Chronic Fatigue Syndrome

SPEAKERS
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Disclosures
The following relationships exist related to this presentation:


Off-Label/Investigational Discussion

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The CFS and Fibromyalgia expert

An expert is one who knows more and more about less and less

Nicholas Murray Butler (1882-1947)
President Columbia University (1901-45)
Case: JI

- 51-year-old Italian-American woman with fatigue dating back 20 years
- May have started as a bout of mononucleosis
- Constant feeling of tiredness, palpitations, tachycardia, shortness of breath, dizziness with minimal exertion
- Arms feel heavy with minimal activities of daily living
- Feet feel numb after standing for 20 minutes
- Foggy feeling in her head
- Very poor sleep pattern, stays awake until 4 AM and naps during the day
- Ringing in her ears, occasional inhaler for asthma
- She DENIES widespread pain

Case: JI

- Physical examination: well-developed, well-nourished woman
- No cervical, axillary or inguinal lymph node enlargement or tenderness
- ENT: normal, normal hearing
- Chest clear, heart sounds normal, no murmurs, no edema
- Joint examination normal; NO tender points
- Neurologic examination normal
- Laboratory studies: CBC, comprehensive metabolic panel, TSH, CK normal
- Full cardiac work-up including tilt-table testing negative

The Evolution of the CFS Concept

- Sir Richard Massingham (1750): febricula
- George Beard (1869): “neurasthenia”
- “epidemic CFS”: Iceland disease, Royal Free Disease, LA County Hospital (1934)
- Chronic active Epstein-Barr Virus (1985)
- Incline Village, Nevada (1985): Yuppie Flu

Chronic mononucleosis syndrome

- 1982 Tobi, et al (Israel)
- 1984 Dubois, et al (U.S.)
- 1985 Behan, et al (Scotland)
Normal serologic response to EBV mononucleosis

<table>
<thead>
<tr>
<th></th>
<th>Infection</th>
<th>1-2 months</th>
<th>Recovery</th>
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<tbody>
<tr>
<td>VCA-IgM</td>
<td>+</td>
<td>-</td>
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<td>VCA-IgG</td>
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<td>EA</td>
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<td>low +</td>
<td>-</td>
</tr>
<tr>
<td>EBNA</td>
<td>-</td>
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Viral serologic findings in persistent EBV infection

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<td>VCA-IgM</td>
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<td>VCA-IgG</td>
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<tr>
<td>EA</td>
<td>+</td>
</tr>
<tr>
<td>EBNA</td>
<td>Deficient</td>
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CFS and EBV infection

- EA found in people who recovered from infectious mononucleosis
- EBV titers do not correlate with disease activity
- Treatment of EBV infection does not improve clinical picture
- EBV titers not useful for recognizing CFS

Proposed infectious agents in CFS

- Epstein-Barr Virus
- Human herpesvirus-6 (HHV-6)
- Cytomegalovirus (CMV)
- Coxsackie B
- Toxoplasmosis
- Chronic Lyme disease
- Retrovirus HTLV-II
- Chronic candidiasis
- Enterovirus
- Ross River virus
- Borna disease virus
- XMRV *
- MLV (both due to contamination of specimens)

* Silverman, et al retracted their original publication in Science. See references.
Brain Perfusion in Chronic Fatigue Syndrome

- Increased perfusion in the right thalamus, pallidum and putamen in patients with CFS (30)
- Similar pattern seen in depression (12)
- CFS patients also increased perfusion in the right thalamus
- Compared to healthy volunteers (15)


CFS Biological Basis

- MRI punctate areas of high signal intensity in white matter
- SPECT abnormalities resemble encephalopathy of AIDS
- Autonomic dysfunction (orthostatic intolerance)
- HPA-axis: mild hypocortisolism

CFS Biological Basis

- Disruption of serotonin and norepinephrine pathways
- Increased CD8+ cytotoxic T cells
- Depressed function of NK cells
- Increased RNase L (80 and 40kDa) activity (2-5A pathway)
- Novel 37kDa protein (72% in CFS)

Chronic Fatigue Syndrome: Revised Definition

- Persistent or relapsing fatigue lasting ≥ 6 months
- 4 or more of following symptoms:
  1. Impaired memory or concentration
  2. Sore throat
  3. Tender cervical or axillary lymph nodes
  4. Muscle pain
  5. Multiple joint pain
  6. New headaches
  7. Unrefreshing sleep
  8. Post-exertion malaise

Chronic Fatigue Syndrome: Revised Definition

Proposed evaluation:
A. History and physical examination
B. Mental status examination
C. Screening laboratory studies: CBC, ESR, ALT, total protein, albumin, globulin, alkaline phosphatase, Ca**, PO4, glucose, BUN, electrolytes, creatinine, TSH, urinalysis
D. Additional tests as needed to exclude other diagnoses


2015 IOM diagnostic criteria for CFS/SEID

Institute of Medicine redefinition of CFS as SEID:
- Systemic Exertion Intolerance Disease

The term “myalgic encephalomyelitis” is no longer used because the brain is normal and there is no evidence of past or present brain inflammation

CFS/SEID patients DO NOT have an immune deficiency


2015 IOM diagnostic criteria for CFS/SEID

Diagnosis requires that the patient have the following three symptoms:
- A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities, that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest, and
- Post-exertional malaise, and
- Unrefreshing sleep


- At least one of the two following manifestations is also required:
  - Cognitive impairment or
  - Orthostatic intolerance

Recommended laboratory studies:
- CBC, comprehensive metabolic panel, TSH, CK

Epidemiology of Fatigue

• 8.5% of patients in a primary care setting had debilitating fatigue of at least 6 months without apparent cause
• Surveys of the general population show 6-7.5% have fatigue
• In patients with fatigue only 10% satisfy CFS/SEID definition

Epidemiology of Fatigue

• Common medical causes of fatigue:
  — Psychiatric illness: depression, anxiety and somatization
  — Chronic heart disease: congestive heart failure
  — COPD
  — Infections: HIV, TB
  — Occult malignancy
  — Sleep apnea

Epidemiology of Fatigue

• Common medical causes of fatigue:
  — Metabolic disorders: hypothyroidism, adrenal insufficiency, uncontrolled diabetes, pituitary failure
  — Renal failure
  — Chronic liver disease
  — Malnutrition
  — Drug addiction
  — Medications that cause fatigue

Case: KM

• 45-year-old woman, currently working part-time as a police officer
• Previously in excellent health
• Pneumonitis April 2013 treated with antibiotics
• Bouts of severe fatigue and muscle weakness
• Alternating constipation and diarrhea, painful urination, swollen glands in her neck and axillae
Case: KM
- Tender nodules on her chest wall
- Breathlessness with exercise
- Returned to full-time work in July with residual fatigue and generalized soreness
- After 2 months had worsening fatigue, sore throat, headaches, spots in front of her eyes, chest pain, memory lapses, sweating
- All laboratory studies normal except for
  - positive ANA 1:80, nucleolar pattern

Case: KM
- Current complaints 5 years later:
  - severe fatigue, sleeps 6-8 hours at night but does not feel refreshed in the morning
  - severe pain and swelling of her hands
  - generalized stiffness lasting over an hour in the morning
  - joints do not move well and she cannot grip objects without pain.
  - arms and legs feel heavy and weak
  - recent memory lapses
  - dry eyes and dry mouth
  - frequent cough, irritated by environment
  - She takes a statin

Case: KM
- Physical examination: hands and wrists show full ROM, very tender at joint margins but no swelling
- Eyes slightly injected; Schirmer’s > 10mm OU
- Mouth show normal dentition, normal salivary pool, no thrush
- Diffuse tender muscles and tender points
- No muscle weakness
- CBC, comprehensive metabolic panel, ESR, CRP, CK normal
- TSH, free T4 normal
- ANA + at 1:160 homogeneous pattern
- Anti-anti-SSA (Ro) Anti-anti-SSB (La) negative
Data from the first 305 patients in the Cleveland Clinic Fibromyalgia Clinic cohort

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Fatigue</td>
<td>98.7%</td>
</tr>
<tr>
<td>Widespread pain for three months or more</td>
<td>97.1%</td>
</tr>
<tr>
<td>Current depression (PHQ-9 score &gt; 10)</td>
<td>88.6%</td>
</tr>
<tr>
<td>Unrefreshing sleep</td>
<td>85.8%</td>
</tr>
<tr>
<td>Headaches</td>
<td>82.5%</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>79.5%</td>
</tr>
<tr>
<td>Memory difficulty</td>
<td>75.5%</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>67.5%</td>
</tr>
<tr>
<td>Constipation alternating with diarrhea</td>
<td>61.8%</td>
</tr>
<tr>
<td>Current severe or moderate-to-severe depression (PHQ-9 score ≥ 15)</td>
<td>45.8%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>41.8%</td>
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PHQ-9 = Patient Health Questionnaire-9


Fibromyalgia

- A clinical syndrome characterized by chronic widespread pain and tenderness to palpation at specific body sites
- Fibromyalgia has no target tissue but an easily recognizable clinical presentation

The Paradox of Fibromyalgia: No Target Tissue

- Normal passive range of joint motion
- Minimal mechanical disability
- Absence of muscle weakness or atrophy
- Normal ESR
- Normal radiographs, electromyogram, etc

Differential Diagnosis

- What symptoms would lead us towards FM?
  - Pain
    - Symptoms start insidiously but then maintain consistent severity for at least 3 months
    - Widespread symmetrical pain: axial and truncal, jaw, shoulder and hip girdles, upper and lower arms and legs
  - The other major symptoms:
    - Fatigue (I feel like I always have the flu)
    - Waking unrefreshed (no matter how much sleep I have had I feel exhausted as if I have not slept at all)
    - Cognitive symptoms (I cannot focus my thoughts, I have trouble remembering, I cannot do simple math)
**Differential Diagnosis**

- What other symptoms would lead us towards FM?
- General Somatic symptoms:
  - Irritable bowel syndrome: abdominal pain and cramping, food intolerance, constipation, diarrhea, nausea, heartburn, vomiting
  - Neurologic: headaches, muscle cramps and weakness, numbness and tingling, loss or change of taste, ringing in the ears, dizziness, seizures
  - Irritable bladder symptoms: frequent urination, painful urination, bladder spasms

- Depression, insomnia, many allergies, chemical sensitivity, nervousness
- Raynaud’s Phenomenon, cold and heat intolerance, sun sensitivity, dry skin, dry eyes and throat
- Hives/welts, easy bruising, hair falling out
- Loss or change of taste, loss of appetite

**Physical examination**

- General examination is normal.
- Musculoskeletal examination is normal:
  - Joints are NOT swollen, range of motion is normal.
  - Strength is limited by pain; no muscle atrophy or fasciculation; reflexes are normal; sensation is intact
  - Widespread tender points are seen in the majority of patients but a formal tender point examination to diagnose FM is no longer used for diagnosis
  - Should we accept a diagnosis of FM in the absence of ANY tender points?
ANA: speckled pattern

15-23% of FMS and CFS patients have a positive ANA

Lupus and Fibromyalgia

- 30% of SLE patients have fibromyalgia
- Fatigue may be caused by either or both
- Importance of restful sleep, conditioning and exercise
- Dangers of a wrong diagnosis
- Pitfalls of a positive ANA

Don’t use ANA as a screening test

Sensitivity 99+ %, specificity 85%
Lupus is a rare disease: highest prevalence (AA women) is 400/100,000 (or 4/1000) = base rate
If 1000 women were screened, 4 would be true positive (all SLE positive)
But 150 would be false positive (15% false positive)

A patient with a positive ANA has 4/154 = 2.6% chance of having lupus

Don’t use ANA as a screening test

In a primary care setting 232 patients referred with positive ANA and widespread pain – 2.1% had lupus, 9.1% had any ANA-associated rheumatic disease; no patient with ANA < 1:160.


Syndromes That Overlap with Fibromyalgia

The neurologist sees chronic headache, the gastroenterologist sees IBS, the otolaryngologist sees TMJ syndrome, the cardiologist sees costochondritis, the rheumatologist sees fibromyalgia, and the gynecologist sees PMS.

The Fibromyalgia Complex: Central Sensitivity Syndromes

- Chronic Fatigue Syndrome
- Fibromyalgia
- Irritable bowel syndrome
- Temporomandibular joint disorder
- Migraine and tension headaches
- Multiple allergies syndrome
- Multiple chemical sensitivities
- Idiopathic low back pain
- Irritable bladder syndrome
- Restless leg syndrome
- Primary dysmenorrhea
- Interstitial cystitis/chronic prostatitis/painful bladder syndrome
- Myofascial pain syndrome
- Regional soft tissue pain syndrome
- Many similarities to generalized anxiety disorder

Proposed Pathogenesis of Fibromyalgia

- Fan: The sensitive to everything syndrome
- Current working hypothesis: FM is a problem of central sensitization.
  - Peripheral and internal (autonomic) sensory inputs are heightened by the brain so that "normal" sensations are experienced as unpleasant
- Caveat: "central sensitivity is an evolving concept"
- Criticized as too broad and non-falsifiable (Wolfe 2015)*

Neuronal plasticity in FM

- Neural plasticity: the capacity of neurons to change their function, chemical profile, or structure
- Primary sensory and dorsal horn neurons undergo activation, modulation and modification.
- Gain is increased and results in hypersensitivity

Despite extensive research, the pathogenesis of pain in FM is not clearly understood. However, central sensitization has emerged as a leading theory of disease mechanism.

1. First, impulses from afferents depolarize dorsal horn neurons.
2. Then, extracellular Ca²⁺ and nitric oxide diffuse into neurons and cause exaggerated release of substance P and glutamate, resulting in neuronal hyperexcitability.
3. Finally, a pain signal is sent to the brain from the dorsal horn.

Current drug treatment is aimed at reducing the ascending “exaggerated” impulse or augmenting the descending “deficient” pain modulating pathway.

Can fibromyalgia pain be explained by an amplification feedback loop?

Can fibromyalgia pain be explained by an amplification feedback loop?

- Pain relief through expectation supersedes descending inhibitory deficits in FM
- After Brian Walitt, MD ACR National Meeting November, 2017

The Key Elements to Managing CFS/ Fibromyalgia

- Cognitive behavioral therapy
  — Includes education of her illness
- Graduated exercise program
  — Perform daily
- Restful Sleep
  — Quiet environment, no distraction

Treatment of Fibromyalgia / CFS

- Cognitive behavioral therapy
  A psychological treatment to modify thoughts and beliefs about FM and modify behavior by teaching coping skills and more effective use of rest, sleep and activity
Components of the Cognitive Behavior Therapy Approach

- Education
- Meditation
- Cognitive restructuring
- Distraction
- Pacing
- Laughter

Treatment of Fibromyalgia / CFS

- Education:
  - CFS / Fibromyalgia are well-recognized disorders
  - Stop further diagnostic studies
  - Reassure benign nature of complaints
  - Amelioration of symptoms is possible although there is no cure

Treatment of Fibromyalgia / CFS

- Exercise: needs to be sustained
  - Aerobic exercise, Tai-Chi, mineral baths, spa therapy proven effective
  - Emphasize that exercises improves energy and well-being but does NOT reduce pain

Pain, stress, and fatigue

- Fatigue ↓
- Inactivity ↓
- Deconditioning ↓ ↑
- Susceptibility to DOMS ↓
- Muscle Pain → Inactivity
Nonpharmacologic Treatment

- Aquatic Exercise
- Tai-Chi
- Program
- Stretching
- Low impact aerobics

Tai-Chi Exercises: Mean Changes in Nine Secondary Outcomes at 12 and 24 Weeks, According to Treatment Group

See in https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3023168/

Pharmacologic Treatment of Fibromyalgia / CFS

- Improve sleep:
  - Pediatric doxepin 10mg/ml, start with 6 drops at bedtime = 3mg
  - Alternative is low-dose amitriptyline 10mg nightly with slow increase to 50mg
  - Cyclobenzaprine 5 – 10mg nightly

Pharmacologic Treatment of Fibromyalgia/ CFS

- Depression:
  - 30% have major depression at time of diagnosis
  - Lifetime prevalence of depression is 74% and anxiety disorder 60%
  - SSRIs are not effective in reducing pain by themselves
  - Teach simple relaxation techniques
  - Formal stress-reduction program
  - Sleep hygiene
  - Correct sleep disorder
Pharmacologic Treatment of Fibromyalgia / CFS

- General rules:
  - Start with a low dose and build up slowly
  - Build upon a tricyclic at bedtime to improve sleep
  - For patients with prominent sleep problems add pregabalin (alternative gabapentin) to tricyclic
  - For patients with poor energy and exhaustion add duloxetine or milnacipran to tricyclic
  - Combining SNRIs with either pregabalin or gabapentin offers synergistic benefit

Pharmacologic Treatment of Fatigue

- An SNRI (dual serotonin and norepinephrine re-uptake inhibitor) may help pain, depression and fatigue
  - Duloxetine, milnacipran, venlafaxine
- Direct CNS stimulants:
  - Modafinil, methylphenidate, dextroamphetamine
  - Caffeine tablets; several cups of strong coffee
- Stimulants may heighten anxiety and provoke palpitations

Pharmacologic Treatment of Fibromyalgia

- Medical cannabis
  - The cannabis plant contains over 60 biologically active chemicals – cannabinoids
  - It is the most commonly used illicit drug in the world – 7% of US adults used it in the last 30 days, 34% sometime in 2015. 47% claim used for medicinal purposes
  - Action based on binding to cannabinoid receptors: 3 varieties: phytocannabinoids, synthetic analogs (e.g. nabilone*), endocannabinoids

Pharmacologic Treatment of Fibromyalgia

- Medical cannabis
  - THC binds CNS receptors and induces analgesia but may induce a “high”, provoke sedation, tachycardia and anxiety
  - CBD (cannabidiol) binds different receptors and ameliorates the psychoactive effects of THC – it is analgesic and anti-inflammatory
  - Potentially useful for neuropathic pain in fibromyalgia

- Nabilone; Cochrane review conclusion: We found no convincing, unbiased, high quality evidence suggesting that nabilone is of value in treating people with fibromyalgia. The tolerability of nabilone was low in people with fibromyalgia. Walit B, et al. Cochrane Database Syst Rev. 2016 Jul 18;7:CD011694
Treatment of Fibromyalgia / CFS

- Dubious treatments:
  - growth hormone
  - pressors: fludrocortisone
  - Botulinum toxin, nerve blocks, trigger point injections, rhizotomies, facet blocks, etc.

Alternative Medicine (none proven):

- Diet: gluten-free (some case reports of improvement with FM)
  - Carbohydrate rich
  - Exclusion
  - Caloric restriction, fasting, ketogenic (mitochondria-specific)


Fibromyalgia: the invisible pain

There was a faith-healer of Deal
Who said, “Although pain isn’t real,
If I sit on a pin
And it punctures my skin,
I dislike what I fancy I feel.”

*The Weekend Book (1925)*
Science and Pseudoscience

THE END
References: CFS


References: MUS


References: Fibromyalgia Diagnosis


References: Fibromyalgia Treatment

References: Fibromyalgia


References: Fibromyalgia Treatment


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