Medical Manifestations of COVID Infection and Long-COVID in Children and Adolescents

April 21, 2023, Woodcock Institute,
Texas Women's University

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Disclosure

- I have no relevant financial relationship with the manufacturer of any commercial product or provider of commercial services discussed in this CME activity.
- I do intend to discuss an unapproved commercial product in my presentation.

Key Points

- Those with substantial impairment following mild COVID-19 infection look virtually identical to pre-pandemic ME/CFS, and satisfy the IOM criteria for that diagnosis
- Orthostatic intolerance, which is almost universal in adolescents with ME/CFS, and affects 90% of adults, is one of the most treatable components of long COVID & ME/CFS
- Individuals with ME/CFS and long COVID have a non-random increase in the prevalence of certain co-morbid conditions, including joint hypermobility, postural dysfunctions, mast cell activation and others, each of which offers potential inroads to improving function

"Long COVID is highly suggestive of myalgic encephalomyelitis and chronic fatigue syndrome [ME/CFS]."

Dr. Anthony Fauci
U.S. National Institutes of Health

Adolescent and Young Adult ME/CFS After Confirmed or Probable COVID-19

Lindsay S. Petracek[1], Stacy J. Suskauer[1,2], Rebecca F. Vickers[3], Neel R. Patel[4], Richard L. Voland[5], Renee L. Swope[1] and Peter C. Rowe[1]*

frontiers in Medicine

ORIGINAL RESEARCH
published: 29 April 2021
doi: 10.3389/fmed.2021.668944

- 2F, 1M
- Ages 19, 22, 30
- All working or studying full-time before illness
- All currently meet IOM criteria for ME/CFS after 12-15 months of illness

Healthcare 2023, 11, 865.

19 yr old with post-infectious ME/CFS symptoms during the Covid-19 pandemic

PMH:

Allergies to pollens, grass (immunotherapy ages 10-13)
Oral allergy syndrome to carrots, cashews, cherries
Mild asthma
Johns Hopkins freshman, runs 60-70 miles weekly as part of cross country team training

19 yr old with post-infectious ME/CFS symptoms during the Covid-19 pandemic

June 17, 2020: cough, sore throat, headache, fatigue, flu-like aches

June 20: PCR test positive

Anosmia for several months, but never hypoxic, not hospitalized

July: Notes elevated HR walking between rooms of the house

August: after playing cornhole, HR 170 bpm for 30 min; 3 days of PEM

CXR, ECG, echo, Troponin, cardiac MRI normal

Main symptoms at 3 months: fatigue, insomnia, disrupted & unrefreshing sleep, PEM, lightheadedness, mild cognitive dysfunction, new sense of being overwhelmed by sensory stimulation. Wellness 45/100

How has clinical experience and published data on Pediatric ME/CFS informed our approach to Post-COVID conditions?

Beyond Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome

Redefining an Illness

Committee on Diagnostic Criteria for ME/CFS
February 10th, 2015

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Advising the nation • Improving health

ME/CFS is a serious, chronic, complex, multisystem disease that often can profoundly limit the health and activities of affected patients.

Core Symptoms

1. Substantial impairment in activities that were well tolerated before the illness, accompanied by profound fatigue
2. Post-exertional malaise (PEM)
3. Unrefreshing sleep

and either

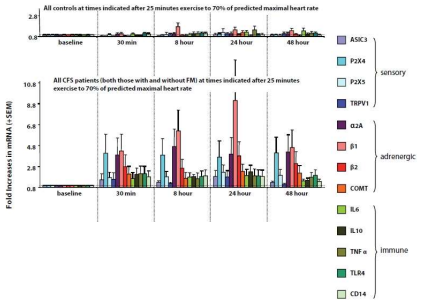
4a. Cognitive impairment or

4b. Orthostatic intolerance

Symptoms present for at least 6 months, at least half the time, and at least moderate severity.

PEM

- PEM refers to an increase in all symptoms after physical or cognitive exertion, including worse fatigue, flu-like symptoms, lightheadedness, cognitive dysfunction, headaches, pain, light/sound sensitivity, and others.
- PEM can extend well beyond 24 hours
- Post-exertional malaise is not unique to ME/CFS, but is more common in ME/CFS than in depression



Light AR, et al. Myalgia and Fatigue: Translation from Mouse Sensory Neurons to Fibromyalgia and Chronic Fatigue Syndromes. Editors In: Kruger L, Light AR. eds. Translational Pain Research: From Mouse to Man. Boca Raton, FL: CRC Press; 2010.

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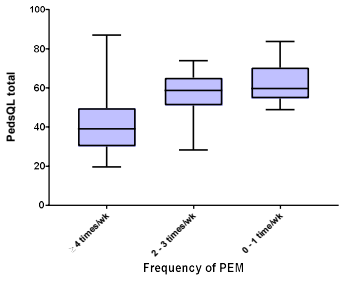


Roma M, Marden CL, Flaherty MAK, Jasion SE, Cranston EM and Rowe PC (2019) Impaired Health-Related Quality of Life in Adolescent Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: The Impact of Core Symptoms. Front. Pediatr. 7:26. doi: 10.3389/fped.2019.00026

15

Orthostatic Intolerance

The term "orthostatic intolerance" refers to a group of clinical conditions in which symptoms worsen with quiet upright posture and many (but not all*) are improved upon lying down.

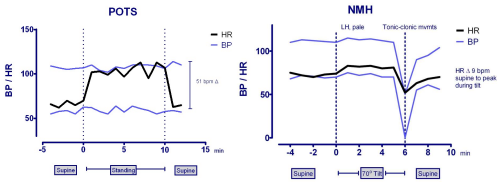
* Fatigue & brain fog can persist long after assuming a recumbent posture

Modified from: Low PA, Sandroni P, Joyner M, Shen WK. Postural tachycardia syndrome (POTS). J Cardiovasc Electrophysiol 2009;20:352-8.

Symptoms Of Orthostatic Intolerance

Lightheadedness	Dyspnea
Syncope	Chest Discomfort
Diminished concentration	Palpitations
Headache	Tremulousness
Blurred vision	Anxiety
Fatigue	Nausea
Exercise intolerance	Nocturia

Common forms of orthostatic intolerance



POTS: In first 10 min standing or HUT, 30 bpm ↑ in HR in adults (40 bpm in < 19 yrs) without OH, with OI symptoms (HR often > 120)

NMH: 25 mm Hg ↓ in SBP, with OI symptoms

Acrocyanosis is common in ME/CFS

Is neurally mediated hypotension an unrecognised cause of chronic fatigue?

Peter C Rowe, Issam Bou-Holaigah, Jean S Kan, Hugh Calkins

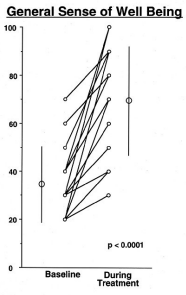
Lancet 1995; **345:** 623–24

The Relationship Between Neurally Mediated Hypotension and the Chronic Fatigue Syndrome

Issam Bou-Holaigah, MD; Peter C. Rowe, MD; Jean Kan, MD; Hugh Calkins, MD

JAMA 1995;274:961-7

Response of CFS subjects to open treatment of orthostatic intolerance



JAMA 1995;274:961-7.

Clinical SCIENCE

www.clinsci.org

Clinical Science (2012) 122, 227–238 (Printed in Great Britain) doi:10.1042/CS20110241 227

Increasing orthostatic stress impairs neurocognitive functioning in chronic fatigue syndrome with postural tachycardia syndrome

Anthony J. OCON*, Zachary R. MESSER†, Marvin S. MEDOW*†
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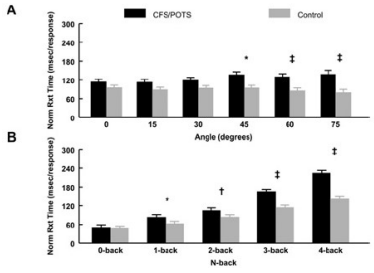
*Department of Physiology, New York Medical College, Valhalla, NY, U.S.A., †Department of Pediatrics, New York Medical College, Valhalla, NY, U.S.A., and ‡Department of Medicine, New York Medical College, Valhalla, NY, U.S.A.



Clinical Neurophysiology Practice 5 (2020) 50–58

Contents lists available at ScienceDirect

Clinical Neurophysiology Practice

journal homepage: www.elsevier.com/locate/cnp

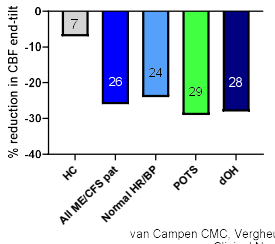
Research paper

Cerebral blood flow is reduced in ME/CFS during head-up tilt testing even in the absence of hypotension or tachycardia: A quantitative, controlled study using Doppler echography

C. (Linda) M.C. van Campen [a,*], Freek W.A. Verheugt [b], Peter C. Rowe [c], Frans C. Visser [a]

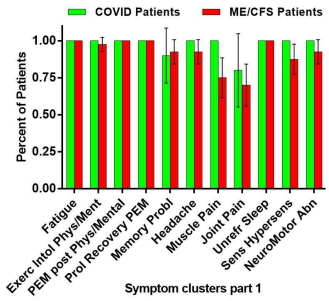
[a] Stichting CardioZorg, Planetenweg 5, 2132 HN Hoofddorp, The Netherlands
[b] Department of Cardiology, Onze Lieve Vrouwe Gasthuis (OLVG), Oosterpark 9, 1091 AC Amsterdam, The Netherlands
[c] Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Changes in CBF during 30 minutes of HUT compared to supine values in 44 HC and 429 ME/CFS

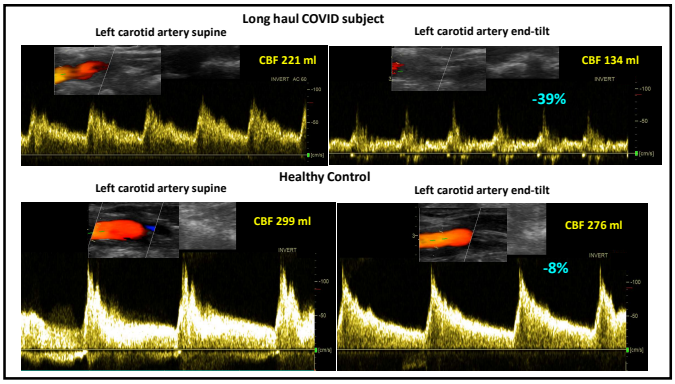


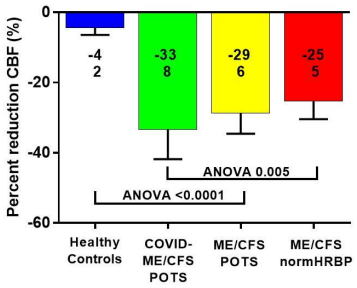
For all ME/CFS groups vs HC, P < 0.001.
(No differences in CBF supine pre-tilt)

van Campen CMC, Vergheut FWA, Rowe PC, Visser FC.
Clinical Neurophysiology Practice 2020.5

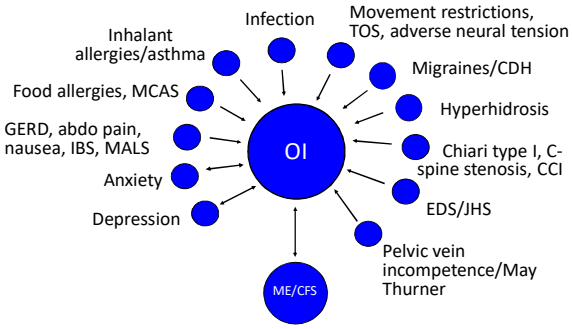


van Campen, C.M.C.; Rowe, P.C.; Visser, F.C. Orthostatic Symptoms and Reductions in Cerebral Blood Flow in Long-Haul COVID-19 Patients: Similarities with Myalgic encephalomyelitis/Chronic Fatigue Syndrome. Medicina 2022, 58, 28. https://doi.org/10.3390/





Van Campen, Rowe, Visser, Medicina 2022



ME/CFS Onset

- Post-infectious onset common; 10-13% meet ME/CFS criteria 6 months after infectious mono. Main risk factor is severity of the initial infection.
- Gradual, insidious onset in 25-40%
- Uncommon before age 10, two peaks in incidence from 10-19 and 30-39 years.

Unger ER, et al. CDC Grand Rounds: Chronic fatigue syndrome. MMWR 2016;65:1434-8.
Bakken IJ, et al. BMC Medicine 2014;12:167; Katz BZ, et al. Pediatrics 2009;124:189-93.

Infection and Immunity

- Active infection hypothesized (and treated) by some groups, but thus far not detected in chronic state
- Does infection trigger some other physiologic dysfunction?
  - a persistent abnormal stress response (autonomic dysfunction, upregulated CRF2 receptor)
  - Neuroinflammation/Mast cell activation
  - auto-immunity
  - reactivation of herpes viruses
  - metabolic dysfunction
  - endothelial dysfunction

Immunoadsorption to remove β2 adrenergic receptor antibodies in Chronic Fatigue Syndrome CFS/ME

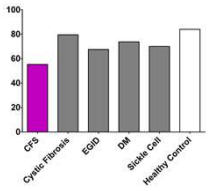
PLoS ONE 201813(3): e0193672

Metabolic features of chronic fatigue syndrome

PNAS 2016

ME/CFS Impact

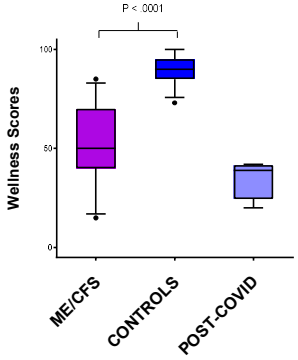
- Severity in adults is comparable to MS, CHF
- Many are disabled
- Most common cause of prolonged school absence in adolescents



Peds QL CFS data from JH Pediatric CFS Cohort Study: Roma M et al, Frontiers Pediatr 2019;

Peds QL data in other conditions from Ingerski LM, et al., J Pediatrics 2010;156:639-44

Komaroff A, et al. Health status in patients with chronic fatigue syndrome and in general population and disease comparison groups. AJM 1992;101:281-90. Crawley E, Sterne JAC. Association between school absence and physical function in paediatric CFS/ME. Arch Dis Child 2009;94:752-6. Winger A, et al. Health-related QOL in adolescents with CFS. Health Quality of Life Outcomes 2015;13:96



N=55 for adolescent ME/CFS and N=55 for HC from Johns Hopkins ME/CFS cohort study.

Roma M, Marden CL, Flaherty MAK, Jasion SE, Cranston EM, Rowe PC (2019) Impaired Health-Related Quality of Life in Adolescent Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: The Impact of Core Symptoms. Front. Pediatr. 7:26. doi: 10.3389/fped.2019.00026

ME/CFS Risk Factors

- Female to male ratio 3-4:1
- Heritability
  - More common in MZ than DZ twins
  - More common in those with Ehlers-Danlos Syndrome
  - Adolescents with ME/CFS have a 3-fold increased risk of having joint hypermobility

Buchwald D, et al. A twin study of Chronic Fatigue. Psychosomatic Medicine 2001; 63:936-43.
Rowe PC, Barron DF, Calkins H, Maumenee IH, Tong PY, Geraghty MT. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. J Pediatr 1999;135:494-9.
Barron DF, Cohen BA, Geraghty MT, Violand R, Rowe PC. Joint hypermobility is more common in children with chronic fatigue syndrome than in healthy controls. J Pediatr 2002;141:421-5.

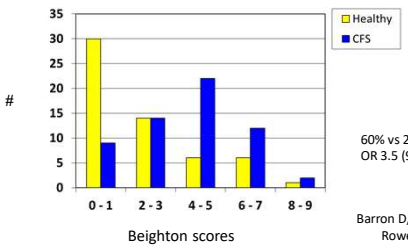
Beighton Score





Maneuver (1 point for each positive)	L	R	Score
Passive dorsiflexion of the fifth finger at the metacarpophalangeal joint > 90 degrees			
Passive apposition of the thumb to the flexor aspect of the forearm			
Hyperextension of the elbow > 190 degrees			
Hyperextension of the knee > 190 degrees			
Forward flexion of the trunk with the knees straight so the palms rest easily on the floor			
Beighton score (≥4 c/w hypermobility; max score=9)			

Beighton Joint Hypermobility Scores in 58 Adolescents With CFS And 58 Healthy Controls



60% vs 24%, P < .0001
OR 3.5 (95% CI, 1.6-7.5)

Barron D, Geraghty, Cohen, Violand, Rowe. J Pediatr 2002;141:421-5

ME/CFS Management

- RCT-proven treatments are limited
- Standard forms of symptomatic therapy can be effective for orthostatic intolerance, headaches, pain, menstrual dysfunction, insomnia, low mood/anxiety, and other co-morbid conditions
- Enthusiasm for cognitive behavioral therapy (CBT) as a *curative* treatment has waned:
  - Treatment effect sizes modest and unsustained
  - No studies in the severely affected
  - PACE trial controversial due to emerging data on research misconduct (*Wilshire et al. BMC Psychology 2018; 6:6)*
  - rigid advancement of graded exercise can provoke PEM

Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection

PLOS ONE

Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. (2020) PLoS ONE 15(11): e0240784

Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection

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Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. (2020) PLoS ONE 15(11): e0240784

"A suite of interventions, ~~including graded exercise and cognitive behavioural therapy~~, are needed to manage CFS and may be relevant to post infectious fatigue."

Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection

PLOS ONE

Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. (2020) PLoS ONE 15(11): e0240784

"A suite of interventions, ~~including graded exercise and cognitive behavioural therapy~~, are needed to manage CFS and may be relevant to post infectious fatigue."

CBT is no longer recommended as the primary therapy of ME/CFS

Friedberg F, Sunnquist MA, Nacul L. Rethinking the standard of care for ME/CFS. JGIM 2019;35(3):906-9.

POTS and orthostatic intolerance are among the most treatable conditions in ME/CFS *Pediatric ME/CFS Primer, Front Pediatr, 19 June 2017;5:121;*

Cognitive behaviour therapy for adolescents with chronic fatigue syndrome: randomised controlled trial

Maja Stulemeijer, Lieke W A M de Jong, Theo J W Fiselier, Sigrid W B Hoogveld, Gijs Bleijenberg

Here's what this [2004 December] BMJ study proved: Ten sessions of something lead to more reports of short-term benefits than no sessions of anything. But ten sessions of what? Maybe ten sessions of poker-playing or ten sessions of watching Seinfeld reruns while holding hands with the therapist and singing "The Girl from Ipanema" in falsetto would have produced the same results. Who knows? To flatly declare that their findings prove that CBT is an effective treatment—without caveats or an iota of caution—is a huge and unacceptable interpretive leap.

David Tuller virology blog About viruses and viral disease

What ME/CFS is not

- It is not school refusal
  - School refusal is seen in much younger children
  - ME/CFS patients want to attend, but can't due to symptoms
- It is not a factitious illness or Munchausen by proxy
  - MBP is rare, average age 4 yrs, with no consistent symptoms
- It is not primary depression
  - Many with ME/CFS become demoralized due to the illness, and rates of depression and anxiety can be increased
  - Anhedonia/feelings of worthlessness/disinterest in friends uncommon
  - In contrast to ME/CFS, exercise improves symptoms in depression

Rowe PC, Underhill RA, Friedman KJ, Gurwitt A, Medow MS, Schwartz MS, Speight N, Stewart JM, Vallings R, Rowe KS. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Diagnosis and Management in Young People: A Primer. Front Pediatr, 19 June 2017;5:121.

ME/CFS and long COVID: educational challenges

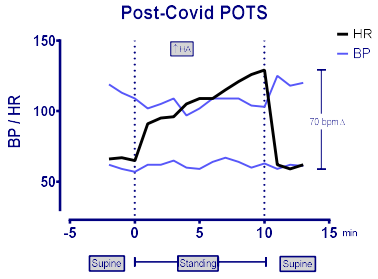
- Individuals feel worse in AM, when blood volume is lowest, and do better in afternoon
- Insomnia and disrupted sleep schedule common
- Symptoms wax and wane, often unpredictably, making planning and attendance a challenge
- Symptoms persist longer after URIs
- Symptoms often worse after vigorous exercise
- Cognitive problems can mimic ADD
- OI symptoms worse with prolonged standing or longer periods of sitting (block classes)

Back to our Long COVID patient …

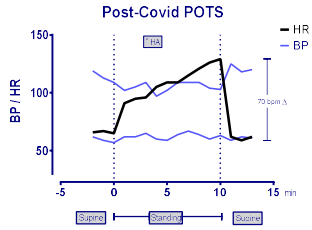
Exam notable for Beighton score of 3/9
Bilaterally positive Hoffman sign
Limited range of motion on PT screening tests
Labs show elevation in plasma histamine 4.2 mg/L (reference ≤1.8)

Healthcare 2023, 11, 865.

Post-Covid POTS



3 months post-onset



Ineffective POTS treatments:

Fludrocortisone
Atenolol
Midodrine
Pyridostigmine bromide
Ivabradine

Partially beneficial treatments:

Clonidine 0.1 mg qHS
Methylphenidate 10 mg qAM
Escitalopram 5 mg qD

LETTER TO THE EDITOR

A case report of postural tachycardia syndrome after COVID-19

Clinical Medicine 2020, Vol 21 No 1 January 2021

Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies

Postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders after COVID-19 infection: a case series of 20 patients

Post COVID-19 syndrome associated with orthostatic cerebral hypoperfusion syndrome, small fiber neuropathy and benefit of immunotherapy: a case report

Peter Nowak

eNeurologicalSci 21 (2020) 100276

New-onset Postural Orthostatic Tachycardia Syndrome Following Coronavirus Disease 2019 Infection

RESEARCH ARTICLE

Autonomic dysfunction following COVID-19 infection: an early experience

"The most common finding was orthostatic intolerance, often without objective hemodynamic abnormalities on testing."

Allergic/inflammatory manifestations

- Pt 1: Asthma, allergies to pollens, grasses; allergies to foods (cashews, carrots, cherries → oral allergy syndrome); positive FH
- Pt 2: Asthma, allergic rhinitis, eczema, urticaria with citrus
- Pt 3: Dermatographism, facial flushing with activity; + FH (father on Cromolyn and H1 antihistamine)
- Elevated histamine levels in two: 3.5, 4.2 (normal ≤ 1.8 ng/dL)

MCAS: Afrin LB, Weinstock LB, Molderings GJ. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. Int J Infect Dis 2020; 100:327-332.
Glynne P, Tahmasebi N, Gant V, Gupta R. Long COVID following mild SARS-CoV- 2 infection: characteristic T cell alterations and response to antihistamines. J Investig Med 2021 doi:10.1136/jim-2021-002051
Weinstock, et al. Mast cell activation symptoms are prevalent in Long COVID. Int J Infect Dis 2021; 217-226.

One year follow-up:

Fall 2020-Spring 2021: Able to take on-line university courses

Summer 2021:Tolerates virtual summer internship 40 hrs/wk

July 2021: main symptoms are fatigue, unrefreshing sleep, PEM; lightheadedness and headaches now infrequent
Walking 15 minutes twice daily; HR reaches 130

Meds: escitalopram 5 mg qD, famotidine 40 mg BID, fexofenadine 180 mg BID, methylphenidate 10 mg qAM, clonidine 0.1 mg nightly; low dose naltrexone 4.5 mg nightly.

49

2nd year of illness:

- Fall of 2021: Able to take in-person university courses, starts manual PT to address movement restrictions, and adds stationary biking, advancing gradually to avoid provoking PEM:
  - 09/2021: 15 min. 2X/week
  - 10/2021: 20 min. 3X/week
  - 11/2021: 25 min. 4X/week
  - 01/2022: 30 min. 4 X/week
  - 03/2022: Resumes running, 10 min QOD, advancing by 2 min each week

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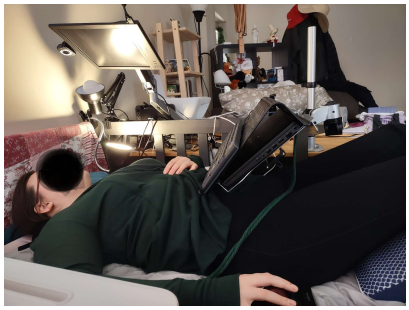
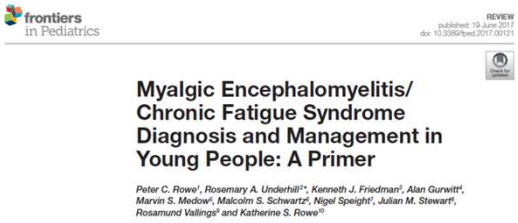


Conclusions

- Long COVID patients meeting criteria for ME/CFS have a serious, chronic, complex, multisystem disease that often can profoundly limit their health and activities
- In Pediatric ME/CFS the physical examination is often abnormal
  - Acrocyanosis [75%]
  - Tachycardia or hypotension [>95%]
  - Joint hypermobility [60%]
  - Movement restrictions [80%]
- Many symptoms of the illness are amenable to established therapies
- Effective treatment for severe ME/CFS and long COVID is a critical need

Resources


frontiers in Pediatrics

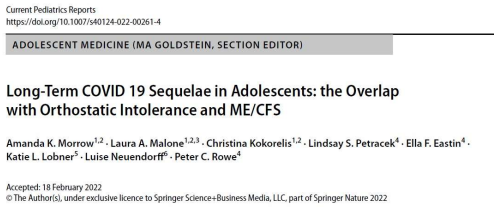
REVIEW
published: 19 June 2017
doi: 10.3389/fped.2017.00121

Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome Diagnosis and Management in Young People: A Primer

Peter C. Rowe[1], Rosemary A. Underhill[2], Kenneth J. Friedman[3], Alan Gurwitt[4], Marvin S. Medow[5], Malcolm S. Schwartz[6], Nigel Speight[7], Julian M. Stewart[8], Rosamund Vallings[9] and Katherine S. Rowe[10]*

Open Access, so available to all free of charge

Resources


Current Pediatrics Reports
https://doi.org/10.1007/s40124-022-00261-4

ADOLESCENT MEDICINE (MA GOLDSTEIN, SECTION EDITOR)

Long-Term COVID 19 Sequelae in Adolescents: the Overlap with Orthostatic Intolerance and ME/CFS

Amanda K. Morrow[1,2] · Laura A. Malone[1,2,3] · Christina Kokorelis[1,2] · Lindsay S. Petracek[4] · Ella F. Eastin[4] · Katie L. Lobner[5] · Luise Neuendorff[6] · Peter C. Rowe[4]

Accepted: 18 February 2022
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Webinars

- Managing Orthostatic Intolerance, 1 Sept 2010

http://www.youtube.com/watch?v=5iF30TVLaRE&playnext=1&list=PLCDC685DB095C02DC&feature=results_video

- Neuromuscular Strain in ME/CFS, 23 October 2014

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- Orthostatic intolerance in EDS, 19 December 2018

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- Pediatric Long COVID Clinical Tips

https://www.hawaiiecho.info/peds-resources-1

- ME/CFS - Solve ME/CFS Initiative
  http://solvecfs.org/
- ME/CFS - International Association for CFS/ME
  www.iacfsme.org
- OI - Dysautonomia International is a non-profit
  www.dysautonomiainternational.org
- Chiari Syringomyelia Foundation
  https://bobbyjonescsf.org/
- EDS - Ehlers-Danlos Society
  http://ehlers-danlos.com/

THANK YOU

- Grants from NIAID, DoD, CFIDS Association of America/SMCI
- Sunshine Natural Wellbeing Foundation (Endowed Chair)
- Boies Family Endowed Fund
- Caldwell Family Endowed FUnd
- Research Coordinator Colleen Marden and Nurse Renee Swope
- Summer students (John Fan, Alli Johns, Marissa Flaherty, Jocelyn Ray, Samantha Jasion, Erica Cranston, Megan Lauver, Maria Roma)
- Rowe's Research Runners--special thanks to Emily Steffensmeier
- Many, many families and patients

57