevated in CFS patients compared to healthy controls and to a fatigued comparison group, GWI patients.

CFS patients as well as patients with general fatigue had abnormally elevated levels of plasma concentrations of high-sensitivity c-reactive protein (hs-CRP).


CFS patients have a variety of problems with their blood, including a decrease in water content and increases in oxyhemoglobin content, oxidation of heme a+a(3) and copper in cytochrome c oxidase.


The fingernails of CF patients showed a decreased alpha-helix content and an increased beta-sheet content, suggesting reduced levels of normal elements in the nail plate.


In a mouse model of CFS, brain-derived neurotrophic factor (BDNF) and Bcl-2 mRNA expression levels in the hippocampus were suppressed.

CFS patients display abnormalities in a variety of blood and urine tests.


Anti-68/48kD protein autoantibodies were found in 13% of 114 CFS patients and 0% in healthy subjects (p < 0.05). Hypersomnia and difficulty in concentration were found more frequently in the CFS patients with this specific autoantibody.


Studies suggest that CFS is closely associated with attenuation of central synaptic transmission mediated by neurotransmitters such as serotonin and glutamate.


Increased excretion of beta-alanine was found in a subgroup of CFS patients.


Vis-NIR spectroscopy for sera combined with chemometrics analysis could provide a promising tool to objectively diagnose CFS.

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There is evidence of decreased 5-HT1A receptor number or affinity in CFS.

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This pilot study detected an identical set of central nervous system, innate immune and amyloidogenic proteins in cerebrospinal fluids from two independent cohorts of subjects with overlapping CFS, PGI and fibromyalgia.

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CFS/fibromyalgia and CFS had significant differences in urine compared to normal controls that may be of significance as biomarkers of illnesses.

*  

Significantly more CFS patients had elevations in spinal fluid in either protein levels or number of cells than healthy controls.


The density of serotonin transporters (5-HTTs) in the brain, as determined by using a radiotracer, [C](+)McN5652, was significantly reduced in the rostral subdivision of the anterior cingulate of CFS patients as compared with that in normal volunteers.


Most diseases are accompanied by a blunted response to acetylcholine but the opposite is true for CFS. Such sensitivity is normally associated with physical training so the finding in CFS is anomalous and may well be relevant to vascular symptoms that characterise many patients. There are several mechanisms that might lead to ACh endothelial sensitivity in CFS patients.


CFS patients showed evidence of reduced hyperemic flow and reduced oxygen delivery but no evidence that this impaired muscle metabolism.

CFS patients have chronic immune activation, compared to normal people. Bronchial hyperresponsiveness is associated with that.


Subgroups of CFS are associated with autoimmune abnormalities of CHRM1.


Attenuated concentration of extracellular serotonin due to longer variants may cause higher susceptibility to CFS.


The mean ratio of choline to creatine in the occipital cortex in CFS was significantly higher than in the controls. Our results suggest that there may be an abnormality of phospholipid metabolism in the brain in CFS.

Beta-endorphin concentrations were significantly lower in patients with chronic fatigue syndrome or fibromyalgia syndrome than in normal subjects and depressed patients. Evaluation of peripheral blood mononuclear cell beta-endorphin concentrations could represent a diagnostic tool for chronic fatigue syndrome.


The presence of the anti-68/48 kDa protein antibodies in a portion of both CFS and primary FM patients suggests the existence of a common immunological background. These antibodies may find utility as possible markers for a clinicoserological subset of CFS/FM patients with hypersomnia and cognitive complaints.


The salivary gland changes in patients with chronic fatigue syndrome show varying degrees of ductal and acinar dilatation, periductal fibrosis, lymphoplasmacytic infiltrates, and occasional lymphocytic foci, all suggestive of primary gland damage. The one parameter that showed statistical significance was the presence of mast cells.

The presence of a 37 kDa 2-5A binding protein in extracts of peripheral blood mononuclear cells may distinguish patients with chronic fatigue syndrome from healthy subjects and those suffering from other diseases.


A new lab panel allows testing for diagnosis as well as monitoring for anticoagulation protocols in CFS patients.

* Vojdani A, Lapp CW. Interferon-induced proteins are elevated in blood samples of patients with chemically or virally induced chronic fatigue syndrome. Immunopharmacol Immunotoxicol. 1999 May;21(2):175-202. PMID: 10319275

Interferon induced proteins 2-5A Synthetase and Protein Kinase RNA (PKR) are not only biomarkers for viral induction of CFS, but biomarkers to other stressors that include MTBE and Benzene.


Patients with CFS were found to have low levels of peripheral blood mononuclear cell beta-endorphin. Beta-endorphin concentrations in PBMC seem to mirror the central nervous system homeostasis of the opioid. Therefore, we would postulate that the fatigue and weakness typical of CFS could be related to low beta-endorphin concentrations at the central nervous system level.

The high frequency of autoantibodies to insoluble cellular antigens in CFS represents a unique feature which might help to distinguish CFS from other rheumatic autoimmune diseases.


Compared to control subjects, mean concentrations of C-reactive protein, beta 2-microglobulin, and neopterin were higher in patients with CFS and chronic fatigue. The presence of several markers was highly correlated, suggesting a subset of patients with immune activation.


In all the subjects in a group of patients having both CFS and fibromyalgia, the homocysteine (HCY) levels were increased in the cerebrospinal fluid (CSF). There was a significant positive correlation between CSF-HCY levels and fatiguability, and the levels of CSF-B12 correlated significantly with the item of fatiguability and with CPRS-15.

We have identified and partially characterized the autoantibodies in sera of 60 patients with chronic fatigue syndrome. Approximately 52% of CFS patients had sera that were found to react with nuclear envelope antigens. Some sera immunoprecipitated the in vitro transcription and translation product of a human cDNA clone encoding the nuclear envelope protein lamin B1. The autoantibodies were of the IgG isotype. It thus seems there is an autoimmune component in chronic fatigue syndrome.


Chronic fatigue syndrome (CFS) patients have a urinary metabolite labeled CFSUM1 with increased incidence (P < 0.004) and relative abundance (P < 0.00003). The relative abundances of urinary CFSUM1 and beta-alanine were associated with alterations in metabolite excretion and symptom incidence. The strong associations of CFSUM1 and beta-alanine with CFS symptom expression provide a molecular basis for developing an objective test for CFS.


Eosinophil cationic protein serum levels were significantly higher in CFS patients than in controls. In the CFS population, the prevalence of RAST positivity to one or more allergens was 77%, while no control showed positive RAST.

Asymmetry (R > L) of tracer uptake at parietotemporal level in the brain is demonstrated in CFS as compared with major depression.


Of 11 immunological tests done on chronic fatigue syndrome patients and on fatigued controls, the best ones to distinguish them from normals were protein A binding, Raji cell, or C3 or C4. Other tests, including immunoglobulin G subclasses, complement component CH50, interleukin-2, and anticardiolipin antibodies, did not discriminate well among the groups.


A variety of immunological and hormonal abnormalities were found in a group of CFS patients.


Serum ACE elevations may be a useful marker for CFIDS.

A group of CFS patients showed a significant reduction in basal plasma levels of MHPG and a significant increase in basal plasma levels of 5-HIAA.


The characteristic abnormality in CFS patients is the low values of 17-Ketosteroid-Sulfates/creatinine in morning urine and the acetylcarnitine deficiency.

**Channelopathies**


The sarcolemmal conduction system and some aspects of Ca(2+) transport are negatively influenced in chronic fatigue syndrome. Both deregulation of pump activities (Na(+)/K(+) and Ca(2+)-ATPase) and alteration in the opening status of ryanodine channels may result from increased membrane fluidity involving sarcoplasmic reticulum membranes.


The authors hypothesize that abnormal ion channel function underlies the symptoms of CFS.


It is suggested that chronic fatigue syndrome/fibromyalgia is caused by virus injury to the calcium channels leading to larger quantities than usual of calcium ions entering the striated muscle cells.

**Lipids**

Maes M, Mihaylova I, Leunis JC. In chronic fatigue syndrome, the decreased levels of omega-3 poly-unsaturated fatty acids are related to lowered serum zinc and defects in T cell activation. Neuro Endocrinol Lett. 2005 Dec;26(6):745-51. PMID: 16380690

The results of this study show that a decreased availability of omega3 poly-unsaturated fatty acids plays a role in the pathophysiology of CFS and is related to the immune pathophysiology of CFS.


Levels of the arachidonic acid (ARA) and docosahexanoic acid (DHA) were decreased in patients suffered from CFS. However, the levels of the palmitic acid and oleic acid were increased. We speculated that there are two possible mechanisms--one of which is that oxidative stress has led to an excessive oxidation and resulting in the above fatty acids. Alternatively, insufficiency of ingestion of fatty acids might not be the major cause.

The authors suggest that essential fatty acids may play a role in CFS.


Some CFS patients in this study had mild elevation of antibodies against Epstein-Barr Virus and immunologic abnormalities (natural killer cell dysfunction and high rates of skin reactivity to house dust, pollen, drugs and common food). In these patients, the researchers found decreases in serum concentrations of arachidonic acid and dihomogamma-linolenic acid.


The authors propose an interaction between infections and essential fatty acid metabolism in post viral fatigue syndrome.

**Carnitine**


CFS patients demonstrate disturbance in carnitine homeostasis, possibly reflective of a reduction in carnitine palmitoyltransferase-I (CPT-I) activity.

CFS patients did not differ from controls in terms of plasma or urinary total, free or esterified (acyl) carnitine or in renal excretion rates of these compounds.

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A significant decrease in the levels of serum acetylcarnitine was found in patients with CFS.

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CFS patients have statistically significantly lower serum total carnitine, free carnitine and acylcarnitine levels. Higher serum carnitine levels correlated with better functional capacity. These findings may be indicative of mitochondrial dysfunction.

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A group of CFS patients had a deficiency of serum acylcarnitine.

**Nutrients**

The researchers determined that NADH levels could be used to gauge health status of CFS patients.

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The current paper will focus on the emerging role of tryptophan deficiencies in CFS and fibromyalgia.

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In patients presenting with chronic fatigue and/or orthostatic intolerance, low ferritin levels and hypovitaminosis D are common, especially in patients with excessive postural tachycardia.

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25-OH vitamin D levels are moderately to severely suboptimal in CFS patients, with a mean of 44.4 nmol/L (optimal levels >75 nmol/L). These levels are lower and the difference is statistically significant (p<0.0004) than those of the general British population from a recent national survey, but similar to those in patients with other chronic conditions.

CFS patients had higher resting free Mg2+ levels compared to sedentary controls.


There is a reduced functional B vitamin status, particularly of pyridoxine, in CFS patients.


Half of a group of CFS patients were deficient in folic acid.

CFS vs. Other Conditions


Differences and similarities between sickness behavior (an adaptive response induced by proinflammatory cytokines) and ME/CFS are discussed. The article concludes that these are two different conditions.

Abbi B, Natelson BH. Is chronic fatigue syndrome the same illness as fibromyalgia: evaluating the 'single syndrome' hypothesis. QJM. 2013 Jan;106(1):3-9. PMID: 22927538
This review presents data showing differences between CFS and FM across a number of parameters.

* 


This study suggests that adolescents who meet criteria for CFS 6 months following infectious mononucleosis do not have, as a group, more standing orthostatic intolerance than recovered controls.

* 


In a group of children, ANA titers were higher and the prevalence of anti-Sa was far more frequent in CFS patients than in FM cases. The authors conclude that CFS and FM are different from each other at least in childhood from the immunological aspects, although a few patients were suffering from both conditions.

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CFS was more likely to present in a sudden flu-like manner in civilians than Gulf War veterans. Comorbid fibromyalgia was more prevalent in civilians.

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Sinaii N, Cleary SD, Ballweg ML, Nieman LK, Stratton P. High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among

A survey showed that about 4.6% of endometriosis sufferers also reported having CFS.


Compared to their nonfatigued co-twins, CFS twins had higher rates of fibromyalgia and irritable bowel syndrome. The strongest associations were observed between chronic fatigue and fibromyalgia, irritable bowel syndrome, chronic pelvic pain, multiple chemical sensitivities, and temporomandibular disorder.


There is significant clinical overlap between CFS and FMS.


Unlike fibromyalgia patients, CFS patients have normal levels of Substance P in their cerebrospinal fluid.

The authors report a relationship between chronic fatigue syndrome and phosphate diabetes.

**HLA**


HLA DQB1*0602 was obtained in 74 patients, and positive in 32 (43%), P < 0.0001. In patients with CFS and fibromyalgia, researchers found a sleep disorder characterized by objective hypersomnia. Seventy-three (80%) were on an abnormal multiple sleep latency testing (MSLT). Some patients had characteristics of narcolepsy. Highly fragmented sleep was seen.


Certain HLA DRB genetic types (related to the acquired immune system) are more associated with CFS than are others.


HLA DRB genetic types are related to symptom presentation and age of onset in CFS.

Forty nine patients with CFS were genotyped for the HLA-DRB1, HLA-DQA1, and HLA-DQB1 alleles and the frequency of these alleles was compared with a control group comprising 102 normal individuals from the UK. Analysis by 2 x 2 contingency tables revealed an increased frequency of HLA-DQA1*01 alleles in patients with CFS (51.0% v 35%; odds ratio (OR), 1.93; p = 0.008). HLA-DQB1*06 was also increased in the patients with CFS (30.2% v 20.0%; OR, 1.73, p = 0.052). Only the association between HLA-DQA1*01 and CFS was significant in logistic regression models containing HLA-DQA1*01 and HLA-DRQ1B*06, and this was independent of HLA-DRB1 alleles. There was a decreased expression of HLA-DRB1*11 in CFS, although this association disappeared after correction for multiple comparisons. CFS may be associated with HLA-DQA1*01, although a role for other genes in linkage disequilibrium cannot be ruled out.


Fifty-eight patients were phenotyped for HLA A and B by microcytotoxicity and genotyped for HLA DRB, DQB and DPB by PCR oligoprobing, and the frequencies of antigens so assigned were compared with those from a control group of 134. No significant differences in HLA frequencies were found between patient and control groups.


We hypothesized that if autoimmune mechanisms did play an important role in the pathogenesis of AIFS, it is possible that it is immunogenetically regulated as observed
in other autoimmune disorders. In order to examine the immunogenetic background of AIFS patients, HLA-A, -B, -C, and -DR loci were analyzed serologically in 61 AIFS patients. AIFS was found to be positively associated with the class I antigen HLA-B61 and with the class II antigen HLA-DR9, with odds ratios of 2.77 (\(p = 0.015, P_{corr} = 0.48\)) and 2.60 (\(p = 0.012, P_{corr} = 0.17\)), respectively. A negative association was also found between AIFS and HLA-DR2 with odds ratio of 0.25 (\(p = 0.029, P_{corr} = 0.041\)). When comparing anti-Sa positive AIFS patients with healthy controls, the odds ratios associated with HLA-B61, DR9, and DR2 were 3.42 (\(p = 0.021, P_{corr} = 0.22\)), 3.96 (\(p = 0.0011, P_{corr} = 0.015\)), and 0.16 (\(p = 0.0022, P_{corr} = 0.031\)), respectively. Thus, the HLA associations observed in this study suggested that immunogenetic background might play a role in AIFS.


CFS patients had significantly increased mean fluorescence intensity readings of HLA-DR in CD4 and CD8 cells (\(P < 0.05\)). Expression of the costimulatory receptor CD28 in CD8 cells was significantly reduced, and the apoptosis repressor ratio of bcl-2/bax in both CD4 and CD8 was increased in patients (\(P < 0.05\)). Patients with increased HLA-DR expression had significantly lower SF-36 total scores, worse body pains, and poorer general health perception and physical functioning scores. Increased spontaneous lymphocyte proliferation was associated with poor general health perception.


**Gene Expression**


The researchers created a valid profile of polymorphisms for CFS, including two known polymorphisms associated with chronic fatigue syndrome, the NR3C1_11159943 major allele and the 5HTT_7911132 minor allele.


This paper summarizes research on genes that may be linked to increased susceptibility in developing and maintaining CFS and fibromyalgia, and research on resting and stressor-evoked changes in leukocyte gene expression, highlighting physiological pathways linked to stress and distress. These include the adrenergic nervous system, the hypothalamic-pituitary-adrenal axis and serotonergic pathways, and exercise responsive metabolite-detecting ion channels. The findings to date provide some support for both inherited susceptibility and/or physiological dysregulation in all three systems, particularly for catechol-O-methyl transferase (COMT) genes, the glucocorticoid and the related mineralocorticoid receptors (NR3C1, NR3C2), and the purinergic 2X4 (P2X4) ion channel involved as a sensory receptor for muscle pain and fatigue and also in upregulation of spinal microglia in chronic pain models.

CFS patients were especially likely to have a number of specific genes, suggesting that CFS might be related to polymorphisms of COMT and the $\beta_2$-adrenergic receptor.


Using an integrated genomic strategy, this study suggests a possible role for genes involved in glutamatergic neurotransmission and circadian rhythm in CFS and supports further study of novel candidate genes in independent populations of CFS subjects.


Reference genes that may be suitable for the analysis of CFS, or human blood RNA derived from whole blood as well as isolated peripheral blood mononuclear cells (PBMCs), have not previously been described. The authors identified PGK1 as a stable reference gene for use with whole blood RNA and RNA.


CFS patients were especially likely to have a number of specific genes, suggesting that CFS might be related to polymorphisms of COMT and the $\beta_2$-adrenergic receptor.

This study of CFS patients suggests that the promoter polymorphism (rs6311) can affect both transcription factor binding and promoter methylation, and this along with an individual's stress response can impact the rate of HTR2A transcription in a genotype and methylation-dependent manner.


The Cys704 allele of Ser704Cys SNP was associated with an increased risk of CFS development compared with the Ser704 allele.


A systems biology approach that includes environmental influences needs to be taken in order to look at the role of genetics in CFS.


Specific genotypes are associated with CFS.

The authors compared computational tools with and without feature selection for predicting chronic fatigue syndrome (CFS) using genetic factors such as single nucleotide polymorphisms (SNPs).


Differentially expressed genes in CFS suggest problems with immune modulation, oxidative stress and apoptosis. These may have the potential of serving as biomarkers for the disease.


The authors were unable to identify a biomarker for chronic fatiguing illness in the transcriptome of peripheral blood leukocytes.


The Bayesian based approach is a promising method to assess the gene-gene and gene-environment interactions in chronic fatigue syndrome patients by using genetic factors, such as SNPs, and demographic factors such as age, gender and BMI.

A defined gene cluster (9 genes) may be useful for detecting pathological responses in CFS patients and for differential diagnosis of this syndrome.

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A total of 88 human genes were upregulated or downregulated in CFS patients, including those related to hematologic function, immunologic function, cancer, cell death, immune response and infection.

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A systems biology approach was used to create a module of 299 highly correlated genes associated with CFS severity.

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The researchers analyzed gene expression in peripheral blood from 25 patients with CFS.

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Clustering of quantitative PCR (qPCR) data from patients with CFS revealed seven distinct subtypes.

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Sequence variation in HTR2A, related to serotonin, may potentially result in its enhanced activity and thus be involved in the pathophysiology of CFS.

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The authors identified 9 genes that were significantly and differentially expressed between CFS patients and healthy subjects.

*  


A significant increase of longer (L and XL) allelic variants for serotonin transporter was found in the CFS patients compared to the controls. Compared to S allele, the L allele is believed to retain higher transcriptional activity, which causes decreased concentration of serotonin in the extracellular space, namely, active serotonin in CFS.

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Rajeevan MS, Smith AK, Dimulescu I, Unger ER, Vernon SD, Heim C, Reeves WC. Glucocorticoid receptor polymorphisms and haplotypes associated with chronic fatigue syndrome. Genes Brain Behav. 2007 Mar;6(2):167-76. PMID: 16740143

The authors observed an association of multiple SNPs with chronic fatigue compared to non-fatigued (NF) subjects.

In a population of CFS sufferers, researchers identified 24 common genes and 11 common pathways.


A total of 839 genes were statistically associated with fatigue measures. These mapped to biological pathways such as oxidative phosphorylation, gluconeogenesis, lipid metabolism, and several signal transduction pathways. The study supports the use of phenotypic measures of CFS and QTA as important for additional studies of this complex illness.


The peripheral blood appears to be facilitating the molecular profiling of several diseases, such as CFS, that involve bodywide perturbations that are mediated by the CNS.

Goertzel BN, Pennachin C, de Souza Coelho L, Gurbaxani B, Maloney EM, Jones JF. Combinations of single nucleotide polymorphisms in neuroendocrine effector and receptor genes predict chronic fatigue syndrome. Pharmacogenomics. 2006 Apr;7(3):475-83. PMID: 16610957
The authors suggest that the fact that only 28 out of several million possible SNPs predict whether a person has CFS with 76% accuracy indicates that CFS has a genetic component that may help to explain some aspects of the illness.


CFS patients showed gene upregulations typical of T cell activation and perturbation of neuronal and mitochondrial function.

* Vernon SD, Reeves WC. Evaluation of autoantibodies to common and neuronal cell antigens in Chronic Fatigue Syndrome. J Autoimmune Dis. 2005 May 25;2:5. PMID: 15916704

Subsets of those with CFS had higher rates of antibodies to microtubule-associated protein 2 (MAP2) and ssDNA. There was no evidence of higher rates for several common nuclear and cellular antigens in people with CFS.


Homozygosity for the serine allele of the CBG gene may predispose to CFS, perhaps due to an effect on hypothalamic-pituitary-adrenal axis function related to altered CBG-cortisol transport function or immune-cortisol interactions.

Differentially expressed genes in CFS were involved in pathways of purine and pyrimidine metabolism, glycolysis, oxidative phosphorylation, and glucose metabolism.


The identification of novel gene tags up-regulated in CFS patients suggests that CFS is a disease characterized by subtle changes in the immune system.


Several of the differentially expressed genes are associated with immunologic functions (e.g., CMRF35 antigen, IL-8, HD protein) and implicate immune dysfunction in the pathophysiology of CFS.


CFS subjects had slightly lower concentrations or no detectable plasma DNA than non-fatigued subjects. There was a diverse array of 16S rDNA sequences in plasma DNA from both CFS and non-fatigued subjects. There were no unique, previously uncharacterized or predominant 16S rDNA sequences in either CFS or non-fatigued subjects.