Systemic Exertion Intolerance Disease/Chronic Fatigue Syndrome-A Route To Resolution

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NHAND Webinar

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www.bornintegrativemedicine.com

Disclosures

- Born Integrative Medicine Specialists, PLLC
  - Co-owner and medical director
    - www.bornintegrativemedicine.com
- Allergy Research Group LLC
  - Director of new product development, Scientific Advisor, Editor-in-chief of Focus Newsletter
- International Medical Wellness Association
  - Medical Wellness Advisor
    - https://www.medicalwellnessassociation.com/

Terminology & Definitions

Chronic Fatigue Syndrome

Myalgic Encephalomyelitis (UK)

Chronic Multifactorial Fatigue (Mayo Clinic)

2015 Institute of Medicine (IOM)

- Redefined diagnostic criteria and suggested name change to Systemic Exertion Intolerance Disease (SEID)

Diagnostic Criteria

Symptoms should be present for at least six months and have moderate, substantial, or severe intensity at least one-half of the time.

2015 IOM diagnostic criteria for CFS/SEID

Diagnosis requires that the patient have the following three symptoms:

1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than six months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest; and
2. Post-exertional malaise;* and
3. Unrefreshing sleep*

At least one of the two following manifestations is also required:

1. Cognitive impairment* or
2. Orthostatic intolerance±

* Frequency and severity of symptoms should be assessed. The diagnosis of CFS/SEID should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.
± Onset of symptoms when standing upright that are improved by lying back down

From: Institute of Medicine of the National Academies. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an illness. Report Brief, February 2015. Reprinted with permission from the National Academies Press, Copyright © 2015 National Academy of Sciences.

CDC Diagnostic Criteria

The fatigue of CFS is accompanied by characteristic illness symptoms lasting at least 6 months. These symptoms include:

- increased malaise (extreme exhaustion and sickness) following physical activity or mental exertion
- problems with sleep
- difficulties with memory and concentration
- persistent muscle pain
- arthralgias (without redness or swelling)
- headache
- cervical or axillary tender lymph nodes
- pharyngitis

http://www.cdc.gov/cfs/symptoms/index.html

Epidemiology

- Prospective cohort study of over 4000 patients in a health maintenance organization, est. crude point prevalence of SEID/CFS ranged from 75 to 267 cases per 100,000 persons.
  - But if you didn't meet the IOM strict definition: 775 to 6321 cases per 100,000 persons.
- Depending on the case definition, prevalence rates of ME/CFS in the United States range from 0.3% to 2.5%.
- Prevalence is generally considered to be under 10%.
- Females comprise 75% of SEID/CFS.
- Primarily affects young to middle aged adults.

Buchwald D, et al. Chronic fatigue and the chronic fatigue syndrome: prevalence in a Pacific Northwest health care system. Ann Intern Med. 1995;123(2):81.

Bates DW, et al. Prevalence of fatigue and chronic fatigue syndrome in a primary care practice. Arch Intern Med. 1993;153(24):2759.

Prins JB, et al. Chronic fatigue syndrome. Lancet 2006;367(9507):346.

Diagnosis and Treatment of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome . Executive Summary. AHRQ. 2014.

Signs and Symptoms

Relatively sudden onset of fatigue.

Often associated with a typical infection such as an URI or true mononucleosis.

Overwhelming fatigue and several additional symptoms, especially altered sleep and cognition.

Excessive physical activity characteristically exacerbates the symptoms.

Affected patients are typically highly functioning individuals who are "struck down" with the disease. There is often, however, a history of psychiatric disorders.

Katon WJ, et al. Psychiatric illness in patients with chronic fatigue and those with rheumatoid arthritis. J Gen Intern Med. 1991;6(4):277.

Lante TJ, et al. Depression and somatization in the chronic fatigue syndrome. Am J Med. 1991;91(4):335.

Diagnostic Difficulty

- Once the inciting illness (if any) is resolved, PE typically is normal.
- Although patients commonly feel febrile, few ever demonstrate elevated temps (po greater than $37.4^0C/99.3^0F$).
- Arthralgias, but no erythema, effusion, nor limitation of motion.
- Easily fatigued muscles (PPR), strength is normal, as are biopsies and electromyograms.
- Mild cervical and/or axillary lymphadenitis, along with painful lymph nodes (lymphadenia) are a frequent complaints, but not true lymphadenopathy, is not present.
    - Biopsied lymph nodes show reactive hyperplasia. The cervical lymph nodes are most commonly involved, but the axillary lymph nodes may also be affected.

Diagnostic Difficulty

"Routine Labs" typically only elucidate causation in about 5% of cases.

No specific tests available.

Many patients are partially or completely disabled by its manifestations.

The illness has a pattern of remission and relapse.

Outward healthy appearance doesn't tell story of how they actually feel.

Accused of malingerers, worsening their physical and mental symptoms.

Lane TJ. The low yield of physical examinations and laboratory investigations of patients with chronic fatigue. Am J Med Sci. 1990;299(5):313.

http://www.cdc.gov/cfs/diagnosis/index.html

Fukuda K, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med. 1994 Dec 15;121(12):953-9.

SEID/CFS & Fibromyalgia

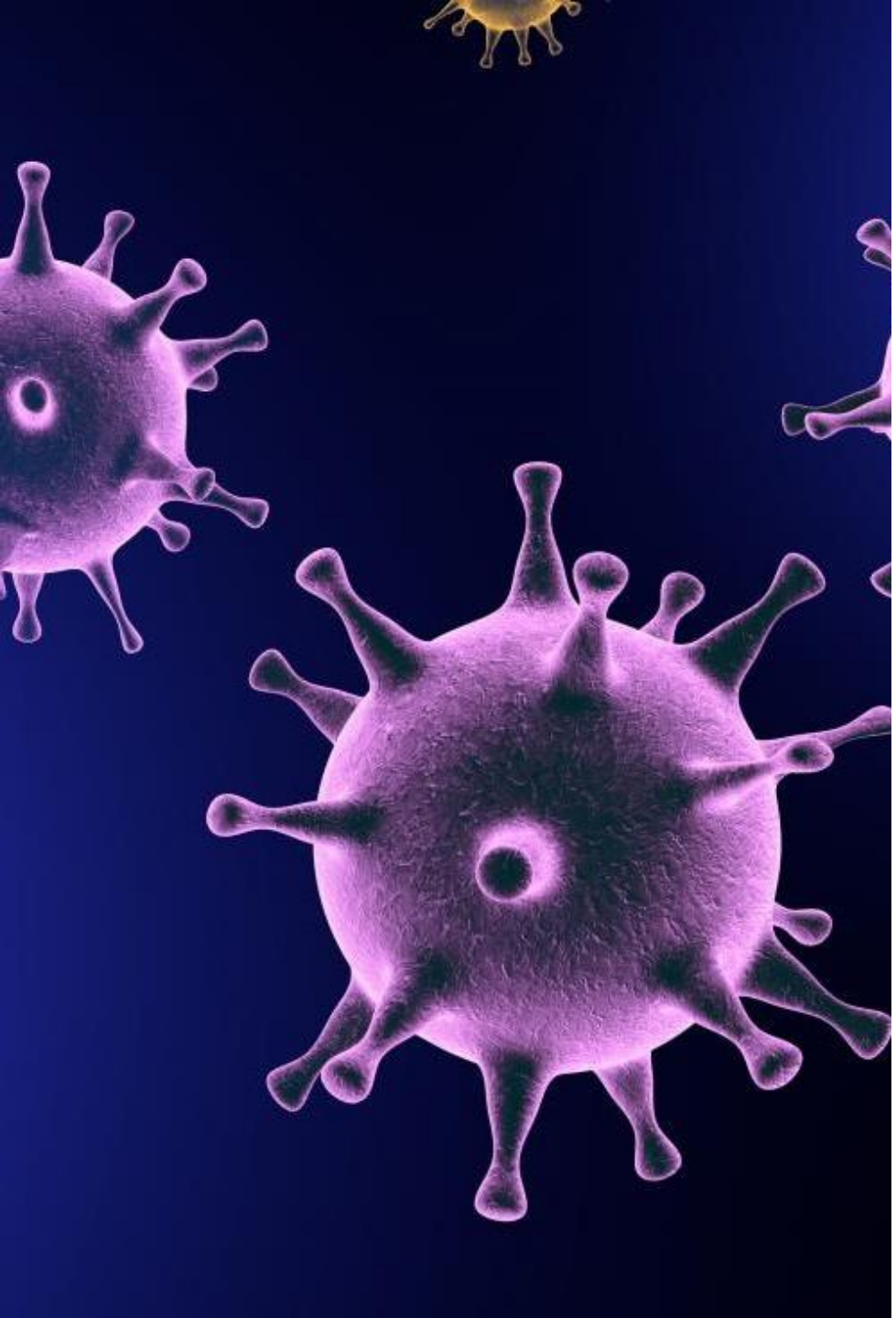
Approximately 70% of patients with fibromyalgia meet the criteria for SEID/CFS.

Clinical similarities between fibromyalgia and systemic exertion intolerance disease (SEID), also known as chronic fatigue syndrome (CFS)

80 to 90% women, usual ages 20 to 55 years
Myalgias and fatigue in more than 90%
Associated common symptoms
Neurocognitive and mood disturbances
Headaches
Sleep disturbances
No identifiable cause
Testing is normal
Physical examination usually normal except for tender points which are required for diagnosis of fibromyalgia and present in most patients with chronic fatigue
Normal laboratory and radiologic tests
Chronic symptoms, no highly effective therapy

UpToDate

Buchwald D, Garrity D. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. Arch Intern Med. 1994;154(18):2049.



Proposed Etiologies

Viruses & Bacteria

- EBV, HHV-6, CMV, enteroviruses, coxsackie B, Ross River, Borna disease, xenotropic murine leukemia virus-related virus (XMRV), murine leukemia virus (MLV), Mycoplasma, Coxiella burnetti (Q Fever), Rubella…

Immune Dysfunction compared to healthy controls

- ↓Immune complexes, NK cells and function; altered IgG levels and CD4/CD8 ratios.
- ↑ interferon and cytokine activity & IL-2

Endocrine-metabolic dysfunction

- Physical or emotional stress, which is commonly reported as a pre-onset condition in CFS patients, alters the activity of the HPA axis.

http://www.cdc.gov/cfs/causes/index.html

Lorusso L, et al. Immunological aspects of chronic fatigue syndrome. Autoimmun Rev. 2009 Feb;8(4):287-91.

Nasralla M, et al. 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.

Proposed Etiologies

Neurally-mediated hypotension (NMH)/Postural Orthostatic Tachycardia (POTS)

- develop lower blood pressure with tilt table testing, as well as other characteristic symptoms, such as lightheadedness, visual dimming, or a slow response to verbal stimuli.

Neuropsychiatric factors (2/3 or more meet criteria)

- Depressive d/o, Anxiety d/o, etc.

Genetics

- DNA sequence changes in three genes associated with brain function, stress reactions, and emotional responses led to differences in how the body responds to hormones and other chemical messengers.

http://www.cdc.gov/cfs/causes/index.html

Taerk GS, et al. Depression in patients with neuromyasthenia (benign myalgic encephalomyelitis). Int J Psychiatry Med. 1987;17(1):49.

Kruesi MJ, et al. Psychiatric diagnoses in patients who have chronic fatigue syndrome. J Clin Psychiatry. 1989;50(2):53.

Manu P, et al. The frequency of the chronic fatigue syndrome in patients with symptoms of persistent fatigue. Ann Intern Med. 1988;109(7):554.

Genetics Always at Play

Pharmacogenomics. 2006 Apr;7(3):387-94.

Polymorphisms in genes regulating the HPA axis associated with empirically delineated classes of unexplained chronic fatigue.

Smith AK[1], White PD, Aslakson E, Vollmer-Conna U, Rajeevan MS.

⊕ **Author information**

Abstract

Chronic fatigue syndrome (CFS) is characterized by persistent or relapsing fatigue that is not alleviated by rest, causes substantial reduction in activities and is accompanied by a variety of symptoms. Its unknown etiology may reflect that CFS is heterogeneous. Latent class analyses of symptoms and physiological systems were used to delineate subgroups within a population-based sample of fatigued and nonfatigued subjects [1] . This study examined whether genetic differences underlie the individual subgroups of the latent class solution. Polymorphisms in 11 candidate genes related to both hypothalamic-pituitary-adrenal (HPA) axis function and mood-related neurotransmitter systems were evaluated by comparing each of the five ill classes (Class 1, n = 33; Class 3, n = 22; Class 4, n = 22; Class 5, n = 17; Class 6, n = 11) of fatigued subjects with subjects defined as well (Class 2, n = 35). Of the five classes of subjects with unexplained fatigue, three classes were distinguished by gene polymorphsims involved in either HPA axis function or neurotransmitter systems, including proopiomelanocortin (POMC), nuclear receptor subfamily 3, group C, member 1 (NR3C1), monoamine oxidase A (MAOA), monoamine oxidase B (MAOB), and tryptophan hydroxylase 2 (TPH2). These data support the hypothesis that medically unexplained chronic fatigue is heterogeneous and presents preliminary evidence of the genetic mechanisms underlying some of the putative conditions.

PMID: 16610949 DOI: 10.2217/14622416.7.3.387

Pharmacogenomics. 2006 Apr;7(3):475-83.

Combinations of single nucleotide polymorphisms in neuroendocrine effector and receptor genes predict chronic fatigue syndrome.

Goertzel BN[1], Pennachin C, de Souza Coelho L, Gurbaxani B, Maloney EM, Jones JF.

⊕ Author information

Abstract

OBJECTIVE: This paper asks whether the presence of chronic fatigue syndrome (CFS) can be more accurately predicted from single nucleotide polymorphism (SNP) profiles than would occur by chance.

METHODS: Specifically, given SNP profiles for 43 CFS patients, together with 58 controls, we used an enumerative search to identify an ensemble of conjunctive rules that predict whether a patient has CFS.

RESULTS: The accuracy of the rules reached 76.3%, with the highest accuracy rules yielding 49 true negatives, 15 false negatives, 28 true positives and nine false positives (odds ratio [OR] 8.94, $p < 0.0001$). Analysis of the SNPs used most frequently in the overall ensemble of rules gave rise to a list of 'most important SNPs', which was not identical to the list of 'most differentiating SNPs' that one would calculate via studying each SNP independently. The top three genes containing the SNPs accounting for the highest accumulated importances were neuronal tryptophan hydroxylase (TPH2), catechol-O-methyltransferase (COMT) and nuclear receptor subfamily 3, group C, member 1 glucocorticoid receptor (NR3C1).

CONCLUSION: 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.

PMID: 16610957 DOI: 10.2217/14622416.7.3.475

Other Proposed Etiologies

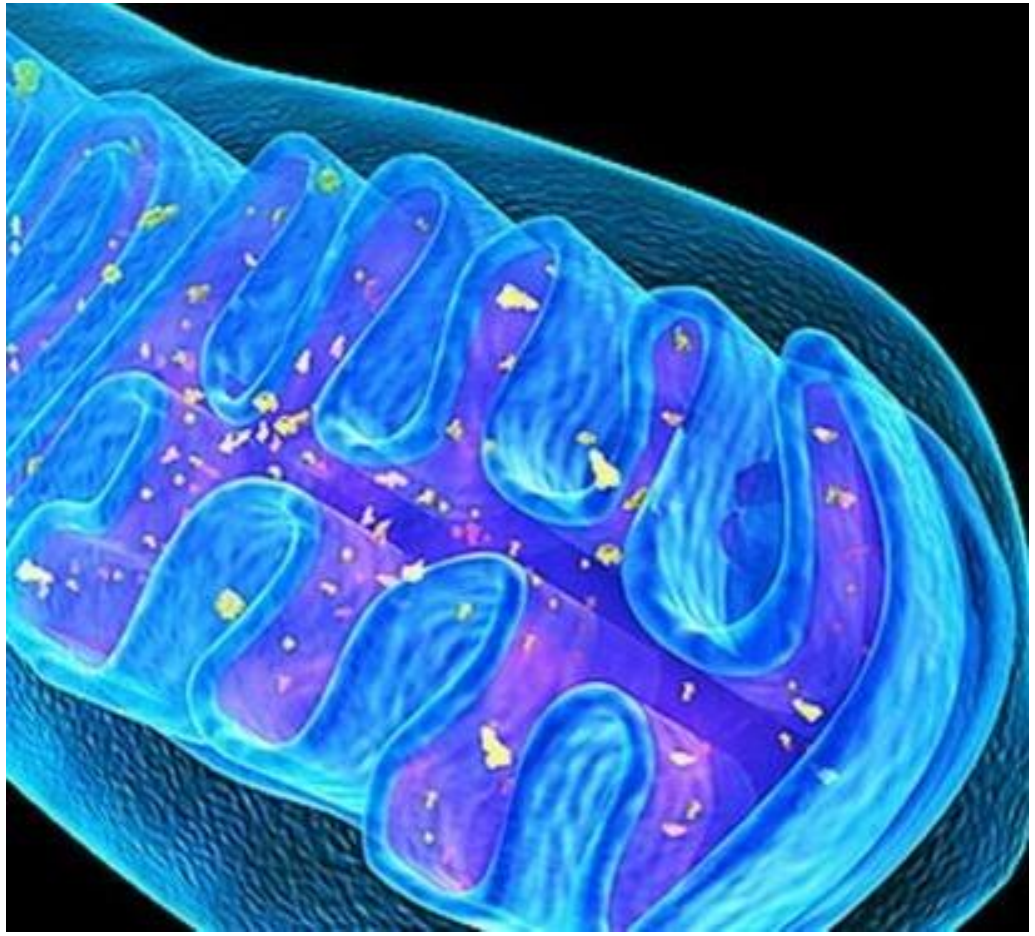
Mitochondrial dysfunction

- Major immediate causes are lack of essential substrates and partial blocking of the translocator protein sites in mitochondria.

Booth NE, et al. Mitochondrial dysfunction and the pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Int J Clin Exp Med. 2012;5(3):208-20. Epub 2012 Jun 15.

Myhill S, et al. Chronic fatigue syndrome and mitochondrial dysfunction. Int J Clin Exp Med. 2009;2(1):1-16. Epub 2009 Jan 15.

Racciatti D, et al. Chronic fatigue syndrome following a toxic exposure. Sci Total Environ. 2001 Apr 10;270(1-3):27-31.



Metabolomics

Metabolic features of chronic fatigue syndrome

Robert K. Naviaux[a,b,c,d,1], Jane C. Naviaux[a,e], Kefeng Li[a,b], A. Taylor Bright[a,b], William A. Alaynick[a,b], Lin Wang[a,b], Asha Baxter[f], Neil Nathan[f,2], Wayne Anderson[f], and Eric Gordon[f]

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92103-8467; [e]Department of Neurosciences, University of California, San Diego School of Medicine,
Associates, Santa Rosa, CA 95403

Edited by Ronald W. Davis, Stanford University School of Medicine, Stanford, CA, and approved July

More than 2 million people in the United States have myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). We performed targeted, broad-spectrum metabolomics to gain insights into the biology of CFS. We studied a total of 84 subjects using these methods. Forty-five subjects (n = 22 men and 23 women) met diagnostic criteria for ME/CFS by Institute of Medicine, Canadian, and Fukuda criteria. Thirty-nine subjects (n = 18 men and 21 women) were age- and sex-matched normal controls. Males with CFS were 53 (±2.8) y old (mean ± SEM; range, 21–67 y). Females were 52 (±2.5) y old (range, 20–67 y). The Karnofsky performance scores were 62 (±3.2) for males and 54 (±3.3) for females. We targeted 612 metabolites in plasma from 63 biochemical pathways by hydrophilic interaction liquid chromatography, electrospray ionization, and tandem mass spectrometry in a single-injection method. Patients with CFS showed abnormalities in 20 metabolic pathways. Eighty percent of the diagnostic metabolites were decreased, consistent with a hypometabolic syndrome. Pathway abnormalities included sphingolipid, phospholipid, purine, cholesterol, microbiome, pyrroline-5-carboxylate, riboflavin, branch chain amino acid, peroxisomal, and mitochondrial metabolism. Area under the receiver operator characteristic curve analysis showed diag

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Significance

Chronic fatigue syndrome is a multisystem disease that causes long-term pain and disability. It is difficult to diagnose because of its protean symptoms and the lack of a diagnostic laboratory test. We report that targeted, broad-spectrum metabolomics of plasma not only revealed a characteristic chemical signature but also revealed an unexpected underlying biology. Metabolomics showed that chronic fatigue syndrome is a highly concerted hypometabolic response to environmental stress that traces to mitochondria and was similar to the classically studied developmental state of dauer. This discovery opens a fresh path for the rational development of new therapeutics and identifies metabolomics as a powerful tool to identify the chemical differences that contribute to health and disease.

Naviaux RK, et al. Metabolic features of chronic fatigue syndrome. Proc Natl Acad Sci U S A. 2016 Sep 13;113(37):E5472-80.

My Approach to DDX

Rule out other etiologies of fatigue

Look at co-morbidities

- Fibromyalgia
- Sleep dysfunction
- Dysglycemia/Hypoglycemia
- Psychiatric illness

Routine Labs

CMP, CBC w/ diff, TSH, FT4, FT3, CRP, hs-CRP, ESR, creatine kinase, vitamin D, HbA1c, ANA, thyroid antibodies

Advanced approach

- Serum MMA, serum + RBC magnesium, ionized calcium, RBC Zn, iron panel w/ ferritin, DHEA-S, pregnenolone, testosterone panel, fractionated estrogens
- Quantitative CMV IgG/IgM and EBV VCA IgG/IgM, EA IgG, EBV NA IgG, human herpsevirus 6 (HHV-6) IgM/IgG.
- Tick-borne illnesses (*Borellia, Babesia, Ehrlichia, Bartonella, Anaplasma)*
- *Mycoplasma pneumoniae*
- Mycotoxins
- Urine and blood heavy metal assessment.

ICD-10: Z00.00, Z11.9 E34.9, E63.9, R53.83, M79.10, R53.82, M25.50, Z11.2, Z11.59, Z13.88…

EBV Interpretation

Marker	Non-Immune	Primary Infection	Past Infection	Reactivation
VCA IgM	N	P	N	N
VCA IgG	N	P	P	P
EA IgG	N	P	N	P
NA IgG	N	N	P	P

N=negative, P=positive

Patterns not falling within one of the above groupings are Indeterminate and it is recommended the patient be redrawn and retested in 1 month.

Notes: Occasionally a false positive result occurs with specimens containing Abs to HIV. With a positive EBV EA IgG result it is essential to exclude HIV disease.
Approximately 5% to 10% of patients with EBV never develop antibodies to EBNA (past).

Conventional Treatment

Systematic reviews of SEID/CFS have determined only two effective treatments: cognitive behavioral therapy (CBT) and graded exercise therapy (GET).

Antidepressants

Sleep hygiene

Support groups

Iron therapy in nonanemic patients with low serum ferritin.

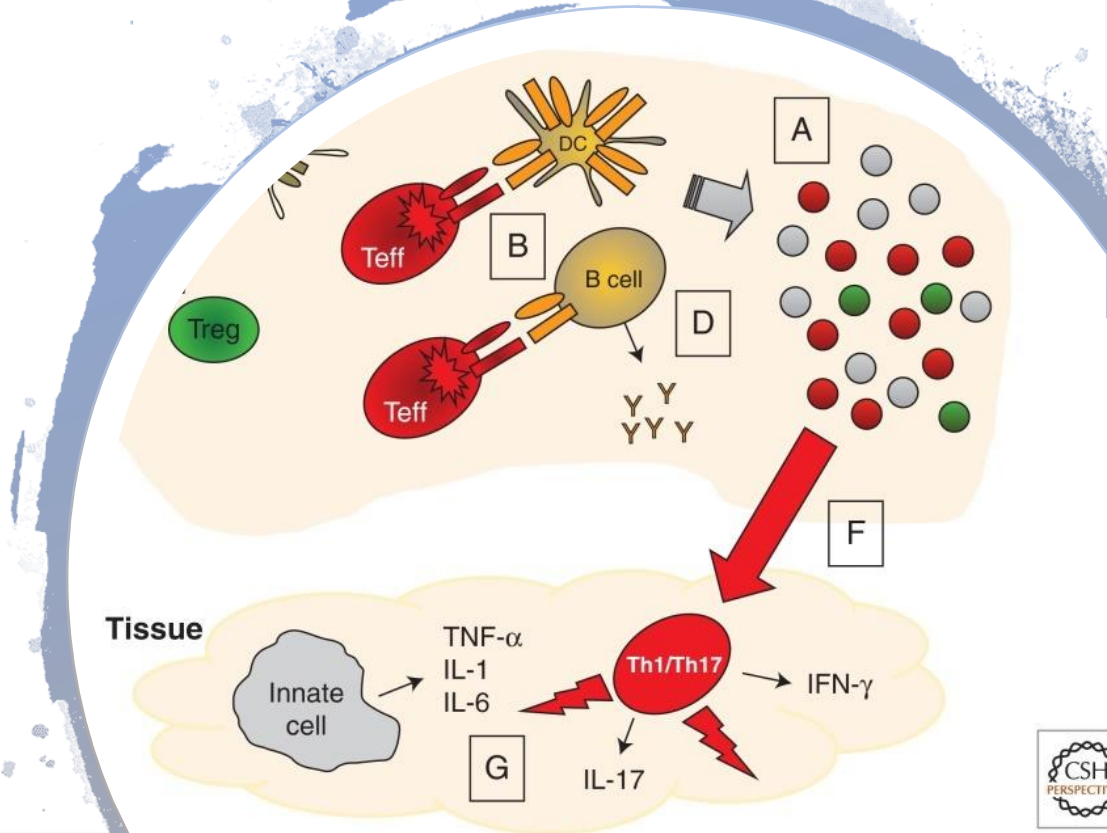
Price JR, et al. Cognitive behaviour therapy for chronic fatigue syndrome in adults. Cochrane Database Syst Rev. 2008 Jul 16;(3):CD001027.

Whiting P, et al. Interventions for the treatment and management of chronic fatigue syndrome: a systematic review. JAMA. 2001;286(11):1360.

Naturopathic Strategies

- Two-thirds of patients with SEID/CFS reported that they were dissatisfied with the quality of their medical care and felt their clinicians lacked communication skills and education regarding their diagnosis.
  - Ergo, support is key.
- Try to find accurate underlying abnormalities and address accordingly.
- Counseling and graded exercise
- Sleep hygiene, if poor sleep present
- Diet
- Constitutional homeopathy
- Mitochondrial support
- Gemmotherapy and Oligotherapy

Deale A, Wessely S. Patients' perceptions of medical care in chronic fatigue syndrome. Soc Sci Med. 2001;52(12):1859.



My Own Clinical Approach

Hx & PE

- Look for themes and trends
- Consider IOM dx, et al criteria.

Constitutional homeopathy

Appropriate blood tests (see slide 17)

Return in 3 weeks for A//

+ EBV, CMV and/or HHV-6

- <u>Gemmotherapy</u>
  - *Acer campestre, Juniperus communis, Tamarix gallica*
- <u>Oligoelement</u>
  - Cu-Au-Ag (Copper/Gold/Silver)

My Own Clinical Approach

- Potent multivitamin/mineral

  Maric D, et al. Multivitamin mineral supplementation in patients with chronic fatigue syndrome. Med Sci Monit. 2014 Jan 14;20:47-53.

- Fermented foods, Stewed apples, Prebiotics (XOS, GOS, FOS) & Probiotics, *Saccharomyces boulardii*

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

  Pothoulakis C. Review article: anti-inflammatory mechanisms of action of Saccharomyces boulardii. Aliment Pharmacol Ther. 2009 Oct 15;30(8):826-33.

- Return in 6 weeks for A//
  - 98% of my patients (over 200 cases so far) are at least 90% better.
    - ***Ribes nigrum* gemmotherapy**
  - For those that aren't substantially better, but responded to therapy, repeat.

My Own Clinical Approach

2% non-responders

Antivirals

- Acyclovir, Valacyclovir, Famciclovir, Valganciclovir
  - 250 mg-1000 mg, TID-QID
    - Adjust for renal impairment.

Humic acid: 750-3000 mg qd, in divided doses

- MOA: interferes with a virus' ability to attach to a host cell, penetrate the host cell, and reproduce itself.

Learner AM, et al. Valacyclovir treatment in Epstein-Barr virus subset chronic fatigue syndrome: thirty-six months follow-up. In Vivo. 2007 Sep-Oct;21(5):707-13.

Watt T, et al. Response to valganciclovir in chronic fatigue syndrome patients with human herpesvirus 6 and Epstein-Barr virus IgG antibody titers. J Med Virol. 2012 Dec;84(12):1967-74.

Montoya JG, et al. Randomized clinical trial to evaluate the efficacy and safety of valganciclovir in a subset of patients with chronic fatigue syndrome. J Med Virol. 2013 Dec;85(12):2101-9.

Laub Biochem Specialty Labs, 2001-2002, research conducted by contract for Virology Branch of the Antiviral Research and Antimicrobial Chemistry Program (Dr. Christopher Tseng, Program Officer), Division of Microbiology and Infectious Diseases (DMID) Screening and Testing Program for Antiviral, Immunomodulatory, Antitumor and/or Drug Delivery Activities, National Institutes of Allergy and Infectious Diseases (NIAID), under the auspices of the National Institutes of Health (NIH, Bethesda, Maryland).

Kloecking R, Helbig B, Schotz G, et al. Anti-HSV-1 Activity of Synthetic Humic Acid-Like Polymers Derived from p-Diphenolic Starting Compounds. Arch. Chem. Chemother. 2002, 13(4), 241-249.

What About Those w/o Infectious Correlations?

- Investigate further
  - ✓Heavy metals
    - ✓ Shin SR & Han AL. Improved Chronic Fatigue Symptoms after Removal of Mercury in Patient with Increased Mercury Concentration in Hair Toxic Mineral Assay. Korean J Fam Med. 2012 Sep;33(5):320-5.
    - ✓ Pacini S, et al. Could cadmium be responsible for some of the neurological signs and symptoms of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Med Hypotheses. 2012 Sep;79(3):403-7.
  - ✓Mold & Mycotoxins
    - ✓ Brewer JH, et al. Detection of Mycotoxins in Patients with Chronic Fatigue Syndrome. Toxins (Basel). 2013 Apr 11;5(4):605-17.
    - ✓ Brewer JH, et al. Chronic Illness Associated with Mold and Mycotoxins: Is Naso-Sinus Fungal Biofilm the Culprit? Toxins (Basel). 2013 Dec 24;6(1):66-80.
    - ✓ Fung F & Clark RF. Health Effects of Mycotoxins: A Toxicological Overview. J Toxicol Clin Toxicol. 2004;42(2):217-34.
  - ✓SIBO
    - ✓ Logan A, et al. Chronic Fatigue Syndrome: Lactic Acid Bacteria May Be of Therapeutic Value. Med Hypotheses. 2003 Jun;60(6):915-23.
  - ✓Dysglycemia and adrenal dysfunction
    - ✓ Zarković M, et al. [Disorder of adrenal gland function in chronic fatigue syndrome]. [Article in Serbian]. Srp Arh Celok Lek. 2003 Sep-Oct;131(9-10):370-4.
  - ✓Food allergies, sensitivities and intolerances

    Loblay RH, Swain AR. The Role of Food Intolerances in Chronic Fatigue Syndrome. The Clinical and Scientific Basis of M.E./CFS. Chapter 58, pg 521-38. 1992.

Still No Luck?

Treat based upon patient symptom picture

Mitochondrial support

- Magnesium (300-600 mg)

  Cox IM, et al. Red blood cell magnesium and chronic fatigue syndrome. Lancet. 1991 Mar 30;337(8744):757-60.

- Coenzyme Q10 (150-600 mg)

  Maes M, et al. 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.

- Lipid Replacement Therapy (1000-6000 mg)

  Nicolson G, et al. Clinical Uses of Membrane Lipid Replacement Supplements in Restoring Membrane Function and Reducing Fatigue in Chronic Diseases and Cancer. DISCOVERIES 2016, Jan-Mar, 4(1): e54.

- Nicotinamide Adenine Dinucleotide (NADH) (10-20 mg)

  Santaella ML, et al. Comparison of oral nicotinamide adenine dinucleotide (NADH) versus conventional therapy for chronic fatigue syndrome. P R Health Sci J. 2004 Jun;23(2):89-93.

  Behan PO, et al. Comparison of oral nicotinamide adenine dinucleotide (NADH) versus conventional therapy for chronic fatigue syndrome. Acta Neurol Scand. 1990 Sep;82(3):209-16.

Mitochondrial Support Cont.

D-Ribose (5 grams tid)

Teitelbaum JE, et al. The use of D-ribose in chronic fatigue syndrome and fibromyalgia: a pilot study. J Altern Complement Med. 2006 Nov;12(9):857-62.

L-carnitine/Acetyl-l-carnitine/Propionylcarnitine (1000-3000 mg)

Vermeulen RC & Scholte HR. Exploratory open label, randomized study of acetyl- and propionylcarnitine in chronic fatigue syndrome. Psychosom Med. 2004 Mar-Apr;66(2):276-82.

Malaguarnera M. Carnitine derivatives: clinical usefulness. Curr Opin Gastroenterol. 2012 Mar;28(2):166-76.

Alpha lipoic acid (300-600 mg)

Nicolson G. Mitochondrial dysfunction and chronic disease: treatment with natural supplements. Altern Ther Health Med. 2014 Winter;20 Suppl 1:18-25.

Kaiser JD. A prospective, proof-of-concept investigation of KPAX002 in chronic fatigue syndrome. Int J Clin Exp Med 2015;8(7):11064-11074.

What Else May Help?

EFA Support (3.6.9) 1-4 grams (10-20 if pain)

Warren G, et al. The role of essential fatty acids in chronic fatigue syndrome. A case-controlled study of red-cell membrane essential fatty acids (EFA) and a placebo-controlled treatment study with high dose of EFA. Acta Neurol Scand. 1999 Feb;99(2):112-6.

Botanical support

Withania somnifera (300-2000 mg) Ashwagandha

Chandrasekhar K, Kapoor J, Anishetty S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. Indian J Psychol Med. 2012;34(3):255-62.

Panax ginseng (500-2000 mg) Asian Ginseng

Kim HG, et al. Antifatigue effects of Panax ginseng C.A. Meyer: a randomised, double-blind, placebo-controlled trial. PLoS One 2013;8(4):e61271.

Botanical Support

- *Glycyrrhiza glabra* (up to 4 grams, limit glycyrrhizic acid to <300 mg)

Baschetti R. Chronic fatigue syndrome and liquorice. N Z Med J. 1995 Apr 26;108(998):156-7.

AARM Reference Review. Treating Adrenal Insufficiency and Hypotension with *Glycyrrhiza* Journal of Restorative Medicine 2012; 1: page 102-6.

- *Ribes nigrum gemmotherapy* (1/2-1 tsp, qd-bid; or 5-10 drops)

Matsumoto H, et al. Effects of blackcurrant anthocyanin intake on peripheral muscle circulation during typing work in humans. Eur J Appl Physiol 2005;94:36-45.

- *Astragalus membranaceus* (500-3000 mg)

Kuo YH. Astragalus membranaceus flavonoids (AMF) ameliorate chronic fatigue syndrome induced by food intake restriction plus forced swimming. J Ethnopharmacol. 2009 Feb 25;122(1):28-34.

Other Integrative Strategies to Consider

- HRT/BHRT
- IM/IV Therapies
- Physiotherapy
- Hydrotherapy
- Acupuncture
- Massage
- CST

Other Integrative Strategies to Consider

- Low-Dose Naltrexone (0.5-4.5 mg hs)
  - Inhibit microglial activation, suppresses activation of NMDA receptors by decreasing the release of glutamate.
  - Increases endorphins
  - ❖ Caveat: not to be used with opiates or synthetic narcotics. Naltrexone blocks opioid receptors.
    - https://ldnresearchtrust.org/content/low-dose-naltrexone-and-chronic-pain-pradeep-chopra-md
    - https://ldnresearchtrust.org/ldn-clinical-trials
    - https://ldnresearchtrust.org/sites/default/files/LDN-2018-Fact-Sheet-USA.pdf
- Organic Germanium (1-3 grams)

  Faloona G & Levine S. The use of organic Germanium in Chronic Epstein-Barr Virus Syndrome (CEBVS): An example of Interferon Modulation of Herpes Reactivation. J. of Orth Med. Vol 3, No 1, 1988.
- Colostrum (5-60 grams)
  - Mero A, et al. Effects of bovine colostrum supplementation on serum IGF-I, IgG, hormone, and saliva IgA during training. J Appl Physiol 1997;83:1144-51.
  - Cesarone MR, et al. Prevention of influenza episodes with colostrum compared with vaccination in healthy and high-risk cardiovascular subjects: the epidemiologic study in San Valentino. Clin Appl Thromb Hemost. 2007 Apr;13(2):130-6.

Take Home Messages

CFS/SEID is a multisystem, multifactorial condition, that when an open heart and scientific inquiry are utilized, patient outcomes dramatically improve.

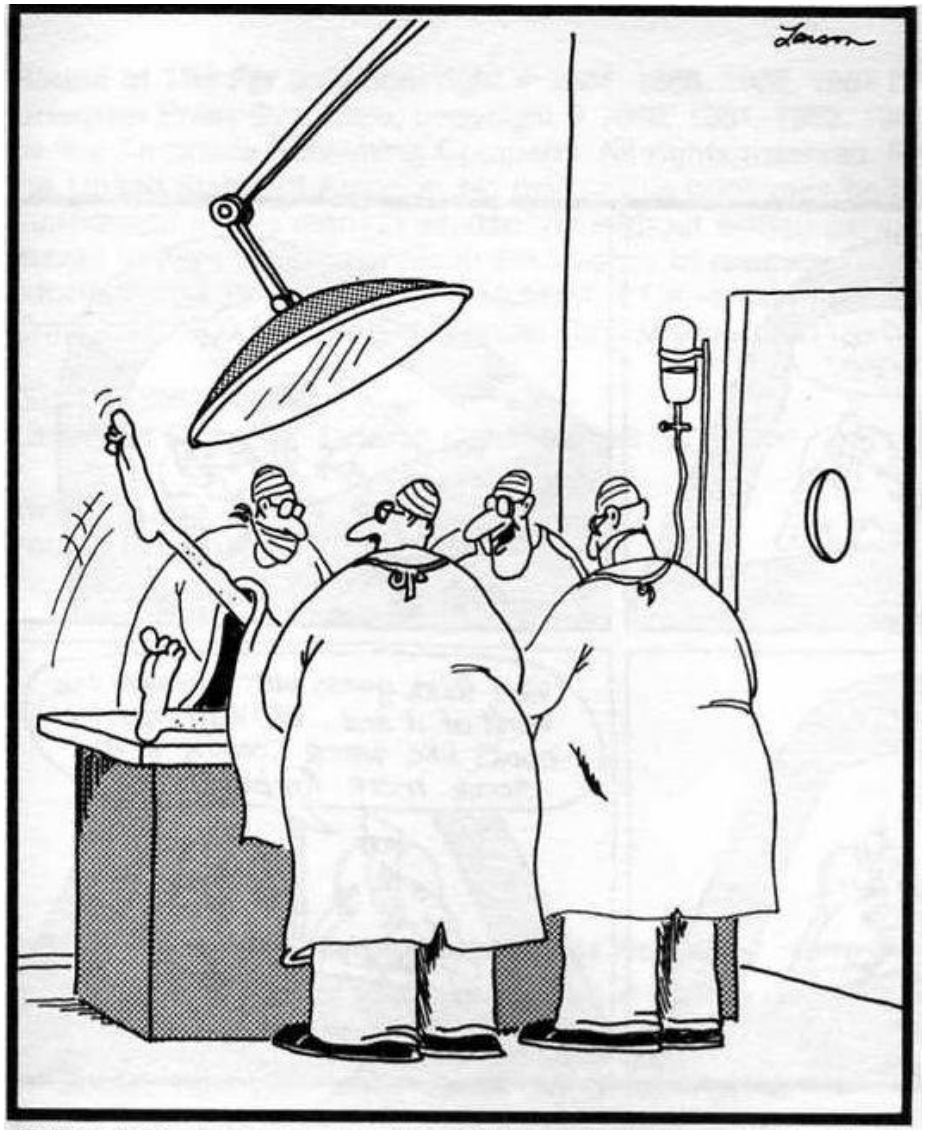
Diagnose first, then treat; don't "shotgun" it.

Consider naturopathic therapeutic order whenever drawing up treatment plans.

Avoid overwhelming.

K.I.S.S.

Thank You!



"Whoa! *That* was a good one! Try it, Hobbs — just poke his brain right where my finger is."