CENTRAL SENSITIZATION SYNDROMES

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GENERAL INTERNAL MEDICINE

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PRESENTER DISCLOSURES

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Other	

CASE

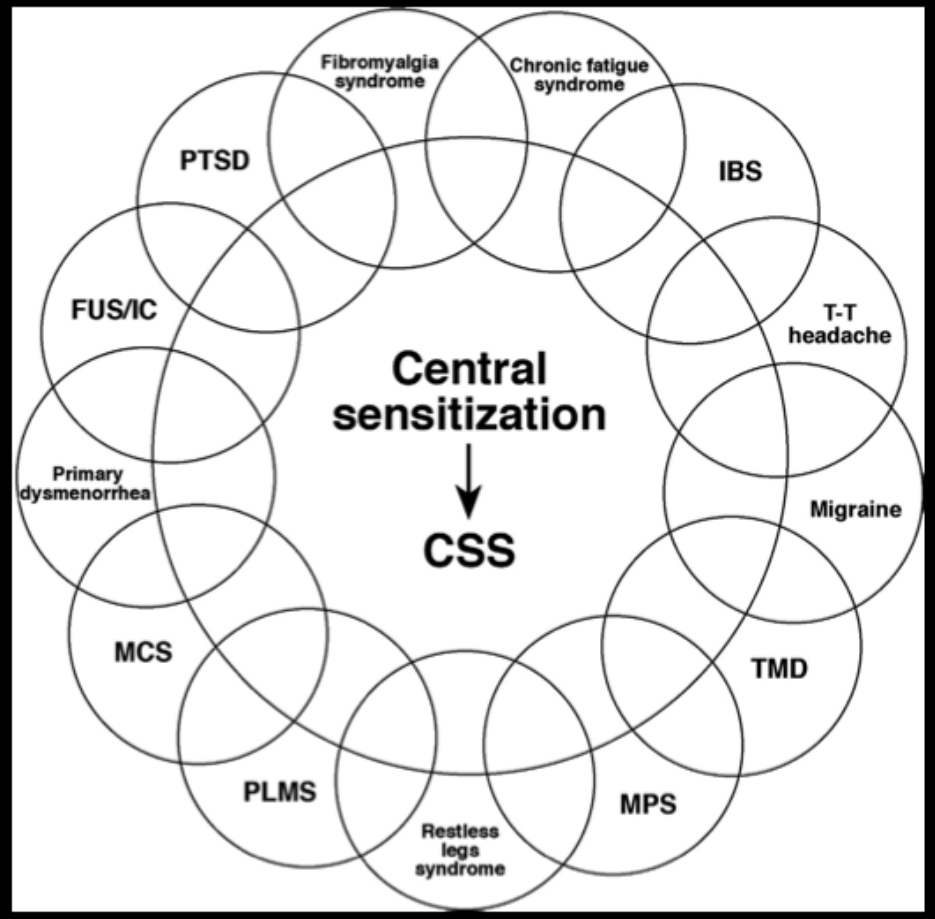
- 45 year old woman presents to your office with a 5 year history of pain all over her body, overwhelming fatigue and brain fog. She is having difficulty managing her work and her household obligations. She was recently in the emergency department for a 1 month history of continuous chest pressure and a sense of being unable to take a full breath. Workup was negative. Prior outpatient evaluations for the chronic symptoms have been inconclusive. She is seeking a second opinion.

WHAT ARE CENTRAL SENSITIZATION SYNDROMES? TERMINOLOGY

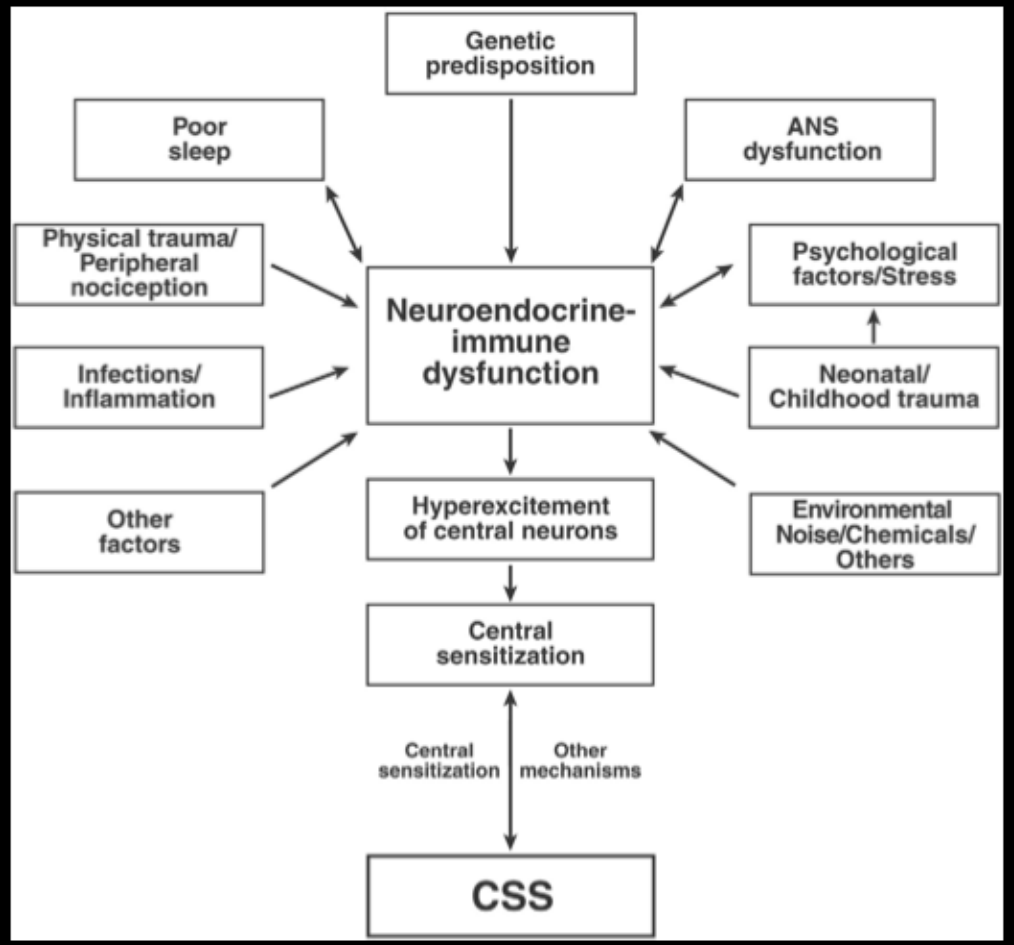
- Chronic fatigue syndrome (systemic exertion intolerance syndrome)
- Myalgic Encephalitis
- Fibromyalgia
- Multiple chemical sensitivities
- Somatoform disorders
- MUPS: Multiple unexplained physical symptoms
- CCS: Central sensitivity syndromes

"Fat File Syndrome"

CURRENTLY PROPOSED MEMBERS OF THE CCS FAMILY



SIMPLIFIED BIOPSYCHOSOCIAL MECHANISMS



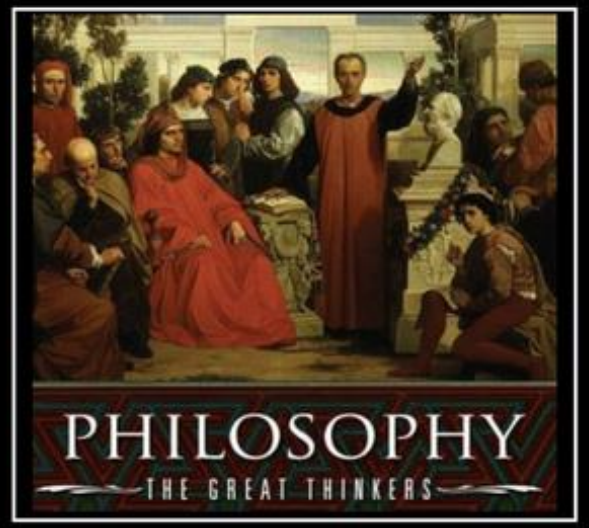
SYMPTOMS

- Fatigue
- Post-exertional malaise (crash)
- Sleep dysfunction
- Pain (arthralgias, myalgias)
- Brain fog, difficulty concentrating
- Dizziness
- Sweating, feeling cold
- Swollen glands, flu like symptoms
- Multiple drug and chemical sensitivities

CHRONIC FATIGUE SYNDROME

What it sounds like I do

What my neighbours think I do



What I think I do

What I want to do

What I should be doing

What I actually do

SCOPE OF THE PROBLEM

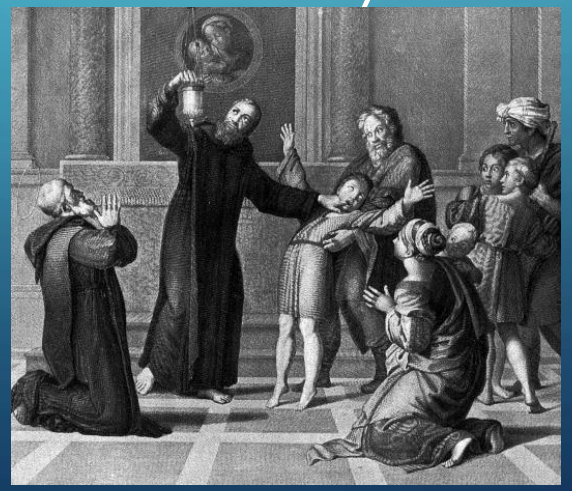
- Central sensitization syndromes are among the most common reasons patients consult a physician
- It is estimated that 2.5 million Americans have ME/CFS with economic costs between 17-24 billion dollars
- Results in considerable psychosocial impairment, work disability and increased health care utilization
- Underrecognized
- Often misconstrued as a diagnosis of exclusion
- Physician and trainee misconceptions still exist (malingering, psychogenic)
- Chronic unexplained symptoms are often experienced as “unsatisfying” for physicians

SCOPE OF THE PROBLEM

- History, physical examination, routine lab investigations, age-appropriate malignancy screening and screening for OSA usually fail to identify an underlying cause
- Patients continue to feel unwell and are not reassured by a negative workup
- The average patient takes 5 years to get diagnosed
- Despite a correct diagnosis, patients continue to feel unsatisfied and continue on their diagnostic and therapeutic quest
- As a group, CSS are some of the least funded diseases

HISTORICAL PERSPECTIVE

- Many diseases were once thought of as psychological until science uncovered their biological mechanisms
- Patients with epilepsy could be forcibly institutionalized until the EEG was able to measure abnormal electrical brain activity
- Multiple sclerosis could be misdiagnosed as hysterical paralysis until brain imaging discovered white matter plaques
- Gastric ulcers were thought to be caused by stress until H. Pylori was discovered



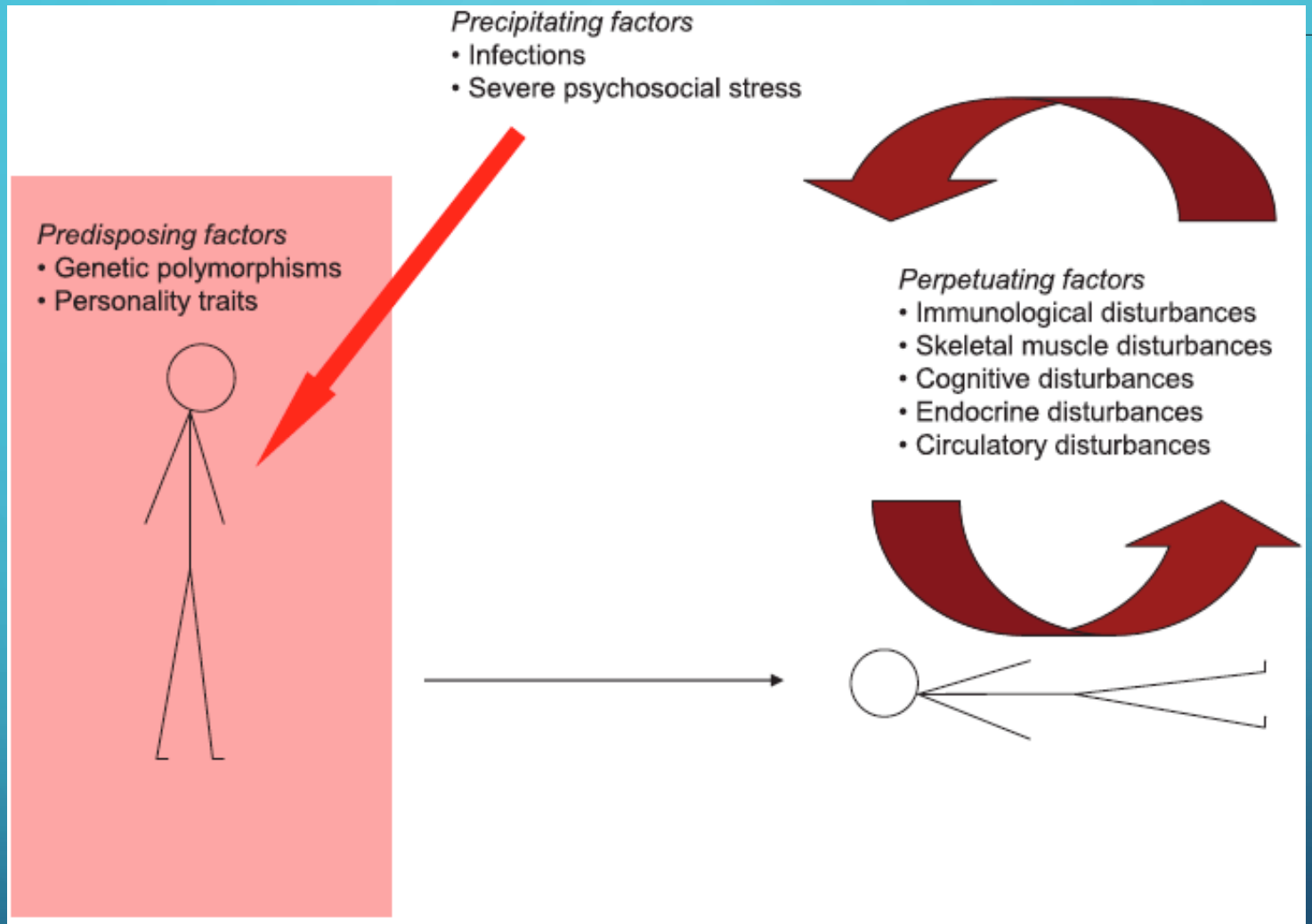


Figure 2. Possible unifying model of the chronic fatigue syndrome based upon differentiation between predisposing, precipitating and perpetuating factors.

Semin Arth Rheum 2007

?ETIOLOGY?

- Humans are “meaning-making machines” and patients need to rationalize their health problems
- If physicians don’t provide an explanatory model to help them understand their illness, patients will create their own or seek one elsewhere
- With the help of the internet, patients often self-diagnose with adrenal fatigue, systemic candidiasis, chronic lyme disease etc.

Research

Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study

Design Prospective cohort study following patients from the time of acute infection with Epstein-Barr virus (glandular fever), *Coxiella burnetii* (Q fever), or Ross River virus (epidemic polyarthritis).
Results Prolonged illness characterised by disabling fatigue, musculoskeletal pain, neurocognitive difficulties, and mood disturbance was evident in 29 (12%) of 253 participants at six months, of whom 28 (11%) met the diagnostic criteria for chronic fatigue syndrome.
Conclusions A relatively uniform post-infective fatigue syndrome persists in a significant minority of patients for six months or more after clinical infection with several different viral and non-viral micro-organisms. Post-infective fatigue syndrome is a valid illness model for investigating one pathophysiological pathway to chronic fatigue syndrome.

- 11% ME/CFS at 6 mo.
- Consistent across infections
- Related to *host response* rather than pathogen

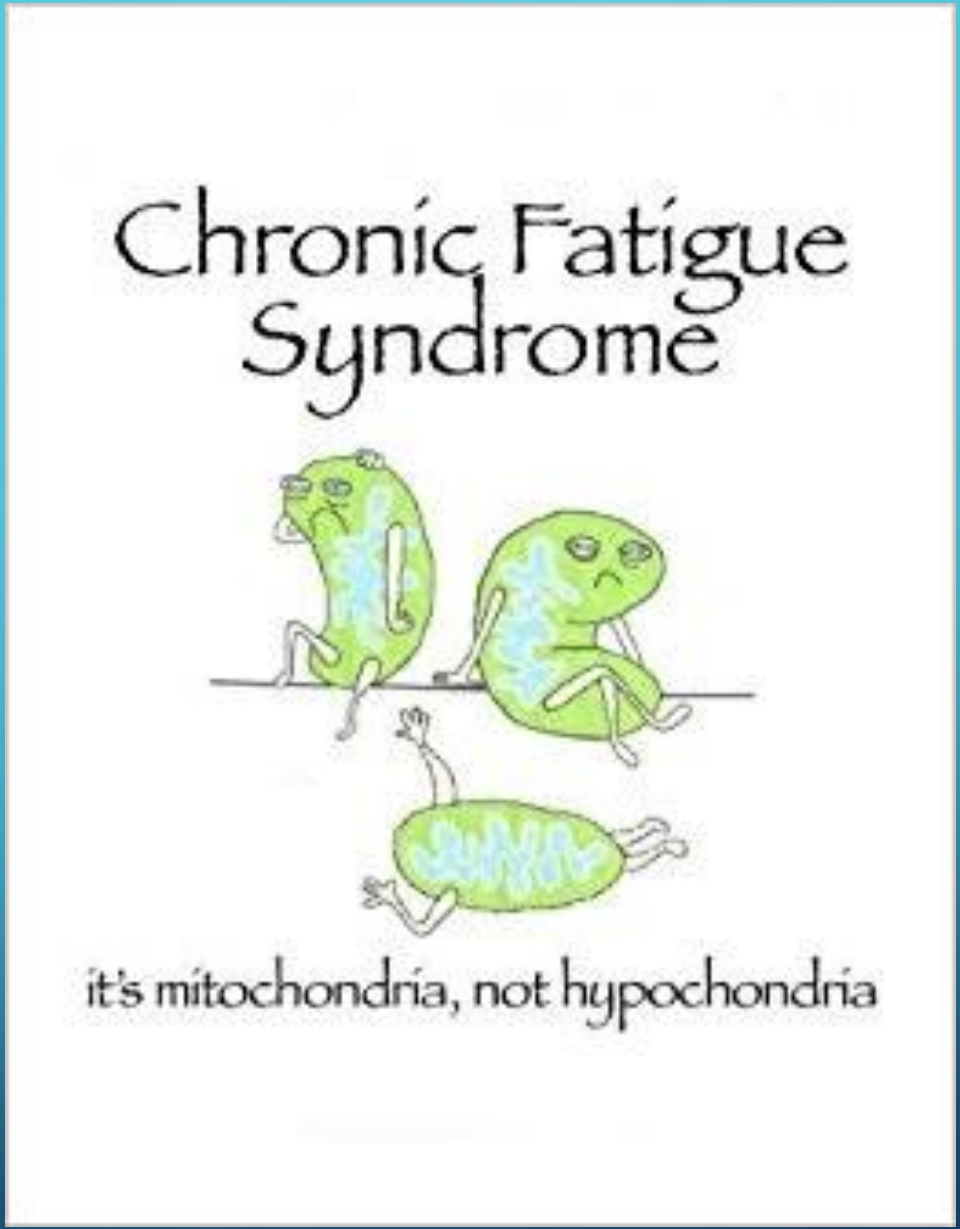
Eur J Clin Invest. 2012 Feb;42(2):186-94

Loss of capacity to recover from acidosis on repeat exercise in chronic fatigue syndrome: a case-control study.

A total of 18 CFS (CDC 1994) patients and 12 sedentary controls underwent assessment of maximal voluntary contraction (MVC), repeat exercise with magnetic resonance spectroscopy and cardio-respiratory fitness test to determine anaerobic threshold.

Resting muscle pH was similar in controls and both CFS patient groups. However, the CFS group achieving normal PCr depletion values showed increased intramuscular acidosis compared to controls after similar work after each of the three exercise periods with no apparent reduction in acidosis with repeat exercise of the type reported in normal subjects. This CFS group also exhibited significant prolongation (almost 4-fold) of the time taken for pH to recover to baseline.

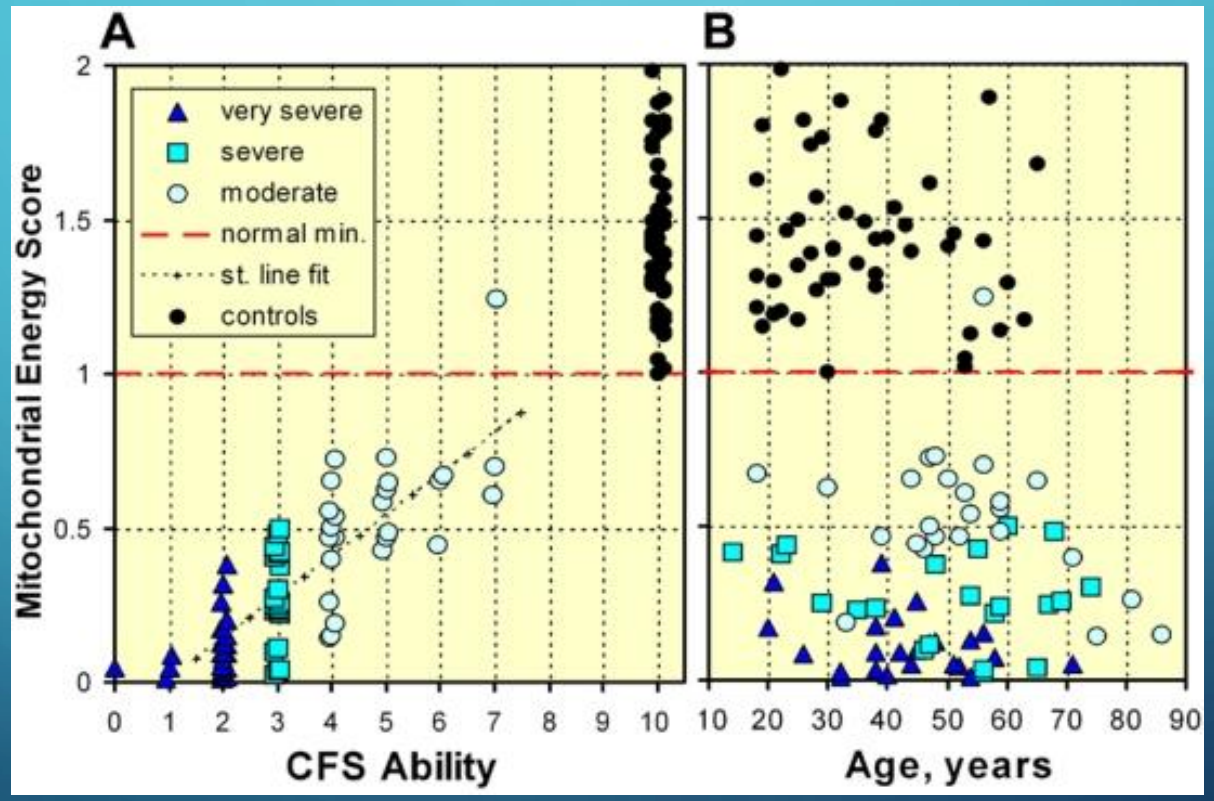
When exercising to comparable levels to normal controls, CFS patients exhibit profound abnormality in bioenergetic function and response to it. Although exercise intervention is the logical treatment for patients showing acidosis, any trial must exclude subjects who do not initiate exercise as they will not benefit. This potentially explains previous mixed results in CFS exercise trials.


Chronic Fatigue Syndrome
it's mitochondria, not hypochondria

Int J Clin Exp Med (2009) 2, 1-16
www.ijcem.com

Chronic fatigue syndrome and mitochondrial dysfunction

Sarah Myhill[1], Norman E. Booth[2], John McLaren-Howard[3]



ATP profile test :"A remarkable correlation is observed between the degree of mitochondrial dysfunction and the severity of illness

Microbiome 2016

Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome

Abstract

Background

Gastrointestinal disturbances are among symptoms commonly reported by individuals diagnosed with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). However, whether ME/CFS is associated with an altered microbiome has remained uncertain. Here, we profiled gut microbial diversity by sequencing 16S ribosomal ribonucleic acid (rRNA) genes from stool as well as inflammatory markers from serum for cases ($n = 48$) and controls ($n = 39$). We also examined a set of inflammatory markers in blood: C-reactive protein (CRP), intestinal fatty acid-binding protein (I-FABP), lipopolysaccharide (LPS), LPS-binding protein (LBP), and soluble CD14 (sCD14).

Conclusions

Our results indicate dysbiosis of the gut microbiota in this disease and further suggest an increased incidence of microbial translocation, which may play a role in inflammatory symptoms in ME/CFS.

Increased nuclear factor-kB and loss of p53 are key mechanisms in Myalgic Encephalomyelitis/chronic fatigue syndrome (ME/CFS)

Medical Hypotheses 79 (2012) 607–613

Activation of immuno-inflammatory pathways

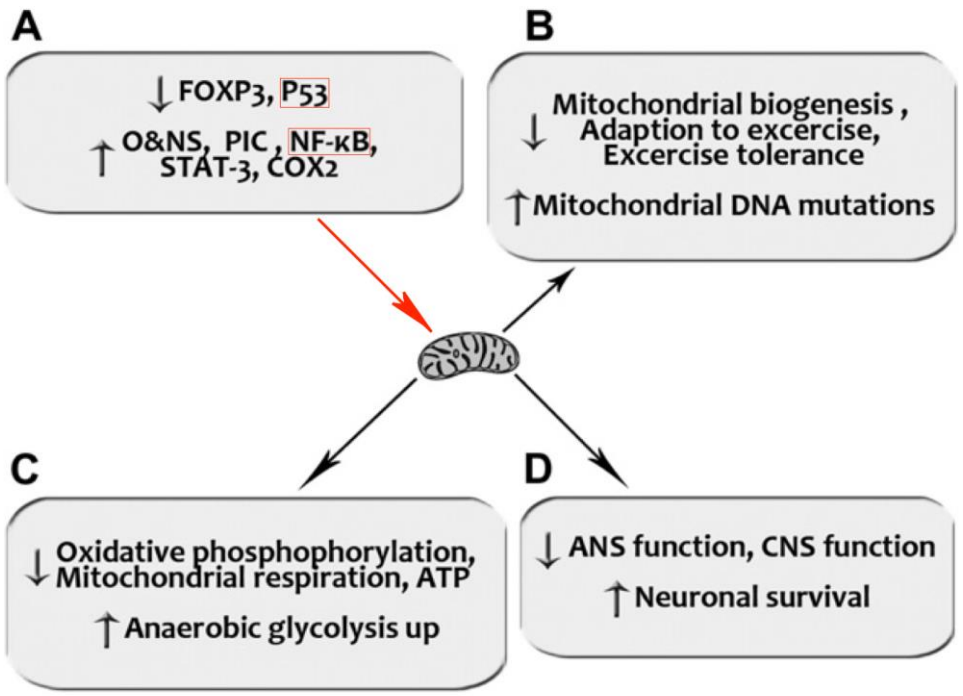


Fig. 2. This Figure shows the functions of p53 in conditions characterized by activation of immuno-inflammatory pathways. FOXP3: forkhead box P3; O&NS: oxidative & nitrosative stress; PIC: pro-inflammatory cytokines; NF-κB: nuclear factor κB; STAT-3: signal transducer and activator of transcription 3; COX2: cyclo-oxygenase 2; ANS: autonomic nervous system; CNS: central nervous system.

Low p53
High NF-ƙB
Low ATP
Mitochondrial dysfunction
Leads to…

- neurocognitive symptoms
- greater muscle fatigability
- reduced exercise capacity due to the inability of mitochondria to increase respiration rates according to increases in demand

Benefit from B-Lymphocyte Depletion Using the Anti-CD20 Antibody Rituximab in Chronic Fatigue Syndrome. A Double-Blind and Placebo-Controlled Study

Øystein Fluge[1]*, Ove Bruland[1,2], Kristin Risa[1], Anette Storstein[3], Einar K. Kristoffersen[4], Dipak Sapkota[1], Halvor Næss[3], Olav Dahl[1,5], Harald Nyland[3], Olav Mella[1,5]

Conclusion: The delayed responses starting from 2–7 months after Rituximab treatment, in spite of rapid B-cell depletion, suggests that CFS is an autoimmune disease and may be consistent with the gradual elimination of autoantibodies preceding clinical responses. The present findings will impact future research efforts in CFS.

RESEARCH ARTICLE

B-Lymphocyte Depletion in Myalgic Encephalopathy/ Chronic Fatigue Syndrome. An Open-Label Phase II Study with Rituximab Maintenance Treatment

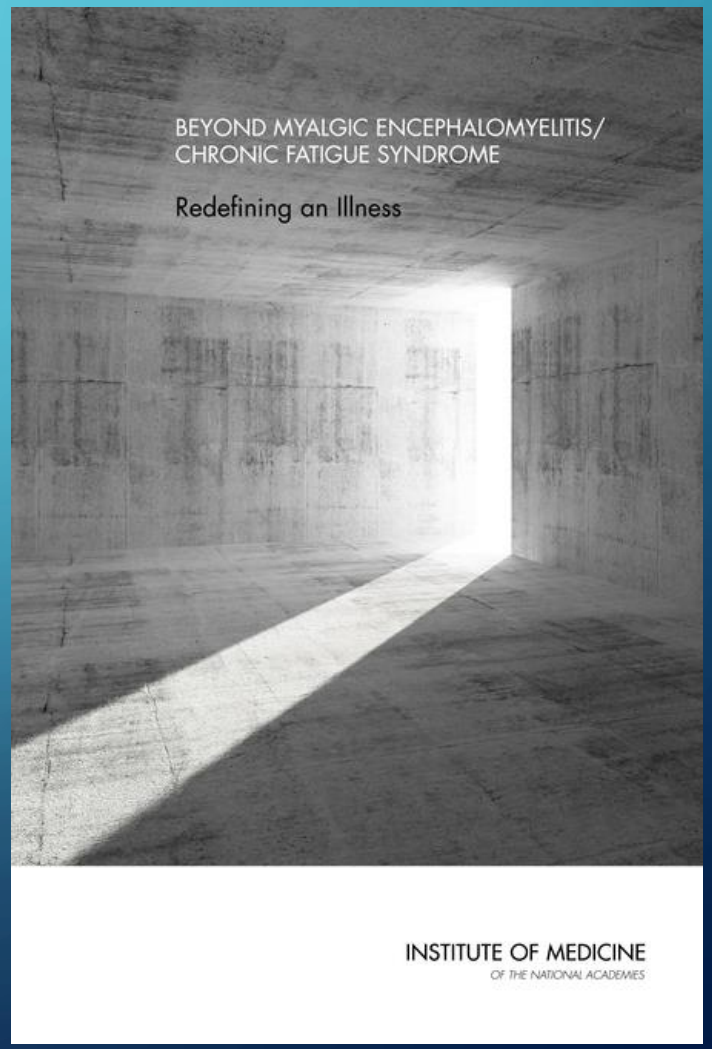
Øystein Fluge[1]*, Kristin Risa[1], Sigrid Lunde[1], Kine Alme[1], Ingrid Gurvin Rekeland[1], Dipak Sapkota[1,2], Einar Kleboe Kristoffersen[3,4], Kari Sørland[1], Ove Bruland[1,5], Olav Dahl[1,4], Olav Mella[1,4]*

“Clinically significant responses were seen in 18 out of 28 patients (64%) receiving rituximab maintenance treatment.”

REPORT BRIEF FEBRUARY 2015

Beyond Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome

Redefining an Illness



SYSTEMIC EXERTION INTOLERANCE SYNDROME

- The brief of the report was 3 fold:

  1- to develop evidence-based new diagnostic criteria for CFS/ME

  2- recommend a new name for the disorder

  3- to develop an outreach strategy to disseminate these changes to clinicians and the public

- Why the name change? Chronic fatigue syndrome gives a negative perception of the illness by trivializing the condition
- Primary message is that SEID is a serious, chronic, complex and systemic disease
- SEID dramatically limits the activities of affected patients
- The goal of the report is to reposition SEID as a legitimate disease

SYSTEMIC EXERTION INTOLERANCE DISEASE (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 6 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 ME/CFS (SEID) should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.

Annals of Internal Medicine

Anthony L. Komaroff, MD
Brigham and Women's Hospital, Harvard Medical School
Boston, Massachusetts

Ann Intern Med. 2015;162:871-872. doi:10.7326/M15-0647

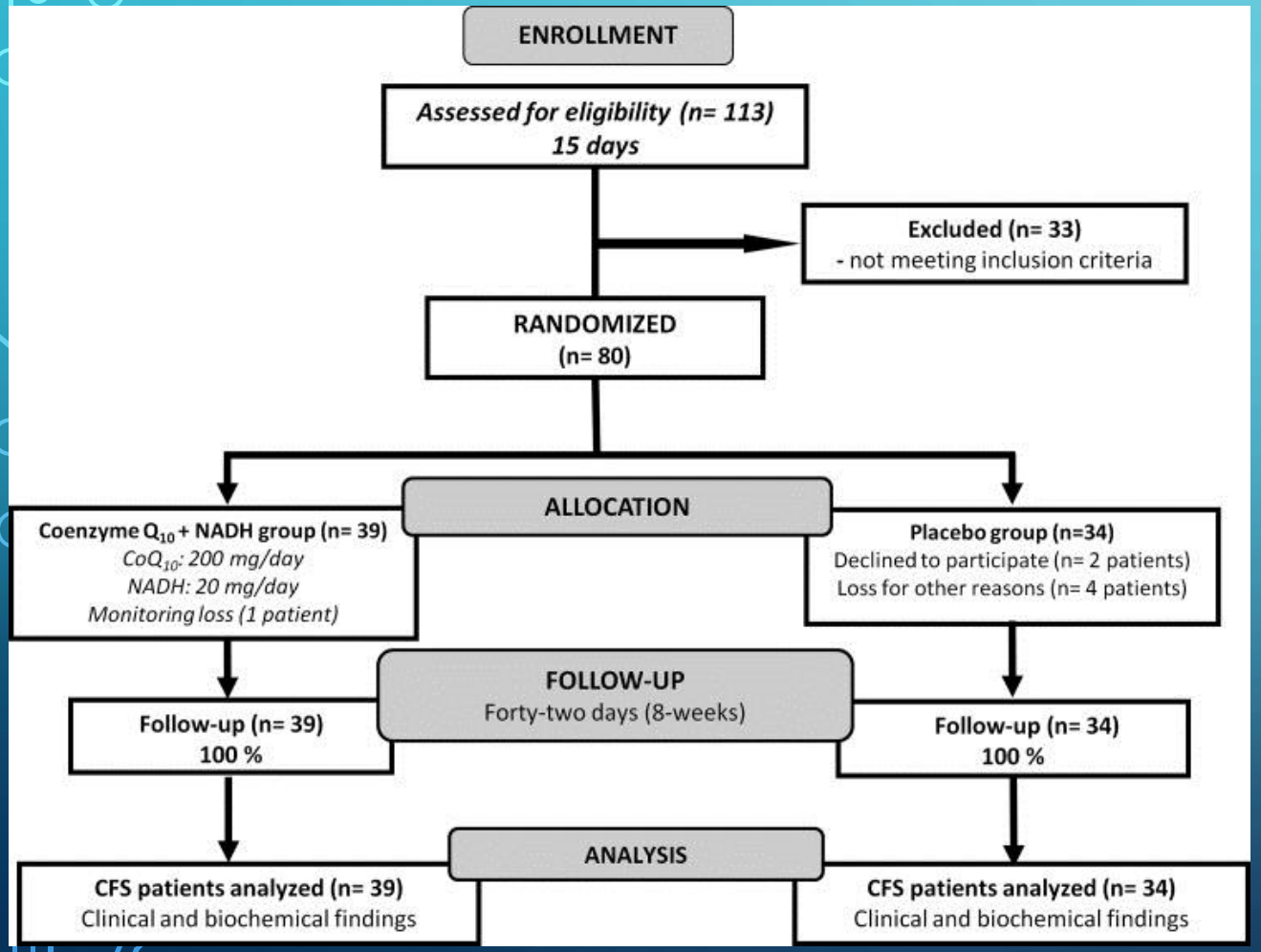
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Real Illness

TREATMENT

- Current treatments for CCS are mostly symptomatic and modestly effective
- Low recovery rate
- Best evidence for cognitive behavioral therapy, graded exercise therapy (2016 Cochrane Review)
- Adaptive pacing therapy was not found to be more effective than CBT/GET in the PACE Trial (2011)
- Perhaps all chronic disease patients could learn to cope better with CBT, but a positive response does imply an effect on the underlying disease mechanisms.

Antioxid Redox Signal. 2015 Mar 10;22(8):679-85. doi: 10.1089/ars.2014.6181. Epub 2014 Dec 18.

Does oral coenzyme Q10 plus NADH supplementation improve fatigue and biochemical parameters in chronic fatigue syndrome?



"A significant improvement of fatigue showing a reduction in fatigue impact scale total score ($p<0.05$) was reported in treated group versus placebo. In addition, a recovery of the biochemical parameters was also reported. NAD+/NADH ($p<0.001$), CoQ10 ($p<0.05$), ATP ($p<0.05$), and citrate synthase ($p<0.05$) were significantly higher, and lipoperoxides ($p<0.05$) were significantly lower in blood mononuclear cells of the treated group"

WHAT I DO NOW

- After an appropriate but limited workup, I diagnose CCS/SEID if diagnostic criteria a met
- Legitimize their symptoms
- Give them a handout explaining in layman's terms what are CCS/SEID

  http://med-fom-tcmp.sites.olt.ubc.ca/files/2015/10/Central-Sensitivity-Syndromes-CSS.pdf
- Focus on self-management (http://www.cfidsselfhelp.org)
- Address sleep and pain issues through both pharmacological and non-pharmacological modalities
- Listen and support patients
- Acknowledge scientific uncertainty

THERAPEUTIC RELATIONSHIP

- Redirect focus from continuously searching for a cause of their symptoms
- Redirect focus from cure
- Provide reassurance
- Focus on coping/adapting
- Encourage work and social activities
- Avoid iatrogenesis

QUESTION 1

CFS/SEID is primarily a psychological illness which is why cognitive behavioral therapy and graded exercise therapy are helpful.

A- TRUE

B- FALSE

QUESTION 2

Which of the following symptoms is NOT a key diagnostic criterion for SEID:

A- Post-exertional malaise

B- Dizziness (ie orthostatic intolerance)

C- Pain

D- Brain fog (ie cognitive impairment)

SYSTEMIC EXERTION INTOLERANCE DISEASE (SEID)

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TAKE HOME MESSAGES

- CFS/SEID is a serious, chronic, complex systemic disease that can profoundly affect the lives of patients
- The disease is not a “psychological problem”, however comorbid psychiatric conditions occur in some patients and need to be appropriately diagnosed/treated
- Etiology remains unclear, however there is emerging evidence that there are immunological, inflammatory and mitochondrial disturbances at play
- Mainstay of therapy for CFS/SEID is CBT and GET, however new treatment options to come in the future
- Telling patients you are tired too and that there is nothing wrong with them will compound their suffering