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

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Disclosures

• Born Naturopathic Associates, Inc.
  • Co-owner and medical director.

• Allergy Research Group LLC
  • Director of new product development, product manager and editor-in-chief of Focus Newsletter.
  • Clinical Education
    • Thought Leader

• International Society for Naturopathic Medicine
  • Lead educator and advisor
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)
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

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
Epidemiology

- Prospective cohort study of over 4000 patients in a health maintenance organization, estimated 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.

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.
- The patient has overwhelming fatigue and a number of 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.


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 37.40C/99.30F).
- Arthralgias, but no erythema, effusion, or 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 only reactive hyperplasia. The cervical lymph nodes are most commonly involved, but the axillary lymph nodes may also be
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.


Approximately 70 percent 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

Proposed Etiologies

• Viruses
  • 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 their 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 or HPA axis.
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


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

Smith AK\textsuperscript{1}, White PD, Aslakson E, Yollmer-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 polymorphisms 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
Genetics Always at Play

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

Combinations of single nucleotide polymorphisms in neuroendocrine effector and receptor genes predict chronic fatigue syndrome.
Goetzte BN1, Pernachini C, de Souza Coelho L, Curbaxani B, Maloney FM, 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: 10.2217/14622415.7.3.475
Other Proposed Etiologies

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


Metabolomics features of chronic fatigue syndrome


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Edited by Ronald W. Davis, Stanford University School of Medicine, Stanford, CA, and approved July 13, 2016 (received for review May 11, 2016)

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 (±28) y old (mean ± SEM; range: 21-67 y). Females were 52 (±20) y old (range: 20-47 y). The Karmovsky performance scores were 62 (±32) for males and 54 (±33) 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-experiment 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, microbiate, pyroline-5-carboxylate, riboflavin, branch chain amino acid, carnitine, and mitochondrial metabolism. Area under the receiver operator characteristic curve analysis showed diagnostic accuracies of 95% (95% confidence interval, 84-100%) in males using eight metabolites and 96% (95% CI, 86-100%) in females using 13 metabolites. Our data show that despite the heterogeneity of factors leading to CFS, the cellular metabolic response in patients was homogeneous, statistically robust, and chemically similar to the evolutionarily conserved response to environmental stress known as crisis.

chronic fatigue syndrome | metabolomics | mitochondria | dauer | cell death response

CFS is a complex, multiorgan system disease for which no single diagnostic test yet exists. The disease is characterized by profound fatigue and disability.
Naturopathic Approach to Dx

- 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, ESR, creatine kinase, vitamin D, HbA1c.
- Advanced approach
  - Serum methylmalonic acid, serum + RBC magnesium, ionized calcium, iron.
  - Serum + RBC methylmalonic acid, serum + RBC homocysteine, vitamin B12.
  - Serum + RBC pyridoxal-5-phosphate.
# EBV Interpretation

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<tr>
<th>Marker</th>
<th>Non-Immune</th>
<th>Primary Infection</th>
<th>Past Infection</th>
<th>Reactivation</th>
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<tbody>
<tr>
<td>VCA IgM</td>
<td>N</td>
<td>P</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>VCA IgG</td>
<td>N</td>
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<td>P</td>
</tr>
<tr>
<td>EA IgG</td>
<td>N</td>
<td>P</td>
<td>N</td>
<td>P</td>
</tr>
<tr>
<td>NA IgG</td>
<td>N</td>
<td>N</td>
<td>P</td>
<td>P</td>
</tr>
</tbody>
</table>

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 effectiveness for only two treatments: cognitive behavioral therapy (CBT) and graded exercise therapy (GET).
- Antidepressants
- Sleep hygiene
- Support groups
- Iron therapy in nonanemic patients with low serum ferritin.


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
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
  - **Gemmotherapy**
    - Acer campestre, Juniperus communis, Tamarix gallica
  - **Oligoelements**
My Own Clinical Approach

- Potent multivitamin/mineral
  

- Prebiotics (XOS, GOS, FOS) & Probiotics, Saccharomyces boulardii
  
  

- Return in 6 weeks for A//
  
  - 98% of my patients (over 150 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.


What About Those w/o Infectious Correlations?

- Investigate further

  - Heavy metals
    
    

  - Mold
    

- Other infections

- Dysglycemia and adrenal dysfunction


- Food allergies, sensitivities and intolerances
Still No Luck?

• Treat based upon patient symptom picture
  • Mitochondrial support
    • **Magnesium (300-600 mg)**
    • **Coenzyme Q10 (150-300 mg)**
    • **Lipid Replacement Therapy (1000-6000 mg)**
    • **Nicotinamide Adenine Dinucleotide (NADH) (10 mg)**
Mitochondrial Support Cont.

· **D-Ribose (5 grams tid)**
  

· **L-carnitine/Acetyl-L-carnitine/Propionylcarnitine (1000-3000 mg)**
  


· **Alpha lipoic acid (300-600 mg)**
  

What Else May Help?

• **EFA Support (3.6.9)**


• **Botanical support**

  • *Withania somnifera* (300-600 mg)


  • *Panax ginseng* (500-2000 mg)


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

Other Integrative Strategies to Consider

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

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.”