Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS)

Medical Abnormalities Research Citations

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Overview

Jason LA, Zinn ML, Zinn MA. Myalgic Encephalomyelitis: Symptoms and Biomarkers. Curr Neuropharmacol. 2015;13(5):701-34. PMID: 26411464

The authors summarize advances in the physiological and neurological approaches to understanding, diagnosing, and treating ME.

*

Fischer DB, William AH, Strauss AC, Unger ER, Jason L, Marshall GD Jr, Dimitrakoff JD. Chronic Fatigue Syndrome: The Current Status and Future Potentials of Emerging Biomarkers. Fatigue. 2014 Jun 1;2(2):93-109. PMID: 24932428

The authors review potential CFS biomarkers related to neurological and immunological components of the illness.

*

Bansal AS, Bradley AS, Bishop KN, Kiani-Alikhan S, Ford B. Chronic fatigue syndrome, the immune system and viral infection. Brain Behav Immun. 2011 Jul 2. PMID: 21756995

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.

*

May M, Emond A, Crawley E. Phenotypes of chronic fatigue syndrome in children and young people. Arch Dis Child. 2010 Apr;95(4):245-9. PMID: 19843509

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, muscoloskeletal, 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.

*

Carlo-Stella N, Cuccia M. Demographic and clinical aspects of an Italian patient population with chronic fatigue syndrome. Reumatismo. 2009 Oct-Dec;61(4):285-9. PMID: 20143004

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

*

Bassi N, Amital D, Amital H, Doria A, Shoenfeld Y. Chronic fatigue syndrome: characteristics and possible causes for its pathogenesis. Isr Med Assoc J. 2008 Jan;10(1):79-82. PMID: 18300582

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.”

*

Klimas NG, Koneru AO. Chronic fatigue syndrome: inflammation, immune function, and neuroendocrine interactions. Curr Rheumatol Rep. 2007 Dec;9(6):482-7. PMID: 18177602

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

*

Miike T. Childhood chronic fatigue syndrome. Nihon Rinsho. 2007 Jun;65(6):1099-104. PMID: 17561704

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

*

Kuratsune H. Overview of chronic fatigue syndrome focusing on prevalence and diagnostic criteria. Nihon Rinsho. 2007 Jun;65(6):983-90. PMID: 17561686

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.

*

Janal MN, Ciccone DS, Natelson BH. Sub-typing CFS patients on the basis of 'minor' symptoms. Biol Psychol. 2006 Aug;73(2):124-31. PMID: 16473456

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.

*

Jason LA, Taylor RR, Kennedy CL, Jordan K, Huang CF, Torres-Harding S, Song S, Johnson D. A factor analysis of chronic fatigue symptoms in a community-based sample. Soc Psychiatry Psychiatr Epidemiol. 2002 Apr;37(4):183-9. PMID: 12027245

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

Chang CM, Warren JL, Engels EA. Chronic fatigue syndrome and subsequent risk of cancer among elderly US adults. Cancer. 2012 Dec 1;118(23):5929-36. PMID: 22648858

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.

*

Levine PH, Fears TR, Cummings P, Hoover RN. Cancer and a fatiguing illness in Northern Nevada--a causal hypothesis. Ann Epidemiol. 1998 May;8(4):245-9. PMID: 9590603

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.

*

Levine PH, Atherton M, Fears T, Hoover R. An approach to studies of cancer subsequent to clusters of chronic fatigue syndrome: use of data from the Nevada State Cancer Registry. Clin Infect Dis. 1994 Jan;18 Suppl 1:S49-53. PMID: 8148453

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.

*

Levine PH, Peterson D, McNamee FL, O'Brien K, Gridley G, Hagerty M, Brady J, Fears T, Atherton M, Hoover R. Does chronic fatigue syndrome predispose to non-Hodgkin's lymphoma? Cancer Res. 1992 Oct 1;52(19 Suppl):5516s-5518s; discussion 5518s-5521s. PMID: 1394166

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.

*

Kossaify A, Kallab K. Neurocardiogenic syncope and associated conditions: insight into autonomic nervous system dysfunction. Turk Kardiyol Dern Ars. 2013 Jan;41(1):75-83. PMID: 23518945

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

*

Wyller VB, Helland IB. Relationship between autonomic cardiovascular control, case definition, clinical symptoms, and functional disability in adolescent chronic fatigue syndrome: an exploratory study. Biopsychosoc Med. 2013 Feb 7;7(1):5. PMID: 23388153

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.

*

Frith J, Zalewski P, Klawe JJ, Pairman J, Bitner A, Tafil-Klawe M, Newton JL. Impaired blood pressure variability in chronic fatigue syndrome--a potential biomarker. QJM. 2012 Sep;105(9):831-8. PMID: 22670061

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.

*

Miwa K, Fujita M. Small Heart With Low Cardiac Output for Orthostatic Intolerance in Patients With Chronic Fatigue Syndrome. Clin Cardiol. 2011 Nov 28. PMID: 22120591

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.

*

Hollingsworth KG, Hodgson T, Macgowan GA, Blamire AM, Newton JL. Impaired cardiac function in chronic fatigue syndrome measured using magnetic resonance cardiac tagging. J Intern Med. 2011 Jul 27. PMID: 21793948

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.

*

Bjerregaard P, Nallapaneni H, Gussak I. Short QT interval in clinical practice. J Electrocardiol. 2010 Sep-Oct;43(5):390-5. PMID: 20667544

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

*

Stewart JM. Chronic fatigue syndrome: comments on deconditioning, blood volume and resulting cardiac function. Clin Sci (Lond). 2009 Oct 19;118(2):121-3. PMID: 19534728

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.

*

Hurwitz BE, Coryell VT, Parker M, Martin P, Laperriere A, Klimas NG, Sfakianakis GN, Bilsker MS. Chronic fatigue syndrome: illness severity, sedentary lifestyle, blood volume and evidence of diminished cardiac function. Clin Sci (Lond). 2009 Oct 19;118(2):125-35. PMID: 19469714

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.

*

Miwa K, Fujita M. Small heart syndrome in patients with chronic fatigue syndrome. Clin Cardiol. 2008 Jul;31(7):328-33. PMID: 18636530

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

*

Naschitz JE, Slobodin G, Sharif D, Fields M, Isseroff H, Sabo E, Rosner I. Electrocardiographic QT interval and cardiovascular reactivity in fibromyalgia differ from chronic fatigue syndrome. Eur J Intern Med. 2008 May;19(3):187-91. PMID: 18395162

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

*

Naschitz J, Fields M, Isseroff H, Sharif D, Sabo E, Rosner I. Shortened QT interval: a distinctive feature of the dysautonomia of chronic fatigue syndrome. J Electrocardiol. 2006 Oct;39(4):389-94. PMID: 16895768

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

*

Lerner AM, Dworkin HJ, Sayyed T, Chang CH, Fitzgerald JT, Beqaj S, Deeter RG, Goldstein J, Gottipolu P, O'Neill W. Prevalence of abnormal cardiac wall motion in the cardiomyopathy associated with incomplete multiplication of Epstein-barr Virus and/or cytomegalovirus in patients with chronic fatigue syndrome. In Vivo. 2004 Jul-Aug;18(4):417-24. PMID: 15369178

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).

*

Peckerman A, LaManca JJ, Dahl KA, Chemitiganti R, Qureishi B, Natelson BH. Abnormal impedance cardiography predicts symptom severity in chronic fatigue syndrome. Am J Med Sci. 2003 Aug;326(2):55-60. PMID: 12920435

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.

*

Dworkin HJ, Lawrie C, Bohdiewicz P, Lerner AM. Abnormal left ventricular myocardial dynamics in eleven patients with chronic fatigue syndrome.Clin Nucl Med. 1994 Aug;19(8):675-7. PMID: 7955743

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.

*

Lerner AM, Lawrie C, Dworkin HS. Repetitively negative changing T waves at 24-h electrocardiographic monitors in patients with the chronic fatigue syndrome. Left ventricular dysfunction in a cohort. Chest. 1993 Nov;104(5):1417-21. PMID: 8222798

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

Miwa K. Variability of postural orthostatic tachycardia in patients with myalgic encephalomyelitis and orthostatic intolerance. Heart Vessels. 2015 Sep 15. PMID: 26374335

In ME patients with orthostatic intolerance, the exaggerated activation of the sympathetic nervous system while standing appears to switch to the impaired sympathetic activation after the system is loaded with the additional accentuated stimuli associated with the preload reduction.

*

Eyskens JB, Nijs J, D'Août K, Sand A, Wouters K, Moorkens G. Timed loaded standing in female chronic fatigue syndrome compared with other populations. J Rehabil Res Dev. 2015;52(1):21-9. PMID: 26230614

The timed loaded standing (TLS) test scores were lower in patients with CFS than in nondisabled controls.

*

Medow MS, Sood S, Messer Z, Dzogbeta S, Terilli C, Stewart JM. Phenylephrine alteration of cerebral blood flow during orthostasis: effect on n-back performance in chronic fatigue syndrome. J Appl Physiol (1985). 2014 Nov 15;117(10):1157-64. PMID: 25277740

Compared with control subjects, CFS subjects are more sensitive both to orthostatic challenge and to baroreflex/chemoreflex-mediated interventions.

*

Van Cauwenbergh D, Nijs J, Kos D, Van Weijnen L, Struyf F, Meeus M. Malfunctioning of the autonomic nervous system in patients with chronic fatigue

syndrome: a systematic literature review. Eur J Clin Invest. 2014 May;44(5):516-26. PMID: 24601948

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.

*

Reynolds GK, Lewis DP, Richardson AM, Lidbury BA. Comorbidity of postural orthostatic tachycardia syndrome and chronic fatigue syndrome in an Australian cohort. J Intern Med. 2014 Apr;275(4):409-17. PMID: 24206536

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.

*

Nijs J, Ickmans K. Postural orthostatic tachycardia syndrome as a clinically important subgroup of chronic fatigue syndrome: further evidence for central nervous system dysfunctioning. J Intern Med. 2013 May;273(5):498-500. PMID: 23331489

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

*

Lewis I, Pairman J, Spickett G, Newton JL. Clinical characteristics of a novel subgroup of chronic fatigue syndrome patients with postural orthostatic tachycardia syndrome. J Intern Med. 2013 May;273(5):501-10. PMID: 23206180

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.

*

Chirilă EL, Postolache P. Orthostatic intolerance and chronic fatigue syndrome--possible related conditions. Rev Med Chir Soc Med Nat Iasi. 2013 Apr-Jun;117(2):388-93. PMID: 24340521

Many patients with chronic fatigue syndrome also had some form of orthostatic intolerance. Some studies suggested that dysautonomia may be the common problem in patients with these syndromes.

*

Okamoto LE, Raj SR, Peltier A, Gamboa A, Shibao C, Diedrich A, Black BK, Robertson D, Biaggioni I. Neurohumoral and haemodynamic profile in postural tachycardia and chronic fatigue syndromes. Clin Sci (Lond). 2012 Feb 1;122(4):183-92. PMID: 21906029

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.

*

Benarroch EE. Postural tachycardia syndrome: a heterogeneous and multifactorial disorder. Mayo Clin Proc. 2012 Dec;87(12):1214-25. PMID: 23122672

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

*

Allen J, Murray A, Di Maria C, Newton JL. Chronic fatigue syndrome and impaired peripheral pulse characteristics on orthostasis--a new potential diagnostic biomarker. Physiol Meas. 2012 Feb;33(2):231-41. PMID: 22273713

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

*

Ocon AJ, Messer Z, Medow M, Stewart J. Increasing orthostatic stress impairs neurocognitive functioning in Chronic Fatigue Syndrome with Postural Tachycardia Syndrome. Clin Sci (Lond). 2011 Sep 15. PMID: 21919887

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.

*

Jones DE, Gray J, Frith J, Newton JL. Fatigue severity remains stable over time and independently associated with orthostatic symptoms in chronic fatigue syndrome: a longitudinal study. J Intern Med. 2011 Feb;269(2):182-8. PMID: 21073560

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

*

Wyller VB, Barbieri R, Saul JP. Blood pressure variability and closed-loop baroreflex assessment in adolescent chronic fatigue syndrome during supine rest and orthostatic stress. Eur J Appl Physiol. 2011 Mar;111(3):497-507. PMID: 20890710

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

*

Costigan A, Elliott C, McDonald C, Newton JL. Orthostatic symptoms predict functional capacity in chronic fatigue syndrome: implications for management. QJM. 2010 Jun 9. PMID: 20534655

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

*

Hollingsworth KG, Jones DE, Taylor R, Blamire AM, Newton JL. Eur J Clin Invest. Impaired cardiovascular response to standing in Chronic Fatigue Syndrome. 2010 May 20. PMID: 20497461

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

*

Wyller VB, Barbieri R, Thaulow E, Saul JP. Enhanced vagal withdrawal during mild orthostatic stress in adolescents with chronic fatigue. Ann Noninvasive Electrocardiol. 2008 Jan;13(1):67-73. PMID: 18234008

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

*

Hoad A, Spickett G, Elliott J, Newton J. Postural orthostatic tachycardia syndrome is an under-recognized condition in chronic fatigue syndrome. QJM. 2008 Dec;101(12):961-5. PMID: 18805903

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.

*

Galland BC, Jackson PM, Sayers RM, Taylor BJ. A matched case control study of orthostatic intolerance in children/adolescents with chronic fatigue syndrome. Pediatr Res. 2008 Feb;63(2):196-202. PMID: 18091356

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

*

Wyller VB, Saul JP, Walløe L, Thaulow E. Sympathetic cardiovascular control during orthostatic stress and isometric exercise in adolescent chronic fatigue syndrome. Eur J Appl Physiol. 2008 Apr;102(6):623-32. PMID: 18066580

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.

*

Agarwal AK, Garg R, Ritch A, Sarkar P. Postural orthostatic tachycardia syndrome. Postgrad Med J. 2007 Jul;83(981):478-80. PMID: 17621618

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

*

Wyller VB, Saul JP, Amlie JP, Thaulow E. Sympathetic predominance of cardiovascular regulation during mild orthostatic stress in adolescents with chronic fatigue. Clin Physiol Funct Imaging. 2007 Jul;27(4):231-8. PMID: 17564672

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

*

Tanaka H. Autonomic function and child chronic fatigue syndrome. Nihon Rinsho. 2007 Jun;65(6):1105-12. PMID: 17561705

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.

*

Naschitz JE, Yeshurun D, Rosner I. Dysautonomia in chronic fatigue syndrome: facts, hypotheses, implications. Med Hypotheses. 2004;62(2):203-6. PMID: 14962627

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

*

Peckerman A, LaManca JJ, Qureishi B, Dahl KA, Golfetti R, Yamamoto Y, Natelson BH. Baroreceptor reflex and integrative stress responses in chronic fatigue syndrome. Psychosom Med. 2003 Sep-Oct;65(5):889-95. PMID: 14508037

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

*

Khan F, Spence V, Kennedy G, Belch JJ. Prolonged acetylcholine-induced vasodilatation in the peripheral microcirculation of patients with chronic fatigue syndrome. Clin Physiol Funct Imaging. 2003 Sep;23(5):282-5. PMID: 12950326

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.

*

Tanaka H, Matsushima R, Tamai H, Kajimoto Y. Impaired postural cerebral hemodynamics in young patients with chronic fatigue with and without orthostatic intolerance. J Pediatr. 2002 Apr;140(4):412-7. PMID: 12006954

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.

*

Naschitz JE, Sabo E, Naschitz S, Shaviv N, Rosner I, Rozenbaum M, Gaitini L, Ahdoot A, Ahdoot M, Priselac RM, Eldar S, Zukerman E, Yeshurun D. Hemodynamic instability in chronic fatigue syndrome: indices and diagnostic significance. Semin Arthritis Rheum. 2001 Dec;31(3):199-208. PMID: 11740800

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

*

Stewart JM. Autonomic nervous system dysfunction in adolescents with postural orthostatic tachycardia syndrome and chronic fatigue syndrome is characterized by attenuated vagal baroreflex and potentiated sympathetic vasomotion. Pediatr Res. 2000 Aug;48(2):218-26. PMID: 10926298

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.

*

Streeten DH, Thomas D, Bell DS. The roles of orthostatic hypotension, orthostatic tachycardia, and subnormal erythrocyte volume in the pathogenesis of the chronic fatigue syndrome. Am J Med Sci. 2000 Jul;320(1):1-8. PMID: 10910366

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.

*

Rowe PC, Barron DF, Calkins H, Maumenee IH, Tong PY, Geraghty MT. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. J Pediatr. 1999 Oct;135(4):494-9. PMID: 10518084

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

*

Stewart JM, Gewitz MH, Weldon A, Munoz J. Patterns of orthostatic intolerance: the orthostatic tachycardia syndrome and adolescent chronic fatigue. J Pediatr. 1999 Aug;135(2 Pt 1):218-25. PMID: 10431117

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.

*

Schondorf R, Benoit J, Wein T, Phaneuf D. Orthostatic intolerance in the chronic fatigue syndrome.J Auton Nerv Syst. 1999 Feb 15;75(2-3):192-201. PMID: 10189122

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.

*

Stewart JM, Gewitz MH, Weldon A, Arlievsky N, Li K, Munoz J. Orthostatic intolerance in adolescent chronic fatigue syndrome. Pediatrics. 1999 Jan;103(1):116-21. PMID: 9917448

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.

*

Streeten DH, Anderson GH Jr. The role of delayed orthostatic hypotension in the pathogenesis of chronic fatigue. Clin Auton Res. 1998 Apr;8(2):119-24. PMID: 9613802

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

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Rowe PC, Calkins H. Neurally mediated hypotension and chronic fatigue syndrome. Am J Med. 1998 Sep 28;105(3A):15S-21S. PMID: 9790477

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.

*

Rowe PC, Bou-Holaigah I, Kan JS, Calkins H. Is neurally mediated hypotension an unrecognised cause of chronic fatigue? Lancet. 1995 Mar 11;345(8950):623-4. PMID: 7898182

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

Tilt Table Test

Wyller VB, Due R, Saul JP, Amlie JP, Thaulow E. Usefulness of an abnormal cardiovascular response during low-grade head-up tilt-test for discriminating adolescents with chronic fatigue from healthy controls. Am J Cardiol. 2007 Apr 1;99(7):997-1001. PMID: 17398200

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

*

Naschitz JE, Mussafia-Priselac R, Kovalev Y, Zaigraykin N, Slobodin G, Elias N, Rosner I. Patterns of hypocapnia on tilt in patients with fibromyalgia, chronic fatigue syndrome, nonspecific dizziness, and neurally mediated syncope. Am J Med Sci. 2006 Jun;331(6):295-303. PMID: 16775435

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.

*

Jones JF, Nicholson A, Nisenbaum R, Papanicolaou DA, Solomon L, Boneva R, Heim C, Reeves WC. Orthostatic instability in a population-based study of chronic fatigue syndrome. Am J Med. 2005 Dec;118(12):1415. PMID: 16378795

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.

*

Yoshiuchi K, Quigley KS, Ohashi K, Yamamoto Y, Natelson BH. Use of time-frequency analysis to investigate temporal patterns of cardiac autonomic response during head-up tilt in chronic fatigue syndrome. Auton Neurosci. 2004 Jun 30;113(1-2):55-62. PMID: 15296795

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.

*

Razumovsky AY, DeBusk K, Calkins H, Snader S, Lucas KE, Vyas P, Hanley DF, Rowe PC. Cerebral and systemic hemodynamics changes during upright tilt in chronic fatigue syndrome. J Neuroimaging. 2003 Jan;13(1):57-67. PMID: 12593133

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.

*

Naschitz JE, Rosner I, Rozenbaum M, Naschitz S, Musafia-Priselac R, Shaviv N, Fields M, Isseroff H, Zuckerman E, Yeshurun D, Sabo E. The head-up tilt test with haemodynamic instability score in diagnosing chronic fatigue syndrome. QJM. 2003 Feb;96(2):133-42. PMID: 12589011

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.

*

Timmers HJ, Wieling W, Soetekouw PM, Bleijenberg G, Van Der Meer JW, Lenders JW. Hemodynamic and neurohumoral responses to head-up tilt in patients with chronic fatigue syndrome. Clin Auton Res. 2002 Aug;12(4):273-80. PMID: 12357281

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.

*

Naschitz JE, Rozenbaum M, Rosner I, Sabo E, Priselac RM, Shaviv N, Ahdoot A, Ahdoot M, Gaitini L, Eldar S, Yeshurun D. Cardiovascular response to upright tilt in fibromyalgia differs from that in chronic fatigue syndrome. J Rheumatol. 2001 Jun;28(6):1356-60. PMID: 11409131

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

*

Karas B, Grubb BP, Boehm K, Kip K. The postural orthostatic tachycardia syndrome: a potentially treatable cause of chronic fatigue, exercise intolerance, and cognitive impairment in adolescents. Pacing Clin Electrophysiol. 2000 Mar;23(3):344-51. PMID: 10750135

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.

*

LaManca JJ, Peckerman A, Walker J, Kesil W, Cook S, Taylor A, Natelson BH. Cardiovascular response during head-up tilt in chronic fatigue syndrome. Clin Physiol. 1999 Mar;19(2):111-20. PMID: 10200892

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

*

Stewart J, Weldon A, Arlievsky N, Li K, Munoz J. Neurally mediated hypotension and autonomic dysfunction measured by heart rate variability during head-up tilt testing in children with chronic fatigue syndrome. Clin Auton Res. 1998 Aug;8(4):221-30. PMID: 9791743

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.

*

De Becker P, Dendale P, De Meirleir K, Campine I, Vandenborne K, Hagers Y. Autonomic testing in patients with chronic fatigue syndrome. Am J Med. 1998 Sep 28;105(3A):22S-26S. PMID: 9790478

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

*

De Lorenzo F, Hargreaves J, Kakkar VV. Pathogenesis and management of delayed orthostatic hypotension in patients with chronic fatigue syndrome. Clin Auton Res. 1997 Aug;7(4):185-90. PMID: 9292244

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.

*

De Lorenzo F, Hargreaves J, Kakkar VV. Possible relationship between chronic fatigue and postural tachycardia syndromes. Clin Auton Res. 1996 Oct;6(5):263-4. PMID: 8899252

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

*

Bou-Holaigah I, Rowe PC, Kan J, Calkins H. The relationship between neurally mediated hypotension and the chronic fatigue syndrome. JAMA. 1995 Sep 27;274(12):961-7. PMID: 7674527

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

Wyller VB, Fagermoen E, Sulheim D, Winger A, Skovlund E, Saul JP. Orthostatic responses in adolescent chronic fatigue syndrome: contributions from expectancies as well as gravity. Biopsychosoc Med. 2014 Sep 15;8:22. PMID: 25237387

At supine rest, CFS patients had significantly higher heart rate, diastolic blood pressure, and mean arterial blood pressure, and lower stroke index and heart rate variability (HRV) indices.

*

Gao J, Gurbaxani BM, Hu J, Heilman KJ, Emanuele Ii VA, Lewis GF, Davila M, Unger ER, Lin JM. Multiscale analysis of heart rate variability in non-stationary environments. Front Physiol. 2013 May 30;4:119. PMID: 23755016

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.

*

Meeus M, Goubert D, De Backer F, Struyf F, Hermans L, Coppieters I, De Wandele I, Da Silva H, Calders P. Heart rate variability in patients with fibromyalgia and

patients with chronic fatigue syndrome: A systematic review. Semin Arthritis Rheum. 2013 Oct;43(2):279-87. PMID: 23838093

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.

*

Hurum H, Sulheim D, Thaulow E, Wyller VB. Elevated nocturnal blood pressure and heart rate in adolescent chronic fatigue syndrome. Acta Paediatr. 2011 Feb;100(2):289-92. PMID: 21059182

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.

*

Burton AR, Rahman K, Kadota Y, Lloyd A, Vollmer-Conna U. Reduced heart rate variability predicts poor sleep quality in a case-control study of chronic fatigue syndrome. Exp Brain Res. 2010 Jul;204(1):71-8. PMID: 20502886

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.

*

Newton JL, Sheth A, Shin J, Pairman J, Wilton K, Burt JA, Jones DE. Lower ambulatory blood pressure in chronic fatigue syndrome. Psychosom Med. 2009 Apr;71(3):361-5. PMID: 19297309

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

*

Newton JL, Okonkwo O, Sutcliffe K, Seth A, Shin J, Jones DE. Symptoms of autonomic dysfunction in chronic fatigue syndrome. QJM. 2007 Aug;100(8):519-26. PMID: 17617647

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

*

Boneva RS, Decker MJ, Maloney EM, Lin JM, Jones JF, Helgason HG, Heim CM, Rye DB, Reeves WC. Higher heart rate and reduced heart rate variability persist during sleep in chronic fatigue syndrome: a population-based study. Auton Neurosci. 2007 Dec 30;137(1-2):94-101. PMID: 17851136

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.

*

Winkler AS, Blair D, Marsden JT, Peters TJ, Wessely S, Cleare AJ. Autonomic function and serum erythropoietin levels in chronic fatigue syndrome. J Psychosom Res. 2004 Feb;56(2):179-83. PMID:15016575

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.

*

Vanness JM, Snell CR, Strayer DR, Dempsey L 4th, Stevens SR. Subclassifying chronic fatigue syndrome through exercise testing. Med Sci Sports Exerc. 2003 Jun;35(6):908-13. PMID: 12783037

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.

*

Naschitz JE, Sabo E, Naschitz S, Rosner I, Rozenbaum M, Fields M, Isseroff H, Priselac RM, Gaitini L, Eldar S, Zukerman E, Yeshurun D. Hemodynamics instability score in chronic fatigue syndrome and in non-chronic fatigue syndrome. Semin Arthritis Rheum. 2002 Dec;32(3):141-8. PMID: 12528078

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.

*

Naschitz JE, Sabo E, Naschitz S, Rosner I, Rozenbaum M, Priselac RM, Gaitini L, Zukerman E, Yeshurun D. Fractal analysis and recurrence quantification analysis of heart rate and pulse transit time for diagnosing chronic fatigue syndrome. Clin Auton Res. 2002 Aug;12(4):264-72. PMID: 12357280

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.

*

Farquhar WB, Hunt BE, Taylor JA, Darling SE, Freeman R. Blood volume and its relation to peak O(2) consumption and physical activity in patients with chronic fatigue. Am J Physiol Heart Circ Physiol. 2002 Jan;282(1):H66-71. PMID: 11748048

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.

*

LaManca JJ, Peckerman A, Sisto SA, DeLuca J, Cook S, Natelson BH. Cardiovascular responses of women with chronic fatigue syndrome to stressful cognitive testing before and after strenuous exercise. Psychosom Med. 2001 Sep-Oct;63(5):756-64. PMID: 11573024

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.

*

Duprez DA, De Buyzere ML, Drieghe B, Vanhaverbeke F, Taes Y, Michielsen W, Clement DL. Long- and short-term blood pressure and RR-interval variability and psychosomatic distress in chronic fatigue syndrome. Clin Sci (Lond). 1998 Jan;94(1):57-63. PMID: 9505867

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

*

Cordero DL, Sisto SA, Tapp WN, LaManca JJ, Pareja JG, Natelson BH. Decreased vagal power during treadmill walking in patients with chronic fatigue syndrome. Clin Auton Res. 1996 Dec;6(6):329-33. PMID: 8985621

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

*

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 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

Shukla SK, Cook D, Meyer J, Vernon SD, Le T, Clevidence D, Robertson CE, Schrodi SJ, Yale S, Frank DN. Changes in Gut and Plasma Microbiome following Exercise Challenge in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). PLoS One. 2015 Dec 18;10(12):e0145453. PMID: 26683192

Following maximal exercise challenge, there was an increase in relative abundance of 6 of the 9 major bacterial phyla/genera in ME/CFS patients from baseline to 72 hours post-exercise compared to only 2 of the 9 phyla/genera in controls ($p = 0.005$). There was also a significant difference in clearance of specific bacterial phyla from blood following exercise with high levels of bacterial sequences maintained at 72 hours post-exercise in ME/CFS patients versus clearance in the controls. These findings suggest a role for an altered gut microbiome and increased bacterial translocation following exercise in ME/CFS patients.

*

Keller BA, Pryor JL, Giloteaux L. Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO2peak indicates functional impairment. J Transl Med. 2014 Apr 23;12(1):104. PMID: 24755065

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.

*

Vermeulen RC, Vermeulen van Eck IW. Decreased oxygen extraction during cardiopulmonary exercise test in patients with chronic fatigue syndrome. J Transl Med. 2014 Jan 23;12:20. PMID: 24456560

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.

*

Learmonth YC, Paul L, McFadyen AK, Marshall-McKenna R, Mattison P, Miller L. McFarlane NG. Short-term effect of aerobic exercise on symptoms in multiple sclerosis and chronic fatigue syndrome: a pilot study. Int J MS Care. 2014 Summer;16(2):76-82. PMID: 25061431

Undertaking 15 minutes of moderate-intensity aerobic cycling exercise had no significant adverse effects on pain or function in people with MS and CFS (with a Karnofsky score of 50-80) within a 24-hour time period.

*

Kishi A, Togo F, Cook DB, Klapholz M, Yamamoto Y, Rapoport DM, Natelson BH. The effects of exercise on dynamic sleep morphology in healthy controls and patients with chronic fatigue syndrome. Physiol Rep. 2013 Nov;1(6):e00152. PMID: 24400154

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

*

Snell CR, Stevens SR, Davenport TE, Van Ness JM. Discriminative validity of metabolic and workload measurements for identifying people with chronic fatigue syndrome. Phys Ther. 2013 Nov;93(11):1484-92. PMID: 23813081

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.

*

Strahler J, Fischer S, Nater UM, Ehlert U, Gaab J. Norepinephrine and epinephrine responses to physiological and pharmacological stimulation in chronic fatigue syndrome. Biol Psychol. 2013 Sep;94(1):160-6. PMID: 23770415

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

*

Nakamura T, Schwander S, Donnelly R, Cook DB, Ortega F, Togo F, Yamamoto Y, Cherniack NS, Klapholz M, Rapoport D, Natelson BH. Exercise and sleep deprivation do not change cytokine expression levels in patients with chronic fatigue syndrome. Clin Vaccine Immunol. 2013 Nov;20(11):1736-42. PMID: 24027260

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 with chronic fatigue syndrome, patients with multiple sclerosis, and healthy controls. Psychosom Med. 2012 Jan;74(1):46-54. PMID: 22210239

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.

*

Cook DB, Stegner AJ, Nagelkirk PR, Meyer JD, Togo F, Natelson BH. Responses to exercise differ for chronic fatigue syndrome patients with fibromyalgia. Med Sci Sports Exerc. 2012 Jun;44(6):1186-93. PMID: 22157881

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.

*

Jammes Y, Steinberg JG, Delliaux S. Chronic fatigue syndrome: acute infection and history of physical activity affect resting levels and response to exercise of plasma oxidant/antioxidant status and heat shock proteins. J Intern Med. 2011 Nov 24. PMID: 22112145

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.

*

Jones DE, Hollingsworth KG, Jakovljevic DG, Fattakhova G, Pairman J, Blamire AM, Trenell MI, Newton JL. Loss of capacity to recover from acidosis on repeat exercise in chronic fatigue syndrome: a case-control study. Eur J Clin Invest. 2011 Jun 10. PMID: 21749371

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.

*

Nijs J, Meeus M, Van Oosterwijck J, Ickmans K, Moorkens G, Hans G, De Clerck LS. In the mind or in the brain? Scientific evidence for central sensitisation in chronic fatigue syndrome. Eur J Clin Invest. 2011 Jul 2. PMID: 21793823

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.

*

Light AR, Bateman L, Jo D, Hughen RW, Vanhaitsma TA, White AT, Light KC. Gene expression alterations at baseline and following moderate exercise in patients with Chronic Fatigue Syndrome and Fibromyalgia Syndrome. J Intern Med. 2011 May 26. PMID: 21615807

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.

*

Davenport TE, Stevens SR, Baroni K, Van Ness M, Snell CR. Diagnostic accuracy of symptoms characterising chronic fatigue syndrome. Disabil Rehabil. 2011 Jan 6. PMID: 21208154

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

*

Vermeulen RC, Kurk RM, Visser FC, Sluiter W, Scholte HR. Patients with chronic fatigue syndrome performed worse than controls in a controlled repeated exercise study despite a normal oxidative phosphorylation capacity. J Transl Med. 2010 Oct 11;8:93.

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.

*

Meeus M, Ickmans K, De Clerck LS, Moorkens G, Hans G, Grosemans S, Nijs J. Serotonergic descending inhibition in chronic pain: design, preliminary results and early cessation of a randomized controlled trial. In Vivo. 2011 Nov-Dec;25(6):1019-25. PMID: 22021700

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.

*

Meeus M, Roussel NA, Truijen S, Nijs J. Reduced pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low back pain: an experimental study. J Rehabil Med. 2010 Oct;42(9):884-90. PMID: 20878051

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

*

Meeus M, van Eupen I, van Baarle E, De Boeck V, Luyckx A, Kos D, Nijs J. Symptom fluctuations and daily physical activity in patients with chronic fatigue syndrome: a case-control study. Arch Phys Med Rehabil. 2011 Nov;92(11):1820-6. PMID: 22032215

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.

*

Suárez A, Guillamo E, Roig T, Blázquez A, Alegre J, Bermúdez J, Ventura JL, García-Quintana AM, Comella A, Segura R, Javierre C. Nitric Oxide Metabolite Production During Exercise in Chronic Fatigue Syndrome: A Case-Control Study. J Womens Health (Larchmt). 2010 May 14. PMID: 20469961

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

*

Nijs J, Van Oosterwijck J, Meeus M, Lambrecht L, Metzger K, Frémont M, Paul L. Unravelling the nature of postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: the role of elastase, complement C4a and interleukin-1beta. J Intern Med. 2010 Apr;267(4):418-35. PMID: 20433584

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

*

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.

*

Jones DE, Hollingsworth KG, Taylor R, Blamire AM, Newton JL. Abnormalities in pH handling by peripheral muscle and potential regulation by the autonomic nervous system in chronic fatigue syndrome. J Intern Med. 2010 Apr;267(4):394-401. PMID: 20433583

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

*

White AT, Light AR, Hughen RW, Bateman L, Martins TB, Hill HR, Light KC. Severity of symptom flare after moderate exercise is linked to cytokine activity in chronic fatigue syndrome. Psychophysiology. 2010 Mar 4. PMID: 20230500

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

*

Robinson M, Gray SR, Watson MS, Kennedy G, Hill A, Belch JJ, Nimmo MA. Plasma IL-6, its soluble receptors and F2-isoprostanes at rest and during exercise in chronic fatigue syndrome. Scand J Med Sci Sports. 2010 Apr;20(2):282-90. PMID: 19422646

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

*

Van Oosterwijck J, Nijs J, Meeus M, Lefever I, Huybrechts L, Lambrecht L, Paul L. Pain inhibition and postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: an experimental study. J Intern Med. 2010 Sep;268(3):265-78. PMID: 20412374

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.

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VanNess JM, Stevens SR, Bateman L, Stiles TL, Snell CR. Postexertional malaise in women with chronic fatigue syndrome. J Womens Health (Larchmt). 2010 Feb;19(2):239-44. PMID: 20095909

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.

*

Light AR, White AT, Hughen RW, Light KC. Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects. J Pain. 2009 Oct;10(10):1099-112. PMID: 19647494

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.

*

Maes M. Inflammatory and oxidative and nitrosative stress pathways underpinning chronic fatigue, somatization and psychosomatic symptoms. Curr Opin Psychiatry. 2009 Jan;22(1):75-83. PMID: 19127706

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.

*

Sorensen B, Jones JF, Vernon SD, Rajeevan MS. Transcriptional control of complement activation in an exercise model of chronic fatigue syndrome. Mol Med. 2009 Jan-Feb;15(1-2):34-42. PMID: 19015737

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.

*

Jammes Y, Steinberg JG, Delliaux S, Brégeon F. Chronic fatigue syndrome combines increased exercise-induced oxidative stress and reduced cytokine and Hsp responses. J Intern Med. 2009 Aug;266(2):196-206. PMID: 19457057

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.

*

Paul L, Rafferty D, Marshal R. Physiological cost of walking in those with chronic fatigue syndrome (CFS): a case-control study. Disabil Rehabil. 2009;31(19):1598-604. PMID: 19848558

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

*

Maes M, Twisk FN. Chronic fatigue syndrome: la bête noire of the Belgian health care system. Neuro Endocrinol Lett. 2009;30(3):300-11. PMID: 19855351

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.

*

Jason L, Benton M, Torres-Harding S, Muldowney K. The impact of energy modulation on physical functioning and fatigue severity among patients with ME/CFS. Patient Educ Couns. 2009 Nov;77(2):237-41. PMID: 19356884

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.

*

Weinstein AA, Drinkard BM, Diao G, Furst G, Dale JK, Straus SE, Gerber LH.

Exploratory analysis of the relationships between aerobic capacity and self-reported fatigue in patients with rheumatoid arthritis, polymyositis, and chronic fatigue syndrome. PM R. 2009 Jul;1(7):620-8. PMID: 19627955

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.

*

Thambirajah AA, Sleigh K, Stiver HG, Chow AW. Differential heat shock protein responses to strenuous standardized exercise in chronic fatigue syndrome patients and matched healthy controls. Clin Invest Med. 2008 Dec 1;31(6):E319-27. PMID: 19032901

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.

*

Patrick Neary J, Roberts AD, Leavins N, Harrison MF, Croll JC, Sexsmith JR. Prefrontal cortex oxygenation during incremental exercise in chronic fatigue syndrome. Clin Physiol Funct Imaging. 2008 Nov;28(6):364-72. PMID: 18671793

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

*

Nijs J, Almond F, De Becker P, Truijen S, Paul L. Can exercise limits prevent post-exertional malaise in chronic fatigue syndrome? An uncontrolled clinical trial. Clin Rehabil. 2008 May;22(5):426-35. PMID: 18441039

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.

*

Nijs J, Zwinnen K, Meeusen R, de Geus B, De Meirleir K. Comparison of two exercise testing protocols in patients with chronic fatigue syndrome. J Rehabil Res Dev. 2007;44(4):553-9. PMID: 18247252

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.

*

Nijs J, Demol S, Wallman K. Can submaximal exercise variables predict peak exercise performance in women with chronic fatigue syndrome? Arch Med Res. 2007 Apr;38(3):350-3. PMID: 17350488

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).

*

Yoshiuchi K, Cook DB, Ohashi K, Kumano H, Kuboki T, Yamamoto Y, Natelson BH. A real-time assessment of the effect of exercise in chronic fatigue syndrome. Physiol Behav. 2007 Dec 5;92(5):963-8. PMID: 17655887

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.

*

Nijs J, Meeus M, De Meirleir K. Chronic musculoskeletal pain in chronic fatigue syndrome: recent developments and therapeutic implications. Man Ther. 2006 Aug;11(3):187-91. PMID: 16781183

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.

*

Cook DB, Nagelkirk PR, Poluri A, Mores J, Natelson BH. The influence of aerobic fitness and fibromyalgia on cardiorespiratory and perceptual responses to exercise in patients with chronic fatigue syndrome. Arthritis Rheum. 2006 Oct;54(10):3351-62. PMID: 17009309

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.

*

Nijs J, Meeus M, McGregor NR, Meeusen R, de Schutter G, van Hoof E, de Meirleir K. Chronic fatigue syndrome: exercise performance related to immune dysfunction. Med Sci Sports Exerc. 2005 Oct;37(10):1647-54. PMID: 16260962

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

*

Jammes Y, Steinberg JG, Mambrini O, Brégeon F, Delliaux S. Chronic fatigue syndrome: assessment of increased oxidative stress and altered muscle excitability in response to incremental exercise. J Intern Med. 2005 Mar;257(3):299-310. PMID: 15715687

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

*

Nijs J, De Meirleir K. Impairments of the 2-5A synthetase/RNase L pathway in chronic fatigue syndrome. In Vivo. 2005 Nov-Dec;19(6):1013-21. PMID: 16277015

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.

*

Black CD, McCully KK. Time course of exercise induced alterations in daily activity in chronic fatigue syndrome. Dyn Med. 2005 Oct 28;4:10. PMID: 16255779

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.

*

Bazelmans E, Bleijenberg G, Voeten MJ, van der Meer JW, Folgering H. Impact of a maximal exercise test on symptoms and activity in chronic fatigue syndrome. J Psychosom Res. 2005 Oct;59(4):201-8. PMID: 16223622

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

*

Snell CR, Vanness JM, Strayer DR, Stevens SR. Exercise capacity and immune function in male and female patients with chronic fatigue syndrome (CFS). In Vivo. 2005 Mar-Apr;19(2):387-90. PMID: 15796202

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.

*

Nijs J, De Meirleir K. Prediction of peak oxygen uptake in patients fulfilling the 1994 CDC criteria for chronic fatigue syndrome. Clin Rehabil. 2004 Nov;18(7):785-92. PMID: 15573835

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

*

Whiteside A, Hansen S, Chaudhuri A. Exercise lowers pain threshold in chronic fatigue syndrome. Pain. 2004 Jun;109(3):497-9. PMID: 15157711

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

*

Nijs J, Vanherberghen K, Duquet W, De Meirleir K. Chronic fatigue syndrome: lack of association between pain-related fear of movement and exercise capacity and disability. Phys Ther. 2004 Aug;84(8):696-705. PMID: 15283620

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.

*

Siemionow V, Fang Y, Calabrese L, Sahgal V, Yue GH. Altered central nervous system signal during motor performance in chronic fatigue syndrome. Clin Neurophysiol. 2004 Oct;115(10):2372-81. PMID: 15351380

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

*

McCully KK, Smith S, Rajaei S, Leigh JS Jr, Natelson BH. Muscle metabolism with blood flow restriction in chronic fatigue syndrome. J Appl Physiol. 2004 Mar;96(3):871-8. PMID: 14578362

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

*

Nijs J, De Meirleir K, Wolfs S, Duquet W. Disability evaluation in chronic fatigue syndrome: associations between exercise capacity and activity limitations/participation restrictions. Clin Rehabil. 2004 Mar;18(2):139-48. PMID: 15053122

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.

*

Sorensen B, Streib JE, Strand M, Make B, Giclas PC, Fleshner M, Jones JF. Complement activation in a model of chronic fatigue syndrome. J Allergy Clin Immunol. 2003 Aug;112(2):397-403. PMID: 12897748

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.

*

Vanness JM, Snell CR, Strayer DR, Dempsey L 4th, Stevens SR. Subclassifying chronic fatigue syndrome through exercise testing. Med Sci Sports Exerc. 2003 Jun;35(6):908-13. PMID: 12783037

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

*

Snell CR, Vanness JM, Strayer DR, Stevens SR. Physical performance and prediction of 2-5A synthetase/RNase L antiviral pathway activity in patients with chronic fatigue syndrome. In Vivo. 2002 Mar-Apr;16(2):107-9. PMID: 12073768

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 V02 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.

*

Farquhar WB, Hunt BE, Taylor JA, Darling SE, Freeman R. Blood volume and its relation to peak O(2) consumption and physical activity in patients with chronic fatigue. Am J Physiol Heart Circ Physiol. 2002 Jan;282(1):H66-71. PMID: 11748048

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

*

Inbar O, Dlin R, Rotstein A, Whipp BJ. Physiological responses to incremental exercise in patients with chronic fatigue syndrome. Med Sci Sports Exerc. 2001 Sep;33(9):1463-70. PMID: 11528333

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

*

Jason LA, Melrose H, Lerman A, Burroughs V, Lewis K, King CP, Frankenberry EL. Managing chronic fatigue syndrome: overview and case study. AAOHN J. 1999 Jan;47(1):17-21. PMID: 10205371

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.

*

McCully KK, Natelson BH. Impaired oxygen delivery to muscle in chronic fatigue syndrome. Clin Sci (Lond). 1999 Nov;97(5):603-8; discussion 611-3. PMID: 10545311

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

*

Mullis R, Campbell IT, Wearden AJ, Morriss RK, Pearson DJ. Prediction of peak oxygen uptake in chronic fatigue syndrome. Br J Sports Med. 1999 Oct;33(5):352-6. PMID: 10522640

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.

*

Paul L, Wood L, Behan WM, Maclaren WM. Demonstration of delayed recovery from fatiguing exercise in chronic fatigue syndrome. Eur J Neurol. 1999 Jan;6(1):63-9. PMID: 10209352

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.

*

LaManca JJ, Sisto SA, DeLuca J, Johnson SK, Lange G, Pareja J, Cook S, Natelson BH. Influence of exhaustive treadmill exercise on cognitive functioning in chronic fatigue syndrome. Am J Med. 1998 Sep 28;105(3A):59S-65S. PMID: 9790484

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

*

Blackwood SK, MacHale SM, Power MJ, Goodwin GM, Lawrie SM. Effects of exercise on cognitive and motor function in chronic fatigue syndrome and depression. J Neurol Neurosurg Psychiatry. 1998 Oct;65(4):541-6. PMID: 9771781

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.

*

Lane RJ, Barrett MC, Woodrow D, Moss J, Fletcher R, Archard LC. Muscle fibre characteristics and lactate responses to exercise in chronic fatigue syndrome. J Neurol Neurosurg Psychiatry. 1998 Mar;64(3):362-7. PMID: 9527150

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.

*

Fischler B, Dendale P, Michiels V, Cluydts R, Kaufman L, De Meirleir K. Physical fatigability and exercise capacity in chronic fatigue syndrome: association with disability, somatization and psychopathology. J Psychosom Res. 1997 Apr;42(4):369-78. PMID: 9160276

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

*

Kent-Braun JA, Sharma KR, Weiner MW, Massie B, Miller RG. Central basis of muscle fatigue in chronic fatigue syndrome. Neurology. 1993 Jan;43(1):125-31.

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

*

Wong R, Lopaschuk G, Zhu G, Walker D, Catellier D, Burton D, Teo K, Collins-Nakai R, Montague T. Skeletal muscle metabolism in the chronic fatigue syndrome. In vivo assessment by 31P nuclear magnetic resonance spectroscopy. Chest. 1992 Dec;102(6):1716-22. PMID: 1446478

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

Maes M, Leunis JC. Attenuation of autoimmune responses to oxidative specific epitopes, but not nitroso-adducts, is associated with a better clinical outcome in Myalgic Encephalomyelitis/chronic fatigue syndrome. Neuro Endocrinol Lett. 2014;35(7):577-85. PMID: 25617880

Autoimmune responses to oxidative specific epitopes are involved in the pathophysiology of ME/CFS.

*

Morris G1, Anderson G, Dean O, Berk M, Galecki P, Martin-Subero M, Maes M. The Glutathione System: A New Drug Target in Neuroimmune Disorders. Mol Neurobiol. 2014 Apr 22. PMID: 24752591

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.

*

Morris G, Maes M. Oxidative and Nitrosative Stress and Immune-Inflammatory Pathways in Patients with Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS). Curr Neuropharmacol. 2014 Mar;12(2):168-85. PMID: 24669210

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.

*

Morris G, Berk M, Galecki P, Maes M. The Emerging Role of Autoimmunity in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Mol Neurobiol. 2013 Sep 26. PMID: 24068616

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.

*

Castro-Marrero J, Cordero MD, Saez-Francas N, Jimenez-Gutiérrez C, Aguilar-Montilla FJ, Aliste L, Alegre-Martin J. Could mitochondrial dysfunction be a differentiating marker between Chronic Fatigue Syndrome and Fibromyalgia? Antioxid Redox Signal. 2013 Apr 22. PMID: 23600892

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.

*

Broderick G, Katz BZ, Fernandes H, Fletcher MA, Klimas N, Smith FA, O'Gorman MR, Vernon SD, Taylor R. Cytokine expression profiles of immune imbalance in post-mononucleosis chronic fatigue. J Transl Med. 2012 Sep 13;10:191. PMID: 22973830

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.

*

Zhang HY, Liu ZD, Hu CJ, Wang DX, Zhang YB, Li YZ. Up-regulation of TGF-β1 mRNA expression in peripheral blood mononuclear cells of patients with chronic fatigue syndrome. J Formos Med Assoc. 2011 Nov;110(11):701-4. PMID: 22118314

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

*

Maes M, Twisk FN, Kubera M, Ringel K. Evidence for inflammation and activation of cell-mediated immunity in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): Increased interleukin-1, tumor necrosis factor-α, PMN-elastase, lysozyme and neopterin. J Affect Disord. 2011 Oct 3. PMID: 21975140

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.

*

Maes M, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. Increased plasma peroxides as a marker of oxidative stress in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Med Sci Monit. 2011 Apr;17(4):SC11-5. PMID: 21455120

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.

*

Brkic S, Tomic S, Maric D, Novakov Mikic A, Turkulov V. Lipid peroxidation is elevated in female patients with chronic fatigue syndrome. Med Sci Monit. 2010 Nov 30;16(12):CR628-32. PMID: 21119582

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.

*

Kennedy G, Khan F, Hill A, Underwood C, Belch JJ. Biochemical and vascular aspects of pediatric chronic fatigue syndrome. Arch Pediatr Adolesc Med. 2010 Sep;164(9):817-23. PMID: 20819963

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.

*

Miwa K, Fujita M. Fluctuation of serum vitamin E (alpha-tocopherol) concentrations during exacerbation and remission phases in patients with chronic fatigue syndrome. Heart Vessels. 2010 Jul;25(4):319-23. PMID: 20676841

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

*

Jason LA, Porter N, Herrington J, Sorenson M, Kubow S. Kindling and Oxidative Stress as Contributors to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. J Behav Neurosci Res. 2009 Jan 1;7(2):1-17. PMID: 21253446

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.

*

Maes M, Twisk FN. Why myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) may kill you: disorders in the inflammatory and oxidative and nitrosative stress (IO&NS) pathways may explain cardiovascular disorders in ME/CFS. Neuro Endocrinol Lett. 2009;30(6):677-93. PMID: 20038921

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 polyunsatutared 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.

*

Miwa K, Fujita M. Increased oxidative stress suggested by low serum vitamin E concentrations in patients with chronic fatigue syndrome. Int J Cardiol. 2009 Aug 14;136(2):238-9. PMID: 18684522

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

*

Spence VA, Kennedy G, Belch JJ, Hill A, Khan F. Low-grade inflammation and arterial wave reflection in patients with chronic fatigue syndrome. Clin Sci (Lond). 2008 Apr;114(8):561-6. PMID: 18031285

Measures related to oxidative stress were studied in CFS patients.

*

Fulle S, Pietrangelo T, Mancinelli R, Saggini R, Fanò G. Specific correlations between muscle oxidative stress and chronic fatigue syndrome: a working hypothesis. J Muscle Res Cell Motil. 2007;28(6):355-62. PMID: 18274865

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

Tinnitis 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.

*

Richards RS, Wang L, Jelinek H. Erythrocyte oxidative damage in chronic fatigue syndrome. Arch Med Res. 2007 Jan;38(1):94-8. PMID: 17174731

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.

*

Maes M, Mihaylova I, De Ruyter M. Lower serum zinc in Chronic Fatigue Syndrome (CFS): relationships to immune dysfunctions and relevance for the oxidative stress status in CFS. J Affect Disord. 2006 Feb;90(2-3):141-7. PMID: 16338007

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 anti-oxidant, the present results further support the findings that CFS is accompanied by increased oxidative stress.

*

Kennedy G, Spence VA, McLaren M, Hill A, Underwood C, Belch JJ. Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms. Free Radic Biol Med. 2005 Sep 1;39(5):584-9. PMID: 16085177

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

*

Pall ML. Nitric oxide and the etiology of chronic fatigue syndrome: giving credit where credit is due. Med Hypotheses. 2005;65(3):631-3.

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Nijs J, Van de Velde B, De Meirleir K. Pain in patients with chronic fatigue syndrome: does nitric oxide trigger central sensitisation? Med Hypotheses. 2005;64(3):558-62. PMID: 15617866

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.

*

Chaudhuri A, Behan PO. In vivo magnetic resonance spectroscopy in chronic fatigue syndrome. Prostaglandins Leukot Essent Fatty Acids. 2004 Sep;71(3):181-3. PMID: 15253888

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.

*

Smirnova IV, Pall ML. Elevated levels of protein carbonyls in sera of chronic fatigue syndrome patients. Mol Cell Biochem. 2003 Jun;248(1-2):93-5. PMID: 12870659

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.

*

Vecchiet J, Cipollone F, Falasca K, Mezzetti A, Pizzigallo E, Bucciarelli T, De Laurentis S, Affaitati G, De Cesare D, Giamberardino MA. Relationship between musculoskeletal symptoms and blood markers of oxidative stress in patients with chronic fatigue syndrome. Neurosci Lett. 2003 Jan 2;335(3):151-4. PMID: 12531455

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

*

Manuel y Keenoy B, Moorkens G, Vertommen J, De Leeuw I. Antioxidant status and lipoprotein peroxidation in chronic fatigue syndrome.Life Sci. 2001 Mar 16;68(17):2037-49. PMID: 11388705

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.

*

Pall ML. Common etiology of posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity via elevated nitric oxide/peroxynitrite. Med Hypotheses. 2001 Aug;57(2):139-45. PMID: 11461161

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

*

Richards RS, Roberts TK, Dunstan RH, McGregor NR, Butt HL. Free radicals in chronic fatigue syndrome: cause or effect? Redox Rep. 2000;5(2-3):146-7. PMID: 10939298

Free radicals may be a problem in CFS.

*

Fulle S, Mecocci P, Fanó G, Vecchiet I, Vecchini A, Racciotti D, Cherubini A, Pizzigallo E, Vecchiet L, Senin U, Beal MF. Specific oxidative alterations in vastus lateralis muscle of patients with the diagnosis of chronic fatigue syndrome. Free Radic Biol Med. 2000 Dec 15;29(12):1252-9. PMID: 11118815

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.

*

Richards RS, Roberts TK, McGregor NR, Dunstan RH, Butt HL. Blood parameters indicative of oxidative stress are associated with symptom expression in chronic fatigue syndrome. Redox Rep. 2000;5(1):35-41. PMID: 10905542

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.

*

Pall ML. Elevated, sustained peroxynitrite levels as the cause of chronic fatigue syndrome. Med Hypotheses. 2000 Jan;54(1):115-25. PMID: 10790736

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

Russell L, Broderick G, Taylor R, Fernandes H, Harvey J, Barnes Z, Smylie A, Collado F, Balbin EG, Katz BZ, Klimas NG, Fletcher MA. Illness progression in chronic

fatigue syndrome: a shifting immune baseline. BMC Immunol. 2016 Mar 10;17(1):3. PMID: 26965484

Preliminary results suggest that IL-1α, 6 and 8 adjusted for illness duration may serve as robust biomarkers, independent of age, in screening for ME/CFS.

*

Landi A, Broadhurst D, Vernon SD, Tyrrell DL, Houghton M. Reductions in circulating levels of IL-16, IL-7 and VEGF-A in myalgic encephalomyelitis/chronic fatigue syndrome. Cytokine. 2016 Feb;78:27-36. PMID: 26615570

The authors measured the plasma levels of 34 cytokines, chemokines and growth factors in 100 ME/CFS patients and controls We observed highly significant reductions in the concentration of circulating interleukin (IL)-16, IL-7, and Vascular Endothelial Growth Factor A (VEGF-A) in ME/CFS patients. In addition, they identified significant reductions in the concentrations of fractalkine (CX3CL1) and monokine-induced-by-IFN-γ (MIG; CXCL9) along with increases in the concentrations of eotaxin 2 (CCL24) in ME/CFS patients.

*

Hardcastle SL, Brenu EW, Johnston S, Nguyen T, Huth T, Ramos S, Staines D, Marshall-Gradisnik S. Serum Immune Proteins in Moderate and Severe Chronic Fatigue Syndrome/Myalgic Encephalomyelitis Patients. Int J Med Sci. 2015 Sep 5;12(10):764-72. PMID: 26516304

IL-1β was significantly reduced in severe compared with moderate CFS/ME patients. IL-6 was significantly decreased in moderate CFS/ME patients compared with healthy controls and severe CFS/ME patients. RANTES was significantly increased in moderate CFS/ME patients compared to severe CFS/ME patients. Serum IL-7 and IL-8 were significantly higher in the severe CFS/ME group compared with healthy controls and moderate CFS/ME patients. IFN-γ was significantly increased in severe CFS/ME patients compared with moderately affected patients.

*

Peterson D, Brenu EW, Gottschalk G, Ramos S, Nguyen T, Staines D, Marshall-Gradisnik S. Cytokines in the cerebrospinal fluids of patients with chronic fatigue syndrome/myalgic encephalomyelitis. Mediators Inflamm. 2015;2015:929720. PMID:25834308

IL-10 was significantly reduced in CFS/ME patients in comparison to controls.

*

Hornig M, Gottschalk G, Peterson DL, Knox KK, Schultz AF, Eddy ML, Che X, Lipkin WI. Cytokine network analysis of cerebrospinal fluid in myalgic encephalomyelitis/chronic fatigue syndrome. Mol Psychiatry. 2016 Feb;21(2):261-9. PMID: 25824300

Researchers found revealed an inverse relationship between interleukin 1 receptor antagonist and colony-stimulating factor 1, colony-stimulating factor 2 and interleukin 17F, without effects on interleukin 1α or interleukin 1β, suggesting a disturbance in interleukin 1 signaling, in a group of ME/CFS patients. Our results indicate a markedly disturbed immune signature in the cerebrospinal fluid of cases that is consistent with immune activation in the central nervous system, and a shift toward an allergic or T helper type-2 pattern associated with autoimmunity.

*

Khaiboullina SF, DeMeirleir KL, Rawat S, Berk GS, Gaynor-Berk RS, Mijatovic T, Blatt N, Rizvanov AA, Young SG, Lombardi VC. Cytokine expression provides clues to the pathophysiology of Gulf War illness and myalgic encephalomyelitis. Cytokine. 2015 Mar;72(1):1-8. PMID: 25514671

The authors identified a group of cytokines that identified ME and GWI cases with sensitivities of 92.5% and 64.9%, respectively. The five most significant cytokines in decreasing order of importance were IL-7, IL-4, TNF-α, IL-13, and IL-17F. When delineating GWI and ME cases from healthy controls, the observed specificity was only 33.3%, suggesting that with respect to cytokine expression, GWI cases resemble control subjects to a greater extent than ME cases across a number of parameters.

*

Nakamura T, Schwander S, Donnelly R, Cook DB, Ortega F, Togo F, Yamamoto Y, Cherniack NS, Klapholz M, Rapoport D, Natelson BH. Exercise and sleep deprivation do not change cytokine expression levels in patients with chronic fatigue syndrome. Clin Vaccine Immunol. 2013 Nov;20(11):1736-42. PMID: 24027260

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.

*

Stringer EA, Baker KS, Carroll IR, Montoya JG, Chu L, Maecker HT, Younger JW. Daily cytokine fluctuations, driven by leptin, are associated with fatigue severity in chronic fatigue syndrome: evidence of inflammatory pathology. J Transl Med. 2013 Apr 9;11:93. PMID: 23570606

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.

*

Smylie AL, Broderick G, Fernandes H, Razdan S, Barnes Z, Collado F, Sol C, Fletcher MA, Klimas N. A comparison of sex-specific immune signatures in Gulf War illness and chronic fatigue syndrome. BMC Immunol. 2013 Jun 25;14:29. PMID: 23800166

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.

*

Nakamura T, Schwander SK, Donnelly R, Ortega F, Togo F, Broderick G, Yamamoto Y, Cherniack NS, Rapoport D, Natelson BH. Cytokines across the night in chronic fatigue syndrome with and without fibromyalgia. Clin Vaccine Immunol. 2010 Apr;17(4):582-7. PMID: 20181767

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.

*

Broderick G, Fuite J, Kreitz A, Vernon SD, Klimas N, Fletcher MA. A formal analysis of cytokine networks in Chronic Fatigue Syndrome. Brain Behav Immun. 2010 May 4. PMID: 20447453

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

*

Fletcher MA, Zeng XR, Barnes Z, Levis S, Klimas NG. Plasma cytokines in women with chronic fatigue syndrome. J Transl Med. 2009 Nov 12;7:96. PMID: 19909538

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.

*

Geller RD, Giclas PC. Chronic fatigue syndrome and complement activation. BMJ Case Rep. 2009;2009. PMID: 21686614

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.

*

Nater UM, Youngblood LS, Jones JF, Unger ER, Miller AH, Reeves WC, Heim C. Alterations in diurnal salivary cortisol rhythm in a population-based sample of cases with chronic fatigue syndrome. Psychosom Med. 2008 Apr;70(3):298-305. PMID: 18378875

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.

*

Vollmer-Conna U, Cameron B, Hadzi-Pavlovic D, Singletary K, Davenport T, Vernon S, Reeves WC, Hickie I, Wakefield D, Lloyd AR; Dubbo Infective Outcomes Study Group. Postinfective fatigue syndrome is not associated with altered cytokine production. Clin Infect Dis. 2007 Sep 15;45(6):732-5. PMID: 17712757

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

*

ter Wolbeek M, van Doornen LJ, Kavelaars A, van de Putte EM, Schedlowski M, Heijnen CJ. Longitudinal analysis of pro- and anti-inflammatory cytokine production in severely fatigued adolescents. Brain Behav Immun. 2007 Nov;21(8):1063-74. PMID: 17544255

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.

*

Carlo-Stella N, Badulli C, De Silvestri A, Bazzichi L, Martinetti M, Lorusso L, Bombardieri S, Salvaneschi L, Cuccia M. A first study of cytokine genomic polymorphisms in CFS: Positive association of TNF-857 and IFNgamma 874 rare alleles. Clin Exp Rheumatol. 2006 Mar-Apr;24(2):179-82. PMID: 16762155

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.

*

Gaab J, Rohleder N, Heitz V, Engert V, Schad T, Schürmeyer TH, Ehlert U. Stress-induced changes in LPS-induced pro-inflammatory cytokine production in chronic fatigue syndrome. Psychoneuroendocrinology. 2005 Feb;30(2):188-98. PMID: 15471616

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.

*

Tomoda A, Joudoi T, Rabab el-M, Matsumoto T, Park TH, Miike T. Cytokine production and modulation: comparison of patients with chronic fatigue syndrome and normal controls. Psychiatry Res. 2005 Mar 30;134(1):101-4. PMID: 15808295

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.

*

Sackner MA, Gummels EM, Adams JA. Say NO to fibromyalgia and chronic fatigue syndrome: an alternative and complementary therapy to aerobic exercise. Med Hypotheses. 2004;63(1):118-23. PMID: 15193362

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

*

Skowera A, Cleare A, Blair D, Bevis L, Wessely SC, Peakman M. High levels of type 2 cytokine-producing cells in chronic fatigue syndrome. Clin Exp Immunol. 2004 Feb;135(2):294-302. PMID: 14738459

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.

*

Shephard RJ. Cytokine responses to physical activity, with particular reference to IL-6: sources, actions, and clinical implications. Crit Rev Immunol. 2002;22(3):165-82. PMID: 12498381

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.

*

Arnold MC, Papanicolaou DA, O'Grady JA, Lotsikas A, Dale JK, Straus SE, Grafman J. Using an interleukin-6 challenge to evaluate neuropsychological performance in chronic fatigue syndrome. Psychol Med. 2002 Aug;32(6):1075-89. PMID: 12214788

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.

*

Kerr JR, Barah F, Mattey DL, Laing I, Hopkins SJ, Hutchinson IV, Tyrrell DA. Circulating tumour necrosis factor-alpha and interferon-gamma are detectable during acute and convalescent parvovirus B19 infection and are associated with prolonged and chronic fatigue. J Gen Virol. 2001 Dec;82(Pt 12):3011-9. PMID: 11714978

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

*

Visser J, Graffelman W, Blauw B, Haspels I, Lentjes E, de Kloet ER, Nagelkerken L. LPS-induced IL-10 production in whole blood cultures from chronic fatigue syndrome patients is increased but supersensitive to inhibition by dexamethasone. J Neuroimmunol. 2001 Oct 1;119(2):343-9. PMID: 11585638

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.

*

Patarca-Montero R, Antoni M, Fletcher MA, Klimas NG. Cytokine and other immunologic markers in chronic fatigue syndrome and their relation to neuropsychological factors. Appl Neuropsychol. 2001;8(1):51-64. PMID: 11388124

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.

*

Hanson SJ, Gause W, Natelson B. Detection of immunologically significant factors for chronic fatigue syndrome using neural-network classifiers. Clin Diagn Lab Immunol. 2001 May;8(3):658-62. PMID: 11329477

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).

*

Cannon JG, Angel JB, Ball RW, Abad LW, Fagioli L, Komaroff AL. Acute phase responses and cytokine secretion in chronic fatigue syndrome. J Clin Immunol. 1999 Nov;19(6):414-21. PMID: 10634215

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

*

Moss RB, Mercandetti A, Vojdani A. TNF-alpha and chronic fatigue syndrome. J Clin Immunol. 1999 Sep;19(5):314-6. PMID: 10535608

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

*

Gupta S, Aggarwal S, Starr A. Increased production of interleukin-6 by adherent and non-adherent mononuclear cells during 'natural fatigue' but not following 'experimental fatigue' in patients with chronic fatigue syndrome. Int J Mol Med. 1999 Feb;3(2):209-13. PMID: 9917531

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.

*

Bennett AL, Chao CC, Hu S, Buchwald D, Fagioli LR, Schur PH, Peterson PK, Komaroff AL. Elevation of bioactive transforming growth factor-beta in serum from patients with chronic fatigue syndrome. J Clin Immunol. 1997 Mar;17(2):160-6. PMID: 9083892

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.

*

Gupta S, Aggarwal S, See D, Starr A. Cytokine production by adherent and non-adherent mononuclear cells in chronic fatigue syndrome. J Psychiatr Res. 1997 Jan-Feb;31(1):149-56. PMID: 9201656

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.

*

Peterson PK, Sirr SA, Grammith FC, Schenck CH, Pheley AM, Hu S, Chao CC. Effects of mild exercise on cytokines and cerebral blood flow in chronic fatigue syndrome patients. Clin Diagn Lab Immunol. 1994 Mar;1(2):222-6. PMID: 7496949

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.

*

Patarca R, Klimas NG, Lugtendorf S, Antoni M, Fletcher MA. Dysregulated expression of tumor necrosis factor in chronic fatigue syndrome: interrelations with cellular sources and patterns of soluble immune mediator expression. Clin Infect Dis. 1994 Jan;18 Suppl 1:S147-53. PMID: 8148443

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

*

Chao CC, Janoff EN, Hu SX, Thomas K, Gallagher M, Tsang M, Peterson PK. Altered cytokine release in peripheral blood mononuclear cell cultures from patients with the chronic fatigue syndrome. Cytokine. 1991 Jul;3(4):292-8. PMID: 1873478

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.

*

Cheney PR, Dorman SE, Bell DS. Interleukin-2 and the chronic fatigue syndrome. Ann Intern Med. 1989 Feb 15;110(4):321. PMID: 2783643

Rnase L

Nijs J, Frémont M. Intracellular immune dysfunction in myalgic encephalomyelitis/chronic fatigue syndrome: state of the art and therapeutic implications. Expert Opin Ther Targets. 2008 Mar;12(3):281-9. PMID: 18269338

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

*

Bisbal C, Silverman RH. Diverse functions of RNase L and implications in pathology. Biochimie. 2007 Jun-Jul;89(6-7):789-98. PMID: 17400356

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

*

Nijs J, De Meirleir K. Impairments of the 2-5A synthetase/RNase L pathway in chronic fatigue syndrome. In Vivo. 2005 Nov-Dec;19(6):1013-21. PMID: 16277015

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.

*

Frémont M, El Bakkouri K, Vaeyens F, Herst CV, De Meirleir K, Englebienne P. 2',5'-Oligoadenylate size is critical to protect RNase L against proteolytic cleavage in chronic fatigue syndrome. Exp Mol Pathol. 2005 Jun;78(3):239-46. PMID: 15924878

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.

*

Tiev KP, Demettre E, Ercolano P, Bastide L, Lebleu B, Cabane J. RNase L levels in peripheral blood mononuclear cells: 37-kilodalton/83-kilodalton isoform ratio is a potential test for chronic fatigue syndrome. Clin Diagn Lab Immunol. 2003 Mar;10(2):315-6. PMID: 12626460

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

*

Demettre E, Bastide L, D'Haese A, De Smet K, De Meirleir K, Tiev KP, Englebienne P, Lebleu B. Ribonuclease L proteolysis in peripheral blood mononuclear cells of chronic fatigue syndrome patients. J Biol Chem. 2002 Sep 20;277(38):35746-51. PMID: 12118002

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.

*

Snell CR, Vanness JM, Strayer DR, Stevens SR. Physical performance and prediction of 2-5A synthetase/RNase L antiviral pathway activity in patients with chronic fatigue syndrome. In Vivo. 2002 Mar-Apr;16(2):107-9. PMID:12073768

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.

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Shetzline SE, Martinand-Mari C, Reichenbach NL, Buletic Z, Lebleu B, Pfleiderer W, Charubala R, De Meirleir K, De Becker P, Peterson DL, Herst CV, Englebienne P, Suhadolnik RJ. Structural and functional features of the 37-kDa 2-5A-dependent RNase L in chronic fatigue syndrome. J Interferon Cytokine Res. 2002 Apr;22(4):443-56. PMID: 12034027

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.

*

Vojdani A, Choppa PC, Lapp CW. Downregulation of RNase L inhibitor correlates with upregulation of interferon-induced proteins (2-5A synthetase and RNase L) in patients with chronic fatigue immune dysfunction syndrome. J Clin Lab Immunol. 1998;50(1):1-16. PMID: 10189612

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.

*

Suhadolnik RJ, Peterson DL, O'Brien K, Cheney PR, Herst CV, Reichenbach NL, Kon N, Horvath SE, Iacono KT, Adelson ME, De Meirleir K, De Becker P, Charubala R, Pfleiderer W. Biochemical evidence for a novel low molecular weight 2-5A-dependent RNase L in chronic fatigue syndrome. J Interferon Cytokine Res. 1997 Jul;17(7):377-85. PMID: 9243369

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

*

Suhadolnik RJ, Reichenbach NL, Hitzges PM, Ablashi DV, Strayer DR, Carter WA. RNA drug therapy acting via the 2-5A synthetase/RNase L pathway. Ann N Y Acad Sci. 1993 Jun 23;685:756-7. PMID: 8363281

Mitochondria

Armstrong CW, McGregor NR, Butt HL, Gooley PR. Metabolism in chronic fatigue syndrome. Adv Clin Chem. 2014;66:121-72. PMID: 25344988

Studies on metabolism and CFS suggest irregularities in energy metabolism, amino acid metabolism, nucleotide metabolism, nitrogen metabolism, hormone metabolism, and oxidative stress metabolism. The overwhelming body of evidence suggests an oxidative environment with the minimal utilization of mitochondria for efficient energy production. This is coupled with a reduced excretion of amino acids and nitrogen in general.

*

Morris G, Maes M. Mitochondrial dysfunctions in myalgic encephalomyelitis/chronic fatigue syndrome explained by activated immuno-

inflammatory, oxidative and nitrosative stress pathways. Metab Brain Dis. 2014 Mar;29(1):19-36. PMID: 24557875

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.

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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.

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Castro-Marrero J, Cordero MD, Sáez-Francas N, Jimenez-Gutierrez C, Aguilar-Montilla FJ, Aliste L, Alegre-Martin J. Could mitochondrial dysfunction be a differentiating marker between chronic fatigue syndrome and fibromyalgia? Antioxid Redox Signal. 2013 Nov 20;19(15):1855-60. PMID: 23600892

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.

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Booth NE, Myhill S, McLaren-Howard J. Mitochondrial dysfunction and the pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Int J Clin Exp Med. 2012;5(3):208-20. PMID: 22837795

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.

*

Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. Coenzyme Q10 deficiency in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is related to fatigue, autonomic and neurocognitive symptoms and is another risk factor explaining the early mortality in ME/CFS due to cardiovascular disorder. Neuro Endocrinol Lett. 2009;30(4):470-6. PMID: 20010505

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.

*

Pietrangelo T, Mancinelli R, Toniolo L, Montanari G, Vecchiet J, Fanò G, Fulle S. Transcription profile analysis of vastus lateralis muscle from patients with chronic fatigue syndrome. Int J Immunopathol Pharmacol. 2009 Jul-Sep;22(3):795-807. PMID: 19822097

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.

*

Hokama Y, Campora CE, Hara C, Kuribayashi T, Le Huynh D, Yabusaki K. Anticardiolipin antibodies in the sera of patients with diagnosed chronic fatigue syndrome. J Clin Lab Anal. 2009;23(4):210-2. PMID: 19623655

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

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Myhill S, Booth NE, McLaren-Howard J. Chronic fatigue syndrome and mitochondrial dysfunction. Int J Clin Exp Med. 2009;2(1):1-16. PMID: 19436827

Mitochondrial dysfunction is strongly associated with CFS.

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Mathew SJ, Mao X, Keegan KA, Levine SM, Smith EL, Heier LA, Otcheretko V, Coplan JD, Shungu DC. Ventricular cerebrospinal fluid lactate is increased in chronic fatigue syndrome compared with generalized anxiety disorder: an in vivo 3.0 T (1)H MRS imaging study. NMR Biomed. 2009 Apr;22(3):251-8. PMID: 18942064

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.

*

Hokama Y, Empey-Campora C, Hara C, Higa N, Siu N, Lau R, Kuribayashi T, Yabusaki K. Acute phase phospholipids related to the cardiolipin of mitochondria in the sera of patients with chronic fatigue syndrome (CFS), chronic Ciguatera fish poisoning (CCFP), and other diseases attributed to chemicals, Gulf War, and marine toxins. J Clin Lab Anal. 2008;22(2):99-105. PMID: 18348309

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

Huth TK, Brenu EW, Ramos S, Nguyen T, Broadley S, Staines D, Marshall-Gradisnik S. Pilot Study of Natural Killer Cells in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis and Multiple Sclerosis. Scand J Immunol. 2016 Jan;83(1):44-51. PMID: 26381393

Co-expression of CD57 and perforin was significantly increased on CD56(dim) CD16(+) NK cells from patients with CFS/ME compared to the MS and non-fatigued control participants. NK cells from patients with CFS/ME and MS may have undergone increased differentiation in response to external stimuli which may affect different mechanisms in the NK cell cytotoxic activity pathway.

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Petty RD, McCarthy NE, Le Dieu R, Kerr JR. MicroRNAs hsa-miR-99b, hsa-miR-330, hsa-miR-126 and hsa-miR-30c: Potential Diagnostic Biomarkers in Natural Killer (NK) Cells of Patients with Chronic Fatigue Syndrome (CFS)/ Myalgic

Encephalomyelitis (ME). PLoS One. 2016 Mar 11;11(3):e0150904. PMID: 26967895

This study demonstrates altered microRNA expression in the peripheral blood mononuclear cells of CFS/ME patients, which are potential diagnostic biomarkers. The greatest degree of miRNA deregulation was identified in NK cells with targets consistent with cellular activation and altered effector function.

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Huth TK, Brenu EW, Ramos S, Nguyen T, Broadley S, Staines D, Marshall-Gradisnik S. Pilot Study of Natural Killer Cells in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis and Multiple Sclerosis. Scand J Immunol. 2016 Jan;83(1):44-51. PMID: 26381393

Co-expression of CD57 and perforin was significantly increased on CD56(dim) CD16(+) NK cells from patients with CFS/ME compared to the MS and non-fatigued control participants. The results suggest that NK cells from patients with CFS/ME and MS may have undergone increased differentiation in response to external stimuli which may affect different mechanisms in the NK cell cytotoxic activity pathway.

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Brenu EW, van Driel ML, Staines DR, Ashton KJ, Hardcastle SL, Keane J, Tajouri L, Peterson D, Ramos SB, Marshall-Gradisnik SM. Longitudinal investigation of natural killer cells and cytokines in chronic fatigue syndrome/myalgic encephalomyelitis. J Transl Med. 2012 May 9;10:88. PMID: 22571715

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.

*

Fletcher MA, Zeng XR, Maher K, Levis S, Hurwitz B, Antoni M, Broderick G, Klimas NG. Biomarkers in chronic fatigue syndrome: evaluation of natural killer cell

function and dipeptidyl peptidase IV/CD26. PLoS One. 2010 May 25;5(5):e10817. PMID: 20520837

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

*

Siegel SD, Antoni MH, Fletcher MA, Maher K, Segota MC, Klimas N. Impaired natural immunity, cognitive dysfunction, and physical symptoms in patients with chronic fatigue syndrome: preliminary evidence for a subgroup? J Psychosom Res. 2006 Jun;60(6):559-66. PMID: 16731230

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.

*

Robertson MJ, Schacterle RS, Mackin GA, Wilson SN, Bloomingdale KL, Ritz J, Komaroff AL. Lymphocyte subset differences in patients with chronic fatigue syndrome, multiple sclerosis and major depression. Clin Exp Immunol. 2005 Aug;141(2):326-32. PMID: 15996197

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

*

Ogawa M, Nishiura T, Yoshimura M, Horikawa Y, Yoshida H, Okajima Y, Matsumura I, Ishikawa J, Nakao H, Tomiyama Y, Kanayama Y, Kanakura Y, Matsuzawa Y. Decreased nitric oxide-mediated natural killer cell activation in chronic fatigue syndrome. Eur J Clin Invest. 1998 Nov;28(11):937-43. PMID: 9824439

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.

*

Whiteside TL, Friberg D. Natural killer cells and natural killer cell activity in chronic fatigue syndrome. Am J Med. 1998 Sep 28;105(3A):27S-34S. PMID: 9790479

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

*

Levine PH, Whiteside TL, Friberg D, Bryant J, Colclough G, Herberman RB. Dysfunction of natural killer activity in a family with chronic fatigue syndrome. Clin Immunol Immunopathol. 1998 Jul;88(1):96-104. PMID: 9683556

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

*

Ojo-Amaize EA, Conley EJ, Peter JB. Decreased natural killer cell activity is associated with severity of chronic fatigue immune dysfunction syndrome. Clin Infect Dis. 1994 Jan;18 Suppl 1:S157-9. PMID: 8148445

This data suggest a correlation between low levels of natural killer cell activity and severity of CFS.

*

Aoki T, Miyakoshi H, Usuda Y, Herberman RB. Low NK syndrome and its relationship to chronic fatigue syndrome. Clin Immunol Immunopathol. 1993 Dec;69(3):253-65. PMID: 8242898

Low natural killer cell function is associated with CFS.

*

Uchida A. Chronic fatigue immune dysfunction syndrome. Nihon Rinsho. 1992 Nov;50(11):2625-9. PMID: 1287238

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

*

Morrison LJ, Behan WH, Behan PO. Changes in natural killer cell phenotype in patients with post-viral fatigue syndrome. Clin Exp Immunol. 1991 Mar;83(3):441-6. PMID: 1706238

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.

*

Caligiuri M, Murray C, Buchwald D, Levine H, Cheney P, Peterson D, Komaroff AL, Ritz J. Phenotypic and functional deficiency of natural killer cells in patients with chronic fatigue syndrome. J Immunol. 1987 Nov 15;139(10):3306-13. PMID: 2824604

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 cytolytic 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

Brenu EW, Broadley S, Nguyen T, Johnston S, Ramos S, Staines D, Marshall-Gradisnik S. A Preliminary Comparative Assessment of the Role of CD8+ T Cells in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis and Multiple Sclerosis. J Immunol Res. 2016;2016:9064529. PMID: 26881265

The study suggests significant deficits in the expression of receptors and adhesion molecules on subsets of CD8+ T cells in both MS and CFS/ME patients.

*

Keijmel SP, Raijmakers RP, Bleeker-Rovers CP, van der Meer JW, Netea MG, Schoffelen T, van Deuren M.Altered interferon-γ response in patients with Q-fever fatigue syndrome. J Infect. 2016 Apr;72(4):478-85. PMID: 26820634

Researchers explored the specific IFNγ production and IFNγ/IL-2 ratio in Q-fever fatigue syndrome (similar to CFS) patients. Results point to an altered cell-mediated immunity in QFS, and suggest a different immune response than in chronic Q-fever.

*

Maes M, Bosmans E, Kubera M. Increased expression of activation antigens on CD8+ T lymphocytes in Myalgic Encephalomyelitis/chronic fatigue syndrome: inverse associations with lowered CD19+ expression and CD4+/CD8+ ratio, but no associations with (auto)immune, leaky gut, oxidative and nitrosative stress biomarkers. Neuro Endocrinol Lett. 2015;36(5):439-46. PMID: 26707044

The study results support that a) increased CD38 and HLA-DR expression on CD8+ T cells are biomarkers of ME/CFS; b) increased CD38 antigen expression may contribute to suppression of the CD4+/CD8+ ratio and CD19+ expression; c) there are different immune subgroups of ME/CFS patients, e.g. increased CD8+

activation marker expression versus inflammation or O&NS processes; and d) viral infections or reactivation may play a role in a some ME/CFS patients.

*

Mensah F, Bansal A, Berkovitz S, Sharma A, Reddy V, Leandro MJ, Cambridge G. Extended B-cell phenotype in patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A cross-sectional study. Clin Exp Immunol. 2015 Dec 8. PMID: 26646713

The authors identified possible changes in B-cell phenotype in patients with ME/CFS. These may reflect altered B-cell function and if confirmed in other patient cohorts, could provide a platform for studies based on clinical course or responsiveness to rituximab-therapy.

*

Guenther S, Loebel M, Mooslechner AA, Knops M, Hanitsch LG, Grabowski P, Wittke K, Meisel C, Unterwalder N, Volk HD, Scheibenbogen C. Frequent IgG subclass and mannose binding lectin deficiency in patients with chronic fatigue syndrome. Hum Immunol. 2015 Oct;76(10):729-35. PMID: 26429318

The authors retrospectively analysed 300 patients with CFS for immunoglobulin and mannose binding lectin (MBL) levels, and B-cell subset frequencies. 25% of the CFS patients had decreased serum levels of at least one antibody class or subclass with IgG3 and IgG4 subclass deficiencies as most common phenotypes. They found elevated immunoglobulin levels with an excess of IgM and IgG2 in particular in another 25% of patients. Deficiency of MBL was found in 15% of the CFS patients in contrast to 6% in a historical control group. Thus, humoral immune defects are frequent in CFS patients and are associated with infections of the respiratory tract.

*

Loebel M, Grabowski P, Heidecke H, Bauer S, Hanitsch LG, Wittke K, Meisel C, Reinke P, Volk HD, Fluge Ø, Mella O,Scheibenbogen C. Antibodies to β adrenergic and muscarinic cholinergic receptors in patients with Chronic Fatigue Syndrome. Brain Behav Immun. 2016 Feb;52:32-9. PMID: 26399744

Serum samples from a patient cohort from Berlin (n=268) and from Bergen with pre- and post-treatment samples from 25 patients treated within the KTS-2 rituximab trial were analysed for IgG against human α and β adrenergic, muscarinic (M) 1-5 acetylcholine, dopamine, serotonin, angiotensin, and endothelin receptors by ELISA and compared to a healthy control cohort (n=108). Antibodies against β2, M3 and M4 receptors were significantly elevated in CFS patients compared to controls. A high correlation was found between levels of autoantibodies and elevated IgG1-3 subclasses, but not with IgG4. Patients with high β2 antibodies had significantly more frequently activated HLA-DR+ T cells and more frequently thyreoperoxidase and anti-nuclear antibodies.

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Hardcastle SL, Brenu EW, Johnston S, Nguyen T, Huth T, Ramos S, Staines D, Marshall-Gradisnik S. Longitudinal analysis of immune abnormalities in varying severities of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis patients. J Transl Med. 2015 Sep 14;13:299. PMID: 26370228

Severe CFS/ME patients differed from controls and moderate CFS/ME patients over time and expressed significant alterations in iNKT cell phenotypes, CD8(+)T cell markers, NK cell receptors and γδT cells at 6 months.

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Fluge Ø, Risa K, Lunde S, Alme K, Rekeland IG, Sapkota D, Kristoffersen EK, Sørland K, Bruland O, Dahl O, Mella O. B-Lymphocyte Depletion in Myalgic Encephalopathy/ Chronic Fatigue Syndrome. An Open-Label Phase II Study with Rituximab Maintenance Treatment. PLoS One. 2015 Jul 1;10(7):e0129898. PMID: 26132314

In a subgroup of ME/CFS patients, prolonged B-cell depletion with rituximab maintenance infusions was associated with sustained clinical responses. The observed patterns of delayed responses and relapse after B-cell depletion and regeneration, a three times higher disease prevalence in women than in men, and a previously demonstrated increase in B-cell lymphoma risk for elderly ME/CFS patients, suggest that ME/CFS may be a variant of an autoimmune disease.

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Hornig M, Montoya JG, Klimas NG, Levine S, Felsenstein D, Bateman L, Peterson DL, Gottschalk CG, Schultz AF, Che X, Eddy ML, Komaroff AL, Lipkin WI. Distinct plasma immune signatures in ME/CFS are present early in the course of illness. Sci Adv. 2015 Feb;1(1). pii: e1400121. PMID: 26079000

The authors leveraged two large, multicenter cohort studies of ME/CFS to assess the relationship of immune signatures with diagnosis, illness duration, and other clinical variables. Early ME/CFS cases had a prominent activation of both pro- and anti-inflammatory cytokines as well as dissociation of intercytokine regulatory networks.

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Hardcastle SL, Brenu EW, Johnston S, Nguyen T, Huth T, Wong N, Ramos S, Staines D, Marshall-Gradisnik S. Characterisation of cell functions and receptors in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME). BMC Immunol. 2015 Jun 2;16:35. PMID: 26032326

CFS/ME patients exhibited alterations in NK receptors and adhesion markers and receptors on CD4(+)T and CD8(+)T cells. Moderate CFS/ME patients had increased CD8(+) CD45RA effector memory T cells, SLAM expression on NK cells, KIR2DL5(+) on CD4(+)T cells and BTLA4(+) on CD4(+)T central memory cells. Moderate CFS/ME patients also had reduced CD8(+)T central memory LFA-1, total CD8(+)T KLRG1, naïve CD4(+)T KLRG1 and CD56(dim)CD16(-) NK cell CD2(+) and CD18(+)CD2(+). Severe CFS/ME patients had increased CD18(+)CD11c(-) in the CD56(dim)CD16(-) NK cell phenotype and reduced NKp46 in CD56(bright)CD16(dim) NK cells.

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Gambuzza ME, Salmeri FM, Soraci L, Soraci G, Sofo V, Marino S, Bramanti P. The Role of Toll-Like Receptors in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: A New Promising Therapeutic Approach? CNS Neurol Disord Drug Targets. 2015;14(7):903-14. PMID: 25808894

The paper examines the role of TLR-mediated innate immunity in CFS/ME with evaluation of the current literature, also discussing about innovative therapeutic approaches represented by immunomodulators TLR-targeting.

*

Nijs J, Nees A, Paul L, De Kooning M, Ickmans K, Meeus M, Van Oosterwijck J. Altered immune response to exercise in patients with chronic fatigue syndrome/myalgic encephalomyelitis: a systematic literature review. Exerc Immunol Rev. 2014;20:94-116. PMID: 24974723

Compared to the normal response of the immune system to exercise as seen in healthy subjects, patients with CFS have a more pronounced response in the complement system (i.e. C4a split product levels), oxidative stress system (i.e. enhanced oxidative stress combined with a delayed and reduced anti-oxidant response), and an alteration in the immune cells' gene expression profile (increases in post-exercise interleukin-10 and toll-like receptor 4 gene expression), but not in circulating pro- or anti-inflammatory cytokines.

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Loebel M, Strohschein K, Giannini C, Koelsch U, Bauer S, Doebis C, Thomas S, Unterwalder N, von Baehr V, Reinke P, Knops M, Hanitsch LG, Meisel C, Volk HD, Scheibenbogen C. Deficient EBV-specific B- and T-cell response in patients with chronic fatigue syndrome. PLoS One. 2014 Jan 15;9(1):e85387. PMID: 24454857

Taken together, the findings of this study give evidence for 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. In addition the diminished EBV response might be suitable to develop diagnostic marker in CFS.

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Brenu EW, Huth TK, Hardcastle SL, Fuller K, Kaur M, Johnston S, Ramos SB, Staines DR, Marshall-Gradisnik SM. Role of adaptive and innate immune cells in chronic fatigue syndrome/myalgic encephalomyelitis. Int Immunol. 2014 Apr;26(4):233-42. PMID: 24343819

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.

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Curriu M, Carrillo J, Massanella M, Rigau J, Alegre J, Puig J, Garcia-Quintana AM, Castro-Marrero J, Negredo E, Clotet B, Cabrera C, Blanco J. Screening NK-, B- and T-cell phenotype and function in patients suffering from Chronic Fatigue Syndrome. J Transl Med. 2013 Mar 20;11:68. PMID:23514202

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.

*

Bradley AS, Ford B, Bansal AS. Altered functional B cell subset populations in patients with chronic fatigue syndrome compared to healthy controls. Clin Exp Immunol. 2013 Apr;172(1):73-80. PMID: 23480187

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.

*

Brenu EW, Ashton KJ, van Driel M, Staines DR, Peterson D, Atkinson GM, Marshall-Gradisnik SM. Cytotoxic lymphocyte microRNAs as prospective biomarkers for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. J Affect Disord. 2012 Dec 10;141(2-3):261-9. PMID: 22572093

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.

*

Bansal AS, Bradley AS, Bishop KN, Kiani-Alikhan S, Ford B. Chronic fatigue syndrome, the immune system and viral infection. Brain Behav Immun. 2011 Jul 2. PMID: 21756995

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.

*

Brenu EW, Staines DR, Baskurt OK, Ashton KJ, Ramos SB, Christy RM, Marshall-Gradisnik SM. Immune and hemorheological changes in chronic fatigue syndrome. J Transl Med. 2010 Jan 11;8:1. PMID: 20064266

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.

*

Meeus M, Mistiaen W, Lambrecht L, Nijs J. Immunological similarities between cancer and chronic fatigue syndrome: the common link to fatigue? Anticancer Res. 2009 Nov;29(11):4717-26. PMID: 20032425

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.

*

Lorusso L, Mikhaylova SV, Capelli E, Ferrari D, Ngonga GK, Ricevuti G. Immunological aspects of chronic fatigue syndrome. Autoimmun Rev. 2009 Feb;8(4):287-91. PMID: 18801465

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.

*

Torres-Harding S, Sorenson M, Jason LA, Maher K, Fletcher MA. Evidence for T-helper 2 shift and association with illness parameters in chronic fatigue syndrome (CFS). Bull IACFS ME. 2008 Fall;16(3):19-33. PMID: 21234277

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.

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Meeus M, Nijs J, McGregor N, Meeusen R, De Schutter G, Truijen S, Frémont M, Van Hoof E, De Meirleir K. Unravelling intracellular immune dysfunctions in

chronic fatigue syndrome: interactions between protein kinase R activity, RNase L cleavage and elastase activity, and their clinical relevance. In Vivo. 2008 Jan-Feb;22(1):115-21. PMID: 18396793

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

*

Aspler AL, Bolshin C, Vernon SD, Broderick G. Evidence of inflammatory immune signaling in chronic fatigue syndrome: A pilot study of gene expression in peripheral blood. Behav Brain Funct. 2008 Sep 26;4:44. PMID: 18822143

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.

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Mihaylova I, DeRuyter M, Rummens JL, Bosmans E, Maes M. Decreased expression of CD69 in chronic fatigue syndrome in relation to inflammatory markers: evidence for a severe disorder in the early activation of T lymphocytes and natural killer cells. Neuro Endocrinol Lett. 2007 Aug;28(4):477-83. PMID: 17693977

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.

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Maher KJ, Klimas NG, Fletcher MA. Chronic fatigue syndrome is associated with diminished intracellular perforin. Clin Exp Immunol. 2005 Dec;142(3):505-11. PMID: 16297163

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

*

Kennedy G, Spence V, Underwood C, Belch JJ. Increased neutrophil apoptosis in chronic fatigue syndrome. J Clin Pathol. 2004 Aug;57(8):891-3. PMID: 15280416

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.

*

Sabath DE, Barcy S, Koelle DM, Zeh J, Ashton S, Buchwald D. Cellular immunity in monozygotic twins discordant for chronic fatigue syndrome. J Infect Dis. 2002 Mar 15;185(6):828-32. PMID: 11920301

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.

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Patarca R. Cytokines and chronic fatigue syndrome. Ann N Y Acad Sci. 2001 Mar;933:185-200. PMID:12000020

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.

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Visser J, Blauw B, Hinloopen B, Brommer E, de Kloet ER, Kluft C, Nagelkerken L. CD4 T lymphocytes from patients with chronic fatigue syndrome have decreased interferon-gamma production and increased sensitivity to dexamethasone. J Infect Dis. 1998 Feb;177(2):451-4. PMID: 9466535

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.

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Vojdani A, Ghoneum M, Choppa PC, Magtoto L, Lapp CW. Elevated apoptotic cell population in patients with chronic fatigue syndrome: the pivotal role of protein kinase RNA. J Intern Med. 1997 Dec;242(6):465-78. PMID: 9437407

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.

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Mawle AC, Nisenbaum R, Dobbins JG, Gary HE Jr, Stewart JA, Reyes M, Steele L, Schmid DS, Reeves WC. Immune responses associated with chronic fatigue syndrome: a case-control study. J Infect Dis. 1997 Jan;175(1):136-41. PMID: 8985207

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.

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Tirelli U, Marotta G, Improta S, Pinto A. Immunological abnormalities in patients with chronic fatigue syndrome. Scand J Immunol. 1994 Dec;40(6):601-8. PMID: 7997849

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.

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Levy JA. Viral studies of chronic fatigue syndrome. Clin Infect Dis. 1994 Jan;18 Suppl 1:S117-20. PMID: 8148437

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.

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Barker E, Fujimura SF, Fadem MB, Landay AL, Levy JA. Immunologic abnormalities associated with chronic fatigue syndrome. Clin Infect Dis. 1994 Jan;18 Suppl 1:S136-41. PMID: 8148441

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.

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Straus SE, Fritz S, Dale JK, Gould B, Strober W. Lymphocyte phenotype and function in the chronic fatigue syndrome. J Clin Immunol. 1993 Jan;13(1):30-40. PMID: 8095270

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.

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Lloyd A, Hickie I, Hickie C, Dwyer J, Wakefield D. Cell-mediated immunity in patients with chronic fatigue syndrome, healthy control subjects and patients with major depression. Clin Exp Immunol. 1992 Jan;87(1):76-9. PMID: 1733640

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

*

Landay AL, Jessop C, Lennette ET, Levy JA. Chronic fatigue syndrome: clinical condition associated with immune activation. Lancet. 1991 Sep 21;338(8769):707-12. PMID: 1679864

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

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Gupta S, Vayuvegula B. A comprehensive immunological analysis in chronic fatigue syndrome. Scand J Immunol. 1991 Mar;33(3):319-27. PMID: 1849315

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 phytohaemoglobulin (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).

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Klimas NG, Salvato FR, Morgan R, Fletcher MA. Immunologic abnormalities in chronic fatigue syndrome. J Clin Microbiol. 1990 Jun;28(6):1403-10. PMID: 2166084

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.

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Lloyd AR, Wakefield D, Boughton CR, Dwyer JM. Immunological abnormalities in the chronic fatigue syndrome. Med J Aust. 1989 Aug 7;151(3):122-4. PMID: 2787888

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

Maes M, Ringel K, Kubera M, Anderson G, Morris G, Galecki P, Geffard M. In myalgic encephalomyelitis/chronic fatigue syndrome, increased autoimmune activity against 5-HT is associated with immuno-inflammatory pathways and bacterial translocation. J Affect Disord. 2013 Sep 5;150(2):223-30. PMID: 23664637

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

Lum E, Medveczky MM, Medveczky PG. Is inherited human herpesvirus 6 the perpetrator behind some cases of chronic fatigue syndrome? Future Microbiol. 2014;9(4):433-6. PMID: 24810341

The authors discuss the possible role of HHV6 in CFS.

*

Jason LA, Katz BZ, Shiraishi Y, Mears CJ, Im Y, Taylor R. Predictors of Post-Infectious Chronic Fatigue Syndrome in Adolescents. Health Psychol Behav Med. 2014 Jan 1;2(1):41-51. PMID: 24660116

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.

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Loebel M, Strohschein K, Giannini C, Koelsch U, Bauer S, Doebis C, Thomas S, Unterwalder N, von Baehr V, Reinke P, Knops M, Hanitsch LG, Meisel C, Volk HD, Scheibenbogen C. Deficient EBV-specific B- and T-cell response in patients with chronic fatigue syndrome. PLoS One. 2014 Jan 15;9(1):e85387. PMID: 24454857

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.

*

Tsai SY, Yang TY, Chen HJ, Chen CS, Lin WM, Shen WC, Kuo CN, Kao CH. Increased risk of chronic fatigue syndrome following herpes zoster: a population-based study. Eur J Clin Microbiol Infect Dis. 2014 Apr 9. PMID: 24715153

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 human herpesvirus-7 viral loads in chronic fatigue patients. Clin Infect Dis. 2013 May;56(10):1394-400. PMID:23408682

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.

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Burbelo PD, Bayat A, Wagner J, Nutman TB, Baraniuk JN, Iadarola MJ. No serological evidence for a role of HHV-6 infection in chronic fatigue syndrome. Am J Transl Res. 2012;4(4):443-51. PMID: 23145212

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

*

Chapenko S, Krumina A, Logina I, Rasa S, Chistjakovs M, Sultanova A, Viksna L, Murovska M. Association of active human herpesvirus-6, -7 and parvovirus b19 infection with clinical outcomes in patients with myalgic encephalomyelitis/chronic fatigue syndrome. Adv Virol. 2012;2012:205085. PMID: 22927850

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.

*

Lerner AM, Ariza ME, Williams M, Jason L, Beqaj S, Fitzgerald JT, Lemeshow S, Glaser R. Antibody to Epstein-Barr virus deoxyuridine triphosphate nucleotidohydrolase and deoxyribonucleotide polymerase in a chronic fatigue syndrome subset. PLoS One. 2012;7(11):e47891. PMID: 23155374

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.

*

Beqaj SH, Lerner AM, Fitzgerald JT. Immunoassay with cytomegalovirus early antigens from gene products p52 and CM2 (UL44 and UL57) detects active infection in patients with chronic fatigue syndrome. J Clin Pathol. 2008 May;61(5):623-6. PMID: 18037660

Immunoassays 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.

*

Bellmann-Weiler R, Schroecksnadel K, Holzer C, Larcher C, Fuchs D, Weiss G. IFN-gamma mediated pathways in patients with fatigue and chronic active Epstein Barr virus-infection. J Affect Disord. 2008 May;108(1-2):171-6. PMID: 17945348

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

*

Kondo K. Chronic fatigue syndrome and herpesvirus reactivation. Nihon Rinsho. 2007 Jun;65(6):1043-8. PMID: 17561695

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

*

Komaroff AL, Jacobson S, Ablashi DV, Yamanishi K. Highlights from 5th International Conference on HHV-6 and -7. Herpes. 2006 Nov;13(3):81-2. PMID: 17147913

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

*

Chapenko S, Krumina A, Kozireva S, Nora Z, Sultanova A, Viksna L, Murovska M. Activation of human herpesviruses 6 and 7 in patients with chronic fatigue syndrome. J Clin Virol. 2006 Dec;37 Suppl 1:S47-51. PMID: 17276369

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

*

Komaroff AL. Is human herpesvirus-6 a trigger for chronic fatigue syndrome? J Clin Virol. 2006 Dec;37 Suppl 1:S39-46. PMID: 17276367

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

*

Kondo K. Human herpesvirus latency and fatigue. Uirusu. 2005 Jun;55(1):9-17. PMID:16308525

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.

*

Koelle DM, Barcy S, Huang ML, Ashley RL, Corey L, Zeh J, Ashton S, Buchwald D. Markers of viral infection in monozygotic twins discordant for chronic fatigue syndrome. Clin Infect Dis. 2002 Sep 1;35(5):518-25. PMID: 12173124

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.

*

Krueger GR, Koch B, Hoffmann A, Rojo J, Brandt ME, Wang G, Buja LM. Dynamics of chronic active herpesvirus-6 infection in patients with chronic fatigue syndrome: data acquisition for computer modeling. In Vivo. 2001 Nov-Dec;15(6):461-5. PMID: 11887330

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

*

Reeves WC, Stamey FR, Black JB, Mawle AC, Stewart JA, Pellett PE. Human herpesviruses 6 and 7 in chronic fatigue syndrome: a case-control study. Clin Infect Dis. 2000 Jul;31(1):48-52. PMID: 10913395

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.

*

Ablashi DV, Eastman HB, Owen CB, Roman MM, Friedman J, Zabriskie JB, Peterson DL, Pearson GR, Whitman JE. Frequent HHV-6 reactivation in multiple sclerosis (MS) and chronic fatigue syndrome (CFS) patients. J Clin Virol. 2000 May;16(3):179-91. PMID: 10738137

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.

*

Wallace HL 2nd, Natelson B, Gause W, Hay J. Human herpesviruses in chronic fatigue syndrome. Clin Diagn Lab Immunol. 1999 Mar;6(2):216-23. PMID: 10066657

Serological analyses of serum anti-EBV and anti-HHV6 antibody titers showed no significant differences between the CFS and control patients.

*

Cuende JI, Civeira P, Diez N, Prieto J. High prevalence without reactivation of herpes virus 6 in subjects with chronic fatigue syndrome. An Med Interna. 1997 Sep;14(9):441-4. PMID: 9453750

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

*

Buchwald D, Ashley RL, Pearlman T, Kith P, Komaroff AL. Viral serologies in patients with chronic fatigue and chronic fatigue syndrome. Med Virol. 1996 Sep;50(1):25-30. PMID: 8890037

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.

*

Schmaling KB, Jones JF. MMPI profiles of patients with chronic fatigue syndrome. J Psychosom Res. 1996 Jan;40(1):67-74. PMID: 8730646

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

*

Patnaik M, Komaroff AL, Conley E, Ojo-Amaize EA, Peter JB. Prevalence of IgM antibodies to human herpesvirus 6 early antigen (p41/38) in patients with chronic fatigue syndrome. J Infect Dis. 1995 Nov;172(5):1364-7. PMID: 7594679

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

*

Swanink CM, van der Meer JW, Vercoulen JH, Bleijenberg G, Fennis JF, Galama JM. Epstein-Barr virus (EBV) and the chronic fatigue syndrome: normal virus load

in blood and normal immunologic reactivity in the EBV regression assay. Clin Infect Dis. 1995 May;20(5):1390-2. PMID: 7620030

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

*

Di Luca D, Zorzenon M, Mirandola P, Colle R, Botta GA, Cassai E. Human herpesvirus 6 and human herpesvirus 7 in chronic fatigue syndrome. J Clin Microbiol. 1995 Jun;33(6):1660-61. PMID: 7650209

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).

*

Sairenji T, Yamanishi K, Tachibana Y, Bertoni G, Kurata T. Antibody responses to Epstein-Barr virus, human herpesvirus 6 and human herpesvirus 7 in patients with chronic fatigue syndrome. Intervirology. 1995;38(5):269-73. PMID: 8724857

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

*

Manian FA. Simultaneous measurement of antibodies to Epstein-Barr virus, human herpesvirus 6, herpes simplex virus types 1 and 2, and 14 enteroviruses in chronic fatigue syndrome: is there evidence of activation of a nonspecific polyclonal immune response? Clin Infect Dis. 1994 Sep;19(3):448-53. PMID: 7811864

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

*

Yalcin S, Kuratsune H, Yamaguchi K, Kitani T, Yamanishi K. Prevalence of human herpesvirus 6 variants A and B in patients with chronic fatigue syndrome. Microbiol Immunol. 1994;38(7):587-90. PMID: 7968694

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

*

Natelson BH, Ye N, Moul DE, Jenkins FJ, Oren DA, Tapp WN, Cheng YC. High titers of anti-Epstein-Barr virus DNA polymerase are found in patients with severe fatiguing illness. J Med Virol. 1994 Jan;42(1):42-6. PMID: 8308519

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

*

Wray BB, Gaughf C, Chandler FW Jr, Berry SS, Latham JE, Wood L, DuRant RH. Detection of Epstein-Barr virus and cytomegalovirus in patients with chronic fatigue. Ann Allergy. 1993 Sep;71(3):223-6. PMID: 8396863

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.

*

Bond PA. A role for herpes simplex virus in the aetiology of chronic fatigue syndrome and related disorders. Med Hypotheses. 1993 May;40(5):301-8. PMID: 8394501

*

Lusso P, Malnati MS, Garzino-Demo A, Crowley RW, Long EO, Gallo RC. Infection of natural killer cells by human herpesvirus 6. Nature. 1993 Apr 1;362(6419):458-62. PMID: 7681936

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

*

Kawai K, Kawai A. Studies on the relationship between chronic fatigue syndrome and Epstein-Barr virus in Japan. Intern Med. 1992 Mar;31(3):313-8. PMID: 1319246

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

*

Woodward CG, Cox RA. Epstein-Barr virus serology in the chronic fatigue syndrome. J Infect. 1992 Mar;24(2):133-9. PMID: 1314860

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.

*

Nishikai M. Chronic fatigue syndrome--study of 51 cases treated at the Second Tokyo National Hospital. Nihon Rinsho. 1992 Nov;50(11):2641-7. PMID: 1337560

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.

*

Josephs SF, Henry B, Balachandran N, Strayer D, Peterson D, Komaroff AL, Ablashi DV HHV-6 reactivation in chronic fatigue syndrome. Lancet. 1991 Jun 1;337(8753):1346-7. PMID: 1674318

HHV-6 is reported to be reactivated in CFS.

*

Bertram G, Dreiner N, Krueger GR, Ramon A, Ablashi DV, Salahuddin SZ, Balachandram N. Frequent double infection with Epstein-Barr virus and human herpesvirus-6 in patients with acute infectious mononucleosis. In Vivo. 1991 May-Jun;5(3):271-9. PMID: 1654150

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

*

Jones JF, Streib J, Baker S, Herberger M. Chronic fatigue syndrome: I. Epstein-Barr virus immune response and molecular epidemiology. J Med Virol. 1991 Mar;33(3):151-8. PMID: 1679118

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.

*

Buchwald D, Freedman AS, Ablashi DV, Sullivan JL, Caligiuri M, Weinberg DS, Hall CG, Ashley RL, Saxinger C, Balachandran N, et al. A chronic "postinfectious" fatigue syndrome associated with benign lymphoproliferation, B-cell proliferation, and active replication of human herpesvirus-6. J Clin Immunol. 1990 Nov;10(6):335-44. PMID: 1964694

A patient with ME and HHV6 is profiled.

*

Gold D, Bowden R, Sixbey J, Riggs R, Katon WJ, Ashley R, Obrigewitch RM, Corey L. Chronic fatigue. A prospective clinical and virologic study. JAMA. 1990 Jul 4;264(1):48-53. PMID: 2162397

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

*

Jones JF, Williams M, Schooley RT, Robinson C, Glaser R. Antibodies to Epstein-Barr virus-specific DNase and DNA polymerase in the chronic fatigue syndrome. Arch Intern Med. 1988 Sep;148(9):1957-60. PMID: 2843138

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.

*

Ablashi DV, Josephs SF, Buchbinder A, Hellman K, Nakamura S, Llana T, Lusso P, Kaplan M, Dahlberg J, Memon S, et al. Human B-lymphotropic virus (human herpesvirus-6). J Virol Methods. 1988 Sep;21(1-4):29-48. PMID: 2846617

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

Chia J, Chia A, Voeller M, Lee T, Chang R. Acute enterovirus infection followed by myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and viral persistence. J Clin Pathol. 2010 Feb;63(2):165-8. PMID: 19828908

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.

*

Chia JK, Chia AY. Chronic fatigue syndrome is associated with chronic enterovirus infection of the stomach. J Clin Pathol. 2008 Jan;61(1):43-8. PMID: 17872383

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

*

Chia JK. The role of enterovirus in chronic fatigue syndrome. J Clin Pathol. 2005 Nov;58(11):1126-32. PMID: 16254097

Enteroviruses may play a role in CFS.

*

Nairn C, Galbraith DN, Clements GB. Comparison of coxsackie B neutralisation and enteroviral PCR in chronic fatigue patients. J Med Virol. 1995 Aug;46(4):310-3. PMID: 7595406

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

*

Galbraith DN, Nairn C, Clements GB. Phylogenetic analysis of short enteroviral sequences from patients with chronic fatigue syndrome. J Gen Virol. 1995 Jul;76 (Pt 7):1701-7. PMID: 9049375

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

*

Clements GB, McGarry F, Nairn C, Galbraith DN. Detection of enterovirus-specific RNA in serum: the relationship to chronic fatigue. J Med Virol. 1995 Feb;45(2):156-61. PMID: 7775934

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.

*

Behan PO, Behan WM, Gow JW, Cavanagh H, Gillespie S. Enteroviruses and postviral fatigue syndrome. Ciba Found Symp. 1993;173:146-54; discussion 154-9. PMID: 8387908

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

*

Gow JW, Behan WM. Amplification and identification of enteroviral sequences in the postviral fatigue syndrome. Br Med Bull. 1991 Oct;47(4):872-85. PMID: 1665380

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

*

Gow JW, Behan WM, Clements GB, Woodall C, Riding M, Behan PO. Enteroviral RNA sequences detected by polymerase chain reaction in muscle of patients with postviral fatigue syndrome. BMJ. 1991 Mar 23;302(6778):692-6. PMID: 1850635

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

Maes M, Leunis JC, Geffard M, Berk M. Evidence for the existence of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) with and without abdominal discomfort (irritable bowel) syndrome. Neuro Endocrinol Lett. 2014;35(6):445-53. PMID: 25433843

Abdominal discomfort symptoms are characteristic of a subset of patients with ME/CFS. Increased bacterial translocation (leaky gut) is associated with ADS symptoms.

*

Frémont M, Coomans D, Massart S, De Meirleir K. High-throughput 16S rRNA gene sequencing reveals alterations of intestinal microbiota in myalgic encephalomyelitis/chronic fatigue syndrome patients. Anaerobe. 2013 Aug;22:50-6. PMID: 23791918

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

*

Lakhan SE, Kirchgessner A. Gut inflammation in chronic fatigue syndrome. Nutr Metab (Lond). 2010 Oct 12;7:79. PMID: 20939923

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.

*

Sheedy JR, Wettenhall RE, Scanlon D, Gooley PR, Lewis DP, McGregor N, Stapleton DI, Butt HL, DE Meirleir KL. Increased d-lactic Acid intestinal bacteria in patients with chronic fatigue syndrome. In Vivo. 2009 Jul-Aug;23(4):621-8. PMID: 19567398

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.

*

Frémont M, Metzger K, Rady H, Hulstaert J, De Meirleir K. Detection of herpesviruses and parvovirus B19 in gastric and intestinal mucosa of chronic fatigue syndrome patients. In Vivo. 2009 Mar-Apr;23(2):209-13. PMID: 19414405

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

*

Maes M, Leunis JC. Normalization of leaky gut in chronic fatigue syndrome (CFS) is accompanied by a clinical improvement: effects of age, duration of illness and the translocation of LPS from gram-negative bacteria. Neuro Endocrinol Lett. 2008 Dec;29(6):902-10. PMID: 19112401

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.

*

Cater RE 2nd. Chronic intestinal candidiasis as a possible etiological factor in the chronic fatigue syndrome. Med Hypotheses. 1995 Jun;44(6):507-15. PMID: 7476598

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.

*

Nijs J, Nicolson GL, De Becker P, Coomans D, De Meirleir K. High prevalence of Mycoplasma infections among European chronic fatigue syndrome patients. Examination of four Mycoplasma species in blood of chronic fatigue syndrome patients. FEMS Immunol Med Microbiol. 2002 Nov 15;34(3):209-14. PMID: 12423773

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.

*

Vojdani A, Choppa PC, Tagle C, Andrin R, Samimi B, Lapp CW. Detection of Mycoplasma genus and Mycoplasma fermentans by PCR in patients with Chronic

Fatigue Syndrome. FEMS Immunol Med Microbiol. 1998 Dec;22(4):355-65. PMID: 9879928

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. fermentas were found in 52% and 24% of CFS samples, vs. 14% and 8% of control subjects (P<0.0001).

*

Choppa PC, Vojdani A, Tagle C, Andrin R, Magtoto L. Multiplex PCR for the detection of Mycoplasma fermentans, M. hominis and M. penetrans in cell cultures and blood samples of patients with chronic fatigue syndrome. Mol Cell Probes. 1998 Oct;12(5):301-8. PMID: 9778455

The percentage of Mycoplasma infection was found to be 52% in CFS patients and 15% in healthy individuals. Mycoplasma fermentans, M. hominis andM. 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

Kerr JR, Gough J, Richards SC, Main J, Enlander D, McCreary M, Komaroff AL, Chia JK. Antibody to parvovirus B19 nonstructural protein is associated with chronic arthralgia in patients with chronic fatigue syndrome/myalgic encephalomyelitis. J Gen Virol. 2010 Apr;91(Pt 4):893-7. PMID: 20007355

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.

*

Seishima M, Mizutani Y, Shibuya Y, Arakawa C. Chronic fatigue syndrome after human parvovirus B19 infection without persistent viremia. Dermatology. 2008;216(4):341-6. PMID: 18277075

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

*

Kerr JR. Pathogenesis of parvovirus B19 infection: host gene variability, and possible means and effects of virus persistence. J Vet Med B Infect Dis Vet Public Health. 2005 Sep-Oct;52(7-8):335-9. PMID: 16316396

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.

*

Jacobson SK, Daly JS, Thorne GM, McIntosh K. Chronic parvovirus B19 infection resulting in chronic fatigue syndrome: case history and review. Clin Infect Dis. 1997 Jun;24(6):1048-51. PMID: 9195056

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

Strauss B, Löschau M, Seidel T, Stallmach A, Thomas A. Are fatigue symptoms and chronic fatigue syndrome following Q fever infection related to psychosocial variables? J Psychosom Res. 2012 Apr;72(4):300-4. PMID: 22405225

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.

*

Ledina D, Bradarić N, Milas I, Ivić I, Brncić N, Kuzmicić N. Chronic fatigue syndrome after Q fever. Med Sci Monit. 2007 Jul;13(7):CS88-92. PMID: 17599032

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

*

Iwakami E, Arashima Y, Kato K, Komiya T, Matsukawa Y, Ikeda T, Arakawa Y, Oshida S. Treatment of chronic fatigue syndrome with antibiotics: pilot study assessing the involvement of Coxiella burnetii infection. Intern Med. 2005 Dec;44(12):1258-63. PMID: 16415546

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.

*

Ayres JG, Flint N, Smith EG, Tunnicliffe WS, Fletcher TJ, Hammond K, Ward D, Marmion BP. Post-infection fatigue syndrome following Q fever. QJM. 1998 Feb;91(2):105-23. PMID: 9578893

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

Nakaya T, Kuratsune H, Kitani T, Ikuta K. Demonstration on Borna disease virus in patients with chronic fatigue syndrome. Nihon Rinsho. 1997 Nov;55(11):3064-71. PMID: 9396313

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.

*

Nakaya T, Takahashi H, Nakamura Y, Asahi S, Tobiume M, Kuratsune H, Kitani T, Yamanishi K, Ikuta K. Demonstration of Borna disease virus RNA in peripheral blood mononuclear cells derived from Japanese patients with chronic fatigue syndrome. FEBS Lett. 1996 Jan 8;378(2):145-9. PMID: 8549821

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).

*

Martin WJ. Severe stealth virus encephalopathy following chronic-fatigue-syndrome-like illness: clinical and histopathological features. Pathobiology. 1996;64(1):1-8. PMID: 8856789

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

*

Martin WJ, Ahmed KN, Zeng LC, Olsen JC, Seward JG, Seehrai JS. African green monkey origin of the atypical cytopathic 'stealth virus' isolated from a patient with chronic fatigue syndrome. Clin Diagn Virol. 1995 Jul;4(1):93-103. PMID: 15566831

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

*

Martin WJ, Glass RT. Acute encephalopathy induced in cats with a stealth virus isolated from a patient with chronic fatigue syndrome. Pathobiology. 1995;63(3):115-8. PMID: 8821627

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

*

Martin WJ, Zeng LC, Ahmed K, Roy M. Cytomegalovirus-related sequence in an atypical cytopathic virus repeatedly isolated from a patient with chronic fatigue syndrome. Am J Pathol. 1994 Aug;145(2):440-51. PMID: 8053501

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

Other Infections

Elfaitouri A, Herrmann B, Bölin-Wiener A, Wang Y, Gottfries CG, Zachrisson O, Pipkorn R, Rönnblom L, Blomberg J. Epitopes of microbial and human heat shock

protein 60 and their recognition in myalgic encephalomyelitis. PLoS One. 2013 Nov 28;8(11):e81155. PMID: 24312270

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).

*

Mørch K, Hanevik K, Rivenes AC, Bødtker JE, Næss H, Stubhaug B, Wensaas KA, Rortveit G, Eide GE, Hausken T, Langeland N. Chronic fatigue syndrome 5 years after giardiasis: differential diagnoses, characteristics and natural course. BMC Gastroenterol. 2013 Feb 12;13:28. PMID:23399438

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.

*

Hanevik K, Kristoffersen EK, Sørnes S, Mørch K, Næss H, Rivenes AC, Bødtker JE, Hausken T, Langeland N. Immunophenotyping in post-giardiasis functional gastrointestinal disease and chronic fatigue syndrome. BMC Infect Dis. 2012 Oct 14;12:258. PMID: 23061432

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.

*

Naess H, Nyland M, Hausken T, Follestad I, Nyland HI. Chronic fatigue syndrome after Giardia enteritis: clinical characteristics, disability and long-term sickness absence. BMC Gastroenterol. 2012 Feb 8;12:13. PMID: 22316329

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.

*

Larbcharoensub N, Boonsakan P, Aroonroch R, Rochanawutanon M, Nitiyanant P, Phongkitkarun S, Poonvutikul S, Watcharananan SP, Ngarmukos C. Adrenal histoplasmosis: a case series and review of the literature. Southeast Asian J Trop Med Public Health. 2011 Jul;42(4):920-5. PMID: 22299474

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.

*

Maes M, Twisk FN, Kubera M, Ringel K, Leunis JC, Geffard M. Increased IgA responses to the LPS of commensal bacteria is associated with inflammation and activation of cell-mediated immunity in chronic fatigue syndrome. J Affect Disord. 2011 Oct 1. PMID: 21967891

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.

*

Grinde B. Is chronic fatigue syndrome caused by a rare brain infection of a common, normally benign virus? Med Hypotheses. 2008 Aug;71(2):270-4. PMID: 18440157

The authors propose that CFS is caused by a circovirus.

*

Sairenji T, Nagata K. Viral infections in chronic fatigue syndrome. Nihon Rinsho. 2007 Jun;65(6):991-6. PMID: 17561687

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.

*

Ikuta K, Yamada T, Shimomura T, Kuratsune H, Kawahara R, Ikawa S, Ohnishi E, Sokawa Y, Fukushi H, Hirai K, Watanabe Y, Kurata T, Kitani T, Sairenji T. Diagnostic evaluation of 2', 5'-oligoadenylate synthetase activities and antibodies against Epstein-Barr virus and Coxiella burnetii in patients with chronic fatigue syndrome in Japan. Microbes Infect. 2003 Oct;5(12):1096-102. PMID: 14554250

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.

*

Nicolson GL, Gan R, Haier J. Multiple co-infections (Mycoplasma, Chlamydia, human herpes virus-6) in blood of chronic fatigue syndrome patients: association with signs and symptoms. APMIS. 2003 May;111(5):557-66. PMID: 12887507

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.

*

Chia JK, Chia LY. Chronic Chlamydia pneumoniae infection: a treatable cause of chronic fatigue syndrome. Clin Infect Dis. 1999 Aug;29(2):452-3. PMID: 10476765

Chlamydia pneumoniae is discussed as a contributor to CFS.

*

Pamphlett R, O'Donoghue P. Antibodies against Sarcocystis and Toxoplasma in humans with the chronic fatigue syndrome. Aust N Z J Med. 1992 Jun;22(3):307-8. PMID: 1497558

*

Komaroff AL, Wang SP, Lee J, Grayston JT. No association of chronic Chlamydia pneumoniae infection with chronic fatigue syndrome. J Infect Dis. 1992 Jan;165(1):184. PMID: 1727893

Endocrine System

Vangeel E, Van Den Eede F, Hompes T, Izzi B, Del Favero J, Moorkens G, Lambrechts D, Freson K, Claes S. Chronic Fatigue Syndrome and DNA

Hypomethylation of the Glucocorticoid Receptor Gene Promoter 1F Region: Associations With HPA Axis Hypofunction and Childhood Trauma. Psychosom Med. 2015 Oct;77(8):853-62. PMID: 26230484

The authors found evidence of NR3C1 promoter hypomethylation in female patients with CFS. The functional relevance of these differences was consistent with the hypothalamic-pituitary-adrenalaxis hypofunction hypothesis (GR hypersuppression).

*

Hall DL, Lattie EG, Antoni MH, Fletcher MA, Czaja S, Perdomo D, Klimas NG. Stress management skills, cortisol awakening response, and post-exertional malaise in Chronic Fatigue Syndrome. Psychoneuroendocrinology. 2014 Nov;49:26-31. PMID: 25049069

In a population of CFS patients, greater perceived stress management skills related to greater cortisol awakening response and greater cortisol awakening response related to less post-exertional malaise severity.

*

Craddock TJ, Fritsch P, Rice MA Jr, del Rosario RM, Miller DB, Fletcher MA, Klimas NG, Broderick G. A role for homeostatic drive in the perpetuation of complex chronic illness: Gulf War Illness and chronic fatigue syndrome. PLoS One. 2014 Jan 8;9(1):e84839. PMID: 24416298

In female CFS subjects, expression of endocrine-immune markers aligned with an alternate homeostatic state displaying hypocortisolism, high estradiol, and a shift towards an anti-inflammatory Th2 activation. These results support a role for homeostatic drive in perpetuating dysfunctional cortisol levels through persistent interaction with the immune system and HPG axis.

*

Nijhof SL1, Rutten JM2, Uiterwaal CS3, Bleijenberg G4, Kimpen JL5, Putte EM6. The role of hypocortisolism in chronic fatigue syndrome. Psychoneuroendocrinology. 2014 Apr;42:199-206. PMID: 24636516

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.

*

Powell DJ, Liossi C, Moss-Morris R, Schlotz W. Unstimulated cortisol secretory activity in everyday life and its relationship with fatigue and chronic fatigue syndrome: A systematic review and subset meta-analysis. Psychoneuroendocrinology. 2013 Nov;38(11):2405-22. PMID: 23916911

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.

*

Aschbacher K, Adam EK, Crofford LJ, Kemeny ME, Demitrack MA, Ben-Zvi A. Linking disease symptoms and subtypes with personalized systems-based phenotypes: a proof of concept study. Brain Behav Immun. 2012 Oct;26(7):1047-56. PMID: 22687333

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.

*

Papadopoulos AS, Cleare AJ. Hypothalamic-pituitary-adrenal axis dysfunction in chronic fatigue syndrome. Nat Rev Endocrinol. 2011 Sep 27. PMID: 21946893

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.

*

Ursini F, Succurro E, Grembiale A, Gagliardi DA, Arturi F. The HPA axis in the pathogenesis of chronic fatigue syndrome. Clin Ter. 2010 Sep-Oct;161(5):461-4. PMID: 20949245

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

*

Shishioh-Ikejima N, Ogawa T, Yamaguti K, Watanabe Y, Kuratsune H, Kiyama H. The increase of alpha-melanocyte-stimulating hormone in the plasma of chronic fatigue syndrome patients. BMC Neurol. 2010 Aug 23;10:73. PMID: 20731841

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

*

Wyller VB, Evang JA, Godang K, Solhjell KK, Bollerslev J. Hormonal alterations in adolescent chronic fatigue syndrome. Acta Paediatr. 2010 May;99(5):770-3. PMID:20199497

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.

*

Fomicheva EE, Filatenkova TA, Rybakina EG. Activity in the hypothalamo-hypophyseal-adrenocortical system on experimental induction of chronic fatigue syndrome. Neurosci Behav Physiol. 2010 Mar;40(3):245-50. PMID: 20146018

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

*

Weaver SA, Janal MN, Aktan N, Ottenweller JE, Natelson BH. Sex differences in plasma prolactin response to tryptophan in chronic fatigue syndrome patients with and without comorbid fibromyalgia. J Womens Health (Larchmt). 2010 May;19(5):951-8. PMID: 20384451

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

*

Evans KM, Flanagan DE, Wilkin TJ. Chronic fatigue: is it endocrinology? Clin Med. 2009 Feb;9(1):34-8. PMID: 19271598

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.

*

Fomicheva EE, Filatenkova TA, Rybakina EG. Activity of hypotnalamic-pituitary-adrenal axis by induction of experimental chronic fatigue syndrome. Ross Fiziol Zh Im I M Sechenova. 2009 Jan;95(1):11-8. PMID: 19323439

CFS patients display disordered HPA axis and adrenal functioning.

*

Van Houdenhove B, Van Den Eede F, Luyten P. Does hypothalamic-pituitary-adrenal axis hypofunction in chronic fatigue syndrome reflect a 'crash' in the stress system? Med Hypotheses. 2009 Jun;72(6):701-5. PMID: 19237251

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.

*

Veldman J, Van Houdenhove B, Verguts J. Chronic fatigue syndrome: a hormonal origin? A rare case of dysmenorrhea membranacea. Arch Gynecol Obstet. 2009 May;279(5):717-20. PMID: 18787800

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.

*

Fuite J, Vernon SD, Broderick G. Neuroendocrine and immune network re-modeling in chronic fatigue syndrome: an exploratory analysis. Genomics. 2008 Dec;92(6):393-9. PMID: 18775774

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.

*

Torres-Harding S, Sorenson M, Jason L, Maher K, Fletcher MA, Reynolds N, Brown M. The associations between basal salivary cortisol and illness symptomatology in chronic fatigue syndrome. J Appl Biobehav Res. 2008 Jan 1;13:157-180. PMID: 19701493

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 persons with chronic fatigue syndrome and well controls. J Clin Endocrinol Metab. 2008 Mar;93(3):703-9. PMID: 18160468

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

*

Van Den Eede F, Moorkens G, Hulstijn W, Van Houdenhove B, Cosyns P, Sabbe BG, Claes SJ. Combined dexamethasone/corticotropin-releasing factor test in chronic fatigue syndrome. Psychol Med. 2008 Jul;38(7):963-73. PMID: 17803834

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.

*

Van Den Eede F, Moorkens G, Van Houdenhove B, Cosyns P, Claes SJ. Hypothalamic-pituitary-adrenal axis function in chronic fatigue syndrome. Neuropsychobiology. 2007;55(2):112-20. PMID: 17596739

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.

*

Jerjes WK, Taylor NF, Wood PJ, Cleare AJ. Enhanced feedback sensitivity to prednisolone in chronic fatigue syndrome. Psychoneuroendocrinology. 2007 Feb;32(2):192-8. PMID: 17276605

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

*

Gräns H, Nilsson M, Dahlman-Wright K, Evengård B. Reduced levels of oestrogen receptor beta mRNA in Swedish patients with chronic fatigue syndrome. J Clin Pathol. 2007 Feb;60(2):195-8. PMID: 16731592

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.

*

Tanriverdi F, Karaca Z, Unluhizarci K, Kelestimur F. The hypothalamo-pituitary-adrenal axis in chronic fatigue syndrome and fibromyalgia syndrome. Stress. 2007 Mar;10(1):13-25. PMID: 17454963

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.

*

Maes M, Mihaylova I, De Ruyter M. Decreased dehydroepiandrosterone sulfate but normal insulin-like growth factor in chronic fatigue syndrome (CFS): relevance for the inflammatory response in CFS. Neuro Endocrinol Lett. 2005 Oct;26(5):487-92. PMID: 16264414

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.

*

Segal TY, Hindmarsh PC, Viner RM. Disturbed adrenal function in adolescents with chronic fatigue syndrome. J Pediatr Endocrinol Metab. 2005 Mar;18(3):295-301. PMID: 15813608

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

*

Di Giorgio A, Hudson M, Jerjes W, Cleare AJ. 24-hour pituitary and adrenal hormone profiles in chronic fatigue syndrome. Psychosom Med. 2005 May-Jun;67(3):433-40. PMID: 15911907

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.

*

Crofford LJ, Young EA, Engleberg NC, Korszun A, Brucksch CB, McClure LA, Basal circadian and pulsatile ACTH and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome. Brain Behav Immun. 2004 Jul;18(4):314-25. PMID: 15157948

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.

*

Gaab J, Engert V, Heitz V, Schad T, Schürmeyer TH, Ehlert U. Associations between neuroendocrine responses to the Insulin Tolerance Test and patient characteristics in chronic fatigue syndrome. J Psychosom Res. 2004 Apr;56(4):419-24. PMID: 15094026

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.

*

Zarković M, Pavlović M, Pokrajac-Simeunović A, Cirić J, Beleslin B, Penezić Z, Ognjanović S, Savić S, Poluga J, Trbojević B, Drezgić M. Disorder of adrenal gland function in chronic fatigue syndrome. Srp Arh Celok Lek. 2003 Sep-Oct;131(9-10) 370-4. PMID: 15058215

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.

*

Gaab J, Hüster D, Peisen R, Engert V, Heitz V, Schad T, Schürmeyer T, Ehlert U. Assessment of cortisol response with low-dose and high-dose ACTH in patients with chronic fatigue syndrome and healthy comparison subjects. Psychosomatics. 2003 Mar-Apr;44(2):113-9. PMID: 12618533

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.

*

Gaab J, Hüster D, Peisen R, Engert V, Heitz V, Schad T, Schürmeyer TH, Ehlert U. Hypothalamic-pituitary-adrenal axis reactivity in chronic fatigue syndrome and health under psychological, physiological, and pharmacological stimulation. Psychosom Med. 2002 Nov-Dec;64(6):951-62. PMID: 12461200

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.

*

Racciatti D, Guagnano MT, Vecchiet J, De Remigis PL, Pizzigallo E, Della Vecchia R, Di Sciascio T, Merlitti D, Sensi S.Chronic fatigue syndrome: circadian rhythm and hypothalamic-pituitary-adrenal (HPA) axis impairment. Int J Immunopathol Pharmacol. 2001 Jan-Apr;14(1):11-15. PMID: 12622884

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

*

van Rensburg SJ, Potocnik FC, Kiss T, Hugo F, van Zijl P, Mansvelt E, Carstens ME, Theodorou P, Hurly PR, Emsley RA, Taljaard JJ. Serum concentrations of some metals and steroids in patients with chronic fatigue syndrome with reference to neurological and cognitive abnormalities. Brain Res Bull. 2001 May 15;55(2):319-25. PMID: 11470334

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.

*

Vassallo CM, Feldman E, Peto T, Castell L, Sharpley AL, Cowen PJ. Decreased tryptophan availability but normal post-synaptic 5-HT2c receptor sensitivity in chronic fatigue syndrome. Psychol Med. 2001 May;31(4):585-91. PMID: 11352361

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.

*

Visser J, Lentjes E, Haspels I, Graffelman W, Blauw B, de Kloet R, Nagelkerken L. Increased sensitivity to glucocorticoids in peripheral blood mononuclear cells of chronic fatigue syndrome patients, without evidence for altered density or affinity of glucocorticoid receptors. J Investig Med. 2001 Mar;49(2):195-204. PMID: 11288761

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

*

Cleare AJ, Blair D, Chambers S, Wessely S. Urinary free cortisol in chronic fatigue syndrome. Am J Psychiatry. 2001 Apr;158(4):641-3. PMID: 11282703

There is mild hypocortisolism in chronic fatigue syndrome.

*

Visser JT, De Kloet ER, Nagelkerken L. Altered glucocorticoid regulation of the immune response in the chronic fatigue syndrome. Ann N Y Acad Sci. 2000;917:868-75. PMID: 11268418

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

*

Ottenweller JE, Sisto SA, McCarty RC, Natelson BH. Hormonal responses to exercise in chronic fatigue syndrome. Neuropsychobiology. 2001 Jan;43(1):34-41. PMID: 11150897

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.

*

Torpy DJ, Bachmann AW, Grice JE, Fitzgerald SP, Phillips PJ, Whitworth JA, Jackson RV. Familial corticosteroid-binding globulin deficiency due to a novel null mutation: association with fatigue and relative hypotension.J Clin Endocrinol Metab. 2001 Aug;86(8):3692-700. PMID: 11502797

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.

*

Altemus M, Dale JK, Michelson D, Demitrack MA, Gold PW, Straus SE. Abnormalities in response to vasopressin infusion in chronic fatigue syndrome. Psychoneuroendocrinology. 2001 Feb;26(2):175-88. PMID: 11087963

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

*

Scott LV, Svec F, Dinan T. A preliminary study of dehydroepiandrosterone response to low-dose ACTH in chronic fatigue syndrome and in healthy subjects. Psychiatry Res. 2000 Dec 4;97(1):21-8. PMID: 11104854

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.

*

Starr A, Scalise A, Gordon R, Michalewski HJ, Caramia MD. Motor cortex excitability in chronic fatigue syndrome. Clin Neurophysiol. 2000 Nov;111(11):2025-31. PMID: 11068238

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

*

Knook L, Kavelaars A, Sinnema G, Kuis W, Heijnen CJ. High nocturnal melatonin in adolescents with chronic fatigue syndrome. J Clin Endocrinol Metab. 2000 Oct;85(10):3690-2. PMID: 11061525

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

*

Berwaerts J, Moorkens G, Abs R. Secretion of growth hormone in patients with chronic fatigue syndrome. Growth Horm IGF Res. 1998 Apr;8 Suppl B:127-9. PMID: 10990147

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

*

Moorkens G, Berwaerts J, Wynants H, Abs R. Characterization of pituitary function with emphasis on GH secretion in the chronic fatigue syndrome. Clin Endocrinol (Oxf). 2000 Jul;53(1):99-106. PMID: 10931086

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.

*

Scott LV, Teh J, Reznek R, Martin A, Sohaib A, Dinan TG. Small adrenal glands in chronic fatigue syndrome: a preliminary computer tomography study. Psychoneuroendocrinology. 1999 Oct;24(7):759-68. PMID: 10451910

Adrenal gland size was reduced by over 50% in CFS patients, indicative of significant adrenal atrophy.

*

Scott LV, Salahuddin F, Cooney J, Svec F, Dinan TG. Differences in adrenal steroid profile in chronic fatigue syndrome, in depression and in health. J Affect Disord. 1999 Jul;54(1-2):129-37. PMID: 10403156

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.

*

Scott LV, Medbak S, Dinan TG. Desmopressin augments pituitary-adrenal responsivity to corticotropin-releasing hormone in subjects with chronic fatigue syndrome and in healthy volunteers. Biol Psychiatry. 1999 Jun 1;45(11):1447-54. PMID: 10356627

Desmopressin was capable of normalizing the pituitary-adrenal response to corticotropin-releasing hormone in 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.

*

De Becker P, De Meirleir K, Joos E, Campine I, Van Steenberge E, Smitz J, Velkeniers B. Dehydroepiandrosterone (DHEA) response to i.v. ACTH in patients with chronic fatigue syndrome. Horm Metab Res. 1999 Jan;31(1):18-21. PMID: 10077344

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

*

Kuratsune H, Yamaguti K, Sawada M, Kodate S, Machii T, Kanakura Y, Kitani T. Dehydroepiandrosterone sulfate deficiency in chronic fatigue syndrome. Int J Mol Med. 1998 Jan;1(1):143-6. PMID: 9852212

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.

*

Scott LV, Medbak S, Dinan TG. The low dose ACTH test in chronic fatigue syndrome and in health. Clin Endocrinol (Oxf). 1998 Jun;48(6):733-7. PMID: 9713562

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

*

Cannon JG, Angel JB, Abad LW, O'Grady J, Lundgren N, Fagioli L, Komaroff AL. Hormonal influences on stress-induced neutrophil mobilization in health and chronic fatigue syndrome. J Clin Immunol. 1998 Jul;18(4):291-8. PMID: 9710746

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

*

Peroutka SJ. Chronic fatigue disorders: an inappropriate response to arginine vasopressin? Med Hypotheses. 1998 Jun;50(6):521-3. PMID: 9710328

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.

*

Scott LV, Medbak S, Dinan TG. Blunted adrenocorticotropin and cortisol responses to corticotropin-releasing hormone stimulation in chronic fatigue syndrome. Acta Psychiatr Scand. 1998 Jun;97(6):450-7. PMID: 9669518

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

*

Demitrack MA, Crofford LJ. Evidence for and pathophysiologic implications of hypothalamic-pituitary-adrenal axis dysregulation in fibromyalgia and chronic fatigue syndrome. Ann N Y Acad Sci. 1998 May 1;840:684-97. PMID: 9629295

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.

*

Scott LV, Burnett F, Medbak S, Dinan TG. Naloxone-mediated activation of the hypothalamic-pituitary-adrenal axis in chronic fatigue syndrome. Psychol Med. 1998 Mar;28(2):285-93. PMID: 9572086

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

*

Dinan TG, Majeed T, Lavelle E, Scott LV, Berti C, Behan P. Blunted serotonin-mediated activation of the hypothalamic-pituitary-adrenal axis in chronic fatigue syndrome. Psychoneuroendocrinology. 1997 May;22(4):261-7. PMID: 9226729

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.

*

Cannon JG, Angel JB, Abad LW, Vannier E, Mileno MD, Fagioli L, Wolff SM, Komaroff AL. Interleukin-1 beta, interleukin-1 receptor antagonist, and soluble interleukin-1 receptor type II secretion in chronic fatigue syndrome. J Clin Immunol. 1997 May;17(3):253-61. PMID: 9168406

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.

*

Allain TJ, Bearn JA, Coskeran P, Jones J, Checkley A, Butler J, Wessely S, Miell JP. Changes in growth hormone, insulin, insulinlike growth factors (IGFs), and IGF-binding protein-1 in chronic fatigue syndrome. Biol Psychiatry. 1997 Mar 1;41(5):567-73. PMID: 9046989

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.

*

Sharpe M, Clements A, Hawton K, Young AH, Sargent P, Cowen PJ. Increased prolactin response to buspirone in chronic fatigue syndrome. J Affect Disord. 1996 Nov 4;41(1):71-6. PMID: 8938208

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

*

Bearn J, Allain T, Coskeran P, Munro N, Butler J, McGregor A, Wessely S. Neuroendocrine responses to d-fenfluramine and insulin-induced hypoglycemia in chronic fatigue syndrome. Biol Psychiatry. 1995 Feb 15;37(4):245-52. PMID: 7711161

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

*

Jefferies WM. Mild adrenocortical deficiency, chronic allergies, autoimmune disorders and the chronic fatigue syndrome: a continuation of the cortisone story. Med Hypotheses. 1994 Mar;42(3):183-9. PMID: 8057974

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

*

Bakheit AM, Behan PO, Watson WS, Morton JJ. Abnormal arginine-vasopressin secretion and water metabolism in patients with postviral fatigue syndrome. Acta Neurol Scand. 1993 Mar;87(3):234-8. PMID: 8475696

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

*

Demitrack MA, Dale JK, Straus SE, Laue L, Listwak SJ, Kruesi MJ, Chrousos GP, Gold PW. Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. J Clin Endocrinol Metab. 1991 Dec;73(6):1224-34. PMID: 1659582

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

Martínez-Martínez LA1, Mora T, Vargas A, Fuentes-Iniestra M, Martínez-Lavín M. Sympathetic nervous system dysfunction in fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, and interstitial cystitis: a review of case-control studies. J Clin Rheumatol. 2014 Apr;20(3):146-50. PMID: 24662556

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

Wu T, Qi X, Su Y, Teng J, Xu X. Electroencephalogram characteristics in patients with chronic fatigue syndrome. Neuropsychiatr Dis Treat. 2016 Jan 28;12:241-9. PMID: 26869792

The spontaneous brain electrical activities in CFS patients were significantly reduced. The abnormal changes in the cerebral functions were localized at the right frontal and left occipital regions in CFS patients.

*

Zinn ML, Zinn MA, Jason LA. Intrinsic Functional Hypoconnectivity in Core Neurocognitive Networks Suggests Central Nervous System Pathology in Patients with Myalgic Encephalomyelitis: A Pilot Study. Appl Psychophysiol Biofeedback. 2016 Feb 11. PMID: 26869373

Exact low resolution electromagnetic tomography (eLORETA) was recorded from nineteen EEG channels in nine patients with myalgic encephalomyelitis (ME) and 9 healthy controls to assess current source density and functional connectivity. The authors found support for all three networks of the triple network model, namely the central executive network (CEN), salience network (SN), and the default mode network (DMN) indicating hypo-connectivity in the Delta, Alpha, and Alpha-2 frequency bands in patients with ME compared to controls.

*

Saury JM. The role of the hippocampus in the pathogenesis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Med Hypotheses. 2016 Jan;86:30-8. PMID: 26804593

ME/CFS triggering factors impact the hippocampus, leading to neurocognitive deficits and disturbances in the regulation of the stress system and pain perception.

*

Boissoneault J, Letzen J, Lai S, O'Shea A, Craggs J, Robinson ME, Staud R. Abnormal resting state functional connectivity in patients with chronic fatigue syndrome: an

arterial spin-labeling fMRI study. Magn Reson Imaging. 2016 May;34(4):603-8. PMID: 26708036

The study used arterial spin labeling functional magnetic resonance imaging (ASL) and demonstrates altered functional connectivity of several regions associated with cognitive, affective, memory, and higher cognitive function in ME/CFS patients. Connectivity to memory related brain areas (parahippocampal gyrus) was correlated with clinical fatigue ratings, providing supporting evidence that brain network abnormalities may contribute to ME/CFS pathogenesis.

*

Kim BH, Namkoong K, Kim JJ, Lee S, Yoon KJ, Choi M, Jung YC. Altered resting-state functional connectivity in women with chronic fatigue syndrome. Psychiatry Res. 2015 Dec 30;234(3):292-7. PMID: 26602611

The posterior cingulate cortex in CFS patients showed increased resting-state functional connectivity with the dorsal and rostral anterior cingulate cortex. Global efficiency of the posterior cingulate cortex was significantly lower in CFS patients, while local efficiency showed no difference from findings in healthy controls.

*

Gay CW, Robinson ME, Lai S, O'Shea A, Craggs JG, Price DD, Staud R. Abnormal Resting-State Functional Connectivity in Patients with Chronic Fatigue Syndrome: Results of Seed and Data-Driven Analyses. Brain Connect. 2016 Feb;6(1):48-56. PMID: 26449441

Results of a functional MRI test confirmed altered resting-state functional connectivity in patients with ME/CFS, which was significantly correlated with the severity of their chronic fatigue.

*

Zeineh MM, Kang J, Atlas SW, Raman MM, Reiss AL, Norris JL, Valencia I, Montoya JG. Right Arcuate Fasciculus Abnormality in Chronic Fatigue Syndrome. Radiology. 2014 Oct 29:141079. PMID: 25353054

Bilateral white matter atrophy of the brain is present in CFS. No differences in perfusion were noted. Right hemispheric increased FA fractional anisotropy may reflect degeneration of crossing fibers or strengthening of short-range fibers. Right anterior arcuate FA fractional anisotropy may serve as a biomarker for CFS.

*

Miller AH, Jones JF, Drake DF, Tian H, Unger ER, Pagnoni G. Decreased basal ganglia activation in subjects with chronic fatigue syndrome: association with symptoms of fatigue. PLoS One. 2014 May 23;9(5):e98156. PMID: 24858857

Data suggest that symptoms of fatigue in CFS subjects were associated with reduced responsivity of the basal ganglia, possibly involving the disruption of projections from the globus pallidus to thalamic and cortical networks.

*

Nakatomi Y, Mizuno K, Ishii A, Wada Y, Tanaka M, Tazawa S, Onoe K, Fukuda S, Kawabe J, Takahashi K, Kataoka Y, Shiomi S, Yamaguti K, Inaba M, Kuratsune H, Watanabe Y. Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An 11C-(R)-PK11195 PET Study. J Nucl Med. 2014 Mar 24. PMID: 24665088

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.

*

Ishii A, Tanaka M, Iwamae M, Kim C, Yamano E, Watanabe Y. Fatigue sensation induced by the sounds associated with mental fatigue and its related neural activities: revealed by magnetoencephalography. Behav Brain Funct. 2013 Jun 13;9:24. PMID: 23764106

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.

*

Higgins N, Pickard J, Lever A. Lumbar puncture, chronic fatigue syndrome and idiopathic intracranial hypertension: a cross-sectional study. JRSM Short Rep. 2013 Nov 21;4(12):2042533313507920. PMID: 24475346

An unknown, but possibly substantial, minority of patients with chronic fatigue syndrome may actually have intracranial hypertension. An unknown, but much larger, proportion of patients with chronic fatigue syndrome do not have IIH by current criteria but respond to lumbar puncture in the same way as patients who do.

*

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

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

*

Puri BK, Jakeman PM, Agour M, Gunatilake KD, Fernando KA, Gurusinghe AI, Treasaden IH, Waldman AD, Gishen P. Regional grey and white matter volumetric changes in myalgic encephalomyelitis (chronic fatigue syndrome): a voxel-based morphometry 3 T MRI study. Br J Radiol. 2012 Jul;85(1015):e270-3. PMID: 22128128

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.

*

Stewart JM, Medow MS, Messer ZR, Baugham IL, Terilli C, Ocon AJ. Postural neurocognitive and neuronal activated cerebral blood flow deficits in young chronic fatigue syndrome patients with postural tachycardia syndrome. Am J Physiol Heart Circ Physiol. 2012 Mar 1;302(5):H1185-94. PMID: 22180650

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.

*

Yamamoto S, Ouchi Y, Nakatsuka D, Tahara T, Mizuno K, Tajima S, Onoe H, Yoshikawa E, Tsukada H, Iwase M, Yamaguti K, Kuratsune H, Watanabe Y. Reduction of [11C](+)3-MPB binding in brain of chronic fatigue syndrome with serum autoantibody against muscarinic cholinergic receptor. PLoS One. 2012;7(12):e51515. PMID: 23240035

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.

*

Puri BK, Jakeman PM, Agour M, Gunatilake KD, Fernando KA, Gurusinghe AI, Treasaden IH, Waldman AD, Gishen P. Regional grey and white matter volumetric changes in myalgic encephalomyelitis (chronic fatigue syndrome): a voxel-based morphometry 3-T MRI study. Br J Radiol. 2011 Nov 29. PMID: 22128128

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.

*

Biswal B, Kunwar P, Natelson BH. Cerebral blood flow is reduced in chronic fatigue syndrome as assessed by arterial spin labeling. J Neurol Sci. 2011 Feb 15;301(1-2):9-11. PMID: 21167506

Most CFS patients have decreases in cerebral blood flow.

*

Perrin R, Embleton K, Pentreath VW, Jackson A. Longitudinal MRI shows no cerebral abnormality in chronic fatigue syndrome. Br J Radiol. 2010 May;83(989):419-23. PMID:20223910

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.

*

Flor-Henry P, Lind JC, Koles ZJ. EEG source analysis of chronic fatigue syndrome. Psychiatry Res. 2010 Feb 28;181(2):155-64. PMID: 20006474

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.

*

Chen R, Liang FX, Moriya J, Yamakawa J, Sumino H, Kanda T, Takahashi T. Chronic fatigue syndrome and the central nervous system. J Int Med Res. 2008 Sep-Oct;36(5):867-74. PMID: 18831878

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.

*

Sakudo A, Kuratsune H, Hakariya Y, Kobayashi T, Ikuta K. Spectroscopic diagnosis of chronic fatigue syndrome by multivariate analysis of visible and near-infrared spectra. Nihon Rinsho. 2007 Jun;65(6):1051-6. PMID: 17561696

*

Yoshiuchi K, Farkas J, Natelson BH. Patients with chronic fatigue syndrome have reduced absolute cortical blood flow. Clin Physiol Funct Imaging. 2006 Mar;26(2):83-6. PMID: 16494597

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.

*

de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I. Gray matter volume reduction in the chronic fatigue syndrome. Neuroimage. 2005 Jul 1;26(3):777-81. PMID: 15955487

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.

*

Okada T, Tanaka M, Kuratsune H, Watanabe Y, Sadato N. Mechanisms underlying fatigue: a voxel-based morphometric study of chronic fatigue syndrome. BMC Neurol. 2004 Oct 4;4(1):14. PMID: 15461817

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.

*

Schmaling KB, Lewis DH, Fiedelak JI, Mahurin R, Buchwald DS. Single-photon emission computerized tomography and neurocognitive function in patients with chronic fatigue syndrome. Psychosom Med. 2003 Jan-Feb;65(1):129-36. PMID: 12554824

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.

*

Chaudhuri A, Condon BR, Gow JW, Brennan D, Hadley DM. Proton magnetic resonance spectroscopy of basal ganglia in chronic fatigue syndrome. Neuroreport. 2003 Feb 10;14(2):225-8. PMID: 12598734

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.

*

Puri BK, Counsell SJ, Zaman R, Main J, Collins AG, Hajnal JV, Davey NJ. Relative increase in choline in the occipital cortex in chronic fatigue syndrome. Acta Psychiatr Scand. 2002 Sep;106(3):224-6. PMID: 12197861

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.

*

Brooks JC, Roberts N, Whitehouse G, Majeed T. Proton magnetic resonance spectroscopy and morphometry of the hippocampus in chronic fatigue syndrome.Br J Radiol. 2000 Nov;73(875):1206-8. PMID: 11144799

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

*

MacHale SM, Lawŕie SM, Cavanagh JT, Glabus MF, Murray CL, Goodwin GM, Ebmeier KP. Cerebral perfusion in chronic fatigue syndrome and depression. Br J Psychiatry. 2000 Jun;176:550-6. PMID: 10974961

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.

*

Tomoda A, Miike T, Yamada E, Honda H, Moroi T, Ogawa M, Ohtani Y, Morishita S. Chronic fatigue syndrome in childhood.Brain Dev. 2000 Jan;22(1):60-4. PMID: 10761837

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.

*

Lange G, DeLuca J, Maldjian JA, Lee H, Tiersky LA, Natelson BH. Brain MRI abnormalities exist in a subset of patients with chronic fatigue syndrome. J Neurol Sci. 1999 Dec 1;171(1):3-7. PMID: 10567042

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.

*

Abu-Judeh HH, Levine S, Kumar M, el-Zeftawy H, Naddaf S, Lou JQ, Abdel-Dayem HM. Comparison of SPET brain perfusion and 18F-FDG brain metabolism in patients with chronic fatigue syndrome. Nucl Med Commun. 1998 Nov;19(11):1065-71. PMID: 9861623

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

*

Tirelli U, Chierichetti F, Tavio M, Simonelli C, Bianchin G, Zanco P, Ferlin G. Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data. Am J Med. 1998 Sep 28;105(3A):54S-58S. PMID: 9790483

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

*

Lane RJ, Barrett MC, Taylor DJ, Kemp GJ, Lodi R. Heterogeneity in chronic fatigue syndrome: evidence from magnetic resonance spectroscopy of muscle. Neuromuscul Disord. 1998 May;8(3-4):204-9. PMID: 9631403

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.

*

Schwartz RB, Garada BM, Komaroff AL, Tice HM, Gleit M, Jolesz FA, Holman BL. Detection of intracranial abnormalities in patients with chronic fatigue syndrome: comparison of MR imaging and SPECT. AJR Am J Roentgenol. 1994 Apr;162(4):935-41. PMID: 8141020

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

*

Natelson BH, Cohen JM, Brassloff I, Lee HJ. A controlled study of brain magnetic resonance imaging in patients with the chronic fatigue syndrome. J Neurol Sci. 1993 Dec 15;120(2):213-7. PMID: 8138812

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

*

Buchwald D, Cheney PR, Peterson DL, Henry B, Wormsley SB, Geiger A, Ablashi DV, Salahuddin SZ, Saxinger C, Biddle R, et al. A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpesvirus type 6 infection. Ann Intern Med. 1992 Jan 15;116(2):103-13. PMID: 1309285

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.

*

Shimizu T. Neuro-psychiatric aspects of chronic fatigue syndrome. Nihon Rinsho. 1992 Nov;50(11):2630-4. PMID: 1287239

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

*

Ichise M, Salit IE, Abbey SE, Chung DG, Gray B, Kirsh JC, Freedman M. Assessment of regional cerebral perfusion by 99Tcm-HMPAO SPECT in chronic fatigue syndrome. Nucl Med Commun. 1992 Oct;13(10):767-72. PMID: 1491843

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

Mizuno K, Tanaka M, Tanabe HC, Joudoi T, Kawatani J, Shigihara Y, Tomoda A, Miike T, Imai-Matsumura K, Sadato N,Watanabe Y. Less efficient and costly processes of frontal cortex in childhood chronic fatigue syndrome. Neuroimage Clin. 2015 Sep 10;9:355-68. PMID: 26594619

The authors conducted a study using a dual verbal task to assess allocation of attentional resources to two simultaneous activities (picking out vowels and reading for story comprehension) and functional magnetic resonance imaging. Patients with childhood CFS exhibited a much larger area of activation, recruiting additional frontal areas. The right middle frontal gyrus (MFG), which is included in the dorsolateral prefrontal cortex, of CCFS patients was specifically activated in

both the single and dual tasks; this activation level was positively correlated with motivation scores for the tasks and accuracy of story comprehension.

*

Nijhof LN, Nijhof SL, Bleijenberg G, Stellato RK, Kimpen JL, Hulshoff Pol HE, van de Putte EM. The impact of chronic fatigue syndrome on cognitive functioning in adolescents. Eur J Pediatr. 2016 Feb;175(2):245-52. PMID: 26334394

Current IQ scores of CFS adolescents were lower than expected on the basis of their school level. Furthermore, there was a difference in intelligence performance across time when current IQ scores were compared with pre-CFS cognitive achievement.

*

Sulheim D, Fagermoen E, Sivertsen ØS, Winger A, Wyller VB, Øie MG. Cognitive dysfunction in adolescents with chronic fatigue: a cross-sectional study. Arch Dis Child. 2015 Sep;100(9):838-44. PMID: 25791841

Adolescents with chronic fatigue had impaired cognitive function of clinical relevance, measured by objective cognitive tests, in comparison to HC. Working memory and processing speed may represent core difficulties.

*

Cockshell SJ, Mathias JL. Cognitive deficits in chronic fatigue syndrome and their relationship to psychological status, symptomatology, and everyday functioning. Neuropsychology. 2013 Mar;27(2):230-42. PMID: 23527651

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.

*

Togo F, Lange G, Natelson BH, Quigley KS. Attention network test: Assessment of cognitive function in chronic fatigue syndrome. J Neuropsychol. 2013 Sep 24. PMID: 24112872

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.

*

Mizuno K, Watanabe Y. Neurocognitive impairment in childhood chronic fatigue syndrome. Front Physiol. 2013 Apr 19;4:87. PMID: 23626579

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

*

Beaumont A, Burton AR, Lemon J, Bennett BK, Lloyd A, Vollmer-Conna U. Reduced cardiac vagal modulation impacts on cognitive performance in chronic fatigue syndrome. PLoS One. 2012;7(11):e49518. PMID: 23166694

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.

*

Cockshell SJ, Mathias JL. Test effort in persons with Chronic Fatigue Syndrome when assessed using the Validity Indicator Profile. J Clin Exp Neuropsychol. 2012;34(7):679-87. PMID: 22440059

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

*

Constant EL, Adam S, Gillain B, Lambert M, Masquelier E, Seron X. Cognitive deficits in patients with chronic fatigue syndrome compared to those with major depressive disorder and healthy controls. Clin Neurol Neurosurg. 2011 Jan 19. PMID: 21255911

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

*

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.

*

Kawatani J, Mizuno K, Shiraishi S, Takao M, Joudoi T, Fukuda S, Watanabe Y, Tomoda A. Cognitive dysfunction and mental fatigue in childhood chronic fatigue syndrome - A 6-month follow-up study. Brain Dev. 2011 Apr 27. PMID: 21530119

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.

*

Kadota Y, Cooper G, Burton AR, Lemon J, Schall U, Lloyd A, Vollmer-Conna U. Autonomic hyper-vigilance in post-infective fatigue syndrome. Biol Psychol. 2010 Sep;85(1):97-103. PMID: 20678991

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.

*

Thomas M, Smith A. An investigation into the cognitive deficits associated with chronic fatigue syndrome. Open Neurol J. 2009 Feb 27;3:13-23. PMID: 19452031

CFS patients demonstrate specific cognitive impairments.

*

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.

*

Schrijvers D, Van Den Eede F, Maas Y, Cosyns P, Hulstijn W, Sabbe BG. Psychomotor functioning in chronic fatigue syndrome and major depressive

disorder: a comparative study. J Affect Disord. 2009 May;115(1-2):46-53. PMID: 18817977

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

*

Haig-Ferguson A, Tucker P, Eaton N, Hunt L, Crawley E. Memory and attention problems in children with chronic fatigue syndrome or myalgic encephalopathy. Arch Dis Child. 2009 Oct;94(10):757-62. PMID: 19001478

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

*

Majer M, Welberg LA, Capuron L, Miller AH, Pagnoni G, Reeves WC. Neuropsychological performance in persons with chronic fatigue syndrome: results from a population-based study. Psychosom Med. 2008 Sep;70(7):829-36. PMID: 18606722

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

*

Claypoole KH, Noonan C, Mahurin RK, Goldberg J, Erickson T, Buchwald D. A twin study of cognitive function in chronic fatigue syndrome: the effects of sudden illness onset. Neuropsychology. 2007 Jul;21(4):507-13. PMID: 17605583

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.

*

Glass JM. Cognitive dysfunction in fibromyalgia and chronic fatigue syndrome: new trends and future directions. Curr Rheumatol Rep. 2006 Dec;8(6):425-9. PMID: 17092441

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

*

Capuron L, Welberg L, Heim C, Wagner D, Solomon L, Papanicolaou DA, Craddock RC, Miller AH, Reeves WC. Cognitive dysfunction relates to subjective report of mental fatigue in patients with chronic fatigue syndrome. Neuropsychopharmacology. 2006 Aug;31(8):1777-84. PMID: 16395303

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.

*

Tanaka M, Sadato N, Okada T, Mizuno K, Sasabe T, Tanabe HC, Saito DN, Onoe H, Kuratsune H, Watanabe Y. Reduced responsiveness is an essential feature of chronic fatigue syndrome: a fMRI study. BMC Neurol. 2006 Feb 22;6:9. PMID: 16504053

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

*

Caseras X, Mataix-Cols D, Giampietro V, Rimes KA, Brammer M, Zelaya F, Chalder T, Godfrey EL. Probing the working memory system in chronic fatigue syndrome: a functional magnetic resonance imaging study using the n-back task. Psychosom Med. 2006 Nov-Dec;68(6):947-55. PMID: 17079703

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

*

Cook DB, Nagelkirk PR, Peckerman A, Poluri A, Mores J, Natelson BH. Exercise and cognitive performance in chronic fatigue syndrome. Med Sci Sports Exerc. 2005 Sep;37(9):1460-7. PMID: 16177595

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.

*

Schillings ML, Kalkman JS, van der Werf SP, van Engelen BG, Bleijenberg G, Zwarts MJ. Diminished central activation during maximal voluntary contraction in chronic fatigue syndrome. Clin Neurophysiol. 2004 Nov;115(11):2518-24. PMID: 15465441

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.

*

Deluca J, Christodoulou C, Diamond BJ, Rosenstein ED, Kramer N, Natelson BH. Working memory deficits in chronic fatigue syndrome: differentiating between speed and accuracy of information processing. J Int Neuropsychol Soc. 2004 Jan;10(1):101-9. PMID: 14751012

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.

*

Davey NJ, Puri BK, Catley M, Main J, Nowicky AV, Zaman R. Deficit in motor performance correlates with changed corticospinal excitability in patients with chronic fatigue syndrome. Int J Clin Pract. 2003 May;57(4):262-4. PMID: 12800454

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.

*

Michiels V, Cluydts R. Neuropsychological functioning in chronic fatigue syndrome: a review. Acta Psychiatr Scand. 2001 Feb;103(2):84-93. PMID: 11167310

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.

*

Friedberg F, Dechene L, McKenzie MJ 2nd, Fontanetta R. Symptom patterns in long-duration chronic fatigue syndrome. J Psychosom Res. 2000 Jan;48(1):59-68. PMID: 10750631

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.

*

Michiels V, Cluydts R, Fischler B. Attention and verbal learning in patients with chronic fatigue syndrome. J Int Neuropsychol Soc. 1998 Sep;4(5):456-66. PMID: 9745235

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

*

Michiels V, Cluydts R, Fischler B, Hoffmann G, Le Bon O, De Meirleir K. Cognitive functioning in patients with chronic fatigue syndrome. J Clin Exp Neuropsychol. 1996 Oct;18(5):666-77. PMID: 8941852

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.

*

Marcel B, Komaroff AL, Fagioli LR, Kornish RJ 2nd, Albert MS. Cognitive deficits in patients with chronic fatigue syndrome. Biol Psychiatry. 1996 Sep 15;40(6):535-41. PMID: 8879474

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

*

Johnson SK, DeLuca J, Diamond BJ, Natelson BH. Selective impairment of auditory processing in chronic fatigue syndrome: a comparison with multiple sclerosis and healthy controls. Percept Mot Skills. 1996 Aug;83(1):51-62. PMID: 8873173

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

*

Joyce E, Blumenthal S, Wessely S. Memory, attention, and executive function in chronic fatigue syndrome. J Neurol Neurosurg Psychiatry. 1996 May;60(5):495-503. PMID: 8778252

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.

*

Johnson SK, DeLuca J, Fiedler N, Natelson BH. Cognitive functioning of patients with chronic fatigue syndrome. Clin Infect Dis. 1994 Jan;18 Suppl 1:S84-5. PMID: 8148459

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

*

Sandman CA, Barron JL, Nackoul K, Goldstein J, Fidler F. Memory deficits associated with chronic fatigue immune dysfunction syndrome. Biol Psychiatry. 1993 Apr 15-May 1;33(8-9):618-23. PMID: 8329493

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

*

DeLuca J, Johnson SK, Natelson BH. Information processing efficiency in chronic fatigue syndrome and multiple sclerosis. Arch Neurol. 1993 Mar;50(3):301-4. PMID: 8442710

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

*

Scheffers MK, Johnson R Jr, Grafman J, Dale JK, Straus SE. Attention and short-term memory in chronic fatigue syndrome patients: an event-related potential analysis. Neurology. 1992 Sep;42(9):1667-75. PMID: 1513453

Cognitive impairment in CFS involves response-related processes.

Gait Abnormalities

Eyskens JB, Nijs J, Wouters K, Moorkens G. Reduced gait automaticity in female patients with chronic fatigue syndrome: Case-control study. J Rehabil Res Dev. 2015;52(7):805-14. PMID: 26745400

Patients with chronic fatigue syndrome (CFS) report difficulties walking for a prolonged period of time. Less automated walking was observed in patients with CFS than in nondisabled controls.

*

Paul L, Rafferty D, Wood L, Maclaren W. Gait characteristics of subjects with chronic fatigue syndrome and controls at self-selected and matched velocities. J Neuroeng Rehabil. 2008 May 27;5:16. PMID: 18505580

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

*

Paul LM, Wood L, Maclaren W. The effect of exercise on gait and balance in patients with chronic fatigue syndrome. Gait Posture. 2001 Jul;14(1):19-27. PMID: 11378421

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.

*

Saggini R, Pizzigallo E, Vecchiet J, Macellari V, Giacomozzi C. Alteration of spatial-temporal parameters of gait in Chronic Fatigue Syndrome patients. J Neurol Sci. 1998 Jan 21;154(1):18-25. PMID: 9543318

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.

*

Boda WL, Natelson BH, Sisto SA, Tapp WN. Gait abnormalities in chronic fatigue syndrome. J Neurol Sci. 1995 Aug;131(2):156-61. PMID: 7595641

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

Russell C, Wearden AJ, Fairclough G, Emsley RA, Kyle SD. Subjective But Not Actigraphy-Defined Sleep Predicts Next-Day Fatigue in Chronic Fatigue Syndrome: A Prospective Daily Diary Study. Sleep. 2015 Dec 22. PMID: 26715232

The authors show that nightly subjective sleep predicts next-day fatigue in CFS and identify important factors driving this relationship.

*

Snodgrass K, Harvey A, Scheinberg A, Knight S. Sleep Disturbances in Pediatric Chronic Fatigue Syndrome: A Review of Current Research. J Clin Sleep Med. 2015 Jul 15;11(7):757-64. PMID: 25766714

A meta review suggests that children and adolescents with CFS experience sleep disturbances.

*

Neu D, Mairesse O, Verbanck P, Le Bon O. Slow wave sleep in the chronically fatigued: Power spectra distribution patterns in chronic fatigue syndrome and primary insomnia. Clin Neurophysiol. 2015 Oct;126(10):1926-33. PMID: 25620040

The authors found consistent evidence for lower proportions of slow oscillations during slow wave sleep in CFS patients.

*

Gotts ZM, Deary V, Newton J, Van der Dussen D, De Roy P, Ellis JG. Are there sleep-specific phenotypes in patients with chronic fatigue syndrome? A cross-

sectional polysomnography analysis. BMJ Open. 2013 Jun 20;3(6). PMID: 23794547

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.

*

Togo F, Natelson BH. Heart rate variability during sleep and subsequent sleepiness in patients with chronic fatigue syndrome. Auton Neurosci. 2013 Jun;176(1-2):85-90. PMID: 23499514

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.

*

Mariman AN, Vogelaers DP, Tobback E, Delesie LM, Hanoulle IP, Pevernagie DA. Sleep in the chronic fatigue syndrome. Sleep Med Rev. 2013 Jun;17(3):193-9. PMID:23046847

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.

*

Le Bon O, Neu D, Berquin Y, Lanquart JP, Hoffmann R, Mairesse O, Armitage R. Ultra-slow delta power in chronic fatigue syndrome. Psychiatry Res. 2012 Dec 30;200(2-3):742-7. PMID: 22771174

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

*

Mariman A, Vogelaers D, Hanoulle I, Delesie L, Pevernagie D. Subjective sleep quality and daytime sleepiness in a large sample of patients with chronic fatigue syndrome (CFS). Acta Clin Belg. 2012 Jan-Feb;67(1):19-24. PMID: 22480034

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

*

Jackson ML, Bruck D. Sleep abnormalities in chronic fatigue syndrome/myalgic encephalomyelitis: a review. J Clin Sleep Med. 2012 Dec 15;8(6):719-28. PMID:23243408

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

*

Mariman A, Vogelaers D, Hanoulle I, Delesie L, Tobback E, Pevernagie D. Validation of the three-factor model of the PSQI in a large sample of chronic fatigue syndrome (CFS) patients. J Psychosom Res. 2012 Feb;72(2):111-3. PMID: 22281451

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

*

Wu HS, Davis JE, Natavio T. Fatigue and disrupted sleep-wake patterns in patients with cancer: a shared mechanism. Clin J Oncol Nurs. 2012 Apr;16(2):E56-68. PMID: 22459538

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.

*

Spitzer AR, Broadman M. Treatment of the narcoleptiform sleep disorder in chronic fatigue syndrome and fibromyalgia with sodium oxybate. Pain Pract. 2010 Jan-Feb;10(1):54-9. PMID: 20629967

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.

*

Kishi A, Natelson BH, Togo F, Struzik ZR, Rapoport DM, Yamamoto Y. Sleep stage transitions in chronic fatigue syndrome patients with or without fibromyalgia. Conf Proc IEEE Eng Med Biol Soc. 2010;2010:5391-4. PMID: 21096267

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

*

Neu D, Kajosch H, Peigneux P, Verbanck P, Linkowski P, Le Bon O. Cognitive impairment in fatigue and sleepiness associated conditions. Psychiatry Res. 2010 Dec 31. PMID: 21196050

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

*

Creti L, Libman E, Baltzan M, Rizzo D, Bailes S, Fichten CS. Impaired sleep in chronic fatigue syndrome: how is it best measured? J Health Psychol. 2010 May;15(4):596-607. PMID: 20460416

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).

*

Togo F, Natelson BH, Cherniack NS, Klapholz M, Rapoport DM, Cook DB. Sleep is not disrupted by exercise in patients with chronic fatigue syndromes. Med Sci Sports Exerc. 2010 Jan;42(1):16-22. PMID: 20010134

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

*

Decker MJ, Tabassum H, Lin JM, Reeves WC. Electroencephalographic correlates of Chronic Fatigue Syndrome. Behav Brain Funct. 2009 Oct 6;5:43. PMID: 19807920

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.

*

Libman E, Creti L, Baltzan M, Rizzo D, Fichten CS, Bailes S. Sleep apnea and psychological functioning in chronic fatigue syndrome. J Health Psychol. 2009 Nov;14(8):1251-67. PMID: 19858344

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.

*

Neu D, Cappeliez B, Hoffmann G, Verbanck P, Linkowski P, Le Bon O. High slow-wave sleep and low-light sleep: chronic fatigue syndrome is not likely to be a primary sleep disorder. J Clin Neurophysiol. 2009 Jun;26(3):207-12. PMID: 19424087

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.

*

Armitage R, Landis C, Hoffmann R, Lentz M, Watson N, Goldberg J, Buchwald D. Power spectral analysis of sleep EEG in twins discordant for chronic fatigue syndrome. J Psychosom Res. 2009 Jan;66(1):51-7. PMID: 19073294

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

*

Neu D, Hoffmann G, Moutrier R, Verbanck P, Linkowski P, Le Bon O. Are patients with chronic fatigue syndrome just 'tired' or also 'sleepy'? J Sleep Res. 2008 Dec;17(4):427-31. PMID: 19021860

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

*

Togo F, Natelson BH, Cherniack NS, FitzGibbons J, Garcon C, Rapoport DM. Sleep structure and sleepiness in chronic fatigue syndrome with or without coexisting fibromyalgia. Arthritis Res Ther. 2008;10(3):R56. PMID: 18474105

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.

*

Kishi A, Struzik ZR, Natelson BH, Togo F, Yamamoto Y. Dynamics of sleep stage transitions in healthy humans and patients with chronic fatigue syndrome. Am J Physiol Regul Integr Comp Physiol. 2008 Jun;294(6):R1980-7. PMID: 18417644

Specific sleep problems in CFS are examined.

*

Majer M, Jones JF, Unger ER, Youngblood LS, Decker MJ, Gurbaxani B, Heim C, Reeves WC. Perception versus polysomnographic assessment of sleep in CFS and non-fatigued control subjects: results from a population-based study. BMC Neurol. 2007 Dec 5;7:40. PMID: 18053240

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.

*

Ohinata J, Suzuki N, Araki A, Takahashi S, Fujieda K, Tanaka H. Actigraphic assessment of sleep disorders in children with chronic fatigue syndrome. Brain Dev. 2008 May;30(5):329-33. PMID: 18031961

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

*

Neu D, Mairesse O, Hoffmann G, Dris A, Lambrecht LJ, Linkowski P, Verbanck P, Le Bon O. Sleep quality perception in the chronic fatigue syndrome: correlations with sleep efficiency, affective symptoms and intensity of fatigue. Neuropsychobiology. 2007;56(1):40-6. PMID: 17986836

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.

*

Tajima S, Kuratsune H, Yamaguti K, Takahashi A, Takashima S, Watanabe Y, Nishizawa Y. Estimation of fatigue state in patient with CFS using actigraph and R-R interval power spectrum analysis. Nihon Rinsho. 2007 Jun;65(6):1057-64. PMID: 17561697

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

*

Kumano-go T, Adachi H, Sugita Y. Sleep disturbance in chronic fatigue syndrome. Nihon Rinsho. 2007 Jun;65(6):1017-22. PMID: 17561691

CFS patients display a variety of sleep disorders.

*

Armitage R, Landis C, Hoffmann R, Lentz M, Watson NF, Goldberg J, Buchwald D. The impact of a 4-hour sleep delay on slow wave activity in twins discordant for chronic fatigue syndrome. Sleep. 2007 May;30(5):657-62. PMID: 17552382

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

*

Van Hoof E, De Becker P, Lapp C, Cluydts R, De Meirleir K. Defining the occurrence and influence of alpha-delta sleep in chronic fatigue syndrome. Am J Med Sci. 2007 Feb;333(2):78-84. PMID: 17301585

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

*

Reeves WC, Heim C, Maloney EM, Youngblood LS, Unger ER, Decker MJ, Jones JF, Rye DB. Sleep characteristics of persons with chronic fatigue syndrome and non-fatigued controls: results from a population-based study. BMC Neurol. 2006 Nov 16;6:41. PMID: 17109739

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.

*

Guilleminault C, Poyares D, Rosa A, Kirisoglu C, Almeida T, Lopes MC. Chronic fatigue, unrefreshing sleep and nocturnal polysomnography. Sleep Med. 2006 Sep;7(6):513-20. PMID: 16934523

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.

*

Unger ER, Nisenbaum R, Moldofsky H, Cesta A, Sammut C, Reyes M, Reeves WC. Sleep assessment in a population-based study of chronic fatigue syndrome. BMC Neurol. 2004 Apr 19;4:6. PMID: 15096280

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.

*

Hamilos DL, Nutter D, Gershtenson J, Ikle D, Hamilos SS, Redmond DP, Di Clementi JD, Schmaling KB, Jones JF. Circadian rhythm of core body temperature in subjects with chronic fatigue syndrome. Clin Physiol. 2001 Mar;21(2):184-95. PMID: 11318826

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.

*

Stores G, Fry A, Crawford C. Sleep abnormalities demonstrated by home polysomnography in teenagers with chronic fatigue syndrome. J Psychosom Res. 1998 Jul;45(1 Spec No):85-91. PMID: 9720858

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

*

Morriss RK, Wearden AJ, Battersby L. The relation of sleep difficulties to fatigue, mood and disability in chronic fatigue syndrome. J Psychosom Res. 1997 Jun;42(6):597-605. PMID: 9226607

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.

*

Bennett AL, Mayes DM, Fagioli LR, Guerriero R, Komaroff AL. Somatomedin C (insulin-like growth factor I) levels in patients with chronic fatigue syndrome. J Psychiatr Res. 1997 Jan-Feb;31(1):91-6. PMID: 9201651

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.

*

Fischler B, Le Bon O, Hoffmann G, Cluydts R, Kaufman L, De Meirleir K. Sleep anomalies in the chronic fatigue syndrome. A comorbidity study. Neuropsychobiology. 1997;35(3):115-22. PMID: 9170115

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

*

Williams G, Pirmohamed J, Minors D, Waterhouse J, Buchan I, Arendt J, Edwards RH. Dissociation of body-temperature and melatonin secretion circadian rhythms in patients with chronic fatigue syndrome. Clin Physiol. 1996 Jul;16(4):327-37. PMID: 8842569

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.

*

Schaefer KM. Sleep disturbances and fatigue in women with fibromyalgia and chronic fatigue syndrome. J Obstet Gynecol Neonatal Nurs. 1995 Mar-Apr;24(3):229-33. PMID: 7782955

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

*

Manu P, Lane TJ, Matthews DA, Castriotta RJ, Watson RK, Abeles M. Alpha-delta sleep in patients with a chief complaint of chronic fatigue. South Med J. 1994 Apr;87(4):465-70. PMID: 8153772

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

*

Buchwald D, Pascualy R, Bombardier C, Kith P. Sleep disorders in patients with chronic fatigue. Clin Infect Dis. 1994 Jan;18 Suppl 1:S68-72. PMID: 8148456

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.

*

Krupp LB, Jandorf L, Coyle PK, Mendelson WB. Sleep disturbance in chronic fatigue syndrome. J Psychosom Res. 1993 May;37(4):325-31. PMID: 8510058

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

*

Morriss R, Sharpe M, Sharpley AL, Cowen PJ, Hawton K, Morris J. Abnormalities of sleep in patients with the chronic fatigue syndrome. BMJ. 1993 May 1;306(6886):1161-4. PMID: 8499816

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

Pain

Terzi R, Altın F. [The prevalence of low back pain in hospital staff and its relationship with chronic fatigue syndrome and occupational factors]. Agri. 2015;27(3):149-54. PMID: 26356104

The study shows a relationship between low back pain and chronic fatigue syndrome in hospital employees. Shift work and length of time in occupation are risk factors for chronic fatigue syndrome.

*

Nijs J, Van de Putte K, Louckx F, Truijen S, De Meirleir K. Exercise performance and chronic pain in chronic fatigue syndrome: the role of pain catastrophizing. Pain Med. 2008 Nov;9(8):1164-72. PMID: 19086101

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

*

Meeus M, Nijs J, Van de Wauwer N, Toeback L, Truijen S. Diffuse noxious inhibitory control is delayed in chronic fatigue syndrome: an experimental study. Pain. 2008 Oct 15;139(2):439-48. PMID: 18617327

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

*

Ullrich PM, Afari N, Jacobsen C, Goldberg J, Buchwald D. Cold pressor pain sensitivity in monozygotic twins discordant for chronic fatigue syndrome. Pain Med. 2007 Apr;8(3):216-22. PMID: 17371408

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.

*

Meeus M, Nijs J, Meirleir KD. Chronic musculoskeletal pain in patients with the chronic fatigue syndrome: a systematic review. Eur J Pain. 2007 May;11(4):377-86. PMID: 16843021

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

*

Geisser ME, Gracely RH, Giesecke T, Petzke FW, Williams DA, Clauw DJ. The association between experimental and clinical pain measures among persons with fibromyalgia and chronic fatigue syndrome. Eur J Pain. 2007 Feb;11(2):202-7. PMID: 16546424

CFS patients' responses to painful experimental stimuli were measured.

Muscles

Rutherford G, Manning P, Newton JL. Understanding Muscle Dysfunction in Chronic Fatigue Syndrome. J Aging Res. 2016;2016:2497348. PMID: 26998359

Bioenergetic muscle dysfunction is evident in CFS/ME, with a tendency towards an overutilisation of the lactate dehydrogenase pathway following low-level exercise, in addition to slowed acid clearance after exercise.

*

Lengert N, Drossel B. In silico analysis of exercise intolerance in myalgic encephalomyelitis/chronic fatigue syndrome. Biophys Chem. 2015 Jul;202:21-31. PMID: 25899994

The authors present a model which simulates metabolite dynamics in skeletal muscles during exercise and recovery. CFS simulations exhibit critically low levels

of ATP, where an increased rate of cell death would be expected. To stabilize the energy supply at low ATP concentrations the total adenine nucleotide pool is reduced substantially causing a prolonged recovery time even without consideration of other factors, such as immunological dysregulations and oxidative stress. Repeated exercises worsen this situation considerably. Furthermore, CFS simulations exhibited an increased acidosis and lactate accumulation consistent with experimental observations.

*

Brown AE, Jones DE, Walker M, Newton JL. Abnormalities of AMPK activation and glucose uptake in cultured skeletal muscle cells from individuals with chronic fatigue syndrome. PLoS One. 2015 Apr 2;10(4):e0122982. doi: 10.1371/journal.pone.0122982. eCollection 2015. PMID: 25836975

The authors found four main differences in cultured skeletal muscle cells from subjects with CFS; increased myogenin expression in the basal state, impaired activation of AMP kinase, impaired stimulation of glucose uptake and diminished release of IL6.

*

Santiago T, Rebelo O, Negrão L, Matos A. Macrophagic myofasciitis and vaccination: Consequence or coincidence? Rheumatol Int. 2014 Jun 13. PMID: 24923906

Macrophagic myofasciitis (MMF) characterized by specific muscle lesions assessing long-term persistence of aluminum hydroxide within macrophages at the site of previous immunization has been reported with increasing frequency in the past 10 years. The authors describe clinical and laboratory findings in patients with MMF. CFS was found in 8 of 16 patients.

*

Nijs J, Aelbrecht S, Meeus M, Van Oosterwijck J, Zinzen E, Clarys P. Tired of being inactive: a systematic literature review of physical activity, physiological exercise capacity and muscle strength in patients with chronic fatigue syndrome. Disabil Rehabil. 2011;33(17-18):1493-500. PMID: 21166613

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

*

Light AR, Vierck CJ, Light KC. Myalgia and Fatigue: Translation from Mouse Sensory Neurons to Fibromyalgia and Chronic Fatigue Syndromes. In: Translational Pain Research: From Mouse to Man. Kruger L, Light AR, editors. Boca Raton, FL: CRC Press; 2010. Chapter 11. PMID: 21882454

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."

*

Pietrangelo T, Toniolo L, Paoli A, Fulle S, Puglielli C, Fanò G, Reggiani C. Functional characterization of muscle fibres from patients with chronic fatigue syndrome: case-control study. Int J Immunopathol Pharmacol. 2009 Apr-Jun;22(2):427-36. PMID:19505395

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.

*

McCully KK, Natelson BH, Iotti S, Sisto S, Leigh JS Jr. Reduced oxidative muscle metabolism in chronic fatigue syndrome. Muscle Nerve. 1996 May;19(5):621-5. PMID: 8618560

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

*

Preedy VR, Smith DG, Salisbury JR, Peters TJ. Biochemical and muscle studies in patients with acute onset post-viral fatigue syndrome. J Clin Pathol. 1993 Aug;46(8):722-6. PMID: 7691895

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

*

Connolly S, Smith DG, Doyle D, Fowler CJ. Chronic fatigue: electromyographic and neuropathological evaluation. J Neurol. 1993 Jul;240(7):435-8. PMID: 8410086

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

*

Behan WM, More IA, Behan PO. Mitochondrial abnormalities in the postviral fatigue syndrome. Acta Neuropathol. 1991;83(1):61-5. PMID:1792865

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

Chao CH, Chen HJ, Wang HY, Li TC, Kao CH. Increased risk of organic erectile dysfunction in patients with chronic fatigue syndrome: a nationwide population-based cohort study. Andrology. 2015 Jul;3(4):666-71. PMID: 26198797

Compared with a non-CFS cohort, the incidence density rate of organic erectile dysfunction was 1.88-fold higher in a CFS cohort.

*

Chen Y, Liu W, Zhang L, Yan M, Zeng Y. Hybrid facial image feature extraction and recognition for non-invasive chronic fatigue syndrome diagnosis. Comput Biol Med. 2015 Sep;64:30-9. PMID: 26117650

Individuals with CFS were found to have specific identifiable facial features, including vertical striped wrinkles on the forehead, puffiness of the lower eyelid, the skin colour of the cheeks, nose and lips, and the shape of the mouth corner.

*

Boneva RS, Lin JM, Unger ER. Early menopause and other gynecologic risk indicators for chronic fatigue syndrome in women. Menopause. 2015 Aug;22(8):826-34. PMID: 25647777

Women with CFS reported significantly more gynecologic conditions and surgical operations than controls.

*

Hutchinson CV, Maltby J, Badham SP, Jason LA. Vision-related symptoms as a clinical feature of chronic fatigue syndrome/myalgic encephalomyelitis? Evidence from the DePaul Symptom Questionnaire. Br J Ophthalmol. 2014 Jan;98(1):144-5. PMID: 24187048

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

*

Rayhan RU, Ravindran MK, Baraniuk JN. Migraine in gulf war illness and chronic fatigue syndrome: prevalence, potential mechanisms, and evaluation. Front Physiol. 2013 Jul 24;4:181. PMID: 23898301

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

*

Ravindran M, Adewuyi O, Zheng Y, Rayhan RU, Le U, Timbol C, Merck S, Esteitie R, Read C, Cooney M, Baraniuk J. Dyspnea in Chronic Fatigue Syndrome (CFS): comparison of two prospective cross-sectional studies. Glob J Health Sci. 2012 Dec 12;5(2):94-110. PMID: 23445698

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

*

Ravindran MK, Zheng Y, Timbol C, Merck SJ, Baraniuk JN. Migraine headaches in Chronic Fatigue Syndrome (CFS): Comparison of two prospective cross-sectional studies. BMC Neurol. 2011 Mar 5;11:30. PMID: 21375763

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

*

Boneva RS, Maloney EM, Lin JM, Jones JF, Wieser F, Nater UM, Heim CM, Reeves WC. Gynecological history in chronic fatigue syndrome: a population-based case-control study. J Womens Health (Larchmt). 2011 Jan;20(1):21-8. PMID: 21091051

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.

*

Nickel JC, Tripp DA, Pontari M, Moldwin R, Mayer R, Carr LK, Doggweiler R, Yang CC, Mishra N, Nordling J. Interstitial cystitis/painful bladder syndrome and associated medical conditions with an emphasis on irritable bowel syndrome, fibromyalgia and chronic fatigue syndrome. J Urol. 2010 Oct;184(4):1358-63. PMID: 20719340

CFS and interstitial cystitis/painful bladder syndrome are related.

*

Baraniuk JN, Zheng Y. Relationships among rhinitis, fibromyalgia, and chronic fatigue. Allergy Asthma Proc. 2010 May-Jun;31(3):169-78. PMID: 20615318

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.

*

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.

*

Meeus M, Nijs J, Huybrechts S, Truijen S. Evidence for generalized hyperalgesia in chronic fatigue syndrome: a case control study. Clin Rheumatol. 2010 Apr;29(4):393-8. PMID: 20077123

CFS patients exhibited more generalized hyperalgesia than controls.

*

Blazquez A, Alegre J, Ruiz E. Women with chronic fatigue syndrome and sexual dysfunction: past, present, and future. J Sex Marital Ther. 2009 Oct;35(5):347-59. PMID: 20183003

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

*

Jhanji V, Beltz J, Vajpayee RB. Contact lens-related acanthamoeba keratitis in a patient with chronic fatigue syndrome. Eye Contact Lens. 2008 Nov;34(6):335-6. PMID: 18997544

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.

*

Fisher MM, Rose M. Anaesthesia for patients with idiopathic environmental intolerance and chronic fatigue syndrome. Br J Anaesth. 2008 Oct;101(4):486-91. PMID: 18782886

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

*

Wyller VB, Godang K, Mørkrid L, Saul JP, Thaulow E, Walløe L. Abnormal thermoregulatory responses in adolescents with chronic fatigue syndrome: relation to clinical symptoms. Pediatrics. 2007 Jul;120(1):e129-37. PMID: 17606539

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

*

Bennett B, Goldstein D, Friedlander M, Hickie I, Lloyd A. The experience of cancer-related fatigue and chronic fatigue syndrome: a qualitative and comparative study. J Pain Symptom Manage. 2007 Aug;34(2):126-35. PMID: 17544246

Qualitatively, cancer related fatigue appears closely related to CFS.

*

Nijs J, Aerts A, De Meirleir K. Generalized joint hypermobility is more common in chronic fatigue syndrome than in healthy control subjects. J Manipulative Physiol Ther. 2006 Jan;29(1):32-9. PMID: 16396727

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

*

van de Putte EM, Uiterwaal CS, Bots ML, Kuis W, Kimpen JL, Engelbert RH. Is chronic fatigue syndrome a connective tissue disorder? A cross-sectional study in adolescents. Pediatrics. 2005 Apr;115(4):e415-22. PMID: 15805343

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

*

Ferré Ybarz L, Cardona Dahl V, Cadahía García A, Ruiz E, Vázquez A, Fernández de Sevilla T, Alegre Martín J. Prevalence of atopy in chronic fatigue syndrome. Allergol Immunopathol (Madr). 2005 Jan-Feb;33(1):42-7. PMID: 15777523

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.

*

Shee CD. Phantom lymphadenopathy. An association with chronic fatigue syndrome. Postgrad Med J. 2003 Jan;79(927):59-60. PMID: 12566557

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

*

Jason LA, Torres-Harding SR, Carrico AW, Taylor RR. Symptom occurrence in persons with chronic fatigue syndrome. Biol Psychol. 2002 Feb;59(1):15-27. PMID: 11790441

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.

*

Barron DF, Cohen BA, Geraghty MT, Violand R, Rowe PC. Joint hypermobility is more common in children with chronic fatigue syndrome than in healthy controls. J Pediatr. 2002 Sep;141(3):421-5. PMID: 12219066

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

*

Baraniuk JN, Clauw DJ, Gaumond E. Rhinitis symptoms in chronic fatigue syndrome. Ann Allergy Asthma Immunol. 1998 Oct;81(4):359-65. PMID: 9809501

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.

*

Harlow BL, Signorello LB, Hall JE, Dailey C, Komaroff AL. Reproductive correlates of chronic fatigue syndrome. Am J Med. 1998 Sep 28;105(3A):94S-99S. PMID: 9790489

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).

*

Gomborone JE, Gorard DA, Dewsnap PA, Libby GW, Farthing MJ. Prevalence of irritable bowel syndrome in chronic fatigue. J R Coll Physicians Lond. 1996 Nov-Dec;30(6):512-3. PMID: 8961203

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.

*

Buchwald D, Umali P, Umali J, Kith P, Pearlman T, Komaroff AL. Chronic fatigue and the chronic fatigue syndrome: prevalence in a Pacific Northwest health care system. Ann Intern Med. 1995 Jul 15;123(2):81-8. PMID: 7778839

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

*

Sisto SA, Tapp W, Drastal S, Bergen M, DeMasi I, Cordero D, Natelson B. Vagal tone is reduced during paced breathing in patients with the chronic fatigue syndrome. Clin Auton Res. 1995 Jun;5(3):139-43. PMID: 7549414

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

*

Caffery BE, Josephson JE, Samek MJ. The ocular signs and symptoms of chronic fatigue syndrome. J Am Optom Assoc. 1994 Mar;65(3):187-91. PMID: 8201170

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.

*

Saisch SG, Deale A, Gardner WN, Wessely S. Hyperventilation and chronic fatigue syndrome. Q J Med. 1994 Jan;87(1):63-7. PMID: 8140219

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

*

Auger PL, Gourdeau P, Miller JD. Clinical experience with patients suffering from a chronic fatigue-like syndrome and repeated upper respiratory infections in relation to airborne molds. Am J Ind Med. 1994 Jan;25(1):41-2. PMID: 8116649

*

Potaznick W, Kozol N. Ocular manifestations of chronic fatigue and immune dysfunction syndrome. Optom Vis Sci. 1992 Oct;69(10):811-4. PMID: 1437004

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

*

Cunha BA. Crimson crescents--a possible association with the chronic fatigue syndrome. Ann Intern Med. 1992 Feb 15;116(4):347. PMID: 1733396

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

Physical Abnormalities

Rowe PC, Marden CL, Flaherty MA, Jasion SE, Cranston EM, Johns AS, Fan J, Fontaine KR, Violand RL. Impaired range of motion of limbs and spine in chronic fatigue syndrome. J Pediatr. 2014 Aug;165(2):360-6. PMID: 24929332

Impaired range of motion is more common in subjects with CFS than in healthy adolescents and young adults matched by sex and joint hypermobility. Adding a longitudinal strain to the nerves and soft tissues provoked symptoms in some subjects with CFS.

*

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 Aug;107(8):635-41. PMID: 24619129

Patients without osteoporosis in a CFS cohort exhibited a 1.16-fold higher risk of fracture than did those in a non-CFS cohort.

*

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.

*

Badham SP, Hutchinson CV. Characterising eye movement dysfunction in myalgic encephalomyelitis/chronic fatigue syndrome. Graefes Arch Clin Exp Ophthalmol. 2013 Aug 6. PMID: 23918092

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).

*

Hutchinson CV, Badham SP. Patterns of abnormal visual attention in myalgic encephalomyelitis. Optom Vis Sci. 2013 Jun;90(6):607-14. PMID: 23689679

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.

*

Sakudo A, Kuratsune H, Kato YH, Ikuta K. Visible and near-infrared spectra collected from the thumbs of patients with chronic fatigue syndrome for diagnosis. Clin Chim Acta. 2012 Oct 9;413(19-20):1629-32. PMID: 22583968

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

*

Newton DJ, Kennedy G, Chan KK, Lang CC, Belch JJ, Khan F. Large and small artery endothelial dysfunction in chronic fatigue syndrome. Int J Cardiol. 2011 Nov 10. PMID: 22078396

Endothelial dysfunction is present in CFS.

*

Ohashi K, Bleijenberg G, van der Werf S, Prins J, Amaral LA, Natelson BH, Yamamoto Y. Decreased fractal correlation in diurnal physical activity in chronic fatigue syndrome. Methods Inf Med. 2004;43(1):26-9.PMID: 15026831

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.

*

Gordon R, Michalewski HJ, Nguyen T, Gupta S, Starr A. Cortical motor potential alterations in chronic fatigue syndrome. Int J Mol Med. 1999 Nov;4(5):493-9. PMID: 10534571

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.

*

Servatius RJ, Tapp WN, Bergen MT, Pollet CA, Drastal SD, Tiersky LA, Desai P, Natelson BH. Impaired associative learning in chronic fatigue syndrome. Neuroreport. 1998 Apr 20;9(6):1153-7. PMID: 9601685

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.

*

Ash-Bernal R, Wall C 3rd, Komaroff AL, Bell D, Oas JG, Payman RN, Fagioli LR. Vestibular function test anomalies in patients with chronic fatigue syndrome. Acta Otolaryngol. 1995 Jan;115(1):9-17. PMID: 7762393

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

Sun Y, Zhang ZX, Liu X. Orosomucoid (ORM) as a Potential Biomarker for the Diagnosis of Chronic Fatigue Syndrome(CFS). CNS Neurosci Ther. 2016 Mar;22(3):251-2. PMID: 26833758

The glycoprotein orosomucoid (ORM) was identified as a potential biomarker for the diagnosis of CFS.

*

Brewer JH, Thrasher JD, Straus DC, Madison RA, Hooper D. Detection of mycotoxins in patients with chronic fatigue syndrome. Toxins (Basel). 2013 Apr 11;5(4):605-17. PMID: 23580077

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%.

*

Ciregia F, Giusti L, Da Valle Y, Donadio E, Consensi A, Giacomelli C, Sernissi F, Scarpellini P, Maggi F, Lucacchini A, Bazzichi L. A multidisciplinary approach to study a couple of monozygotic twins discordant for the chronic fatigue syndrome: a focus on potential salivary biomarkers. J Transl Med. 2013 Oct 2;11:243. PMID: 24088505

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.

*

Klimas NG, Broderick G, Fletcher MA. Biomarkers for chronic fatigue. Brain Behav Immun. 2012 Nov;26(8):1202-10. PMID: 22732129

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.

*

Medow MS, Aggarwal A, Baugham I, Messer Z, Stewart JM. Modulation of the axon-reflex response to local heat by reactive oxygen species in subjects with chronic fatigue syndrome. J Appl Physiol. 2013 Jan 1;114(1):45-51. PMID: 23139367

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.

*

Stringer EA, Baker KS, Carroll IR, Montoya JG, Chu L, Maecker HT, Younger JW. Daily cytokine fluctuations, driven by leptin, are associated with fatigue severity in chronic fatigue syndrome: evidence of inflammatory pathology. J Transl Med. 2013 Apr 9;11:93. PMID: 23570606

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

*

Fukuda S, Horiguchi M, Yamaguti K, Nakatomi Y, Kuratsune H, Ichinose H, Watanabe Y. Association of monoamine-synthesizing genes with the depression tendency and personality in chronic fatigue syndrome patients. Life Sci. 2013 Feb 27;92(3):183-6. PMID: 23246742

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.

*

Maes M, Ringel K, Kubera M, Anderson G, Morris G, Galecki P, Geffard M. In myalgic encephalomyelitis/chronic fatigue syndrome, increased autoimmune activity against 5-HT is associated with immuno-inflammatory pathways and bacterial translocation. J Affect Disord. 2013 May 9. PMID: 23664637

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.

*

Tomic S, Brkic S, Maric D, Mikic AN. Lipid and protein oxidation in female patients with chronic fatigue syndrome. Arch Med Sci. 2012 Nov 9;8(5):886-91. PMID: 23185200

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.

*

Armstrong CW, McGregor NR, Sheedy JR, Buttfield I, Butt HL, Gooley PR. NMR metabolic profiling of serum identifies amino acid disturbances in chronic fatigue syndrome. Clin Chim Acta. 2012 Oct 9;413(19-20):1525-31. PMID: 22728138

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.

*

Shungu DC, Weiduschat N, Murrough JW, Mao X, Pillemer S, Dyke JP, Medow MS, Natelson BH, Stewart JM, Mathew SJ. Increased ventricular lactate in chronic fatigue syndrome. III. Relationships to cortical glutathione and clinical symptoms implicate oxidative stress in disorder pathophysiology. NMR Biomed. 2012 Sep;25(9):1073-87. PMID: 22281935

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.

*

Murrough JW, Mao X, Collins KA, Kelly C, Andrade G, Nestadt P, Levine SM, Mathew SJ, Shungu DC. Increased ventricular lactate in chronic fatigue syndrome measured by 1H MRS imaging at 3.0 T. II: comparison with major depressive disorder. NMR Biomed. 2010 Jul;23(6):643-50. PMID: 20661876

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.

*

Schutzer SE, Angel TE, Liu T, Schepmoes AA, Clauss TR, Adkins JN, Camp DG, Holland BK, Bergquist J, Coyle PK, Smith RD, Fallon BA, Natelson BH. Distinct cerebrospinal fluid proteomes differentiate post-treatment lyme disease from chronic fatigue syndrome. PLoS One. 2011 Feb 23;6(2):e17287. PMID: 21383843

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

*

Fletcher MA, Rosenthal M, Antoni M, Ironson G, Zeng XR, Barnes Z, Harvey JM, Hurwitz B, Levis S, Broderick G, Klimas NG. Plasma neuropeptide Y: a biomarker for symptom severity in chronic fatigue syndrome. Behav Brain Funct. 2010 Dec 29;6:76. PMID: 21190576

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

*

Raison CL, Lin JM, Reeves WC. Association of peripheral inflammatory markers with chronic fatigue in a population-based sample. Brain Behav Immun. 2009 Mar;23(3):327-37. PMID: 19111923

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

*

Sakudo A, Kato YH, Tajima S, Kuratsune H, Ikuta K. Visible and near-infrared spectral changes in the thumb of patients with chronic fatigue syndrome. Clin Chim Acta. 2009 May;403(1-2):163-6. PMID: 19248775

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.

*

Sakudo A, Kuratsune H, Kato YH, Ikuta K. Secondary structural changes of proteins in fingernails of chronic fatigue syndrome patients from Fourier-transform infrared spectra. Clin Chim Acta. 2009 Apr;402(1-2):75-8. PMID: 19150612

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.

*

Chen R, Moriya J, Yamakawa J, Takahashi T, Li Q, Morimoto S, Iwai K, Sumino H, Yamaguchi N, Kanda T. Brain atrophy in a murine model of chronic fatigue syndrome and beneficial effect of Hochu-ekki-to (TJ-41). Neurochem Res. 2008 Sep;33(9):1759-67. PMID: 18317925

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

*

Niblett SH, King KE, Dunstan RH, Clifton-Bligh P, Hoskin LA, Roberts TK, Fulcher GR, McGregor NR, Dunsmore JC, Butt HL, Klineberg I, Rothkirch TB. Hematologic and urinary excretion anomalies in patients with chronic fatigue syndrome. Exp Biol Med (Maywood). 2007 Sep;232(8):1041-9. PMID: 17720950

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

*

Nishikai M. Antinuclear antibodies in patients with chronic fatigue syndrome. Nihon Rinsho. 2007 Jun;65(6):1067-70. PMID: 17561698

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.

*

Miwa S, Takikawa O. Chronic fatigue syndrome and neurotransmitters. Nihon Rinsho. 2007 Jun;65(6):1005-10. PMID: 17561689

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

*

Hannestad U, Theodorsson E, Evengård B. beta-Alanine and gamma-aminobutyric acid in chronic fatigue syndrome. Clin Chim Acta. 2007 Feb;376(1-2):23-9. PMID: 16934791

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

*

Sakudo A, Kuratsune H, Kobayashi T, Tajima S, Watanabe Y, Ikuta K. Spectroscopic diagnosis of chronic fatigue syndrome by visible and near-infrared spectroscopy in serum samples. Biochem Biophys Res Commun. 2006 Jul 14;345(4):1513-6. PMID: 16730652

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

*

Cleare AJ, Messa C, Rabiner EA, Grasby PM. Brain 5-HT1A receptor binding in chronic fatigue syndrome measured using positron emission tomography and [11C]WAY-100635. Biol Psychiatry. 2005 Feb 1;57(3):239-46. PMID: 15691524

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

*

Baraniuk JN, Casado B, Maibach H, Clauw DJ, Pannell LK, Hess S S. A Chronic Fatigue Syndrome - related proteome in human cerebrospinal fluid. BMC Neurol. 2005 Dec 1;5:22. PMID: 16321154

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.

*

Casado B, Zanone C, Annovazzi L, Iadarola P, Whalen G, Baraniuk JN. Urinary electrophoretic profiles from chronic fatigue syndrome and chronic fatigue syndrome/fibromyalgia patients: a pilot study for achieving their normalization. J Chromatogr B Analyt Technol Biomed Life Sci. 2005 Jan 5;814(1):43-51. PMID: 15607706

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

*

Natelson BH, Weaver SA, Tseng CL, Ottenweller JE. Spinal fluid abnormalities in patients with chronic fatigue syndrome. Clin Diagn Lab Immunol. 2005 Jan;12(1):52-5. PMID: 15642984

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

*

Yamamoto S, Ouchi Y, Onoe H, Yoshikawa E, Tsukada H, Takahashi H, Iwase M, Yamaguti K, Kuratsune H, Watanabe Y. Reduction of serotonin transporters of patients with chronic fatigue syndrome. Neuroreport. 2004 Dec 3;15(17):2571-4. PMID: 15570154

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.

*

Spence VA, Khan F, Kennedy G, Abbot NC, Belch JJ. Acetylcholine mediated vasodilatation in the microcirculation of patients with chronic fatigue syndrome. Prostaglandins Leukot Essent Fatty Acids. 2004 Apr;70(4):403-7. PMID: 15041034

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.

*

McCully KK, Smith S, Rajaei S, Leigh JS Jr, Natelson BH. Muscle metabolism with blood flow restriction in chronic fatigue syndrome. J Appl Physiol. 2004 Mar;96(3):871-8. PMID: 14578362

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

*

Nijs J, De Becker P, De Meirleir K, Demanet C, Vincken W, Schuermans D, McGregor N. Associations between bronchial hyperresponsiveness and immune cell parameters in patients with chronic fatigue syndrome. Chest. 2003 Apr;123(4):998-1007. PMID: 12684286

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

*

Tanaka S, Kuratsune H, Hidaka Y, Hakariya Y, Tatsumi KI, Takano T, Kanakura Y, Amino N. Autoantibodies against muscarinic cholinergic receptor in chronic fatigue syndrome. Int J Mol Med. 2003 Aug;12(2):225-30. PMID: 12851722

Subgroups of CFS are associated with autoimmune abnormalities of CHRM1.

*

Narita M, Nishigami N, Narita N, Yamaguti K, Okado N, Watanabe Y, Kuratsune H. Association between serotonin transporter gene polymorphism and chronic fatigue syndrome. Biochem Biophys Res Commun. 2003 Nov 14;311(2):264-6. PMID: 14592408

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

*

Puri BK, Counsell SJ, Zaman R, Main J, Collins AG, Hajnal JV, Davey NJ. Relative increase in choline in the occipital cortex in chronic fatigue syndrome. Acta Psychiatr Scand. 2002 Sep;106(3):224-6. PMID: 12197861

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.

*

Panerai AE, Vecchiet J, Panzeri P, Meroni P, Scarone S, Pizzigallo E, Giamberardino MA, Sacerdote P. Peripheral blood mononuclear cell beta-endorphin concentration is decreased in chronic fatigue syndrome and fibromyalgia but not in depression: preliminary report. Clin J Pain. 2002 Jul-Aug;18(4):270-3. PMID: 12131069

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.

*

Nishikai M, Tomomatsu S, Hankins RW, Takagi S, Miyachi K, Kosaka S, Akiya K. Autoantibodies to a 68/48 kDa protein in chronic fatigue syndrome and primary fibromyalgia: a possible marker for hypersomnia and cognitive disorders. Rheumatology (Oxford). 2001 Jul;40(7):806-10. PMID: 11477286

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.

*

Woo SB, Schacterle RS, Komaroff AL, Gallagher GT. Salivary gland changes in chronic fatigue syndrome: a case-controlled preliminary histologic study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000 Jul;90(1):82-7. PMID: 10884641

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.

*

De Meirleir K, Bisbal C, Campine I, De Becker P, Salehzada T, Demettre E, Lebleu B. A 37 kDa 2-5A binding protein as a potential biochemical marker for chronic fatigue syndrome. Am J Med. 2000 Feb;108(2):99-105. PMID: 11126321

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.

*

Berg D, Berg LH, Couvaras J, Harrison H. Chronic fatigue syndrome and/or fibromyalgia as a variation of antiphospholipid antibody syndrome: an explanatory model and approach to laboratory diagnosis. Blood Coagul Fibrinolysis. 1999 Oct;10(7):435-8. PMID: 10695770

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.

*

Conti F, Pittoni V, Sacerdote P, Priori R, Meroni PL, Valesini G. Decreased immunoreactive beta-endorphin in mononuclear leucocytes from patients with chronic fatigue syndrome. Clin Exp Rheumatol. 1998 Nov-Dec;16(6):729-32. PMID: 9844768

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.

*

von Mikecz A, Konstantinov K, Buchwald DS, Gerace L, Tan EM. High frequency of autoantibodies to insoluble cellular antigens in patients with chronic fatigue syndrome. Arthritis Rheum. 1997 Feb;40(2):295-305. PMID: 9041942

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.

*

Buchwald D, Wener MH, Pearlman T, Kith P. Markers of inflammation and immune activation in chronic fatigue and chronic fatigue syndrome. J Rheumatol. 1997 Feb;24(2):372-6. PMID: 9034999

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.

*

Regland B, Andersson M, Abrahamsson L, Bagby J, Dyrehag LE, Gottfries CG. Increased concentrations of homocysteine in the cerebrospinal fluid in patients with fibromyalgia and chronic fatigue syndrome. Scand J Rheumatol. 1997;26(4):301-7. PMID: 9310111

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.

*

Konstantinov K, von Mikecz A, Buchwald D, Jones J, Gerace L, Tan EM. Autoantibodies to nuclear envelope antigens in chronic fatigue syndrome. J Clin Invest. 1996 Oct 15;98(8):1888-96. PMID: 8878441

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.

*

McGregor NR, Dunstan RH, Zerbes M, Butt HL, Roberts TK, Klineberg IJ. Preliminary determination of the association between symptom expression and urinary metabolites in subjects with chronic fatigue syndrome. Biochem Mol Med. 1996 Jun;58(1):85-92. PMID: 8809350

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.

*

Conti F, Magrini L, Priori R, Valesini G, Bonini S. Eosinophil cationic protein serum levels and allergy in chronic fatigue syndrome. Allergy. 1996 Feb;51(2):124-7. PMID: 8738520

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.

*

Fischler B, D'Haenen H, Cluydts R, Michiels V, Demets K, Bossuyt A, Kaufman L, Comparison of 99m Tc HMPAO SPECT scan between chronic fatigue syndrome, major depression and healthy controls: an exploratory study of clinical correlates of regional cerebral blood flow. Neuropsychobiology. 1996;34(4):175-83. PMID: 9121617

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

*

Natelson BH, Ellis SP, Braonáin PJ, DeLuca J, Tapp WN. Frequency of deviant immunological test values in chronic fatigue syndrome patients. Clin Diagn Lab Immunol. 1995 Mar;2(2):238-40. PMID: 7697537

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.

*

Hilgers A, Frank J. Chronic fatigue syndrome: immune dysfunction, role of pathogens and toxic agents and neurological and cardial changes. Wien Med Wochenschr. 1994;144(16):399-406. PMID: 7856214

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

*

Lieberman J, Bell DS. Serum angiotensin-converting enzyme as a marker for the chronic fatigue-immune dysfunction syndrome: a comparison to serum angiotensin-converting enzyme in sarcoidosis. Am J Med. 1993 Oct;95(4):407-12. PMID: 8213873

Serum ACE elevations may be a useful marker for CFIDS.

*

Demitrack MA, Gold PW, Dale JK, Krahn DD, Kling MA, Straus SE. Plasma and cerebrospinal fluid monoamine metabolism in patients with chronic fatigue syndrome: preliminary findings. Biol Psychiatry. 1992 Dec 15;32(12):1065-77. PMID: 1282370

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.

*

Kuratsune H, Yamaguti K, Hattori H, Tazawa H, Takahashi M, Yamanishi K, Kitani T. Symptoms, signs and laboratory findings in patients with chronic fatigue syndrome. Nihon Rinsho. 1992 Nov;50(11):2665-72. PMID: 1337562

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

Channelopathies

Fulle S, Belia S, Vecchiet J, Morabito C, Vecchiet L, Fanò G. Modification of the functional capacity of sarcoplasmic reticulum membranes in patients suffering from chronic fatigue syndrome. Neuromuscul Disord. 2003 Aug;13(6):479-84. PMID: 12899875

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.

*

Chaudhuri A, Watson WS, Pearn J, Behan PO. The symptoms of chronic fatigue syndrome are related to abnormal ion channel function. Med Hypotheses. 2000 Jan;54(1):59-63. PMID: 10790725

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

*

Waxman SG, Ptacek LJ. Chronic fatigue syndrome and channelopathies. Med Hypotheses. 2000 Nov;55(5):457. PMID: 11058431

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Lund-Olesen LH, Lund-Olesen K. The etiology and possible treatment of chronic fatigue syndrome/fibromyalgia. Med Hypotheses. 1994 Jul;43(1):55-8. PMID: 7968720

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.

*

Liu Z, Wang D, Xue Q, Chen J, Li Y, Bai X, Chang L. Determination of fatty acid levels in erythrocyte membranes of patients with chronic fatigue syndrome. Nutr Neurosci. 2003 Dec;6(6):389-92.

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.

*

Gray JB, Martinovic AM. Eicosanoids and essential fatty acid modulation in chronic disease and the chronic fatigue syndrome. Med Hypotheses. 1994 Jul;43(1):31-42. PMID: 7968718

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

*

Ogawa R, Toyama S, Matsumoto H. Chronic fatigue syndrome--cases in the Kanebo Memorial Hospital. Nihon Rinsho. 1992 Nov;50(11):2648-52. PMID: 1337561

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.

*

Horrobin DF. Post-viral fatigue syndrome, viral infections in atopic eczema, and essential fatty acids. Med Hypotheses. 1990 Jul;32(3):211-7. PMID: 2204789

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

Carnitine

Reuter SE, Evans AM. Long-chain acylcarnitine deficiency in patients with chronic fatigue syndrome. Potential involvement of altered carnitine palmitoyltransferase-I activity. J Intern Med. 2010 Dec 22. PMID: 21205027

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

*

Jones MG, Goodwin CS, Amjad S, Chalmers RA. Plasma and urinary carnitine and acylcarnitines in chronic fatigue syndrome. Clin Chim Acta. 2005 Oct;360(1-2):173-7. PMID: 15967423

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.

*

Kuratsune H, Yamaguti K, Lindh G, Evengard B, Takahashi M, Machii T, Matsumura K, Takaishi J, Kawata S, Långström B, Kanakura Y, Kitani T, Watanabe Y. Low levels of serum acylcarnitine in chronic fatigue syndrome and chronic hepatitis type C, but not seen in other diseases. Int J Mol Med. 1998 Jul;2(1):51-6. PMID: 9854142

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

*

Plioplys AV, Plioplys S. Serum levels of carnitine in chronic fatigue syndrome: clinical correlates. Neuropsychobiology. 1995;32(3):132-8. PMID: 8544970

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.

*

Kuratsune H, Yamaguti K, Takahashi M, Misaki H, Tagawa S, Kitani T. Acylcarnitine deficiency in chronic fatigue syndrome. Clin Infect Dis. 1994 Jan;18 Suppl 1:S62-7. PMID: 8148455

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

Nutrients

Witham M, Kennedy G, Belch J, Hill A, Khan F. Association between vitamin D status and markers of vascular health in patients with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). Int J Cardiol. 2014 Jun 1;174(1):139-40. PMID: 24726169

An association between vitamin D status and vascular health was found in CFS/ME patients.

*

Mikirova N, Casciari J, Hunninghake R. The assessment of the energy metabolism in patients with chronic fatigue syndrome by serum fluorescence emission. Altern Ther Health Med. 2012 Jan-Feb;18(1):36-40. PMID: 22516851

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

*

Blankfield A. A Brief Historic Overview of Clinical Disorders Associated with Tryptophan: The Relevance to Chronic Fatigue Syndrome (CFS) and Fibromyalgia (FM). Int J Tryptophan Res. 2012;5:27-32. PMID: 23032646

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

*

Antiel RM, Caudill JS, Burkhardt BE, Brands CK, Fischer PR. Iron insufficiency and hypovitaminosis D in adolescents with chronic fatigue and orthostatic intolerance. South Med J. 2011 Aug;104(8):609-11. PMID: 21886073

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.

*

Berkovitz S, Ambler G, Jenkins M, Thurgood S. Serum 25-hydroxy vitamin D levels in chronic fatigue syndrome: a retrospective survey. Int J Vitam Nutr Res. 2009 Jul;79(4):250-4. PMID: 20209476

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.

*

McCully KK, Malucelli E, Iotti S. Increase of free Mg2+ in the skeletal muscle of chronic fatigue syndrome patients. Dyn Med. 2006 Jan 11;5:1. PMID: 16405724

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

*

Heap LC, Peters TJ, Wessely S. Vitamin B status in patients with chronic fatigue syndrome. J R Soc Med. 1999 Apr;92(4):183-5. PMID: 10450194

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

*

Jacobson W, Saich T, Borysiewicz LK, Behan WM, Behan PO, Wreghitt TG. Serum folate and chronic fatigue syndrome. Neurology. 1993 Dec;43(12):2645-7. PMID: 8255470

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

Other Conditions

Lau CI, Lin CC, Chen WH, Wang HC, Kao CH. Increased risk of chronic fatigue syndrome in patients with migraine: A retrospective cohort study. J Psychosom Res. 2015 Dec;79(6):514-8. PMID: 26505533

The current study demonstrated an increased risk of CFS in patients with migraines. Proposed mechanisms in previous studies such as mitochondrial dysfunction and central sensitization may underlie the shared pathophysiology of these seemingly distinct but potentially overlapping disorders.

*

Magnus P, Gunnes N, Tveito K, Bakken IJ, Ghaderi S, Stoltenberg C, Hornig M, Lipkin WI, Trogstad L, Håberg SE. Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is associated with pandemic influenza infection, but not with an adjuvanted pandemic influenza vaccine. Vaccine. 2015 Nov 17;33(46):6173-7. PMID: 26475444

Pandemic influenza A (H1N1) infection was associated with a more than two-fold increased risk of CFS/ME.

*

Yang TY, Kuo HT, Chen HJ, Chen CS, Lin WM, Tsai SY, Kuo CN, Kao CH. Increased Risk of Chronic Fatigue Syndrome Following Atopy: A Population-Based Study. Medicine (Baltimore). 2015 Jul;94(29):e1211. PMID: 26200644

Atopy is associated with CFS, particularly in patients with numerous atopic syndromes.

*

Gaber TA, Oo WW, Ringrose H. Multiple Sclerosis/Chronic Fatigue Syndrome overlap: When two common disorders collide. NeuroRehabilitation. 2014;35(3):529-34. PMID: 25238862

MS and CFS/ME are two common conditions with increased prevalence in middle aged females. The study results suggest that the two conditions may co-exist.

*

Morris G, Anderson G, Galecki P, Berk M, Maes M. A narrative review on the similarities and dissimilarities between myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and sickness behavior. BMC Med. 2013 Mar 8;11(1):64. PMID: 23497361

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.

*

Katz BZ, Stewart JM, Shiraishi Y, Mears CJ, Taylor R. Orthostatic tolerance testing in a prospective cohort of adolescents with chronic fatigue syndrome and recovered controls following infectious mononucleosis. Clin Pediatr (Phila). 2012 Sep;51(9):835-9. PMID:22850676

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.

*

Itoh Y, Shigemori T, Igarashi T, Fukunaga Y. Fibromyalgia And Chronic Fatigue Syndrome In Children. Pediatr Int. 2011 Nov 24. PMID: 22115414

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.

*

Ciccone DS, Weissman L, Natelson BH. Chronic fatigue syndrome in male Gulf war veterans and civilians: a further test of the single syndrome hypothesis. J Health Psychol. 2008 May;13(4):529-36. PMID: 18420761

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.

*

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 women with endometriosis: a survey analysis. Hum Reprod. 2002 Oct;17(10):2715-24. PMID: 12351553

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

*

Aaron LA, Herrell R, Ashton S, Belcourt M, Schmaling K, Goldberg J, Buchwald D. Comorbid clinical conditions in chronic fatigue: a co-twin control study. J Gen Intern Med. 2001 Jan;16(1):24-31. PMID: 11251747

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.

*

White KP, Speechley M, Harth M, Ostbye T. Co-existence of chronic fatigue syndrome with fibromyalgia syndrome in the general population. A controlled study. Scand J Rheumatol. 2000;29(1):44-51. PMID: 10722257

There is significant clinical overlap between CFS and FMS.

*

Evengard B, Nilsson CG, Lindh G, Lindquist L, Eneroth P, Fredrikson S, Terenius L, Henriksson KG. Chronic fatigue syndrome differs from fibromyalgia. No evidence for elevated substance P levels in cerebrospinal fluid of patients with chronic fatigue syndrome. Pain. 1998 Nov;78(2):153-5. PMID: 9839828

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

*

De Lorenzo F, Hargreaves J, Kakkar VV. Phosphate diabetes in patients with chronic fatigue syndrome. Postgrad Med J. 1998 Apr;74(870):229-32. PMID: 9683977

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

HLA

Spitzer AR, Broadman M. A retrospective review of the sleep characteristics in patients with chronic fatigue syndrome and fibromyalgia. Pain Pract. 2010 Jul-Aug;10(4):294-300.PMID: 20230458

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.

*

Carlo-Stella N, Bozzini S, De Silvestri A, Sbarsi I, Pizzochero C, Lorusso L, Martinetti M, Cuccia M. Molecular study of receptor for advanced glycation endproduct gene promoter and identification of specific HLA haplotypes possibly involved in chronic fatigue syndrome. Int J Immunopathol Pharmacol. 2009 Jul-Sep;22(3):745-54. PMID: 19822091

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

*

Ortega-Hernandez OD, Cuccia M, Bozzini S, Bassi N, Moscavitch S, Diaz-Gallo LM, Blank M, Agmon-Levin N, Shoenfeld Y. Autoantibodies, polymorphisms in the serotonin pathway, and human leukocyte antigen class II alleles in chronic fatigue syndrome: are they associated with age at onset and specific symptoms? Ann N Y Acad Sci. 2009 Sep;1173:589-99. PMID: 19758204

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

*

Smith J, Fritz EL, Kerr JR, Cleare AJ, Wessely S, Mattey DL. Association of chronic fatigue syndrome with human leucocyte antigen class II alleles. J Clin Pathol. 2005 Aug;58(8):860-3. PMID: 16049290

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-DRQB1*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.

*

Underhill JA, Mahalingam M, Peakman M, Wessely S. Lack of association between HLA genotype and chronic fatigue syndrome. Eur J Immunogenet. 2001 Jun;28(3):425-8. PMID:11422420

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.

*

Itoh Y, Igarashi T, Tatsuma N, Imai T, Yoshida J, Tsuchiya M, Murakami M, Fukunaga Y. Immunogenetic background of patients with autoimmune fatigue syndrome. Autoimmunity. 2000 Oct;32(3):193-7. PMID: 11092699

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, Pcorr = 0.48) and 2.60 (p= 0.012, Pcorr = 0.17), respectively. A negative association was also found between AIFS and HLA-DR2 with odds ratio of 0.25 (p = 0.029, Pcorr = 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, Pcorr = 0.22), 3.96 (p = 0.0011, Pcorr = 0.015), and 0.16 (p =

0.0022, Porr = 0.031), respectively. Thus, the HLA associations observed in this study suggested that immunogenetic background might play a role in AIFS.

*

Hassan IS, Bannister BA, Akbar A, Weir W, Bofill M. A study of the immunology of the chronic fatigue syndrome: correlation of immunologic parameters to health dysfunction. Clin Immunol Immunopathol. 1998 Apr;87(1):60-7. PMID: 9576011

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.

*

Keller RH, Lane JL, Klimas N, Reiter WM, Fletcher MA, van Riel F, Morgan R. Association between HLA class II antigens and the chronic fatigue immune dysfunction syndrome. Clin Infect Dis. 1994 Jan;18 Suppl 1:S154-6. PMID: 8148444

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Middleton D, Savage DA, Smith DG. No association of HLA class II antigens in chronic fatigue syndrome. Dis Markers. 1991 Jan-Feb;9(1):47-9. PMID: 1683826

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van Greure CH, Bouic PJ. Aberrant in vitro HLA-DR expression in patients with chronic fatigue. S Afr Med J. 1990 Aug 18;78(4):219-20. PMID: 2382182

Genetics

Schlauch KA, Khaiboullina SF, De Meirleir KL, Rawat S, Petereit J, Rizvanov AA, Blatt N, Mijatovic T, Kulick D, Palotás A,Lombardi VC. Genome-wide association analysis identifies genetic variations in subjects with myalgic encephalomyelitis/chronic fatigue syndrome. Transl Psychiatry. 2016 Feb 9;6: PMID: 26859813

The authors used a DNA single-nucleotide polymorphism (SNP) chip representing over 906,600 known SNPs to analyze DNA from ME/CFS subjects and healthy controls. Twelve SNPs were identified in the coding region of their respective gene.

*

Billing-Ross P, Germain A, Ye K, Keinan A, Gu Z, Hanson MR. Mitochondrial DNA variants correlate with symptoms in myalgic encephalomyelitis/chronic fatigue syndrome. J Transl Med. 2016 Jan 20;14(1):19. PMID: 26791940

Analysis of mitochondrial genomes in ME/CFS cases indicates that individuals of a certain haplogroup or carrying specific SNPs are more likely to exhibit certain neurological, inflammatory, and/or gastrointestinal symptoms.

*

Meyer B, Nguyen CB, Moen A, Fagermoen E, Sulheim D, Nilsen H, Wyller VB, Gjerstad J. Maintenance of Chronic Fatigue Syndrome (CFS) in Young CFS Patients Is Associated with the 5-HTTLPR and SNP rs25531 A > G Genotype. PLoS One. 2015 Oct 16;10(10):e0140883. PMID: 26473596

CFS patients with the 5-HTT SS or SLG genotype had worse 30 weeks outcome than CFS patients with the 5-HTT LALG, SLA or LALA genotype. The 5-HTT genotype may be a factor that contributes to maintenance of CFS.

*

Löbel M, Mooslechner AA, Bauer S, Günther S, Letsch A, Hanitsch LG, Grabowski P, Meisel C, Volk HD, Scheibenbogen C. Polymorphism in COMT is associated with

IgG3 subclass level and susceptibility to infection in patients with chronic fatigue syndrome. J Transl Med. 2015 Aug 14;13:264. PMID: 26272340

The study results indicate a relationship of COMT polymorphism rs4680 with immune dysregulation in CFS providing a potential link for the association between stress and infection susceptibility in CFS.

*

Rajeevan MS, Dimulescu I, Murray J, Falkenberg VR, Unger ER. Pathway-focused genetic evaluation of immune and inflammation related genes with chronic fatigue syndrome. Hum Immunol. 2015 Aug;76(8):553-60. PMID: 26116897

CFS was associated with 32 functionally important single nucleotide polymorphisms(SNPs): 11 missense variants, 4 synonymous variants, 11 untranslated regulatory region (UTR) variants and 6 intronic variants. Of particular interest is association of CFS with two missense variants in genes of complement activation, rs4151667 (L9H) in CFB and rs1061170 (Y402H) in CFH. A 5' UTR polymorphism (rs11214105) in IL18 also associated with physical fatigue, body pain and score for CFS case defining symptoms.

*

Iacob E, Light AR, Donaldson GW, Okifuji A, Hughen RW, White AT, Light KC. Gene Expression Factor Analysis to Differentiate Pathways Linked to Fibromyalgia, Chronic Fatigue Syndrome, and Depression in a Diverse Patient Sample. Arthritis Care Res (Hoboken). 2016 Jan;68(1):132-40. PMID: 26097208

Expression of candidate genes can be grouped into meaningful clusters, and CFS and depression are associated with the same 2 clusters, but in opposite directions, when controlling for comorbid fibromyalgia.

*

Shimosako N, Kerr JR. Use of single-nucleotide polymorphisms (SNPs) to distinguish gene expression subtypes of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). J Clin Pathol. 2014 Dec;67(12):1078-83. PMID: 25240059

This study provides evidence that human SNPs located within CFS/ME associated genes are associated with particular genomic subtypes of CFS/ME. Further work is required to develop this into a clinically useful subtype-specific diagnostic test.

*

Brenu EW, Ashton KJ, Batovska J, Staines DR, Marshall-Gradisnik SM. High-throughput sequencing of plasma microRNA in chronic fatigue syndrome/myalgic encephalomyelitis. PLoS One. 2014 Sep 19;9(9):e102783. PMID: 25238588

The authors identified 19 miRNAs that were differentially expressed in the plasma of CFS/ME patients in comparison to non-fatigued controls. Following RT-qPCR analysis, they confirmed the significant up-regulation of three miRNAs (hsa-miR-127-3p, hsa-miR-142-5p and hsa-miR-143-3p) in the CFS/ME patients.

*

de Vega WC, Vernon SD, McGowan PO. DNA methylation modifications associated with chronic fatigue syndrome. PLoS One. 2014 Aug 11;9(8):e104757. PMID: 25111603

The authors found an increased abundance of differentially methylated genes related to the immune response, cellular metabolism, and kinase activity. Genes associated with immune cell regulation, the largest coordinated enrichment of differentially methylated pathways, showed hypomethylation within promoters and other gene regulatory elements in CFS. These data are consistent with evidence of multisystem dysregulation in CFS and implicate the involvement of DNA modifications in CFS pathology.

*

Cifuentes RA, Barreto E. Supervised selection of single nucleotide polymorphisms in chronic fatigue syndrome. Biomedica. 2011 Oct-Dec;31(4):613-21.PMID: 22674373

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.

*

Light KC, White AT, Tadler S, Iacob E, Light AR. Genetics and Gene Expression Involving Stress and Distress Pathways in Fibromyalgia with and without Comorbid Chronic Fatigue Syndrome. Pain Res Treat. 2012;2012:427869. PMID: 22110941

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.

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Sommerfeldt L, Portilla H, Jacobsen L, Gjerstad J, Wyller VB. Polymorphisms of adrenergic cardiovascular control genes are associated with adolescent chronic fatigue syndrome. Acta Paediatr. 2011 Feb;100(2):293-8. PMID: 21059181

CFS patients were especially likely to have a number of specific genes, suggesting that CFS might be related to polymorphisms of COMT and the β_2 -adrenergic receptor.

*

Smith AK, Fang H, Whistler T, Unger ER, Rajeevan MS. Convergent Genomic Studies Identify Association of GRIK2 and NPAS2 with Chronic Fatigue Syndrome. Neuropsychobiology. 2011;64(4):183-94. PMID: 21912186

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.

*

Falkenberg VR, Whistler T, Murray JR, Unger ER, Rajeevan MS. Identification of Phosphoglycerate Kinase 1 (PGK1) as a Reference Gene for Quantitative Gene Expression Measurements in Human Blood RNA. BMC Res Notes. 2011 Sep 6;4(1):324. PMID: 21896205

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.

*

Sommerfeldt L, Portilla H, Jacobsen L, Gjerstad J, Wyller VB. Polymorphisms of adrenergic cardiovascular control genes are associated with adolescent chronic fatigue syndrome. Acta Paediatr. 2011 Feb;100(2):293-8. PMID: 21059181

CFS patients were especially likely to have a number of specific genes, suggesting that CFS might be related to polymorphisms of COMT and the β_2 -adrenergic receptor.

*

Falkenberg VR, Gurbaxani BM, Unger ER, Rajeevan MS. Functional Genomics of Serotonin Receptor 2A (HTR2A): Interaction of Polymorphism, Methylation, Expression and Disease Association. Neuromolecular Med. 2011 Mar;13(1):66-76. PMID: 20941551

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.

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Fukuda S, Hashimoto R, Ohi K, Yamaguti K, Nakatomi Y, Yasuda Y, Kamino K, Takeda M, Tajima S, Kuratsune H, Nishizawa Y, Watanabe Y. A functional polymorphism in the disrupted-in schizophrenia 1 gene is associated with chronic fatigue syndrome. Life Sci. 2010 May 8;86(19-20):722-5. PMID: 20227423

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

*

Landmark-Høyvik H, Reinertsen KV, Loge JH, Kristensen VN, Dumeaux V, Fosså SD, Børresen-Dale AL, Edvardsen H. The genetics and epigenetics of fatigue. PM R. 2010 May;2(5):456-65. PMID: 20656628

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

*

Zhang L, Gough J, Christmas D, Mattey DL, Richards SC, Main J, Enlander D, Honeybourne D, Ayres JG, Nutt DJ, Kerr JR. Microbial infections in eight genomic subtypes of chronic fatigue syndrome/myalgic encephalomyelitis. J Clin Pathol. 2010 Feb;63(2):156-64. PMID: 19955554

Specific genotypes are associated with CFS.

*

Huang LC, Hsu SY, Lin E. A comparison of classification methods for predicting Chronic Fatigue Syndrome based on genetic data. J Transl Med. 2009 Sep 22;7:81. PMID:19772600

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).

*

Gow JW, Hagan S, Herzyk P, Cannon C, Behan PO, Chaudhuri A. A gene signature for post-infectious chronic fatigue syndrome. BMC Med Genomics. 2009 Jun 25;2:38. PMID: 19555476

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.

*

Byrnes A, Jacks A, Dahlman-Wright K, Evengard B, Wright FA, Pedersen NL, Sullivan PF Gene expression in peripheral blood leukocytes in monozygotic twins discordant for chronic fatigue: no evidence of a biomarker. PLoS One. 2009 Jun 5;4(6):e5805. PMID: 19503787

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

*

Lin E, Hsu SY. A Bayesian approach to gene-gene and gene-environment interactions in chronic fatigue syndrome. Pharmacogenomics. 2009 Jan;10(1):35-42. PMID: 19102713

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.

*

Saiki T, Kawai T, Morita K, Ohta M, Saito T, Rokutan K, Ban N. Identification of marker genes for differential diagnosis of chronic fatigue syndrome. Mol Med. 2008 Sep-Oct;14(9-10):599-607. PMID: 18596870

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

*

Kerr JR. Gene profiling of patients with chronic fatigue syndrome/myalgic encephalomyelitis. Curr Rheumatol Rep. 2008 Dec;10(6):482-91. PMID: 19007540

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.

*

Presson AP, Sobel EM, Papp JC, Suarez CJ, Whistler T, Rajeevan MS, Vernon SD, Horvath S. Integrated weighted gene co-expression network analysis with an application to chronic fatigue syndrome. BMC Syst Biol. 2008 Nov 6;2:95. PMID: 18986552

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

*

Kerr JR, Petty R, Burke B, Gough J, Fear D, Sinclair LI, Mattey DL, Richards SC, Montgomery J, Baldwin DA, Kellam P, Harrison TJ, Griffin GE, Main J, Enlander D, Nutt DJ, Holgate ST. Gene expression subtypes in patients with chronic fatigue syndrome/myalgic encephalomyelitis. J Infect Dis. 2008 Apr 15;197(8):1171-84. PMID: 18462164

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

*

Kerr JR, Burke B, Petty R, Gough J, Fear D, Mattey DL, Axford JS, Dalgleish AG, Nutt DJ. Seven genomic subtypes of chronic fatigue syndrome/myalgic encephalomyelitis: a detailed analysis of gene networks and clinical phenotypes. J Clin Pathol. 2008 Jun;61(6):730-9. PMID: 18057078

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

*

Smith AK, Dimulescu I, Falkenberg VR, Narasimhan S, Heim C, Vernon SD, Rajeevan MS. Genetic evaluation of the serotonergic system in chronic fatigue syndrome. Psychoneuroendocrinology. 2008 Feb;33(2):188-97. PMID: 18079067

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

*

Kawai T, Rokutan K. Identification and application of marker genes for differential diagnosis of chronic fatigue syndrome. Nihon Rinsho. 2007 Jun;65(6):1029-33. PMID: 17561693

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

*

Narita M, Narita N. Genetic background of chronic fatigue syndrome. Nihon Rinsho. 2007 Jun;65(6):997-1002. PMID: 17561688

A significant increase of longer (L and XL) alleic 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.

*

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.

*

Fang H, Xie Q, Boneva R, Fostel J, Perkins R, Tong W. Gene expression profile exploration of a large dataset on chronic fatigue syndrome. Pharmacogenomics. 2006 Apr;7(3):429-40. PMID: 16610953

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

*

Whistler T, Taylor R, Craddock RC, Broderick G, Klimas N, Unger ER. Gene expression correlates of unexplained fatigue. Pharmacogenomics. 2006 Apr;7(3):395-405. PMID: 16610950

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.

*

Vernon SD, Whistler T, Aslakson E, Rajeevan M, Reeves WC. Challenges for molecular profiling of chronic fatigue syndrome. Pharmacogenomics. 2006 Mar;7(2):211-8. PMID: 16515400

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.

*

Kaushik N, Fear D, Richards SC, McDermott CR, Nuwaysir EF, Kellam P, Harrison TJ, Wilkinson RJ, Tyrrell DA, Holgate ST, Kerr JR. Gene expression in peripheral blood mononuclear cells from patients with chronic fatigue syndrome. J Clin Pathol. 2005 Aug;58(8):826-32. PMID: 16049284

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.

*

Torpy DJ, Bachmann AW, Gartside M, Grice JE, Harris JM, Clifton P, Easteal S, Jackson RV, Whitworth JA. Association between chronic fatigue syndrome and the corticosteroid-binding globulin gene ALA SER224 polymorphism. Endocr Res. 2004 Aug;30(3):417-29. PMID: 15554358

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.

*

Whistler T, Unger ER, Nisenbaum R, Vernon SD. Integration of gene expression, clinical, and epidemiologic data to characterize Chronic Fatigue Syndrome. J Transl Med. 2003 Dec 1;1(1):10. PMID: 14641939

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

*

Powell R, Ren J, Lewith G, Barclay W, Holgate S, Almond J. Identification of novel expressed sequences, up-regulated in the leucocytes of chronic fatigue syndrome patients. Clin Exp Allergy. 2003 Oct;33(10):1450-6. PMID: 14519154

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.

*

Vernon SD, Unger ER, Dimulescu IM, Rajeevan M, Reeves WC. Utility of the blood for gene expression profiling and biomarker discovery in chronic fatigue syndrome. Dis Markers. 2002;18(4):193-9. PMID: 12590173

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.

*

Vernon SD, Shukla SK, Conradt J, Unger ER, Reeves WC. Analysis of 16S rRNA gene sequences and circulating cell-free DNA from plasma of chronic fatigue syndrome and non-fatigued subjects. BMC Microbiol. 2002 Dec 23;2:39. PMID:12498618

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.

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