The Biology of Chronic Fatigue Syndrome

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Simcox-Clifford-Higby Professor of Medicine, Harvard Medical School
Is Chronic Fatigue Syndrome Real?

CFS is a syndrome defined just by symptoms, not by objective abnormalities. Are the symptoms imaginary, and not real?

• Are there objective biological markers that are abnormal in CFS?

• Do we understand the pathogenesis of CFS?
International Research/Recognition

- Intramural and extramural research programs at NIH and CDC
- Many international research conferences
- Over 4,500 peer-reviewed publications
- CDC survey of U.S. physicians finds that today over 40% have seen patients with CFS in their practices
Causes of Fatigue in a Primary Care Practice

- Depression
- Overwork
- Organic Diseases
- Chronic Fatigue Syndrome
CDC Case Definition of Chronic Fatigue Syndrome

Severe fatigue that persists or relapses for > 6 months, of new or definite onset, not substantially alleviated by rest, resulting in substantial reduction in activities;

AND four or more of the following symptoms are currently present for > 6 months:

- Impaired memory/concentration
- Sore throat
- Multi-joint pain
- Unrefreshing sleep
- Neck/axillary adenopathy
- Muscle pain
- New headaches
- Post-exertional malaise

AND does not have active medical condition to explain the chronic fatigue, nor any psychosis, melancholic depression, substance abuse, dementia, or anorexia nervosa/bulimia

Who Are The Patients?

- **Age**: Mid-30’s (5-65 years)
- **Sex**: 65% female
- **Socioeconomic**: Middle-class, but more common among African-American/Latino minority populations on population-based surveys
- **Education**: 50% college graduates in office-based samples
- **Severity**: 50% intermittently bedridden/shut-in
- **Duration**: 14 years (4-36 years) in our patients
Sudden Onset

In 80-90% of our patients, the chronic fatigue syndrome started suddenly with a “flu”, “virus”, “bad cold”:  

- Sore throat
- Cough
- Rhinorrhea
- Swollen glands
- Myalgias
- Fever
- Headache
- Diarrhea
Why Isn’t Chronic Fatigue Syndrome “Just” Depression?

- Differences in objective neuroendocrine studies
- Results of treatment studies
- Results of formal psychiatric assessment
Hypothalamic-Pituitary Abnormalities in Chronic Fatigue Syndrome

ACTH release after stimulation

Prolactin release after stimulation

CFS Depression

Hypothalamic-Pituitary Abnormalities In Chronic Fatigue Syndrome

ACTH release after stimulation

Prolactin release after stimulation

CFS   Depression

The Biology of CFS Involves...

- The brain and autonomic nervous system
- Chronic activation of the immune system
- Oxidative/nitrosative stress and abnormalities in energy metabolism
- Possible role of infectious agents in triggering and perpetuating the illness
Studies of the Brain and Autonomic Nervous System
Evidence of CNS Involvement in CFS

- **MRI:** Punctate areas of high signal in white matter
- **SPECT:** Areas of reduced signal
- **Cognition:** Impairments in information processing speed, memory and attention - not explained by concomitant psychiatric disorders
- **Autonomic dysfunction:** Impaired sympathetic and parasympathetic function, 30-80%
- **Sleep disorders:** Disrupted sleep architecture
- **Neuroendocrine dysfunction:** Impairment of multiple limbic-hypothalamic-pituitary axes (involving cortisol, prolactin, & growth hormone) and serotonin (5-HT) system
## Hyperintense Signal In White Matter On Magnetic Resonance Imaging

<table>
<thead>
<tr>
<th></th>
<th>Epidemic</th>
<th>Endemic</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>71/91 (78%)</td>
<td>42/53 (79%)</td>
<td>10/47 (21%)</td>
</tr>
</tbody>
</table>

P < 0.000000001

Interobserver agreement 97% between 3 neuroradiologists

# SPECT Scan Results:
**Mid-Cerebral Uptake Index in 4 Groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>CFS (N=45)</th>
<th>AIDS (N=27)</th>
<th>Depression (N=14)</th>
<th>Healthy (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Index</strong></td>
<td>.67 ± .05</td>
<td>.65 ± .05</td>
<td>.73 ± .16</td>
<td>.72 ± .10</td>
</tr>
</tbody>
</table>

P<0.006

# MRI/SPECT Studies in CFS: Results of Studies

## # of Patients in Yes vs. No Studies

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>375</td>
</tr>
<tr>
<td>NO</td>
<td>161</td>
</tr>
</tbody>
</table>

## # of Studies

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>12.5</td>
</tr>
<tr>
<td>NO</td>
<td>4.5</td>
</tr>
</tbody>
</table>

### Studies

- MRI/SPECT Studies in CFS: 
- Results of Studies
Autonomic Abnormalities in CFS: Results of Studies

# Yes vs. No Studies

# of Patients in Yes vs. No Studies
Studies of Cognition in CFS

- IQ “normal”, but unclear if IQ has fallen from previous levels
- Deficiencies of:
  - Complex information processing (dealing simultaneously with multiple tasks)
  - Information processing speed
  - Initial acquisition of new information
  - Learning/recalling complex verbal material
- Higher order skills (e.g. planning, verbal fluency) intact
- Deficiencies not explained by coexistent psychiatric disorders

# EEG: Spectral Coherence Studies

<table>
<thead>
<tr>
<th>Group</th>
<th>Classified Accurately</th>
<th># Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFS- Unmedicated</td>
<td>89.4%</td>
<td>47</td>
</tr>
<tr>
<td>CFS- Medicated</td>
<td>73.9%</td>
<td>23</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>87.4%</td>
<td>390</td>
</tr>
<tr>
<td>Depressed controls</td>
<td>100.0% (none Dx CFS)</td>
<td>24</td>
</tr>
<tr>
<td>Putative “CFS”</td>
<td>46.6%</td>
<td>148</td>
</tr>
</tbody>
</table>

## Proteomic Markers in Spinal Fluid

<table>
<thead>
<tr>
<th></th>
<th>CFS N=10</th>
<th>Healthy N=10</th>
<th>P-Value</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>α2-macroglobulin</td>
<td>36%</td>
<td>0%</td>
<td>0.01</td>
<td>Protease</td>
</tr>
<tr>
<td>Orosomucoid</td>
<td>36%</td>
<td>0%</td>
<td>0.01</td>
<td>Protease</td>
</tr>
<tr>
<td>Pigment epith. derived factor</td>
<td>45%</td>
<td>0%</td>
<td>0.005</td>
<td>Anti-oxidant</td>
</tr>
<tr>
<td>Keratin 16</td>
<td>45%</td>
<td>0%</td>
<td>0.005</td>
<td>Meningeal inflamm.</td>
</tr>
<tr>
<td>BEHAB</td>
<td>36%</td>
<td>0%</td>
<td>0.06</td>
<td>Structural repair</td>
</tr>
</tbody>
</table>

Lactate in Spinal Fluid in CFS: *In vivo* Proton MR Spectroscopy

- CFS: 0.86 ±0.5
- Anxiety: 0.29 ±0.3
- Healthy: 0.25 ±0.2

P<0.001 for each, compared to CFS

Fatigue & Pain Sensing Molecules: Normals vs. CFS, Post-Exercise

All controls at times indicated after 25 minutes exercise to 70% of predicted maximal heart rate (N=15)

All CFS patients (both those with and without FM) at times indicated after 25 minutes exercise to 70% of predicted maximal heart rate (N=19)

Alan Light, et al. J Pain 2009 (published online)
Well documented disorders of the autonomic nervous system, sleep disorders, defective attention, abnormalities in cognition, information processing and recall, stress and hypothalamus–pituitary axis abnormalities, altered sensory and pain perception, and reduced motor speed...point to major CNS involvement.

Stephen T. Holgate, UK MRC professor of immunopharmacology at the School of Medicine, University of Southampton, UK.

I would be surprised if the pathology does not involve some dysfunction within the CNS.

Simon Wessely, professor and Chair of the Department of Psychological Medicine and also Vice Dean for Academic Psychiatry at the Institute of Psychiatry, King’s College London, UK.
Studies of the Immune System
Immunological Abnormalities in CFS

- **CD8 + “cytotoxic” T cells bearing activation antigens (CD38 +, HLA-DR)**
  

- **Poorly functioning natural killer (NK) cells**


- **Upregulation of the 2,5A system**


- **Increased production of pro-inflammatory cytokines**

## Common Laboratory Abnormalities in CFS

### A Case-Control Study Involving Over 20,000 Laboratory Tests, in Over 700 Patients, in Two Geographic Areas, Over 10 Years

<table>
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<th>Odds Ratios</th>
<th>95% C.I.</th>
<th>P-Value</th>
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<tbody>
<tr>
<td>Immune complexes</td>
<td>26.5</td>
<td>3.4 - 206</td>
<td>0.002</td>
</tr>
<tr>
<td>Immunoglobulin G</td>
<td>8.5</td>
<td>2.0 - 37</td>
<td>0.004</td>
</tr>
<tr>
<td>Atypical lymphocyte count above 2%</td>
<td>11.4</td>
<td>1.4 - 94</td>
<td>0.03</td>
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35% of cases had elevated levels (>0.23 g/L) vs. 2% of controls.

Cytokine Abnormalities in CFS

- Dysregulated pro-inflammatory cytokines, primarily TNF-α, IL-1 family, IL-6, IF-γ
- Increased TGF-β, possibly in response to upregulation of pro-inflammatory cytokines

References:
Up-Regulation of 2-5A System in CFS

Studies of Infectious Agents
Viruses and CFS—My View

- Infectious agents probably can trigger and perpetuate CFS—but no proof yet.
- Agents associated with CFS typically share two properties: they cannot be fully eradicated by the immune system, and they can infect the CNS.
- There now is solid evidence that CFS can follow a new infection.
- It is possible that in CFS different infectious agents interact to cause symptoms.
Documentation of Post-Infectious Chronic Fatigue Syndrome

- 256 patients with acute laboratory-documented EBV, Q fever, or Ross River virus infection in one town, followed systematically for over 12 months

- 11% develop CFS—similar with each pathogen

- CFS more likely to occur in patients with initially severe clinical symptoms, which were associated with higher ex vivo production of pro-inflammatory cytokines

- CFS not more likely in patients with particular premorbid psychiatric and demographic factors

Infectious Agents Linked to CFS

- Epstein-Barr Virus\textsuperscript{1,2}
- Post Q fever (Coxiella burnetii)\textsuperscript{2,6,7}
- Ross River virus\textsuperscript{2}
- Lyme (\textit{B burgdorferi}) (yes, but unusual)\textsuperscript{3}
- Parvovirus (yes, but unusual)\textsuperscript{4}
- Enteroviruses (probably sometimes)\textsuperscript{5}
- \textit{Borna disease virus}
- Human herpesvirus-6 (HHV-6)\textsuperscript{8}
- \textit{Xenotropic murine leukemia-related virus (XMRV)} and other murine leukemia retroviruses (???)

HHV-6 and the Brain

- Infects neuroblastoma and glioma cells, glial cells (astrocytes, oligodendrocytes) & neurons
- Most common cause of infant febrile seizures
- Persists in CNS after primary infection
- Causes encephalitis in immunosuppressed and (commonly) in immunocompetent
- Causes demyelination in immunosuppressed and in immunocompetent infants/children
- Associated with multiple sclerosis
- Associated with temporal lobe seizure disorders
Evidence of Active HHV-6 Infection

Criteria: Primary cell culture produces large refractile giant cells in 4-8 days which fluoresce with antisera known to have high levels of antibody to HHV-6.

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<td>34/42 (81%)</td>
<td>8/40 (20%)</td>
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P < 0.00000001

Active HHV-6 Infection in CFS: Results of Studies

# of Positive vs. Negative Studies

- # of Positive: 9
- # of Negative: 2

# of Patients in Pos. vs. Neg. Studies

- # of Positive: 1061
- # of Negative: 122
Energy Metabolism/
Oxidative and Nitrosative Stress/
Inflammation
Mitochondrial dysfunction

- \( \uparrow \) anaerobic metabolism: lactate

- \( \uparrow \) COX-2

- \( \uparrow \) NFκB

- \( \uparrow \) iNOS

Oxidative Stress

- \( \downarrow \) antioxidant levels (Zn, DHEA)
- \( \uparrow \) peroxide & superoxide
- \( \uparrow \) isoprostan & oxidized LDL
- \( \downarrow \) \( \alpha \)-tocopherol

Nitrosative Stress

- \( \uparrow \) NO, nitrate, peroxynitrite
- \( \uparrow \) IgM against nitro-[amino acids]

Damage to nucleic acids and lipid membranes

- \( \downarrow \) \( \alpha \)-tocopherol

- \( \uparrow \) IgM against nitro-[amino acids]

Mitochondrial dysfunction

- \( \downarrow \) \( \alpha \)-tocopherol

- \( \uparrow \) NO, nitrate, peroxynitrite

- \( \uparrow \) IgM against nitro-[amino acids]
The Biology of Chronic Fatigue Syndrome

- The CNS and autonomic nervous systems are involved
- There is a state of chronic immune activation, as if the immune system is attacking something foreign
- There are oxidative/nitrosative stress
- Energy metabolism is impaired
- Infection can trigger the illness in many, if not all, patients. Can it perpetuate illness??
Is Chronic Fatigue Syndrome Real?

• Do we understand the causes or pathogenesis of CFS?
• Are there objective biological markers that are abnormal in CFS?

Is CFS “real”? 