Chronic Fatigue Syndrome and its Related Disorders

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Presenter Disclosure Information

Peter C. Rowe, MD

• No relationships to disclose
CFS and its related disorders

- CFS definition and epidemiology
- Recent research findings of note
- Treating related disorders
  - Orthostatic intolerance
  - Joint hypermobility and the paradox of movement restrictions
  - Delayed milk protein intolerance
Fatigue in CFS

Self-reported persistent or relapsing fatigue lasting ≥ 6 consecutive months, which:

• Is of new or definite onset (not lifelong)
• Is not the result of ongoing exertion
• Is not substantially alleviated by rest
• Results in substantial reduction in previous levels of occupational, educational, social, or personal activities

Symptom Criteria For CFS
4 of 8 needed for diagnosis

- unrefreshing sleep
- postexertional malaise lasting > 24 hours
- self reported impairment in short-term memory or concentration
- sore throat
- tender cervical or axillary glands
- muscle pain
- multijoint pain without swelling
- headaches of a new type, pattern, severity
Clinical Evaluation

- History, physical, mental status exam
- Screening labs:
  - CBC, ESR/CRP, Chemistries, TSH
  - Urinalysis
  - Most would now add iron studies, vitamin B12, celiac screening, and, in endemic areas, labs for Lyme and other tick-borne infections
- Other labs as clinically indicated
# Prevalence of Fukuda Criteria Symptoms

Nijhof SL, Pediatrics 2011;127:e1169-1175  
National survey of 4.1% of Dutch General Practitioners

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrefreshing sleep</td>
<td>84%</td>
</tr>
<tr>
<td>Post-exertional malaise &gt; 24h</td>
<td>80%</td>
</tr>
<tr>
<td>Memory/concentration probs</td>
<td>79%</td>
</tr>
<tr>
<td>Headaches</td>
<td>78%</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>59%</td>
</tr>
<tr>
<td>Joint pain</td>
<td>48%</td>
</tr>
<tr>
<td>Sore throat</td>
<td>43%</td>
</tr>
<tr>
<td>Tender lymph nodes</td>
<td>31%</td>
</tr>
</tbody>
</table>
# Prevalence of Other (Non-Fukuda) Symptoms

Johns Hopkins Pediatric CFS Cohort Study  
SCL-90 symptom reports of at least moderate severity

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>70%</td>
</tr>
<tr>
<td>Nausea</td>
<td>56%</td>
</tr>
<tr>
<td>Hot/cold temp fluctuations</td>
<td>48%</td>
</tr>
<tr>
<td>Numbness &amp; tingling</td>
<td>48%</td>
</tr>
<tr>
<td>Heart racing</td>
<td>43%</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>37%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>37%</td>
</tr>
<tr>
<td>Diminished appetite</td>
<td>24%</td>
</tr>
</tbody>
</table>
Ruling in CFS

- Post-exertional malaise lasting 1-3 days is more common in CFS than depression
- Post-exertional worsening of symptoms extends past fatigue to include cognitive dysfunction, lightheadedness, pain.
- Cognitive problems common (difficulty with attention, short-term memory)
Helpful clinical questions

• What happens when you try to do normal activities that you tolerated before? (e.g., reading, studying, walking 20 min, exercising)
• How long can you be upright before having to sit?
• What activities have you had to limit since you got sick? (school, after-school activities, shopping)
• How often do you get out of the house?
• How many chores can you manage in a day, or on consecutive days? If you do more, what are the consequences?
# Clinical Discriminators of Fatigue

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical pearl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuromuscular</td>
<td>Weakness</td>
</tr>
<tr>
<td>OSA</td>
<td>Daytime somnolence, snoring</td>
</tr>
<tr>
<td>Heart/lung disease</td>
<td>SOB, effort intolerance</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>↓ BP on orthostatics, ↓ Na. Bronzing, ↓ K less common</td>
</tr>
<tr>
<td>Chiari I</td>
<td>Occipital HA, brisk DTRs</td>
</tr>
</tbody>
</table>
Red Flags for Serious Conditions other than CFS

- Weight loss
- Fevers
- Sleep paralysis, cataplexy
- Clubbing
- Erythematous, swollen joints
- Abnormalities on neuro exam
CFS and its related disorders

• CFS definition and epidemiology
• Recent research findings of note
• Treating related disorders
  – Orthostatic intolerance
  – Joint hypermobility and the paradox of movement restrictions
  – Delayed milk protein intolerance
CFS

• Affects previously active individuals in all SES strata
• Female to male ratio 2:1 to 5:1
• Uncommon before 10 yrs; peaks at 40-49
• Prevalence estimated at 4/1,000 adults
• Heterogeneous precipitating & perpetuating factors
• More common in MZ than DZ twins
• Proven treatments are limited: CBT and graded exercise help, but effects are modest
• Severity in adults comparable to MS, CHF; common cause of prolonged school absence in adolescents
• Estimated $24 billion in losses annually
Health-related QOL: CFS vs. other pediatric chronic conditions

CFS data from Johns Hopkins Pediatric CFS Cohort Study; other conditions from Ingerski LM, et al., J Pediatrics 2010;156:639-44
Infection and Immunity

• Debate about whether infection acts as a “hit and run” phenomenon, triggering some other physiologic dysfunction but not directly causing symptoms, or whether persistent symptoms are due to active infection

• After EBV, Q-fever, other illnesses, ~10% get CFS; main risk factor is severity of the initial infection

• Evidence of active infection thus far not detected in chronic state
301 adolescents with infectious mono: % with CFS over time

Pediatric CFS Impact: School Attendance
Crawley E, Sterne JAC. Arch Dis Child 2009;94:752-6

- 211 with CFS, 69% F, median age 14.6
- Evaluated in CFS specialist clinic in UK
- 56.9% attended school 20% or less
- Those with better physical function were more likely to attend school (OR 1.70; 95% CI, 1.36-2.13)
- No association between attendance rates and anxiety, gender, age, FH of ME/CFS
A Fatigue: all participants

- Specialist medical care
- Adaptive pacing therapy
- Graded exercise therapy
- Cognitive behaviour therapy

Unadjusted fatigue score

12 wks 24 wks 52 wks

White PD et al. PACE trial. Lancet 2011
Measurements of workload at peak exercise (A) and at the ventilatory threshold (B) in individuals with CFS and control subjects obtained during cardiopulmonary exercise test #1 (blue bars) and cardiopulmonary exercise test #2 (gold bars).

Light AR, et al. Myalgia and Fatigue: Translation from Mouse Sensory Neurons to Fibromyalgia and Chronic Fatigue Syndromes.

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Is neurally mediated hypotension an unrecognised cause of chronic fatigue?

Peter C Rowe, Issam Bou-Holaigah, Jean S Kan, Hugh Calkins


The Relationship Between Neurally Mediated Hypotension and the Chronic Fatigue Syndrome

Issam Bou-Holaigah, MD; Peter C. Rowe, MD; Jean Kan, MD; Hugh Calkins, MD

JAMA 1995;274:961-7
Symptoms of Orthostatic Intolerance

Lightheadedness  Dysspnear
Syncope         Chest Discomfort
Diminished concentration  Palpitations
Headache        Tremulousness
Blurred vision  Anxiety
Fatigue         Nausea
Exercise intolerance  Nocturia
Dependent acrocyanosis
Response of CFS subjects to open treatment of orthostatic intolerance

JAMA
**Common forms of orthostatic intolerance in pediatric CFS**

**POTS:** 30 bpm increase (40 bpm in adolescents) in HR with symptoms, or HR > 120 bpm, in first 10 min of standing or HUT
CFS and POTS in adults

- Prevalence of severe fatigue
- Unrefreshing sleep
- Impaired memory or concentration
- Muscle pain
- Post-exertional fatigue
- New or worse headaches
- Joint pain
- Tender lymph nodes
- Sore throat
Increasing orthostatic stress impairs neurocognitive functioning in chronic fatigue syndrome with postural tachycardia syndrome

Anthony J. OCON*, Zachary R. MESSER†, Marvin S. MEDOW*†
and Julian M. STEWART*‡†

*Department of Physiology, New York Medical College, Valhalla, NY, U.S.A., †Department of Pediatrics, New York Medical College, Valhalla, NY, U.S.A., and ‡Department of Medicine, New York Medical College, Valhalla, NY, U.S.A.
N-back testing

- Tests working memory, concentration, attention, information processing
  - 0-back: subject responds if the character on screen is the one they were told to expect
  - 1-back: subject responds when the current character is the same as displayed “1” back
  - 2-back: same character as was displayed 2 characters back
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EDS/
Joint hypermobility

Orthostatic Intolerance

CFS
CFS Associated With EDS and Orthostatic Intolerance

Among 100 adolescents in the CFS clinic at JHH over a 1 year period, we identified 12 with EDS (P < 0.01)

6 classical-type, 6 hypermobile-type EDS

12/12 with OI (9 NMH, 10 POTS)

Rowe PC, Barron DF, Calkins H, Maumanee IH, Tong PY, Geraghty MT.

Beighton Joint Hypermobility Scores in 58 Adolescents With CFS And 58 Healthy Controls

Observations in Adolescents with CFS

- Increased prevalence of postural abnormalities and movement restrictions
Abnormal postures
Restricted Ankle Dorsiflexion

Healthy

CFS
Restricted Prone Knee Bend

Healthy

CFS
Restricted Straight Leg Raise

Healthy

CFS
ROM in 48 CFS subjects 10-23 yrs old matched on sex and Beighton score (Rowe PC, et al. J Pediatrics 2014)

<table>
<thead>
<tr>
<th>Maneuver</th>
<th>CFS %</th>
<th>Controls %</th>
<th>P Wilcoxon signed ranks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slump Left Leg &lt; 170</td>
<td>13</td>
<td>8</td>
<td>.48</td>
</tr>
<tr>
<td>Slump Right Leg &lt; 170</td>
<td>10</td>
<td>2</td>
<td>.10</td>
</tr>
<tr>
<td>ADF Left &lt; 95</td>
<td>15</td>
<td>0</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>ADF Right &lt; 95</td>
<td>13</td>
<td>0</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>SLR Left &lt; 45 onset</td>
<td>69</td>
<td>38</td>
<td>.001</td>
</tr>
<tr>
<td>SLR Right &lt; 45 onset</td>
<td>71</td>
<td>31</td>
<td>.001</td>
</tr>
<tr>
<td>ULTT Left &lt; 170 onset</td>
<td>71</td>
<td>56</td>
<td>.13</td>
</tr>
<tr>
<td>ULTT Right &lt; 170 onset</td>
<td>65</td>
<td>31</td>
<td>.001</td>
</tr>
<tr>
<td>PKB Left &lt; 130 onset</td>
<td>46</td>
<td>35</td>
<td>.41</td>
</tr>
<tr>
<td>PKB Right &lt; 130 onset</td>
<td>38</td>
<td>33</td>
<td>.66</td>
</tr>
<tr>
<td>Prone press-up</td>
<td>52</td>
<td>17</td>
<td>.002</td>
</tr>
</tbody>
</table>
Abnormal ROM in 48 pairs matched on gender and joint hypermobility score

(Composite score range: 0-11)

<table>
<thead>
<tr>
<th>ROM score</th>
<th>CFS, median score (range)</th>
<th>Controls, median score (range)</th>
<th>P Wilcoxon signed ranks</th>
</tr>
</thead>
<tbody>
<tr>
<td>At onset of stretch</td>
<td>5 (0-9)</td>
<td>2 (0-7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>At end-range</td>
<td>2 (0-7)</td>
<td>0 (0-3)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Observations in Adolescents with CFS

• Increased prevalence of postural abnormalities and movement restrictions

• CFS symptoms can be reproduced by selectively placing mechanical tension on the neural tissues
Symptom Changes with SLR over 12 minutes in Adolescent with CFS

Severity

Degrees of SLR

Fatigue
LH
Cog Fog
Vis Blur
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IgE mediated

Production of allergen-specific IgE by B cells

Epitopes encounter specialized dendritic cells, leading to T-cell priming

Non-IgE mediated

Dendritic or other antigen-presenting cells

Genetic disposition

Environmental factors

Allergic reactions occur when these reactive cells (with adjacent IgE molecules bound to their surface) are re-exposed to allergen

Abrogation of oral tolerance → cellular mechanisms leading to allergic reactions
Non-IgE mediated food allergy:
3 cardinal features

1. Recurrent vomiting or GER
2. Recurrent epigastric or abdominal pain
3. Food refusal, picky eating, early satiety

Other: aphthous ulcers, unexplained fevers, diarrhea or constipation, headache, myalgias, fatigue, asthma

Non-IgE mediated food allergy

- Reaction to suspected food usually delayed by 2-6 hours
- IgE level, prick skin tests, RAST tests often negative
- Eosinophilic colitis or esophagitis only the tip of the iceberg
Treatment of non-IgE mediated food allergy

1. Strict avoidance of offending food proteins (Milk > soy > egg)
2. Amino-acid formula (Neocate, EO28, Elecare) sometimes needed for infants, those with many allergies
3. Multivitamins, Ca supplements
Improvements in esophageal eosinophils after amino acid formula diet
Non-IgE mediated food allergy

Diagnosis supported by clinical response to diet, recurrence of symptoms 2-6 hours after inadvertent dietary challenge, confirmed by DBPCOFC
Delayed milk protein hypersensitivity: data from the Johns Hopkins CFS cohort

- 55 subjects with CFS
- Followed for 2 years and treated with multimodal therapy
- Subjects with delayed hypersensitivity to milk protein compared to those without milk sensitivity on history, current symptoms, and quality of life
<table>
<thead>
<tr>
<th>Baseline feature</th>
<th>Milk sensitive (N=17)</th>
<th>Not milk sensitive (N=38)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased vomiting in infancy</td>
<td>47%</td>
<td>13%</td>
<td>.01</td>
</tr>
<tr>
<td>Early satiety</td>
<td>69%</td>
<td>26%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>75%</td>
<td>26%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>GER</td>
<td>69%</td>
<td>29%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Aphthous ulcers</td>
<td>56%</td>
<td>8%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Worse with milk</td>
<td>43%</td>
<td>10%</td>
<td>.01</td>
</tr>
<tr>
<td>Peds QL score</td>
<td>47.4</td>
<td>58.0</td>
<td>.01</td>
</tr>
</tbody>
</table>
Response to multi-modal therapy (including milk-free diet in those with milk sensitivity)
Conclusions

• Adolescents and young adults with CFS have a higher than expected (31%) prevalence of DMPH

• Specific symptoms significantly more common among those with DMPH include reflux, aphthous ulcers, early satiety, and abdominal/epigastric pain
Conclusions

• DMPH contributes to worse health-related QOL in those with CFS
• Treatment with a milk-free diet and multi-modal CFS therapy was associated with improvement in the magnitude of differences in HRQOL after 6 months
• DMPH thus deserves further attention as a treatable contributor to CFC symptoms and HRQOL in CFS
Johns Hopkins CFS Cohort Study: Outcomes with individualized treatment
Resources

• ME/CFS: a primer for clinical practitioners, 2014: Downloaded from www.iacfsme.org
• The CFIDS Association webinars are an excellent source of information on various topics related to CFS: http://solvecfs.org/
• Search “Dr. Peter Rowe” on YouTube for webinar on “Managing Orthostatic Intolerance.”
• Dysautonomia International is a non-profit group. This site has fact sheets, exercise guides, and regular research updates. Talks from conferences are available: www.dysautonomiainternational.org
• Co-cure is a patient-run CFS information exchange: http://www.co-cure.org/
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• Summer students (John Fan, Alli Johns, Marissa Flaherty, Jocelyn Ray, Samantha Jasion, Erica Cranston)
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  – Special thanks to the following:
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  – Megan Lauver, Hannah Vogel