Chronic Fatigue Syndrome and Myalgic Encephalomyelitis: An Unsolved Spectrum of Disorders

By: Emily Villar
Objectives

- Know the current definitions of CFS / ME
- Recognize differences in pediatrics vs. adults
- Understand emerging evidence about the disease
- Be familiar with the current recommendations & challenges in treating this disease
What is CFS/ME?

CDC

“Chronic fatigue syndrome (CFS) is a debilitating and complex disorder characterized by intense fatigue that is not improved by bed rest and that may be worsened by physical activity or mental exertion.”
Fukuda Criteria

- >6mo fatigue
- Significant impairment with ADL/Work

- 4 or more:
  - Post exertion malaise > 24 hrs
  - Un refreshing sleep
  - Significant cognitive impairment
  - Myalgia
  - Arthralgia
  - HA
  - Sore throat
  - Tender LAD
Carruther’s Criteria: Intl. Consensus

- Myalgic Encephalomyelitis  2011
  - Profound muscle weakness/tenderness
  - Fatigue
  - Neurological abnormalities
  - Circulatory abnormalities
  - Post exertional “malaise”

- Estimated 30-50% of CFS
A Timeline

- 1934: “Atypical Poliomyelitis”  ⇒  “epidemic neuromyasthenia”
  - 100,000 ppl California

- 1940-1980: Various Outbreaks across the World
  - 1948: Iceland “Akureyri Disease” 500 ppl
  - 1955: Royal Free Hospital London “Benign ME” 300 ppl

- 1969: Acknowledged by WHO
  - Benign Myalgic Encephalomyelitis
  - CNS disease entity
A Timeline

• 1970’s Theory of Mass Hysteria
  • McEvedy and Beard

• Mid 1980’s: Lake Tahoe Epidemic
  • “Raggedy Ann Syndrome”
  • 260 ppl

• 1988: Clinical Picture Defined
  • Ramsay et al: Myalgic Encephalitis
  • Holmes et al: CFS

• 1994: CFS Redefined
ME vs. CFS

- Considered to be interchangeable

- Distinct but overlapping clinical entities
  - Post exertion malaise & cognitive dysfunction not required for dx of CFS
  - Obligatory for dx ME

- Distinction +/- post exertion malaise considered hallmark for diagnosis
Figure 1 ME and CFS case definitions.
CDC

- Complex and debilitating disease
- Follows Fukuda Criteria

Complications in Diagnosis:
- No lab test or biomarker
- Fatigue common to many illnesses
- Illness may not be obvious
- Pattern of remission and relapse
- Heterogeneous severity
Etiology

- No known etiology
- Several etiologic theories
  - Infectious/Post infectious
  - Immune dysfunction
  - Neurotransmitter d/o
  - Metabolism d/o
  - Genetic
Epidemiology

- More likely in females
  - 2-4:1

- Most common in young adults and middle aged

- 2 peaks: 10-19 yo & 30-39 yo

- Estimated 0.1-2% of adolescents
  - Largest single cause of long-term school absence in the UK
  - 2.6% Jr High and 5-10% Sr High in Japan
CFS/ME in Children vs. Adults: UK & Dutch cohorts

- UK
  - 210 Kids < 12yo
  - 1568 Adolescents
  - 10,675 Adults
  - CDC Criteria

- The Netherlands
  - 135 12-18yo from FITNET Cohort
  - Severe fatigue
  - <85% school performance & attendance
Results

- Children <12 yo
  - More Gender Balanced
    - 56.7% F : 74-82% FA
  - More likely to present with sore throat
    - 62% vs. 56% Adult
  - Cognitive Symptoms
    - 76.5% : 86.7%/95% A/A
  - Problems with Sleeping
    - 85% vs. 96% Adult
  - Less likely to have post exertion malaise
Results

• Adolescents (12-18 yo)
  • More likely to present w/ HA
    • 81% : 75% & 74 % in young children & adults respectively
  • Less likely to have cognitive dysfunction vs. Adults
  • Less likely to have tender LAD, palpitations, dizziness, malaise

• Adults
  • Lower mean physical function (-8.2 pts)
  • Higher mean fatigue (2.1 pts)
Childhood CFS and Neuro-cognitive impairment

- Problems w/ attention control
  - Previously demonstrated in studies prior to 2008

- ERP in CCFS pts
  - 414 CCFS (9-18 yo)
    - Types 1-3 per ERP findings
  - 190 HC

- Frontal Lobe, Autonomic, & ERP fx

http://reposit.lib.kumamoto-u.ac.jp/bitstream/2298/15257/2/JPN5-2007r.pdf
Results
Impact of CFS on Cognitive Fx in Adolescents

- Cross sectional & retrospective studies
  - Change in cognitive fx w/ poor performance in school

- IQ correlation pre & post CFS symptoms

- Current IQ data: retrospective CITO data
  - 59 pts recruited from FITNET Trial
  - 40 HC
## Results

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Intelligence assessment scores of adolescents with CFS and healthy adolescents</th>
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<tbody>
<tr>
<td></td>
<td>CFS (SD)a  n=59</td>
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<td>CTTO score(c) (501–550)</td>
<td>540.4 (7.0)</td>
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<td>Vocabulary (1–19)</td>
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<td>Intelligence quotient (IQ)(^a)</td>
<td>Educational level 1 (VMBO)(^c)</td>
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<tr>
<td>CFS</td>
<td>96.8 (8.6)</td>
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<td>Controls(^b)</td>
<td>104.1 (14.0)</td>
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</table>

There are significant differences between groups at all school levels, \(p=0.005\)

\(VMBO\) Voorbereidend Middelbaar Beroeps Onderwijs, \(HAVO\) Hoger Algemeen Voortgezet Onderwijs, \(VWO\) Voorbereidend Wetenschappelijk Onderwijs, \(CFS\) chronic fatigue syndrome

\(^a\) Values are means (SD)

\(^b\) CFS \(n=59\), Controls \(n=39\) (1 participant incomplete due to illness)

\(^c\) VMBO, HAVO and VWO correspond, respectively, to ‘average’, ‘above average’ and ‘high’ levels of attainment
Treatment for Attention Control

- Data from 2004 suggesting CBT potentially beneficial
- 2009 CBT described as ineffective & potentially harmful
- Recent randomized control studies → SSRI + CBT effective for teen depression
Combination Therapy in CCFS

- 19 CCFS and 25 HC
  - mATMT

- Improved
  - Motor Skill
  - Attention
  - Spatial working memory

P=0.002
P=0.037  P<0.001
5-HTTLPR & SNP rs25531 A>G genotype in young CFS pts

- Serotonin transporter 5-HTT important for CNS re-uptake

- 5-HTT genotype affects transcription rate
  - Short: SS or SLg
  - Long: LaLg, SLa, LaLa
A short allele and a long allele of the 5-HTT gene are shown. The short allele has 14 repeats, while the long allele has 16 repeats. An A → G transition is indicated, with the sequence CCCCCC[G]GCAT, and the AP2 binding site is highlighted.

B shows the predicted rate of transcription for different genotypes: SS, SL_G, L_A L_G, SL_A, and L_A L_A.

C displays the 5-HTT mRNA expression in blood for different genotypes, with fold expression values and sample sizes (n=14, n=13, n=38, n=5, n=22) indicated.
Methods

• 120 pediatric patients
  • Dept of Peds: Oslo University Hospital, Norway
  • National Referral Center for CFS pts 12-18 yo

• 38 age/gender matched HC

• Main Outcomes
  • Steps/Day
  • Functional Disability Inventory
    • Range 0-60
    • Subcategories 0-4: No Trouble – Impossible
Results

A

Number of steps (at inclusion)

SS SLG LALG SLA LAL

n=17 n=14 n=8 n=53 n=28

P = 0.008

B

FDI (at inclusion)

SS SLG LALG SLA LAL

n=17 n=14 n=8 n=53 n=28

P = 0.006

C

Number of steps in controls

SS SLG LALG SLA LAL

n=5 n=3 n=3 n=16 n=11

D

FDI in controls

SS SLG LALG SLA LAL

n=5 n=3 n=3 n=16 n=11
Results

- **SS & SLg**
  - Sig lower steps/day
  - Sig higher FDI score
  - Worse 30 week outcomes

- 5-HTT genotype
  maybe a factor in maintenance of CFS
CFS & Mitochondrial Dysfunction

- Mounting evidence of dysfunctions on cellular level

- ATP Profiles
  - Very Severe – Severe – Moderate

- 71 CFS Patients
  - Ages 14-75 (mean 47 yo)
  - 54 female
  - 17 male

- 50 Healthy Controls
Chronic fatigue syndrome and mitochondrial dysfunction

Energy metabolism in a cell and in a mitochondrion

- O₂ → ATP
- Cytosol → glucose, glycerol, fatty acid synthesis
- Mitochondrion → ATP, CO₂, NAD⁺, NADH
- Ox Phos: ATP synthase, ADP/ATP Translocator
- TL IN: ATP, ADP
- TL OUT: ATP, ADP, Pi, CO₂

Krebs TCA Cycle:
- Oxidation of acetyl CoA
- β-oxidation of fatty acids
- Pyruvate → CO₂
- Link reaction

Food molecules from cytosol: fatty acids, pyruvate, food molecules from cytosol

Phosphate carrier, inner membrane, outer membrane, mitochondrial cristae
Figure 3. Scatter plots of correlations between pairs of factors measured in the “ATP profile”. 
P < 0.001  RR = 0.677
Post Viral/Infectious Etiologies

- EBV – HHV6 – Coxsackie B – HTLV – XMRV – Lyme

- Mostly ruled out as directly causative

- Post Viral Immune Dysfunction
Reduced NK cell activity in CFS

- CFS w/ known reduced NK cytotoxic & lytic activity
  - Demonstrated in numerous studies
  - Maintained throughout course of disease
Longitudinal investigation of NK cells in CFS

- Investigating NK cell cytotoxic activity
- 65 CFS vs 21 HC
- Flow cytometry protocols
  - K652 cells: erythroleukemia
  - Baseline → 6mo → 12mo
  - T1 → T2 → T3
Figure 1: NK Cytotoxic activity was decreased at all time points in the CFS/ME patients. (A) Cytotoxic activity presented as % lysis of K562 cells by NK cells assessed over time at T1, T2 and T3 in the CFS/ME patients (black bars) and control (white bars) participants. (B) Cluster analysis showing the overall cytotoxic activity in the whole participant group. *Indicates statistical significant results relative to controls. Statistics are presented as mean ± SEM.
Benefit from B-Lymphocyte Depletion Using Rituximab in CFS pts

- Double blind Placebo-controlled
- 30 CFS patients
  - 15 Rituximab
  - 15 Saline
- f/u 12 mo
Results

67% improvement w/Rituximab
13% w/placebo
P = 0.003
Altered functional B cell subset populations in CFS

- Response to Rituximab suggests B-cell pathology
- 33 CFS vs. 24 HC
- Differences noted in transitional and naïve B-cell expression
B-Cell Depletion in CFS: Open Label Phase II w/Rituximab Maintenance Tx

• 29 CFS pts
  • Rituximab x2 – 2wks apart
  • Maintenance @ 3, 6, 10, 15 mo
  • f/u 36 mo

• 18 or 64% w/clinically significant responses
  • 14 major
  • 4 moderate
  • Mean response 26 mo
Self-reported Fatigue score
18 patients with, and 10 patient without, clinically significant response

Fatigue score (mean, 95%CI)

Time (months)

Baseline 0-6 6-12 12-18 18-24 24-30 30-36

- Major (n=14) and moderate (n=4) responders
- Nonresponders (n=9) and Marginal responder (n=1)

Fatigue scores (mean, SEM)

Time (months)

p=0.003 for interaction Time*Group (until 12 months)
### NIH Funding per FY 2011-2016

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Figure 1. Algorithm for Evaluating Chronic Fatigue Syndrome (CFS)

Fatigue

Detailed History and Exam

Initial CDC Recommended Tests:
- Urinalysis, Total Protein, Glucose, C-Reactive Protein, Phosphorus, Electrolyte, Complete Blood Count with Leukocyte Differential, Alkaline Phosphatase, Creatinine, Blood Urea Nitrogen, Albumin, Antinuclear Antibody and Rheumatoid Factor, Globulin, Calcium, Alanine Aminotransferase or Aspartate Transaminase Serum Level, Thyroid Function Tests (Thyroid Stimulating Hormone and Free T4).

Specific Diagnoses:
- Psychiatric Disorders
- Infectious Diseases
- Endocrinologic/Metabolism Disorders
- Immunologic/Rheumatologic Disorders
- Hematologic/Oncologic Disorders

Evaluate and Manage Individually

Able to reach a specific diagnosis?

Further Tests or Referral to a Specialist

Able to reach a specific diagnosis?

Fatigue of Unknown Etiology

> 1 month and < 6 months

Prolonged Fatigue

> 6 months

Diagnostic Criteria

1. Unexplained, persistent fatigue that is not due to ongoing exertion, is not substantially relieved by rest, is of new onset (not lifelong), and results in a significant reduction in previous levels of activity.
   AND
2. Four or more of the following symptoms are present for 6 months or more:
   - Impaired memory or concentration
   - Postexertional malaise (extreme, prolonged exhaustion and exacerbation of symptoms following physical or mental exertion)
   - Unrefreshing sleep
   - Muscle pain
   - Multijoint pain without swelling or redness
   - Headaches of a new type or severity
   - Sore throat that's frequent or recurring
   - Tender cervical or axillary lymph nodes

CFS
Conclusions

- Heterogeneous severity of disorders
- Lacking clear diagnostic criteria
- Concrete reproducible evidence and research lacking and underfunded
- No specific treatment guidelines
- Treatment based on symptom relief
References


References Continued


