Epidemiology of Chronic Fatigue Syndrome (CFS)

Elizabeth Maloney, MS, DrPH

Chronic Viral Diseases Branch
National Center for Zoonotic, Vector-borne and Enteric Diseases
Centers for Disease Control and Prevention
Fatigue in Clinical Practice

10 - 40% of primary care visits

Various Outpatient Studies

Percent Reporting Fatigue
Fatigue in Clinical Practice

Diagnoses in 200 Patients with Fatigue

- Psychiatric Dx 74%
- Medical Dx 5%
- Unexplained 21%
CFS Case Definition

FATIGUE
Persistent/relapsing > 6 Mo
Not alleviated by rest
Substantial reduction in activities

No explanatory medical or psychiatric causes

Accompanying Symptoms
- impaired memory/concentration
- post exertional fatigue
- unrefreshing sleep
- headaches
- muscle pain
- multi-joint pain
- sore throat
- tender lymph nodes

Medical Psychiatric Evaluation
CFS in the U.S.

- ~ 4 million CFS

### Clinic Populations
- Primarily middle-aged women
- Upper middle class professionals
- Primarily white
- Most report sudden onset
- Ave duration illness 5+ years
- Ave 22 physician visits annually

### General Population
- Primarily middle-aged women
- Lower socioeconomic
- Racial ethnic minorities
- Most report gradual onset
- Ave duration illness 5+ years
- Only 16% Dx/Tx
Economic Impact of CFS
Indirect Costs
Lost Employment & Earnings

Annual wage loss to each family with CFS $15 – $20K

* Primarily loss of employment
  (19% lower probability of working)
* Early onset CFS significantly reduces educational attainment
  (CFS ≤ 25yrs probability college degree 25%)
  [otherwise 50+%]

$###$
Case-Control Study: Georgia Screening Telephone Interview

Random-digit dialing

10,837 Households (79%)
19,807 Adult Residents

Screen for unwellness
1 month or more:
Severe fatigue not alleviated by rest,
Joint or muscle pain
Unrefreshing sleep
Concentration or memory problems

10,834 Well;
8,973 Unwell: 3,851 Unwell with fatigue; 5,122 Unwell without fatigue
Case-Control Study: Georgia
Detailed Telephone Interview

5,623 CATI

2,438 Unwell with fatigue (71%)
1,429 Unwell without fatigue (67%)
1,756 Well (56%)

Symptoms: duration/severity
Economic data
Health care utilization

Screen for exclusionary med/psych conditions (1,609 with exclusions)

Classify as Well (1,782),
Chronically Unwell (1,763),
CFS-like (469)
Case-Control Study: Georgia Clinical Evaluation

783 to clinic: 53% response rate

CFS-like (all)
Well (1:1 matched age, sex, race, geographic area)
Unwell (random selection)

280 had exclusionary med/psych conditions

501 no exclusions:
113 CFS
124 Well
264 Unwell
Data Collection - Clinic

Past Medical/Psych History
Review of Systems
Medications (current)
Physical Exam
Lab (Blood/urine/saliva: standard labs, endocrine tests)
Psychiatric interview (administered by trained clinicians)
Childhood trauma
Traumatic life events –past year
Chronic stress
Zung depression inventory
Spielberger state trait anxiety
Davidson PTSD Scale
Ways of coping
Cognitive assessment
## Demographic Factors - Georgia

<table>
<thead>
<tr>
<th>Factor</th>
<th>CFS (n=113)</th>
<th>Well (n=124)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean years)</td>
<td>44.3</td>
<td>44.5</td>
<td>p = 0.78</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>81.1</td>
<td>75.6</td>
<td>p = 0.23</td>
</tr>
<tr>
<td>Race (% White)</td>
<td>74.3</td>
<td>76.6</td>
<td>p = 0.68</td>
</tr>
<tr>
<td>Geog. Stratum (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metro</td>
<td>20.3</td>
<td>17.7</td>
<td>p = 0.88</td>
</tr>
<tr>
<td>Urban</td>
<td>32.7</td>
<td>33.9</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>46.9</td>
<td>48.4</td>
<td></td>
</tr>
<tr>
<td>Education (% &gt; High School)</td>
<td>95.5</td>
<td>98.3</td>
<td>p = 0.20</td>
</tr>
<tr>
<td>Body Mass Index (mean)</td>
<td>28.1</td>
<td>26.5</td>
<td>p = 0.01</td>
</tr>
</tbody>
</table>
Outline

• Working model
• Theory
• Factors associated with CFS: Results from Wichita and Georgia Studies
• Building a CFS Model
Working Model

Targets for Controlling CFS

- Biomarkers
- Provider Education
- Symptom management
Pathways to Pathology
Factors Examined

• Stress
  – Early life stress
• HPA-axis
  – Cortisol
• Allostatic Load
  – C-reactive protein
• Metabolic Syndrome
  – Insulin resistance
• Autonomic nervous system
  – Heart rate variability
Early Life Stress

*significant; adjusted for age, sex, race, ethnicity

Heim C, et al., Arch Gen Psychiatry 2008 (In Press)
Morning Salivary Cortisol Profile

Nater U et al., J Clin Endocrinol Metab 2008;93:703-9
Morning Salivary Cortisol Profile

Men

<table>
<thead>
<tr>
<th>Measurement Time Point</th>
<th>Well</th>
<th>CFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awakening</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

Women

<table>
<thead>
<tr>
<th>Measurement Time Point</th>
<th>Well</th>
<th>CFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awakening</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

(Not significant) (p < 0.05)

Nater U et al., J Clin Endocrinol Metab 2008;93:703-9
Morning Cortisol Response in CFS: Role of Early Life Stress (ELS)

Allostatic Load

Environmental stressors
(work, home, neighborhood)

Major life events

Trauma, abuse

Perceived Stress

Host factors:
genes, development, experience

Behavioral Responses:
(fight/flight, diet, smoking, drinking, exercise)

Physiologic responses

Allostasis

Adaptation

Allostatic load

McEwen BS, Seeman T. Ann NY Acad Sci 992:306:47
# Allostatic Load

## Cardiovascular Factors
- Systolic blood pressure ≥ 130.0 mm Hg
- Diastolic blood pressure > 83.0 mm Hg
- Heart rate > 72.0 beats per minute

## Inflammatory Factors
- C-reactive protein > 3.0 mg/L
- Albumin < 4.0 g/dL

## Metabolic Factors
- Waist-hip ratio
  - Males > 0.94
  - Females > 0.86
- High density lipids < 38.0 mg/dL
- Cholesterol (total) > 206.0 mg/dL
- Glucose > 96.0 mg/dL
- Insulin > 7.1 uU/ml

## HPA Axis Factor
- Salivary cortisol (AUC ≤ 0.31 or ≥ 0.95)

## High Allostatic Load and CFS

\[ \text{OR}^* = 3.32 \ (1.68 - 6.54) \]

*Adjusted for age, sex, education

\[ \text{OR}^{**} = 2.75 \ (1.24-6.10) \]

***Adjusted for age, sex, education, BMI

Maloney EM et al., Psychosomatic Med 2008 (Submitted)
Significant Allostatic Load Factors

Proportion of Subjects in CRP Category

<table>
<thead>
<tr>
<th>CRP mg/L</th>
<th>CFS</th>
<th>Well</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.0</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>1.0-3.0</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>&gt; 3.0</td>
<td>30</td>
<td>25</td>
</tr>
</tbody>
</table>

Waist-hip ratio in females

<table>
<thead>
<tr>
<th>Waist-hip ratio</th>
<th>CFS</th>
<th>Well</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.775</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>0.780</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>0.785</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>0.790</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>0.795</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

Mean waist-hip ratio

<table>
<thead>
<tr>
<th>Waist-hip ratio</th>
<th>CFS</th>
<th>Well</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.815</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>0.805</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>0.795</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>0.785</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>0.775</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

Total Cholesterol

<table>
<thead>
<tr>
<th>Cholesterol, mg/dL</th>
<th>CFS</th>
<th>Well</th>
</tr>
</thead>
<tbody>
<tr>
<td>172</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>174</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>176</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>178</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>180</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

Mean cholesterol, mg/dL

<table>
<thead>
<tr>
<th>Cholesterol, mg/dL</th>
<th>CFS</th>
<th>Well</th>
</tr>
</thead>
<tbody>
<tr>
<td>172</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>174</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>176</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>178</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>180</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

Insulin

<table>
<thead>
<tr>
<th>Insulin, uU/ml</th>
<th>CFS</th>
<th>Well</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0001</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>0.0002</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>0.0003</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>0.0004</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>0.0005</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

Mean insulin uU/ml

*p = 0.01
*p = 0.02
*p < 0.0001
### CFS and C-Reactive Protein

<table>
<thead>
<tr>
<th>CRP Level</th>
<th>OR*</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.0 mg/L</td>
<td>1.00</td>
<td>---</td>
</tr>
<tr>
<td>1.0 - 3.0 mg/L</td>
<td>1.73</td>
<td>(0.84 – 3.35)</td>
</tr>
<tr>
<td>&gt; 3.0 mg/L</td>
<td>3.04</td>
<td>(1.53 – 6.03)</td>
</tr>
</tbody>
</table>

*adjusted for age, sex, education; p-trend = 0.001

Raison CL, Lin J-M, Reeves WC.
Brain, Behavior, and Immunity (Under Review)
## Metabolic Syndrome*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cut-Off for Risk Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abdominal Obesity</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>Waist &gt; 102 cm (&gt; 40 inches)</td>
</tr>
<tr>
<td>Women</td>
<td>Waist &gt; 88 cm (&gt; 35 inches)</td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td>&gt; 150 mg/dL or taking lipid lowering medication</td>
</tr>
<tr>
<td><strong>High Density Lipids (HDL-C)</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>&lt; 40 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>&lt; 50 mg/dL</td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td>&gt; 130/ &gt; 85 mm Hg</td>
</tr>
<tr>
<td></td>
<td>or taking blood pressure medication</td>
</tr>
<tr>
<td><strong>Fasting Glucose</strong></td>
<td>&gt;100 mg/dL (5.6 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>or taking medications to lower glucose</td>
</tr>
</tbody>
</table>

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cm = centimeter; mg = milligram; mmol = micromole; dL = deciliter

*National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Definition*
CFS and Metabolic Syndrome

<table>
<thead>
<tr>
<th>OR*</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.39</td>
<td>(1.29 – 4.45)</td>
</tr>
</tbody>
</table>

*adjusted for age, sex and education

Maloney EM et al. JAMA (Under Review)
Prevalence of Metabolic Factors among CFS and Well

Maloney EM et al. Metabolism (Submitted)
### CFS and Insulin Resistance

<table>
<thead>
<tr>
<th>OR*</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.35</td>
<td>(1.29 – 4.28)</td>
</tr>
</tbody>
</table>

*adjusted for age, sex, education
# Factors Associated with CFS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Life Stress</td>
<td>5.6</td>
<td>(3.1 - 10.0)</td>
</tr>
<tr>
<td>High CRP</td>
<td>3.0</td>
<td>(1.5 - 6.0)</td>
</tr>
<tr>
<td>High Allostatic Load</td>
<td>3.3</td>
<td>(1.7 - 6.5)</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>2.4</td>
<td>(1.3 - 4.4)</td>
</tr>
<tr>
<td>Insulin Resistance</td>
<td>2.3</td>
<td>(1.3 - 4.3)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, education*
Correlation of Insulin Resistance Index with Other Factors in Females by CFS Status

<table>
<thead>
<tr>
<th>Factor</th>
<th>CFS</th>
<th>Well</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Partial r-coefficient</td>
<td>p-value</td>
</tr>
<tr>
<td>Childhood Trauma Score</td>
<td>0.32</td>
<td>0.02</td>
</tr>
<tr>
<td>Cortisol</td>
<td>-0.30</td>
<td>0.03</td>
</tr>
<tr>
<td>CRP</td>
<td>0.40</td>
<td>0.003</td>
</tr>
<tr>
<td>Waist Circumf.</td>
<td>0.71</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>0.77</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
Summary

• Developmental stress and a flattened morning cortisol response were associated with CFS, supporting roles for emotional stress and HPA-axis hypoactivity in CFS.

• Alterations in the stress-response system may relate to alterations in homeostatic mechanisms of other systems: immune and metabolic.

• The stress response system includes not only the HPA-axis but also the sympathetic nervous system.
Relationship between HPA and SNS

Hypothalamic paraventricular nucleus ↓ ACTH ↓ Cortisol

Brain stem (Locus Caeruleus) ← SNS Activity

Stress

Full lines, positive feedback; dashed lines, negative feedback. ACTH: adrenocorticotropin

Tentolauris N et al., Annals NY Acad Sci 2006;1083:129-52
**Autonomic Nervous System**

**Wichita study**

Mean values of heart rate (HR) and HR variability parameters during sleep

*Adjusted for age, sex, BMI, medication use;
Heart rate differences remained significant after further adjusting for limitations in physical activity

Hypothetical Model of CFS

Hypothalamic and Brain Stem SNS

↑ Heart Rate Variability

↓ Insulin

↑ SNS Activity

↓ Metabolic Syndrome

↑ Adipose Tissue

↑ IL-6

↓ C-reactive protein

↓ Liver

↑ IL-6

↑ CRP

Stress

Tentolauris N et al., Annals NY Acad Sci 2006;1083:129-52
Conclusions

• Our results support a role for stress and an altered neuroendocrine response to stress, evidenced by hypofolitisolism in CFS. HPA axis hypoactivity and increased SNS activity may be playing parallel roles in altering homeostasis of metabolic and innate immune systems in CFS.

• The epidemiology of CFS, as presented, points to the need to study HPA and autonomic nervous systems under stressful conditions.

• The elevated risk for metabolic syndrome in CFS suggests that persons with CFS may be at increased risk for diabetes and cardiovascular disease.

• Our Registry Study will follow persons with CFS over time to assess development of diabetes and cardiovascular disease.
Acknowledgements

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Roumiana Boneva, MD, PhD
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James Jones, MD
Elizabeth Unger, MD
William C. Reeves, MD, MSc

Emory University
Christine Heim, PhD
Urs Nater, PhD
Charles Raison, MD
Andrew Miller, MD
Genetic Polymorphisms in CFS

- Glucocorticoid receptor – NR3C1
- ACTH precursor – POMC
- Monoamine catabolism – MAOA, MAOB
- Serotonin synthesis – TPH2
- Serotonin receptor – HTR2A
CFS Case Definition

1994

FATIGUE
Persisting/relapsing > 6 mo.
Not alleviated by rest
Substantial reduction in activities
No explanatory medical or psychiatric causes

Accompanying Symptoms
impaired memory/concentration
post exertional fatigue
unrefreshing sleep
headaches

1994

Physical Function \( \leq 70 \)
Social Function \( \leq 75 \)
Role physical \( \leq 50 \)
Role Emotional \( \leq 67 \)

General fatigue \( \geq 13 \)
Reduced activity \( \geq 10 \)

Post-exertional malaise
Unrefreshing sleep
Impaired memory/concentration
Muscle pain
Multi-joint pain
Headaches
Sore throat
Tender cervical/axillary nodes

\( \geq 4 \) Symptoms
Score > 24