Activity Intolerance, Post exertional malaise (PEM) Cognitive impairment

FIBROMYALGIA (FM) MYALGIC ENCEPHALOMYELITIS (ME) CHRONIC FATIGUE SYNDROME (CFS)



Behavioral Objectives Session 2

The participant will be able to:

Determine if **activity impairment and post-exertional malaise** are part of the clinical presentation, and use the information to confirm the diagnosis and counsel patients about activity management

Distinguish between the **PEM of ME/CFS** and the **post-exertional pain and fatigue amplification of FM.**

Appreciate fibromyalgia "brain fog" as an aspect of sensory amplification and central fatigue.

Recognize **cognitive slowing**, cognitive fatigue, memory and concentration deficits in a patient with ME/CFS and adopt communication strategies that will improve patient comprehension and compliance.



Alternate "new" Fibromyalgia Criteria (ACR 2010)



> 3 months in duration and without other apparent explanation



olf F, et al. The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia d Measurement of Symptom Severity. Arthritis Care & Research. Vol. 62, No. 5, May 2010, pp 600–610

ME/CFS Clinical Diagnostic Criteria:

CORE/REQUIRED criteria: Must be <u>mod-severe</u> and <u>frequent</u> (present >50% of time)

- 1) Impaired function related to exhaustion/fatigue
- 2) PEM: Post Exertional Malaise
- 3) Unrefreshing sleep
- 4) A. Cognitive impairment and/or
 - B. Orthostatic intolerance

Other common symptoms, not core:

Chronic widespread pain, Immune manifestations (allergy, inflammation, sensitivities). Infection manifestations, Neuroendocrine dysregulation



1. Fatigue and impaired function of ME/CFS

(IOM/NAM Report Chapter 4, pp 73-78)

- Profound exhaustion and debilitation
- Fatigue negatively impacts function. Useful diagnostic sign
- More severe than many other chronic illnesses.
- Explore the impact of "fatigue" on the patient's occupational, educational, social and personal activities. Ask the right questions!



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Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. Juenger J. Heart. 2002 Mar;87(3):235-41



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Clinical significance: ME/CFS "fatigue"

The low stamina and activity tolerance of ME/CFS are different than depression, and functional limitations are more severe than most chronic illness conditions.

Patients have a lower "threshold" of activity intolerance that may impact all cellular activities---physical and cognitive

Illness severity and functional capacity ranges from:



Clinical significance: FM fatigue

Patients with FM experience a pervasive physical and cognitive fatigue, but determined patients can "push" through, although pain flares. FM fatigue responds well to reduced stress, better sleep, activating medications and improves with low impact physical conditioning/exercise.

If a patient with "FM" can't tolerate low impact exercise and doesn't respond to sensible symptom management, they probably meet ME/CFS criteria as well (or have an undiagnosed underlying medical condition)

Typical for FM

Mild to moderate impairment and difficulty maintaining a normal schedule of full time work, school or family and pain flares with exercise





2. PEM: post exertional malaise of ME/CFS

(IOM/NAM Report, Chapter 4, pp 78-86)

- Exacerbation (relapse) of symptoms after physical, cognitive, emotional, orthostatic or other stress.
- MANY triggers reported and described.
- Duration: days, weeks, months...
- PEM has been objectively measured



Leonard Jason and colleagues (2013) compared **236** well defined ME/CFS patients with **86 healthy** controls rating the <u>frequency</u> and <u>severity</u> of 54 symptoms. This study was used in the IOM report.

This is the PEM symptom graph in the IOM report when symptoms are **moderate to severe** and **present at least 50% of the time**...

Jason LA, et al. Examining case definition criteria for chronic fatigue syndrome and myalgic encephalomyelitis. Fatigue: Biomedicine, Health and Behavior 2(1) 2013.



FIGURE 1 Percentage of ME/CFS patients and healthy controls reporting post-exertional malaise symptoms of at least moderate severity that occurred at least half of the time during the past 6 months.



NOTE: See the complete report for note and source information (available at www.iom.edu/MECFS).



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Scientific measures of low activity tolerance and PEM:

✓ Gene expression following an exercise stressor

 Cardiopulmonary Exercise Testing (CPET) on two serial days.

Metabolomics research (since the IOM report)



Gene Expression following an exercise stressor

University of Utah Alan Light PhD and Kathy Light PhD





2009 2011 2017-18?



The research team used **exercise as a stressor** to study post-exertional gene expression in patients with CFS, CFS/FM and FM-only.

Patients exercised on an Airdyne bike at 70% of age-predicted max heart rate for 25 minutes (moderate sustained activity approximating daily needs)

Blood was drawn:

Before exercise

with with with with

After_exercise at 30 min, 8 hours, 24 and 48 hours

Gene expression changes were analyzed.

Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects. Light AR, White AT, Hughen RW, Light KC. J Pain. 2009 Oct;10(10):1099-112. doi: 10.1016/j.jpain.2009.06.003. Epub 2009 Jul 31. PMID: 19647494

Gene expression alterations at baseline and following moderate exercise in patients with Chronic Fatigue Syndrome and Fibromyalgia Syndrome. Light AR, Bateman L, Jo D, Hughen RW, Vanhaitsma TA, White AT, Light KC. J Intern Med. 2012 Jan;271(1):64-81. doi: 10.1111/j.1365-2796.2011.02405.x. PubMed PMID: 21615807; PubMed Central PMCID: PMC3175315.





All controls at times indicated after 25 minutes exercise

Fold Increases in mRNA (+SEM)

Light A, et al. Journal of Pain. Nov 2010.





Patient 091006CFIDS1 ARUP vs Control subjects

10 ASIC3 P2X4 P2X5 TRPV1 AD2A ADB1 Fold increases in mRNA ADB2 1 baseline baseline 8 hr 24 hr 48 hr COMT 30 min 🗖 IL6 IL10 TNF beta TLR4 □ CD14 0.1 0.01 091006CFIDS1 Controls

Male engineer in 50s, severely disabled, severe OI and cognitive dysfunction



Courtesy of Alan Light.





Courtesy of Alan Light.











Cardiopulmonary Exercise Testing (CPET)

Patients with ME/CFS are unable to replicate the CPET parameters if the test is conducted 2 days in a row.



CPET 24 hr Test-Retest

Demonstrates objectively that CFS patients have a <u>physiologic basis</u> for postexertional malaise and symptoms of syndrome "flare" after increased activity. (VanNess, et al)

	TEST 1	TEST 2
CFS peak VO2 ml/kg/min	25	20
Controls peak VO2	25	25

19% reduction in peak aerobic activity on day 2

Using serial cardiopulmonary exercise tests to support a diagnosis of Chronic Fatigue Syndrome. VanNess, JM, et al. Med. Sci. Sports. Exerc. 38(5), 2006.



Peak Oxygen Consumption (VO2) in ME/CFS compared to Healthy Controls



Using serial cardiopulmonary exercise tests to support a diagnosis of Chronic Fatigue Syndrome. VanNess, JM, et al. Med. Sci. Sports. Exerc. 38(5), 2006.



Test 1 = dark grey bars Test 2= light grey bars

Figure 1: ** p < 0.01, * p < 0.05 see Table 2



VO2 peak/O2 pulse@peak/Work@peak/Vepeak



VO2@VT/O2pulse@VT/Work@VT/Ve@VT

Inability of ME/CFS patients to reproduce VO2 impairment. Keller B, et al. Journal of Translational Medicine 2014, 12:104. ME/CFS n=22



ME/CFS Metabolomics:

People with ME/CFS appear to have a very low metabolic capacity at a cellular level, similar to mitochondrial deficiency. The details of this phenomenon are under study.



Metabolomic diagnosis of CFS. Naviaux et al. Α

С

E

(A,C) Males. (B,D) Females ME/CFS n=45 Controls N=39

The products of several metabolic pathways distinguish ME/CFS from controls.

Male and Female ME/CFS share common pathways, but also have sex-specific pathways

Sphingolipids stand out

Metabolic features of chronic fatigue syndrome.

Robert K. Naviaux et al. PNAS PNAS September 13, 2016 vol. 113 no. 37 E5472-E5480





ME/CFS Metabolomics: (Hansen et al)

17 patients and 15 matched controls

74 differentially accumulating metabolites, out of 361 (P < 0.05), and 35 significantly altered after statistical correction (Q < 0.15)



Pathway analysis points to a few pathways with high impact:

- •taurine and glycerophospholipid metabolism,
- bile acid metabolism
- glyoxylate and dicarboxylate metabolism
- Purines, including **ADP and ATP**, pyrimidines and several amino acid metabolic pathways significantly disturbed.
- Glucose and oxaloacetate were two main metabolites affected that have a major effect on sugar and energy levels.

Metabolic profiling of a myalgic encephalomyelitis/chronic fatigue syndrome discovery cohort reveals disturbances in fatty acid and lipid metabolism. Germain A, Ruppert D, Levine SM, Hanson MR. Mol. BioSyst., 2017 Jan 31;13(2):371-379. doi: 10.1039/c6mb00600k



ME/CFS Metabolomics: (Fluge et al)

Metabolic profiling suggests impaired pyruvate dehydrogenase function in myalgic encephalopathy/chronic fatigue syndrome,

suggesting inadequate ATP generation by oxidative phosphorylation and excessive lactate generation upon exertion. Analysis in **200 ME/CFS patients** and **102 healthy individuals** showed a specific reduction of amino acids that fuel oxidative metabolism via the TCA cycle, mainly in female ME/CFS patients

Serum 3-methylhistidine, a marker of endogenous protein catabolism, was significantly increased in male patients.

Metabolic profiling indicates impaired pyruvate dehydrogenase function in myalgic encephalopathy/chronic fatigue syndrome. Øystein Fluge ... Olav Dahl, Karl J. Tronstad. January 3, 201 JCI Insight. 2017;1(21):e89376



Clinical significance of PEM:

Exceeding cellular energy capacity results in "payback" symptoms that we call PEM.

PEM is physiologic and multisystem.

PEM is illness relapsing or worsening.

The PEM may impact recovery and worsen illness.

The key to ME/CFS management is understanding these physical and cognitive limitations, "pacing" all activity, and preventing severe or prolonged PEM.



3. Cognitive impairment in ME/CFS

Neurocognitive manifestations (IOM Report Chap 4, pp 96-107)

- Impairments in cognitive function are frequently reported
- Cognitive impairment can be measured. The strongest evidence demonstrates *slowed information processing*. There are some data to support *deficits in working memory* and *reduced attention*.



98 **COGNITIVE COMPLAINTS** BEYOND ME/CFS



FIGURE 4-3 Percentage of ME/CFS patients and healthy controls reporting neurocognitive manifestations of at least moderate severity that occurred at least half of the time during the past 6 months.

NOTE: All patients fulfilled the Fukuda definition for CFS. SOURCE: Jason et al., 2013b.



Cognitive impairment in FM

The "brain fog" of FM is similar to the memory and attention problems of depression, anxiety, feeling over-stressed or exhausted. It is a cognitive fatigue that improves when more rested or less stressed, and responds to stimulant medications.



ME/CFS and FM cognitive impairment is often difficult to measure objectively

Neuropsychometric testing is expensive and not often covered by insurance but can be helpful.

Many of the typical neurocognitive tests are within normal limits.

FM brain fog and ME/CFS cognitive impairment are not dementia. IQ is intact.

Slowed information processing is the best documented cognitive deficit in ME/CFS.

Difficulty with timed tests or time limited tasks

 Difficulty multi-tasking (which is actually moving quickly from task to task)



Brain research in ME/CFS

mostly small unreplicated studies

Lactate is increased in the brain ventricles of ME/CFS [and FM*] by proton magnetic resonance spectroscopy (MRS) (Murrough 2010, Shungu 2012, Natelson 2017) and improves with administration of IV N-acetylcysteine (scientific meeting presentation 2016)

Spinal fluid proteins are elevated in some patients with ME/CFS (Natelson 2005)

Proteomics demonstrate distinct signatures but the significance is unknown (Schutzer SE,...Natelson BH).

* Elevations of Ventricular Lactate Levels Occur in Both Chronic Fatigue Syndrome and Fibromyalgia. Fatigue. 2017; 5(1): 15–20. Published online 2017 Feb 20. doi: 10.1080/21641846.2017.1280114 Benjamin H Natelson... and Dikoma C. Shungu



Venn diagram of the qualitative distribution of proteins identified in the pooled, immunodepleted, and fractionated cerebrospinal fluid (CSF) from normal healthy control subjects n=21, Chronic Fatigue Syndrome (*CFS*) n=43, and Neurologic Post Treatment Lyme Syndrome (*nPTLS*) n=25.



Brain research in ME/CFS

Activated microglia and astrocytes (neuroinflammation) were demonstrated in the brain using PET scans in a small but elegant study of 10 ME/CFS patients (Nakatomi 2014)

Functional MRI and spin-echo MRI have demonstrated changes in the brain but are not all in agreement (numerous studies)

Quantitative EEG techniques can differentiate ME/CFS from controls but aren't standardized for clinical use. In a Harvard study of 390 HC, 70 CFS, 24 MDD, 148 fatigue controls, EEG spectral coherence analysis correctly identified unmedicated CFS vs HC vs MDD. (P<0.001) (Komaroff 2011)



Neural Consequences of PEM in ME/CFS. Cook et al. 2017.

Acute exercise exacerbated symptoms, impaired cognitive performance and affected brain function in ME/CFS patients.

Neural Consequences of Post-Exertion Malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Brain Behav Immun. 2017 Feb 16. Cook DB1, Light AR2, Light KC2, Broderick G3, Shields MR4, Dougherty RJ4, Meyer JD4, VanRiper S4, Stegner AJ4, Ellingson LD5, Vernon SD6. Neural Consequences of exercise and cognitive work in ME/CFS.

15 female ME/CFS and 15 female HC.

30 min sub max exercise (70% peak HR) cycle ergometer.

fMRI during a fatiguing cognitive task.
PASAT: paced auditory serial addition task



Fig. 1. Total symptom changes for ME/CFS and control pre- to 24-h post-exercise Total symptoms are based on the sum of 10 VAS ratings derived from 10 items contained in the CDC symptom inventory





Total errors on PASAT testing

Total errors represent both incorrect responses and missed responses (i.e. errors of omission). There was a significant Group by Time Interaction (F = 8.4, p = 0.007).



fMRI results

The primary brain regions that distinguished brain responses between ME/CFS and controls and that were sensitive to acute exercise and symptoms of PEM were the inferior frontal, parietal and cingulate cortices.

These regions are critical for efficient cognitive processing involving processes associated with attention, error detection, and cognitive control/central executive function ME/CFS:



Brain activity during PASAT

pre-exercise



CONTROLS

Clinical significance of cognitive impairment in ME/CFS and FM:

Cognitive slowing, cognitive fatigability and cognitive PEM may be the most limiting aspects of ME/CFS illness, and a primary reason people with ME/CFS are unable to sustain employment or succeed in school.

Brain fog is a distressing symptom in FM and warrants ongoing pacing and management.

General Principles of Supportive Management:

possible contributors to cognitive complaints

- 1) Address all other conditions (complete a good medical work-up)
- i.e. anemia, thyroid, diabetes, sleep apnea, low Vit B12, polypharmacy
- 2) "<u>Pace</u>" to prevent symptom escalation
- 3) Address the major aspects of illness
 - PAIN: reduce severe pain
 - SLEEP: achieve restorative sleep
 - MENTAL HEALTH: insight and support
 - FITNESS: sluggish circulation
 - Orthostatic Intolerance reduced brain blood flow



Address potential contributors to "brain fog" and cognitive slowing

- Medications for sleep, pain, anxiety, migraine---minimize meds when possible, especially during the daytime.
- Chronic sleep disturbances ---continue to improve restorative sleep
- Secondary mental health conditions---depression, anxiety. Address mental health.
- Orthostatic intolerance and other causes of reduced cerebral blood flow and perfusion. "Perfusion" is the circulation or delivery of blood to every cell, bringing oxygen, glucose, everything needed for cell function... Improve cerebral blood flow and perfusion
- Cognitive fatigue and fatigability. Engage in "pacing" cognitively as well as physically
- Low cellular energy production. Capacity for "function" may be reduced in ME/CFS. Pacing critical!
- PEM—the consequences of exceeding cell energy capacity. Avoid severe/prolonged PEM



Medications that might help brain fog and cognitive impairment

- Wellbutrin/bupropion 75-300 mg (FDA approved for ADHD)
- Stimulants (examples) (FDA approved for ADHD)
 - methylphenidate
 - Mixed salts of dexadrine ---can raise BP and HR
- Newer drugs for daytime somnolence (FDA ind: OSA, SWSD, MS fatigue)
 - Modafinil and armodafinil --- can disrupt sleep T 1/2=15h
- Supplements (a few examples, not supported by strong evidence)
 - Fish oil, omega 3 fatty acids
 - Phosphatidyl serine 100 mg 2x or 3x daily
 - Curcumin (from turmeric)
 - B vitamins (B6, B9, B12) related to homocysteine metabolism
 - Vitamin E (tocopherol), Vitamin A, Vitamin C

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC33113 Common dietary supplements for cognitive health. Aging Health. Gestuvo and Hung. 2012 Additional behavioral strategies for managing cognitive impairment

- Complete cognitive tasks when more rested or at best time of day
- Allow more time and minimize interruptions
- Utilize day-timer, iphone, other external memory devices
- Dampen or remove other sensory input to the brain
 - Quiet room, ear plugs or sound-reducing headphones
 - Low or less-glaring lights
 - Reduce #people or other chaotic signaling/disruption

