Fatigue in Medicine
Chronic Fatigue Syndrome
The Chicken and The Egg

The germ is nothing; the terrain is everything.

Attributed to Louis Pasteur on his death bed, 1985

Fatigue in Medicine
Definition

• **What is fatigue?**
• Why do up to 20% of general medical office visits involve fatigue?
Interactive

- Compared to healthy people who have a vitality score of 60-70, what is the vitality score of patients with severe fatigue or CFS/ME?
  - A. 50-60
  - B. 40-50
  - C. 30-40
  - D. 10-20

Impact of Fatigue on Function

<table>
<thead>
<tr>
<th></th>
<th>Vitality Score**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy People</td>
<td>60-70</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>29</td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>48</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>43-52</td>
</tr>
<tr>
<td>ME/CFS/SEID</td>
<td>15-20</td>
</tr>
</tbody>
</table>

From SF 36 form

Fatigue in Medicine

Definition

- Lassitude or weariness resulting from either bodily or mental exertion. 1719 De Foe Carusae: “A Day of great fatigue to me.”
- The perception of the inability to work after a reasonable period of recovery (JFJ 1999/2014)
- Subjective: different for each person
- Acute versus chronic
- Associated with many illnesses
Interactive Nomenclature

- What is the best name for the illness?
  - A. Myalgic encephalitis
  - Chronic Fatigue Syndrome
  - Dropsy
  - Severe exertional intolerance disease
  - Chronic Ebstein Barr disease

Fatigue in Medicine Nomenclature

- Vapors: Jane Austin
- Neurasthenia: Mark Twain
- Cytokine syndrome: Japan
- Hyperventilation syndrome
- Acute neuromyasthenia: Britain
- Chronic Epstein-Barr virus infection: U.S.A.
- Post viral fatigue syndrome
- Stealth infection syndrome
- Chronic Fatigue Syndrome
- Myalgic encephalomyelitis (ME)/CFS

Fatigue in Medicine Approaching Fatigue

- History for THAT patient
  - What is usual output of energy?
  - What is a typical day?
  - What percent have they lost?
- Ways to quantitate or monitor
  - Treadmill testing
  - Chronologic graphics
  - SF-36 Form

Day of Month

0 = good
10 = bad
Fatigue in Medicine

Known Causes

- Endocrine: thyroid disorders
- Neoplastic: CML, Lung Ca; chemotherapy
- Gastrointestinal: Adult coeliac disease (Al Ph Th 2005)
- Metabolic: periodic paralysis; drug use
- Psychiatric: depression, dysthymia
- Infectious: toxoplasmosis, HIV, EBV
- Vascular: CHF; Giant-cell arteritis
- Immunologic: Rheumatoid arthritis
- Nutritional: starvation

Fatigue in Medicine

CFS: Difficult Differential Diagnosis

- Brucellosis
- Periodic Fevers:
  -- Familial Mediterranean Fever
  -- Muckle Wells
- Seasonal affective disorder
- Periodic paralysis
- Cytomegalovirus infection
- Hypothyroidism
- Atopy
Fatigue in Medicine
Definition of Chronic Fatigue Syndrome

• **Major Criteria***
  - New onset
  - No previous history
  - Does not resolve with bed rest
  - Activity reduction ≥50%
  - Exclusion of all other illnesses
  - Exclusion of all psychiatric disorders (+)


Fatigue in Medicine
Chronic Fatigue Syndrome: Criteria

• **Minor Criteria***
  - Low-grade fever
  - Sore throat
  - Painful lymph nodes
  - Generalized weakness
  - Muscle discomfort
  - Generalized (new) headaches
  - Migratory arthralgias


Redefing an Illness
SEID Diagnosis Requirements

Three of These Symptoms
1. Substantial reduction of crucial activities
2. Post exertional Malaise
3. Unrefreshing sleep

At Least One of These
1. Cognitive impairment or
2. Orthostatic intolerance

Institute of Medicine Recommended Diagnostic Criteria

CFS Epidemiology

- Women:men 2:1
- 25-40 years of age
- Worldwide but occurs in clusters: i.e. Incline Village 1985
- As frequent as new diabetes in Topeka, median age 35
- Rural Australia 37/100,000
- 7% CFS in Persian Gulf War Vets (n=1549 in Kansas)*
  - 35% had multisystem complaints
- CFSers had more diarrhea, skin rashes, and night sweats
- Dutch study of Cambodian Veterans (fatigue severity index)**
  - 19% full recovery
  - 20% improvement
  - 57% same complaints
- Hong Kong (traditional Chinese)**
  - Trudie Chalder fatigue scale
  - 1994 CDC criteria
  - 65/583 (6.4%) met CFS criteria

*Steel et al. AACFS 2001; ** de Vries et al AACFS 2001

Pathogenesis of CFS

<table>
<thead>
<tr>
<th>Onset Parameter</th>
<th>Total CFS N (%)</th>
<th>Holmes Criteria N (%)</th>
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</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>376 (24.3)</td>
<td>207 (48.0)*</td>
</tr>
<tr>
<td>Unknown origin</td>
<td>237 (15.3)</td>
<td>206 (33.6)*</td>
</tr>
<tr>
<td>Flu-like illness</td>
<td>213 (13.8)</td>
<td>47 (7.6)*</td>
</tr>
<tr>
<td>Viral infection</td>
<td>170 (11.0)</td>
<td>35 (5.7)*</td>
</tr>
<tr>
<td>Other infection (bacterial)</td>
<td>163 (10.5)</td>
<td>23 (3.7)*</td>
</tr>
<tr>
<td>Stress</td>
<td>152 (9.8)</td>
<td>33 (3.3)*</td>
</tr>
<tr>
<td>Mononucleosis</td>
<td>148 (9.3)</td>
<td>31 (9.0)**</td>
</tr>
<tr>
<td>Motor vehicle accident</td>
<td>140 (6.7)</td>
<td>27 (4.4)**</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>101 (6.4)</td>
<td>16 (2.5)**</td>
</tr>
<tr>
<td>Travel stress</td>
<td>98 (6.4)</td>
<td>31 (5.0)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>79 (5.1)</td>
<td>14 (2.3)**</td>
</tr>
<tr>
<td>Hepatitis B, B, C, D</td>
<td>75 (4.8)</td>
<td>20 (3.2)</td>
</tr>
<tr>
<td>Gastrointestinal infections</td>
<td>59 (3.8)</td>
<td>22 (3.6)</td>
</tr>
<tr>
<td>Postpartum</td>
<td>58 (3.8)</td>
<td>23 (5.0)</td>
</tr>
<tr>
<td>Surgery</td>
<td>47 (3.0)</td>
<td>10 (2.9)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>45 (2.8)</td>
<td>10 (2.4)</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>22 (1.4)</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>21 (1.4)</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>20 (1.3)</td>
<td>2 (0.3)***</td>
</tr>
<tr>
<td>CMV</td>
<td>18 (1.2)</td>
<td>6 (1.0)</td>
</tr>
<tr>
<td>Mental trauma</td>
<td>10 (0.6)</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>11 (0.7)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Intoxication</td>
<td>10 (0.6)</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>5 (0.3)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Neurological problems</td>
<td>4 (0.3)</td>
<td>2 (0.3)</td>
</tr>
</tbody>
</table>

Note: Holmes were compared with the Fukuda criteria. Statistical method = p* analysis; P-values: * p<0.05; ** p<0.01; *** p<0.001.
Fatigue in Medicine
CFS: Pathophysiology

• Role of EBV
  - Persistence of certain antibodies
  - Viral capsid antigen
  - Nuclear antigen
  - Early antigen

• Role of HHV-6
  - Presence of viremia in 60% (Knox et al-1998)
  - Persistence of IgM
  - Isolation from CFS (Levine S, 2001 AACFS-Seattle)

• Hypothalamic-adrenal-pituitary axis
  - Immune dysregulation (controversial)
  - Neuromediated hypotension
  - Role of CRH dysregulation

• Neurological: Abnormal MRI and SPECT
• Immunologic: <NK Cell # and Dysfunction

Fatigue in Medicine
CFS: RNA Dysregulation


Chronic Fatigue Syndrome
Degradation of RNA

Immunosciences Lab, Inc. Beverly Hills, CA 90211
Dysregulation of 2-5A: An Antiviral Response

The 2-5A synthetase/ribonuclease L (RNase L) pathway in normal subjects (left) and in patients with chronic fatigue syndrome (right)

What Do We Know About LMW Rnase L*

- LMW produced from proteolytic cleavage of 80 kDa monomeric protein (? Calpain for some cleavage)
- Most commonly found in monocytes
- LMW hydrolyzes poly(U) but not poly(C)
- LMW is an inactive heterodimer with Rnase activity
- 2-5A binds more avidly to LMW than HMW
- VO2max inversely related to elevated RNaseL
- LMW associated with a 26kDa actin fragment**
- May block apoptotic pathways
- May block ion channels

*Herst CF et al. AACFS 2001 Seattle Abst:163
Grey and White Matter Changes

![Brain MRI images](image)


**Interactive**

What would be a central abnormality in SEID that may serve as a biomarker?

A. MRI abnormalities  
B. Antibody to HHV-6  
C. NK Cell depletion  
D. RNAse dysfunction  
E. None of the above

**Fatigue in Medicine**

**CFS Case Presentation: TT#1**

- **HISTORY.** TT is a 43-year-old lawyer from Philadelphia who presents with a one-year history of fatigue, muscle pain, post-exercise fatigue, insomnia, short term memory defects, serial task dysfunction and decreased libido. There is no significant past medical history save mild L-S spine disease.
- **PHYSICAL EXAM.** Gait is measured. Pharynx red with tender cervical adenopathy. Poor performance of serial 7’s.
- **LAB.** □ CD4+ / □ CD8+, □ NK Cells. □ EBV antibodies to VCA and EBNA
Fatigue in Medicine
CFS Case Presentation: TT#2

- Course. Trials of multiple medications including Klonopin, Florinef, Co-enzyme Q, NDAD produced little improvement.
- Exercise tolerance increased in the summer months
- Cognition not improved
- Prognosis guarded
- Disability through Law Firm otherwise would need to apply for SS disability

Fatigue in Medicine
CFS: Reported Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>100</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>90</td>
</tr>
<tr>
<td>Headache</td>
<td>90</td>
</tr>
<tr>
<td>Sore Throat</td>
<td>85</td>
</tr>
<tr>
<td>Tender lymph nodes</td>
<td>80</td>
</tr>
<tr>
<td>Muscle aches</td>
<td>80</td>
</tr>
<tr>
<td>Joint aches</td>
<td>75</td>
</tr>
<tr>
<td>Feverishness</td>
<td>75</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>70</td>
</tr>
<tr>
<td>Psychiatric problems</td>
<td>65</td>
</tr>
<tr>
<td>Allergies</td>
<td>55</td>
</tr>
<tr>
<td>Abdominal cramps</td>
<td>40</td>
</tr>
<tr>
<td>Rash</td>
<td>10</td>
</tr>
<tr>
<td>Rash</td>
<td>10</td>
</tr>
</tbody>
</table>

Fatigue in Medicine
CFS: Workup

- ESR
- CBC
- Chemistries
- Hepatitis C, B
- CD4/CD8
- Cortisol
- RNaseL
- Bartonella Ab
- Lyme Serology/PCR
- ? EBV DNA
- Thyroid panel
- ? SF36 or another health instrument
Fatigue in Medicine
CFS: Target Organs

- Brain
- Pharynx
- Lymph nodes
- Ovaries
- Muscles
- Joints

Fatigue in Medicine
Management of CFS
SEID

Fatigue in Medicine
CFS: Principles of Management

- Support and attention to symptomatic treatment
- Graded monitored exercise*
- Cognitive behavior therapy
- Evaluation of new symptoms as a new disorder
- Implement Social Security Disability Application
- Physical therapy
- Acupuncture
- Psychotherapy
- Drug therapy

Pharmacologic Therapy-1

• Psychotropic drugs
• Drugs targeting endocrine dysfunction
• Immunodulating and Antiviral Drugs
  — Ampligen: polyI polyC
• Antibiotics
  — Mycoplasma fermentans hypothesis
• Antivirals
  • Thymidine kinase inhibitors
    — ? Control of HHV-6
    — Other antivirals, antiEBV
• Other drugs

Pharmacologic Therapy-2

• Treat the fibromyalgia
  — simple analgesics
  — Lyrica
  — opiates
• Non-steroidal antiinflammatory agents
• Psychoactive agents
  — Tricyclic antidepressants
  — Serotonin uptake inhibitors
  — Others
• Volume expanders
• Stimulants: modafinil + others
• Herbal remedies: coenzyme Q

Pharmacologic Therapy-3

• Poly-PolyC (Ampligen)
  — ongoing trials AMP-516
  — cost recovery trial AMP-511
• NADH (ENADA)
• New Agents
  — Anti dementia agents
  — Interferon agonists and antagonists
  — Role of glucocorticoids
    • Safe doses?
• Immunomodulator
Fatigue in Medicine
CFS: Disability Considerations

• CDS Code 780.1: CFS
• Role of legal counsel
• Meticulous attention to documentation
• Variability of judges
• Necessity for patience, patience, patience and then patience

Fatigue in Medicine
CFS: Desirable Physician Attitudes

• Unqualified acceptance of validity of patient’s illness
• Willingness to listen to patient’s view
• A positive attitude to therapy
• Ability to tolerate slow progress and setbacks
• Willingness to give patient credit for success
• Knowledge of holistic approaches (JFJ)

Levine PH. What we know about chronic fatigue syndrome and its relevance to the practicing physician.
American Journal of Medicine 1998;105(Suppl 5A):100S-103S

Fatigue in Medicine
CFS: Epidemiology/Pathophysiology

• Bottom Line
  – No question that CFS follows certain acute viral infections (60%), particularly EBV.
  – Other viruses are likely involved
  – Non-infectious stressors trigger a significant proportion of the cases.
    • Motor vehicle trauma
    • Closed head injury
    • Emotional trauma
Gene expression in gradual onset CFS

CFS/SEID
Additional Approaches from Clinical Trials

CFS: Cognitive Behavior Model

Wallman KE et al. Randomized controlled trial of graded exercise in chronic fatigue syndrome. MJA 2004; 180:444-8

Fatigue in Medicine
Chronic Fatigue Syndrome
The Future

• Advances in pathogenesis
• Advances in staging
• Advances in drug therapy
• Advances in genomics/prevention
• Advances in medical acceptance
• Advances in social acceptance
Candidate Genes: Fatigue in Sjorgrens
Rheumatology 2014

- APOA2 Apolipoprotein A2
- EIF2BF Eukaryotic initiation factor
- EIF4G1 EIF4G1
- SLC5A40 SLC5A40
- CRAT Carnitine acetyltransferase
- MRPL23 Mitochondrial ribosomal protein
- PEX16 PEX16
- COX8A COX8A
- COX11 Cytochrome oxidases
- ABCD4 ATP binding cassette transporter
- PKNI Protein kinase C superfamily

Are Myalgic Encephalomyelitis and chronic fatigue syndrome different illnesses? A preliminary analysis

Major References

- Leonard A Jason et al. J Health Psychology 2014: Subset of patients with ME have more functional impairment

Fatigue in Medicine
Chronic Fatigue Syndrome
The Chicken and The Egg

The germ is nothing; the terrain is everything.

Attributed to Louis Pasteur on his death bed, 1985
You Don’t Know the Time or the Place!!

Acute disease becomes chronic.