

NOW MORE THAN EVER

BE A DETECTIVE

BE A CLINICIAN

DON'T BE AN EYE-ROLLER!!

Dr. Anthony Fauci, July 2020 IAS COVID-19 Press Conference

*“If you look anecdotally there is no question that there are a considerable number of individuals who have a **post-viral syndrome** that really in many respects can incapacitate them for weeks and weeks following so-called recovery and clearing of the virus....you can see people who’ve recovered who really do not get back to normal that they have things that are highly suggestive of **myalgic encephalomyelitis and chronic fatigue syndrome**. Brain fog, fatigue, and difficulty in concentrating so this is something we really need to seriously look at because it very well might be a **post-viral syndrome associated with COVID-19.**”*

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

- A chronic, multi-system disease that affects approximately 1.3 MILLION Americans
- Affects the central and autonomic nervous system, the cardiovascular system, the gastrointestinal system, and the immune system

Onset and Risk Factors

- 65%-80% of patients describe onset of symptoms after an acute viral or bacterial infection
- Herpesviruses especially EBV-Mononucleosis

Sex Distribution

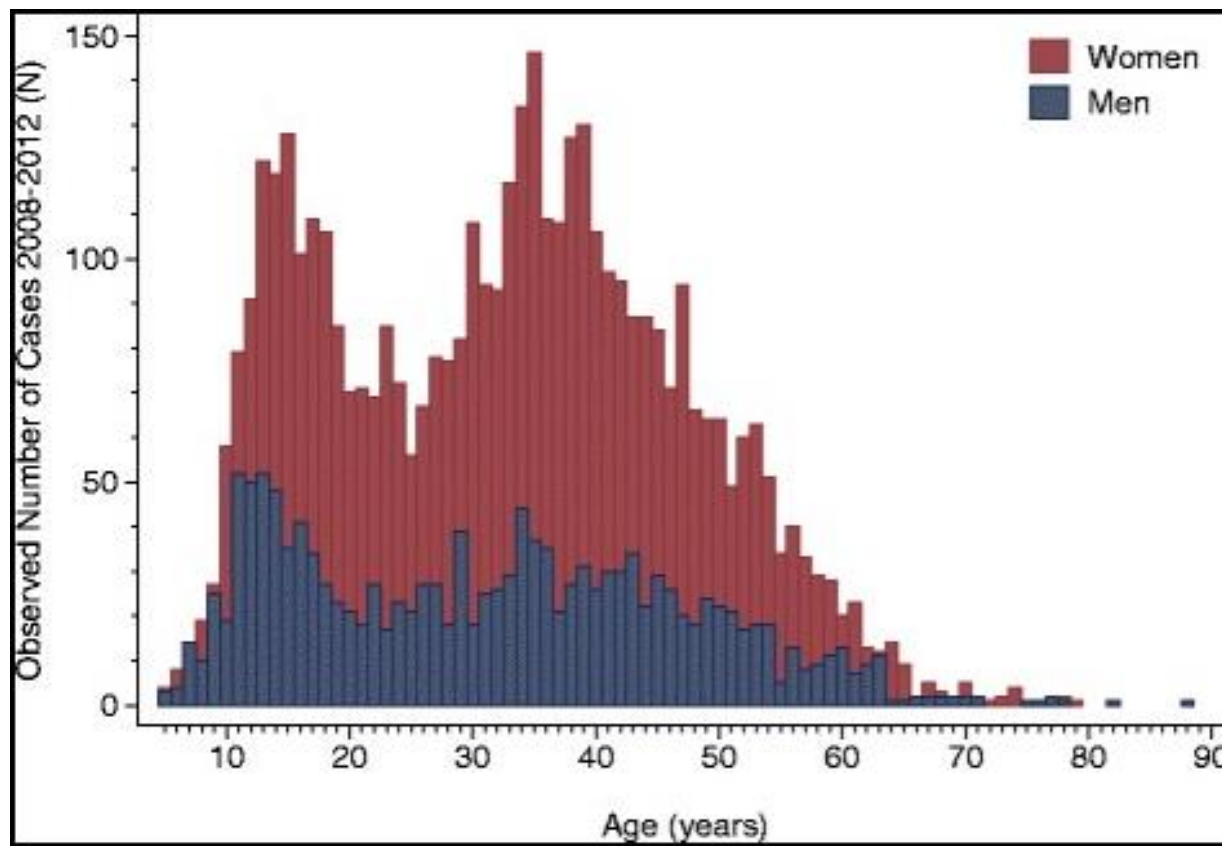


Figure 1 Observed number of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) cases by sex and one-year age groups (age in 2008). Data from the Norwegian Patient Register 2008 to 2012.

Source: Bakken et al. 2014

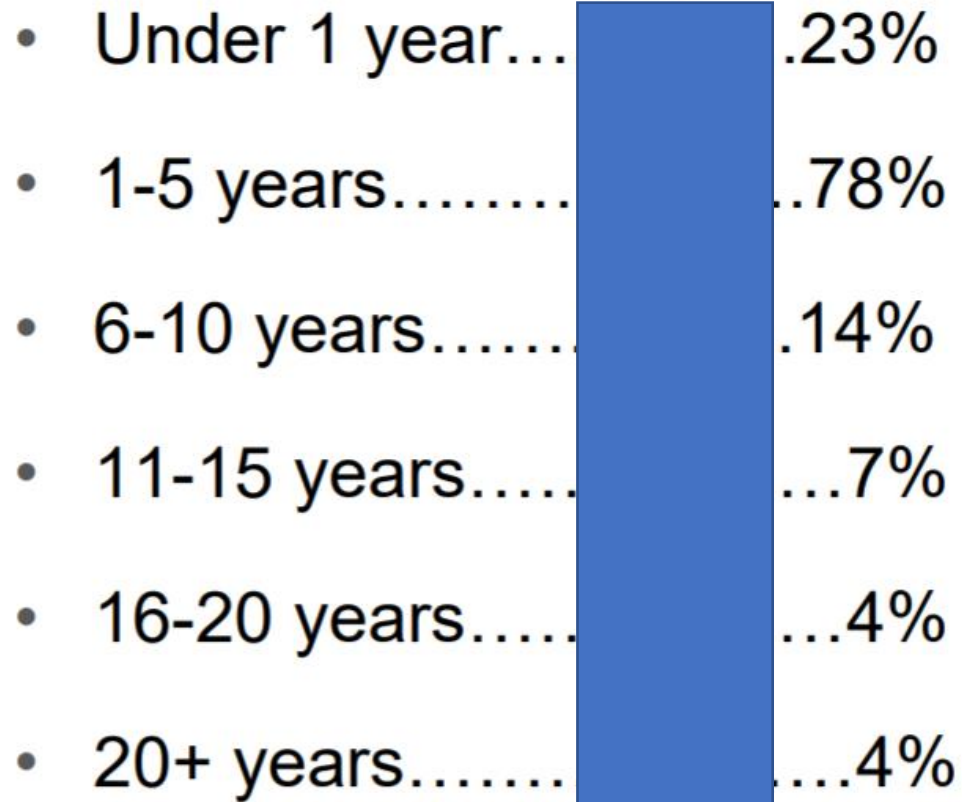
Genetic Risk Factors

- First degree relative with ME/CFS doubles the risk for other family members
- Female to Male=3:1
- White=African American=Hispanic/Latinx

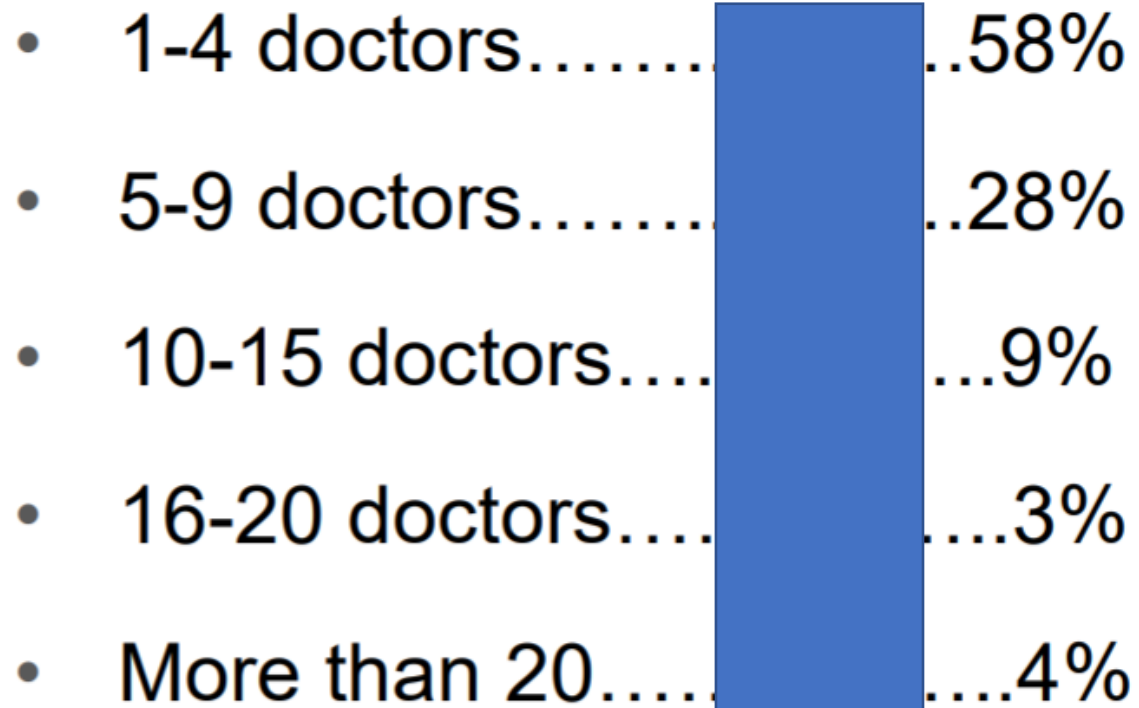
Prevalence

Disease	# US 2017	Prevalence	NIH \$ 2017
ME/CFS	1.7-3.75 M		15M
LUPUS	785,000		109M
MS	486,000		111M

Time to Diagnosis—29% No Dx 6-20 Years



Number of Clinicians Seen Before Dx of ME/CFS



Common MD Experiences/Common Diagnoses

- Depression
- Anxiety
- Conversion Reaction
- Malingering
- Menopausal
- Munchausen (patient and by proxy)



Say It Again: NOT a Psychiatric Disease and NOT a Disease of Deconditioning

- “Just go out and exercise”= NO
- “Just get Cognitive Behavioral Therapy”=NO
- “Just get Graded Exercise Therapy”=NO
- Self Pacing=YES

Never Forget–Post Exertional Malaise

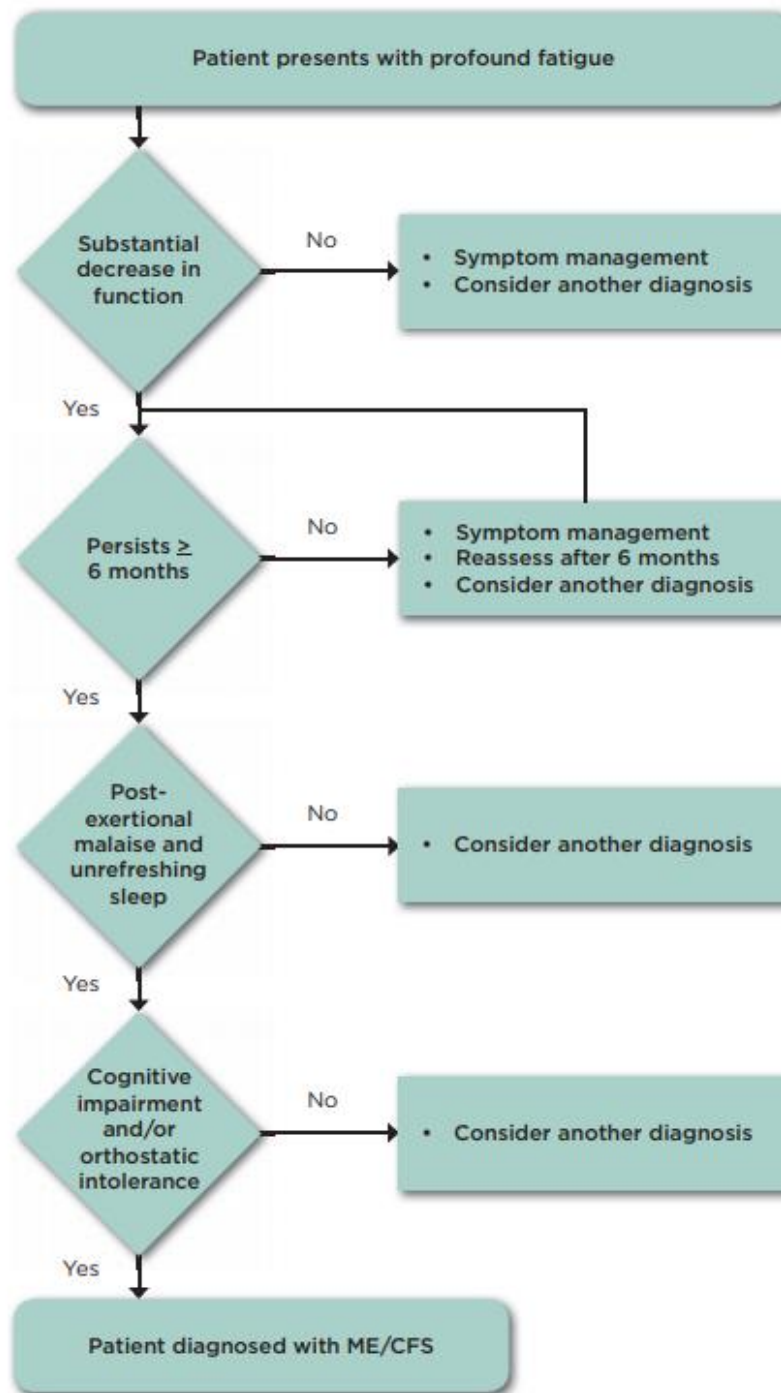


Figure 4 Diagnostic Algorithm for ME/CFS

Source: Beyond ME/CFS Report Guide for Clinicians 2015

NATIONAL ACADEMY OF MEDICINE CLINICAL CRITERIA—SYMPTOMS AND PHENOTYPE

- A substantial reduction or impairment in ability to engage in pre-illness activity that persists for 6 months or more
- Fatigue that is profound, not lifelong, not the result of ongoing exertion, and not alleviated by rest
- Post-exertional malaise (PEM) in which physical or mental activities result in a delayed exacerbation of symptoms and reduction in functioning
- Unrefreshing sleep
- And either cognitive impairment and/or orthostatic intolerance

Post-exertional Malaise Prevalence

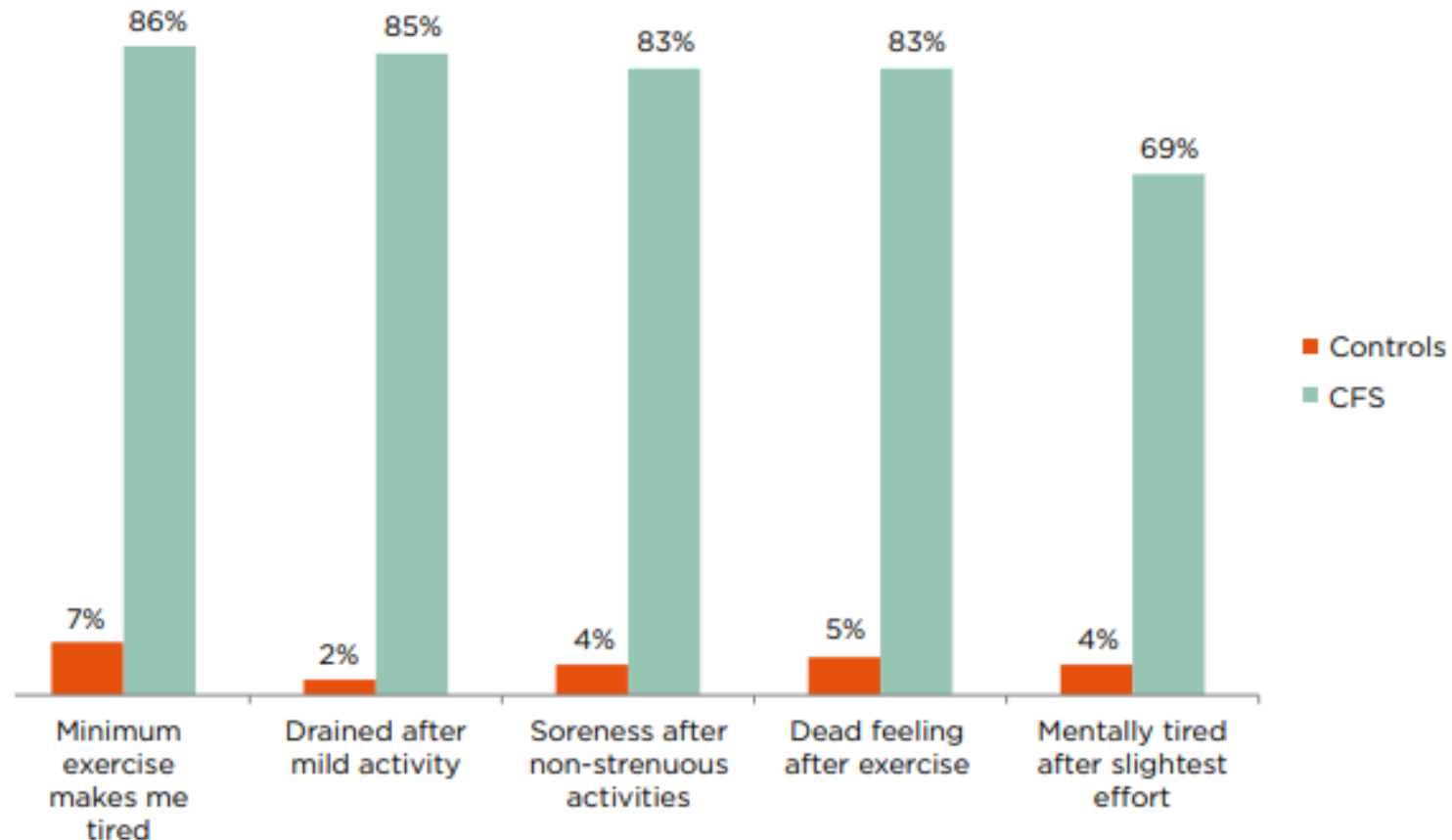


Figure 5 Percentage of ME/CFS patients and healthy controls reporting PEM symptoms of at least moderate severity that occurred at least half of the time during the past 6 months.

Source: Beyond ME/CFS Report Guide for Clinicians 2015

How ME/CFS Patients Describe Their Post-exertional Malaise

- “crash”
- “literally, it's an eye movement, like I'm looking here, I look over there and, boom, I know I'm going to have a crash because I can feel my whole body changing.”
- “When people talk about being bedbound, I mean, we're like bricks, we can't be moved. My wife would come in and check on me to see if I was breathing because I would sleep for days at a time. I didn't get up to eat, I didn't get up to go to the rest room.”
- “[A crash is] not just the physical pain or it's not just the head pain, it's also more cognitive impairment, more orthostatic intolerance, more neurological issues...they're very interrelated.”
- “my head feels like it's going to explode...and I really have to have total silence, 9 total darkness.”

Source: FDA 2013

How ME/CFS Patients Describe Their Fatigue

- “too exhausted to change clothes more than every 7-10 days”
- “exhaustion to the point that speaking is not possible”
- “exertion of daily toileting, particularly bowel movements, sends me back to bed struggling for breath and feeling like I just climbed a mountain”
- “slowed processing speed”
- “tired but wired”

Source: FDA 2013

ME/CFS Patients' Sleep Quality

- 19-69% of patients have comorbid sleep disorder
- Unrefreshing sleep
- Difficulty falling asleep
- Frequent awakenings
- Nonrestorative sleep
- “I could sleep 10 to 12 hours a night, and I do, and I still don't feel good in the morning... if I get less than 10 to 12 [hours] or if I have a bad night for whatever reason, I feel even worse.”

Source: Jason et al. 2014, FDA 2013

COGNITIVE DYSFUNCTION—BRAIN FOG

- Executive function/multi-tasking
- Word finding problems
- Memory impairment
- Reading, writing, television



Source: Google photos

How ME/CFS Patients Describe Their Neurocognitive Symptoms

- “brain fog”
- “I read [what I’ve written] the next day and it's not making sense to me. Now, does that mean I was confused when I wrote it and the writing is actually no good, or am I confused now and unable to read a perfectly good sentence?”
- “inverting words and numbers when speaking or reading”
- “inability to process information”
- “short-term memory loss”
- Difficulty watching television
- “mapping dyslexia, where I lose all sense of how to get from place to place, even with familiar locations”

Source: FDA 2013

Neurocognitive Deficits Prevalence

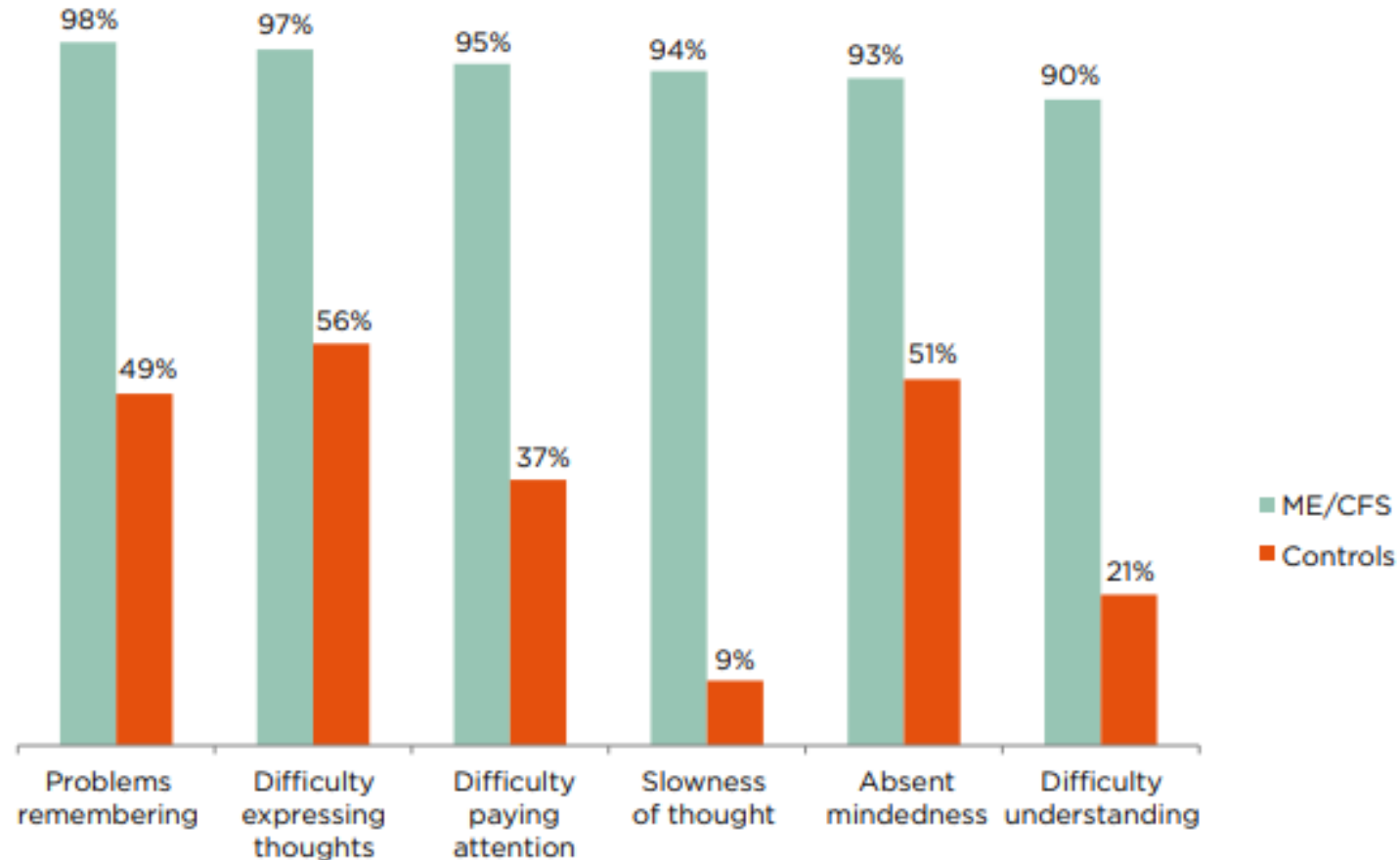


Figure 7 Percentage of ME/CFS patients and healthy controls reporting neurocognitive manifestations of at least moderate severity that occurred at least half of the time during the past 6 months.

Source: Beyond ME/CFS Report Guide for Clinicians 2015

Pain Prevalence

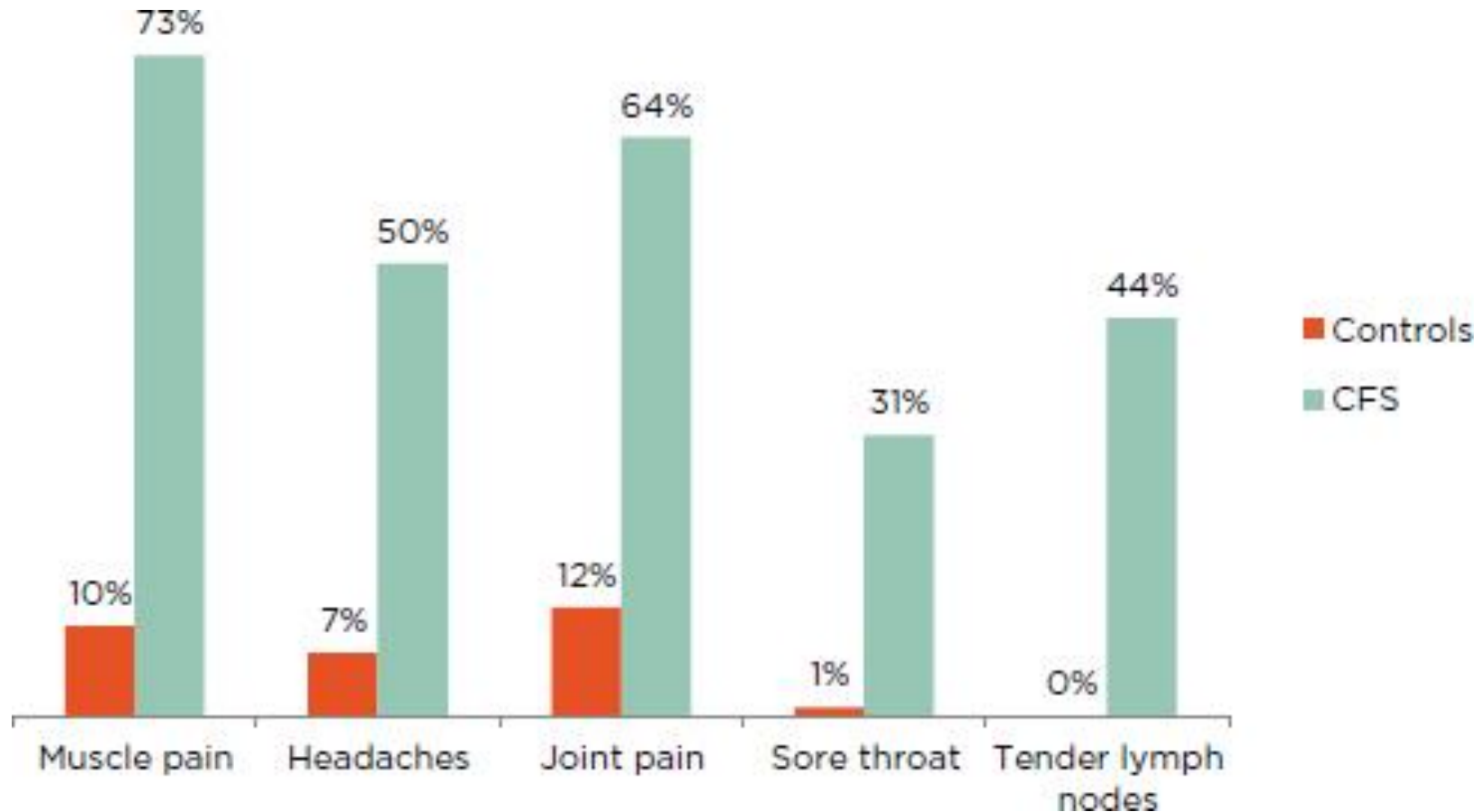


Figure 8 Percentage of ME/CFS patients and healthy controls reporting pain symptoms of at least moderate severity that occurred at least half of the time for the past 6 months.

Source: Beyond ME/CFS Report Guide for Clinicians 2015

How ME/CFS Patients Describe Their Pain

- “full-body ice-cream-headache-like-pains”
- “like if you had run a marathon.... I can barely put one foot in front of the other, barely lift my arm, I jerk”
- “my brain was going to explode”
- “when I finish a workweek..., I spend the entire day Saturday in the midst of recovery and fog and pain and exhaustion”
- “I've probably tried at least 25 drugs [for pain], maybe more, and over time they lose effectiveness. I have to switch it up”

Source: FDA 2013

Immune Impairment in ME/CFS

- swollen lymph nodes
- sore throats, muscle pains
- achy joints
- Headaches
- Chills
- “feverishness” without meeting the criteria for fever
- sensitivities to certain substances
- continual flu-like state

Source: FDA 2013

Immune-related Symptoms Prevalence

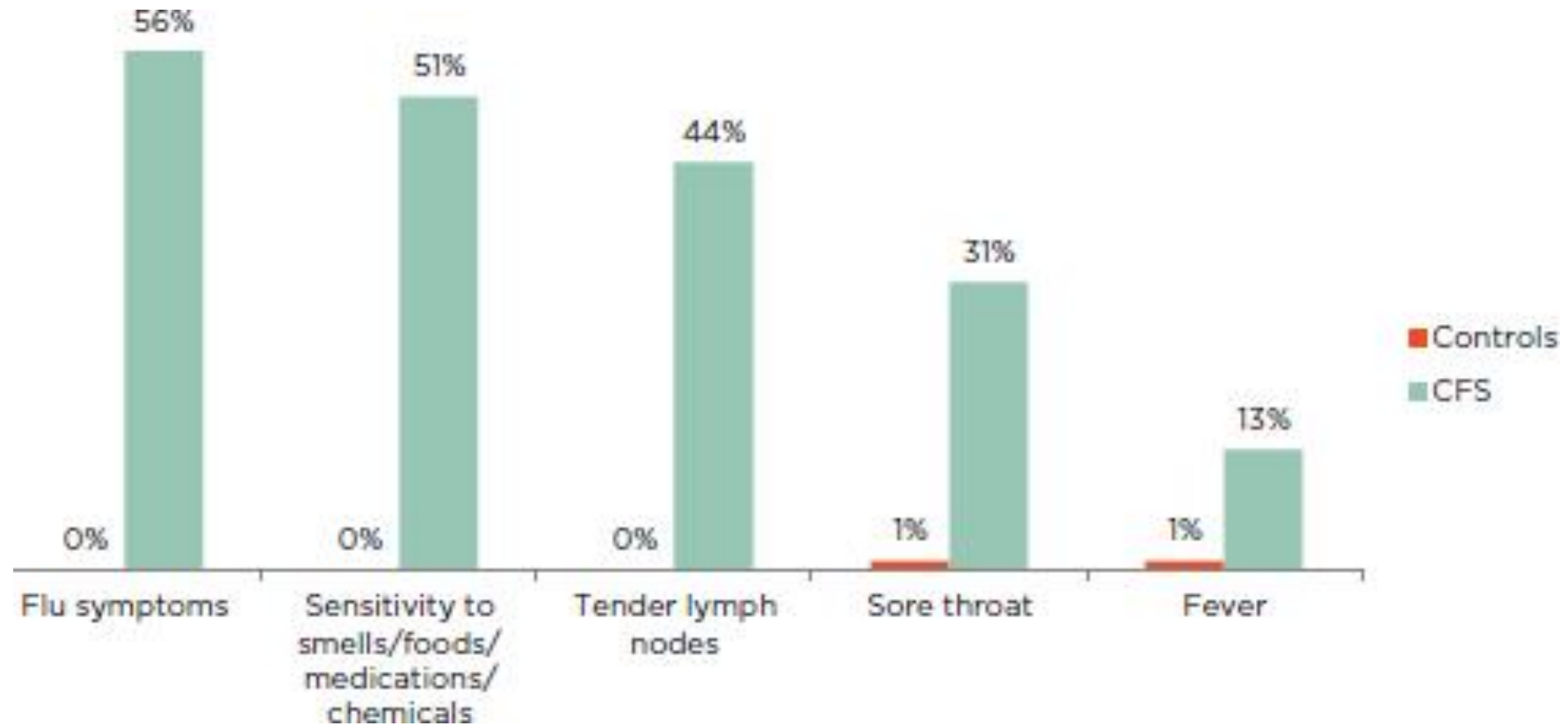


Figure 9 Percentage of ME/CFS patients and healthy controls reporting immune-related symptoms of at least moderate severity that occurred at least half of the time for the past 6 months.

Source: Beyond ME/CFS Report Guide for Clinicians 2015

Pediatric vs Adult ME/CFS

<u>Pediatric</u>	<u>Adult</u>
<ul style="list-style-type: none"> • Gradual onset common 	<ul style="list-style-type: none"> ◦ Acute, episodic onset of illness
<ul style="list-style-type: none"> • Acute infectious onset more common 	<ul style="list-style-type: none"> ◦ Variable cause of onset
<ul style="list-style-type: none"> • Decreased endurance with symptoms 	<ul style="list-style-type: none"> ◦ Fatigue very prevalent
<ul style="list-style-type: none"> • Pain is variable across studies 	<ul style="list-style-type: none"> ◦ Pain very prevalent
<ul style="list-style-type: none"> • PEM onset more likely within hours 	<ul style="list-style-type: none"> ◦ PEM onset can be over minutes to days
<ul style="list-style-type: none"> • Low prevalence of sleep disorders • Dizziness more prevalent • Flu-like symptoms • Worse cognitive abnormalities under orthostatic stress 	<ul style="list-style-type: none"> ◦ High prevalence of sleep disorders

Source: Review of the Evidence on Major ME/CFS Symptoms and Manifestations 2015

New clinical observational studies suggest that Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a sequela of Covid-19 infection, but whether there is an exact causal relationship between Covid-19 and ME/CFS remains to be verified.

These results suggest that SARS-Cov-2 infection may not significantly contribute to the elevated risk of developing CFS, and therefore ME/CFS may not be a sequela of Covid-19 but may simply present with symptoms similar to those of CFS after Covid-19 infection, and thus should be judged and differentiated by physicians when diagnosing and treating the disease in clinical practice.

Results from this international online survey of 3762 individuals with suspected or confirmed COVID-19 illness suggest that Long COVID is composed of heterogeneous sequelae that often affect multiple organ systems, with impact on functioning and ability to work.

POST EXERTIONAL MALAISE—PEM/CRASH

- PEM--worsening of symptoms after physical or cognitive effort
- Often delayed by 8, 24, or 48 hours post-exertion
- Walking, dressing, showering, keyboarding, talking
- Impaired aerobic metabolism, lowered anaerobic threshold, orthostatic stress, **mitochondrial dysfunction**

Fatigue vs Post Exertional Malaise

- Many fatiguing illnesses—SLE, MS, RA, Mono
- PEM is unique to this phenotype which includes ME/CFS, Gulf War Illness, and “Long COVID”
- (and don’t forget SARS, MERS, Ebola....)
- **PEM is DEFINING and DISABLING**

AUTONOMIC NERVOUS SYSTEM DYSFUNCTION

- Orthostatic Intolerance-Orthostatic Hypoperfusion
- Postural Orthostatic Tachycardia Syndrome-POTS
- Neurally Mediated Hypotension-NMH
- Hyperadrenergic POTS
- Sx: dizzy, weak, palpitations, nausea, diaphoresis

MORE COMMON SYMPTOMS: THE DREADED POSITIVE ROS

- Pain-muscles and joints
- Headaches
- Light, sound, chemical hypersensitivity
- GI-nausea, bloating, pain, constipation, diarrhea
- Temperature dysregulation, cold/hot intolerance



Source: Google photos

“Listen to your patient, they are telling you the diagnosis.” –William Osler

- History history history—in these patients the HPI, the PMH, and the ROS really are the CC.
- Think BIG, Cast a WIDE Net, BE A DETECTIVE

Initial Evaluation

- Physical Exam: Expect the supine “usual” exam to be unremarkable.
- Dysautonomia—NASA Lean Test



Orthostatic Vital Signs/The NASA 10-minute Lean Test

	Blood Pressure (BP)		Pulse	Comments
	Systolic	Diastolic		
Supine 1 minute				
Supine 2 minute				
Standing 0 minute				
Standing 1 minute				
Standing 2 minute				
Standing 3 minute				
Standing 4 minute				
Standing 5 minute				
Standing 6 minute				
Standing 7 minute				
Standing 8 minute				
Standing 9 minute				
Standing 10 minute				

Orthostatic intolerance (OI) is an umbrella term used to describe abnormal autonomic nervous system response to orthostatic challenge.

Orthostatic hypotension (OH), neurally mediated hypotension (NMH)] and postural orthostatic tachycardia syndrome (PoTS) are terms used to describe variants of this response.

The new evidence-based IOM clinical criteria for ME/CFS establish that orthostatic intolerance is a common and often overlooked feature of illness that is objectively measurable.

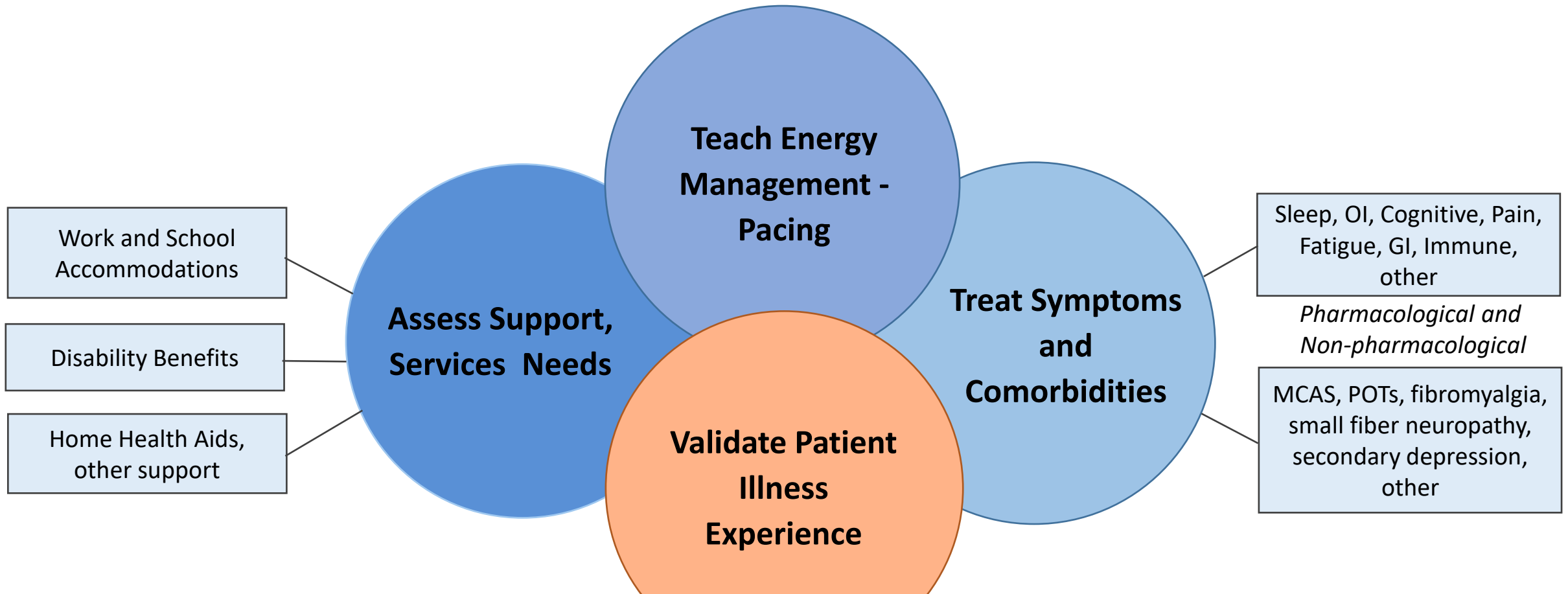
Diagnostic Testing

- Immunology Panel—IgG subclasses, IgA, IgM, IgE, Lymphocyte Subsets
- Viral Serology—esp. EBV, CMV, HHV6
- Hormone Panel—esp. Thyroid, Testosterone, Saliva Cortisol, consider ACTH stim testing

Initial Treatment

- Fluids, Salt, Compression Garments
- Consider Low Dose Naltrexone Titration
- Consider Trial Histamine 1 and 2 receptor blockers with Quercetin

Management Approach



Primary Care Providers in Collaboration with Patient/Caregiver, OTs, PTs, and Sub-specialties

Account of Long Haul COVID Experience

A 26-year-old high school teacher from Georgia described the symptoms as such:

My chest hurts and head pounds

The body aches and heart races

I can hardly move, it's extreme fatigue

Brain's in a fog, can't remember the name of my dog

Lost my sleep and my appetite

Feet are tingling and ears are ringing

It's the Long-Haul COVID

Source: Nath 2020

The Real World: Managed Care and 20 Min Visits

- Initial Visit—Comprehensive history, start at the beginning
- Visit 2—Physical Exam with Lean Test and labs ordered, ? LDN/Mast Cell meds
- Visit 3—Review tests, results of home Lean tests and response to meds

A New Paradigm–Future Research Directions

- A multi-organ, multi-pathogen progressive syndrome driven by chronic inflammation and immune activation leading to the ME/CFS phenotype, often complicated by increasingly fragile connective tissue and mitochondrial dysfunction

