Unexplained Symptoms

Tips and Pearls

Kevin C. Fleming, MD
Day 12. No one had yet discovered that I am a polar bear.
Brain areas identified as related to the sensation of fatigue: Prefrontal cortex, insular cortex, and the anterior and posterior cingulate gyrus.

Tips and Pearls

Serotonin system in CFS

Accumulating evidence shows that 5-HT neurotransmission may be altered in CFS.

5-HT pathways from the dorsal raphe nuclei to the paraventricular nucleus of the hypothalamus seem to bring about secretion of hypothalamic-pituitary-releasing peptides involved in the release of prolactin and ACTH from the anterior pituitary.

Serotonin pathways project to the frontal cortex, striatum, hippocampus and hypothalamus.

Neuroinflammation is present in widespread brain areas in CFS/ME patients and was associated with the severity of neuropsychologic symptoms. Neuroinflammation is evidenced by activation of microglia or astrocytes, and activated glial cells exhibit an increase in expression of the 18-kDa translocator protein (TSPO). (R)-PK11195) is a ligand of PET for the TSPO that is expressed in activated microglia or astrocytes and is widely used to assess neuroinflammation in neurologic diseases.
Daily fatigue severity is significantly correlated with daily serum leptin levels in women with CFS but not in healthy controls. In a widened analysis to 50 other cytokines, the relationship between immune factors and fatigue was so strong that they were able to distinguish low fatigue days from high fatigue days with 78.3% accuracy, using only cytokines as predictors in patients with CFS.
Pressure algometer-induced pain: Temporal summation in fingers was higher in patients with CFS.

Deep-tissue hyperalgesia: Lower cuff pressure pain threshold in CFS.

Patients with **CFS** had lower pain thresholds than controls and patients with MS ... *even though they did not have daily/chronic pain symptoms* - for pressure, temporal summation, and conditioned pain modulation.
Evidence found for **sensitized fatigue pathways in CFS** and contributions of peripheral tissues to fatigue, most likely from muscles. Forearm occlusion appears to trap metabolites from exercised muscles resulting in increased overall and not just local fatigue. **Trapped muscle metabolites** may have activated peripheral and central fatigue pathways via **metabo-receptors**, including ASIC, TRPV1, and P2X.

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CFS patients experience fatigue from ↑ peripheral nerve sensitivity to normal muscle function, also provoking post-exercise central fatigue.
Normal vs. CFS compared doing intermittent and sustained leg exercises. Measured:
1. Max voluntary muscle contraction force (= fatigue)
2. MR spectroscopy (muscle metabolism)
3. Surface EMGs (neurophysiology)
4. VO2max (conditioning)

CFS and normal patients:
CFS did not demonstrate more muscle fatigue. Muscle metabolism was the same. EMGs were the same.

CFS had a progressive failure to voluntarily activate the muscle during strenuous exercise, but no defect of neuromuscular function (such as MS, ALS) = CENTRAL fatigue

In CFS, physical fatigue during and following exercise is perceived mentally rather than there being true peripheral muscle exhaustion.

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CFS had a progressive failure to fully activate the muscle during strenuous exercise, despite no detectable metabolic or functional changes occurring (this is not seen in ALS) = CENTRAL fatigue.

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CFS had a progressive failure to voluntarily activate the muscle during strenuous exercise, but no defect of neuromuscular function (such as MS, ALS)

= **CENTRAL fatigue**

In CFS, physical fatigue during and following exercise is **perceived in the brain** rather than there being true peripheral muscle exhaustion or a neurologic disorder.

Lidocaine injections improved resting fatigue in patients with chronic fatigue syndrome.

Fig. 5
Histogram of the LDA scores computed for genera differentially abundant between ME/CFS and healthy individuals. ME/CFS-enriched genera are indicated with a positive LDA score, and genera enriched in healthy individuals have a negative score. The LDA score indicates the effect size and ranking of each differentially abundant taxon.


Gut microbiome in CFS
CFS: altered gut microbiome

• Gastrointestinal tract in CFS is a pro-inflammatory environment

• Ongoing damage to gut mucosa in CFS leads to ↑microbial translocation from the gut into peripheral blood, which alters antimicrobial regulators and dysregulates the immune system

• CFS gut bacteria/microbiomes are less diverse and more unstable, abundance of specific genera

• Gut dysbiosis could be contributing to some of the symptoms and their severity in CFS
The gut microbiome shows that metabolic features of CFS are consistent with a hypometabolic state. The decreases in these metabolites correlated with CFS disease severity.
Fatigue: Is it a sleep problem?

- **Sleep is non-restorative in CFS**
  But ...PSGs have not shown a significant difference between CFS and normal controls

- **Subjectively poor but objectively normal sleep**
  suggests a psychosocial factors negatively affecting perception of sleep quality

- **Primary sleep disorders are often detected in CFS**
  BUT insufficient evidence that treatment improves fatigue (e.g., OSA) ...EXCEPT
Fatigue: Is it a sleep problem?

Improvement in **Insomnia** significantly improves fatigue

- Insomnia EEG: ↑ frontal alpha, beta and sigma power proportions, cortical hyper-arousal and ↑ wake-drive pressure, ↓ power proportions of slow oscillations in slow wave sleep

**Better sleep hygiene reduces total sleep time**

- (Goal: Max 8 hr)

**There is ↓ HRV in CFS only during sleep**

- ↓ parasympathetic, ↑ sympathetic activity
- ?? due to pain
- Training improves (increases) HRV (e.g., Heartmath)

**High fear avoidance** beliefs about CBT and graduated exercise in patients with CFS
Fatigue: Is it a sleep problem?

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- Power proportions of slow oscillations in slow wave sleep

- **Nightmares and insomnia** are a central feature of post-traumatic stress disorder (PTSD).
- Emerging evidence suggests that specific treatment of PTSD-related sleep disturbance improves PTSD symptoms.

**PTSD, PTSD with nightmares, and nightmares alone** can respond to a bedtime dose of **Prazosin**
- Training improves (increases) HRV (e.g., Heartmath)

High **fear avoidance** beliefs about CBT and graduated exercise in patients with CFS
Dizzy and/or lightheaded

Case: 51 year old female.
7/2016: Vertigo spell, moderately severe.
Acute symptoms resolved in 3 days.

Ever since then felt increasingly dizzy, never resolving.
Quit work. Can’t leave home.

2 head MRIs, 3 Neuro consults, 4 ENT consults, vestibular tests normal/negative.
Dizzy and/or lightheaded

Nonvertiginous dizziness, unsteadiness, unreal, floating, lightheadedness, spaced out or zoned out

Symptoms wax and wane, but usually persist throughout the day

Walking, standing, changing positions are typically worst, but some symptoms sitting or even supine

Symptoms worse in busy environment (malls), escalator, computer work, intense TV/movies, patterns

Triggers: Vertigo, TBI, syncope/presyncope, migraine, panic attacks
Dizzy and/or lightheaded

“Anxiety is not simply a cause or consequence of disturbances in spatial perception or locomotion, but one manifestation of a threat assessment system that is every bit as essential to mobility as the labyrinth, retina, and sensorimotor cortex.”

BRAIN components that control GAIT and EYE MOVEMENTS, emphasizing pathways that process vestibular and threat information.
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receives information about head, body, and external motion via the vestibular nuclei and cerebellum

centerpiece of the Threat System; will increase size in TRAIT anxiety
Acute Dizziness (Vertigo)

“Vestibular disorders are anxiety provoking medical crises, providing a strong incentive for the threat system to alter postural control.”

Anxiety TRAIT: FKBP5 Gene

Cytogenetic band: 6p21.31
Subcellular locations: nucleus, mitochondrion, cytosol
Glucocorticoid receptor regulatory network
Estrogen signaling pathway
TNF-alpha/NF-kB Signaling Pathway
Anxiety TRAIT : FKBP5 Gene

Introverts
Worriers
Anxious
Self-critical, people-pleasing perfectionists

I'd love to hang out, but I have to go sit in my house by myself...
1971: Tippi Hedren and daughter Melanie Griffith, in the swimming pool and reading the newspaper with their pet lion, Neil.
Chronic Subjective Dizziness

Failure of Readaptation
- Dizziness
- Fear of falling
- Functional gait disorder

Provoked by:
1. Standing upright
2. Motion
   - self
   - environment
3. Visual demands
   - complex
   - precise

CNS processes involved in control of posture and locomotion

Cortex
- Awareness of Motion Stimuli
- Conscious Control of Movement

Amygdala
- Threat Evaluation

Autonomic Nuclei

Sensory End Organs
- Visual, Vestibular & Somatosensory Motion Cues

Central Vestibular Processing
- Multisensory integration

Voluntary Locomotion and Oculomotor Control

Autonomic Responses

Reflexive Postural and Oculomotor Control
Persistent Postural Perceptual Dizziness (PPPD)

• PPPD (formerly CSD) is the 2nd most common cause of dizziness in tertiary neuro-otology centers

• Typical cases develop after acute vestibular neuritis, or between recurrences of episodic vestibular syndromes, such as BPPV or vestibular migraine
Tips and Pearls

spaced out, zoned out, disconnected or floating

Dizziness Trigger (e.g., head injury, migraine, labyrinthitis)

Avoidance of going out

Brain hypersensitivity

PPPD/Chronic Subjective Dizziness

Avoidance of Neck Movement

Neck Pain and headache

Anxiety (e.g., fear of falling)

Dissociation

Fatigue

spaced out, zoned out, disconnected or floating
Dizzy and/or lightheaded:

EXAM

1. Walk, turn, stand still with eyes closed
   Romberg: ↑ sway
   Ask: ‘How do you feel?’

2. Rapid head turn x 10 sec.
   Ask: ‘How did that make you feel?’
   Ask: ‘Is that the same sx, or different?’

3. Hyperventilate x 30 sec.
   Ask: ‘How did that make you feel?’
   Ask: ‘Is that the same sx, or different?’

4. ??Tilt Table (ANS) ?? Vestibular Clinic
PPPD treatments

Vestibular rehabilitation

SSRI/SNRI

CBT
Vestibular rehabilitation

Successful treatment requires a gentler approach than typically used for treatment of acute vestibular deficits.

Desensitization: Patient exposed to provocative stimuli in a controlled fashion

Exercises must be less intense at the beginning

Therapy must be increased very gradually

...or will exacerbate symptoms, stop therapy

Maximum benefit requires 3-6 months of diligent treatment.

Vestibular Exercises patient education form MCJ6508-05rev0912
Vestibular-Ocular Reflex Exercises for Dizziness form MC4383-01
Dizzy patient: Outcome

Improved!!
Dizzy patient: Outcome

Improved!!

...mostly
Funny gait: what to do?
Funny gait: what to do?

CNS processes involved in control of posture and locomotion

- **Cortex**
  - Awareness of Motion Stimuli
  - Conscious Control of Movement

- **Amygdala**
  - Threat Evaluation

- **Autonomic Nuclei**

- **Sensory End Organs**
  - Visual, Vestibular & Somatosensory Motion Cues

- **Central Vestibular Processing**
  - Multisensory integration

- **Voluntary Locomotion and Oculomotor Control**
- **Autonomic Responses**
- **Reflexive Postural and Oculomotor Control**
Funny gait? Search “motion”

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<td><strong>X</strong></td>
<td>Gait Analysis-EMG &amp; Physical Exam CGAITEMG</td>
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<td>Plantar Foot Pressure Study CFTPR</td>
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<td>Quantitative Strength Analysis CSTRENG</td>
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<td>Upper Extremity Motion Analysis EMG &amp; Exam CUEMOPE</td>
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Dynamic upper and lower extremity motion analysis

- 10 camera motion capture system
- 5 force platforms embedded in floor
- 2 force platforms in steps
Funny gait? Motion Analysis lab

Gait lab is a 3 hour appointment

Allow 2 weeks for full data interpretation

They can schedule a conference with ordering provider to go over results
Sinus symptoms
Sinus symptoms that aren't

Chronic/recurrent sinusitis, refractory congestion
— ‘Sinus’ headaches, pressure, congestion
— Multiple courses of antibiotics per year

Get CT sinuses during typical spell
— ‘Would you ask for ABX for these symptoms?’
— excessive inflammation within sinus/nasal cavity, edema within sinus/nasal cavity
— If absent: consider Sensitization effect
飞往 厦门 的航班 MU2970
由于某些原因延误
FLT No. MU2970 To XIAMEN
DELAYED DUE TO SOME REASONS
Pelvic floor dysfunction: Clues

Constipation unresponsive to usual Treatment

- Straining (+/- ineffective) even w/o hard stools, incomplete evacuation, splinting, or digital removal
- Maalox: no better (or worse), ↑ bloating
- Pelvic pain or pressure

Recurrent “UTIs” that aren’t

- Frequency, urgency, incontinence, straining, incomplete voiding, splinting, digital maneuvers to void, pelvic pressure, ‘interstitial cystitis’
- Could be PFD or irritable bladder
The last signs of life slip over the horizon.
Finally, I am alone with my crimes, unrepentant.