Chronic Fatigue Syndrome and its Related Disorders

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Presenter Disclosure Information

Peter C. Rowe, MD

- No relationships to disclose

CFS and its related disorders

- CFS definition and epidemiology
- Recent research findings of note
- Treating related disorders
  - Orthostatic intolerance
  - Joint hypermobility and the paradox of movement restrictions
  - Delayed milk protein intolerance

Fatigue in CFS

Self-reported persistent or relapsing fatigue lasting ≥ 6 consecutive months, which:

- Is of new or definite onset (not lifelong)
- Is not the result of ongoing exertion
- Is not substantially alleviated by rest
- Results in substantial reduction in previous levels of occupational, educational, social, or personal activities

Fukuda et al. Ann Int Med 1994;121:953-9.

Symptom Criteria For CFS
4 of 8 needed for diagnosis

- unrefreshing sleep
- postexertional malaise lasting > 24 hours
- self reported impairment in short-term memory or concentration
- sore throat
- tender cervical or axillary glands
- muscle pain
- multijoint pain without swelling
- headaches of a new type, pattern, severity

Clinical Evaluation

- History, physical, mental status exam
- Screening labs:
  - CBC, ESR/CRP, Chemistries, TSH
  - Urinalysis
  - Most would now add iron studies, vitamin B12, celiac screening, and, in endemic areas, labs for Lyme and other tick-borne infections
- Other labs as clinically indicated

Prevalence of Fukuda Criteria Symptoms

Nijhof SL, Pediatrics 2011;127:e1169-1175

National survey of 4.1% of Dutch General Practitioners

Unrefreshing sleep	84%
Post-exertional malaise > 24h	80%
Memory/concentration probs	79%
Headaches	78%
Muscle pain	59%
Joint pain	48%
Sore throat	43%
Tender lymph nodes	31%

Prevalence of Other (Non-Fukuda) Symptoms

Johns Hopkins Pediatric CFS Cohort Study

SCL-90 symptom reports of at least moderate severity

Dizziness	70%
Nausea	56%
Hot/cold temp fluctuations	48%
Numbness & tingling	48%
Heart racing	43%
Shortness of breath	37%
Chest pain	37%
Diminished appetite	24%

Ruling in CFS

- Post-exertional malaise lasting 1-3 days is more common in CFS than depression
- Post-exertional worsening of symptoms extends past fatigue to include cognitive dysfunction, lightheadedness, pain.
- Cognitive problems common (difficulty with attention, short-term memory)

Helpful clinical questions

- What happens when you try to do normal activities that you tolerated before?

  (e.g., reading, studying, walking 20 min, exercising)
- How long can you be upright before having to sit?
- What activities have you had to limit since you got sick? (school, after-school activities, shopping)
- How often do you get out of the house?
- How many chores can you manage in a day, or on consecutive days? If you do more, what are the consequences?

Clinical Discriminators of Fatigue

Condition	Clinical pearl
Neuromuscular	Weakness
OSA	Daytime somnolence, snoring
Heart/lung disease	SOB, effort intolerance
Adrenal insufficiency	↓ BP on orthostatics, ↓ Na. Bronzing, ↓ K less common
Chiari I	Occipital HA, brisk DTRs

Red Flags for Serious Conditions other than CFS

- Weight loss
- Fevers
- Sleep paralysis, cataplexy
- Clubbing
- Erythematous, swollen joints
- Abnormalities on neuro exam


1.5T GEMSOW
Ex: 18852
T2 SAG FSE
Se: 2/7
Im: 7/12
Sag: L2.9 (COI)
S R
Medical
1990 May 18 F MAR051890
Acc: 0013256000094046
2010 Oct 19
Acq Tm: 17:28:00
288 x 224
A R
P L
ET: 23
TR: 3266.7
TE: 86.4
MEDRAD NVPA8
3.0thk/1.0sp
Id:DCM / Lin:DCM / Id:ID
W:491 L:195
I L
DFOV: 24.0 x 24.0cm

CFS and its related disorders

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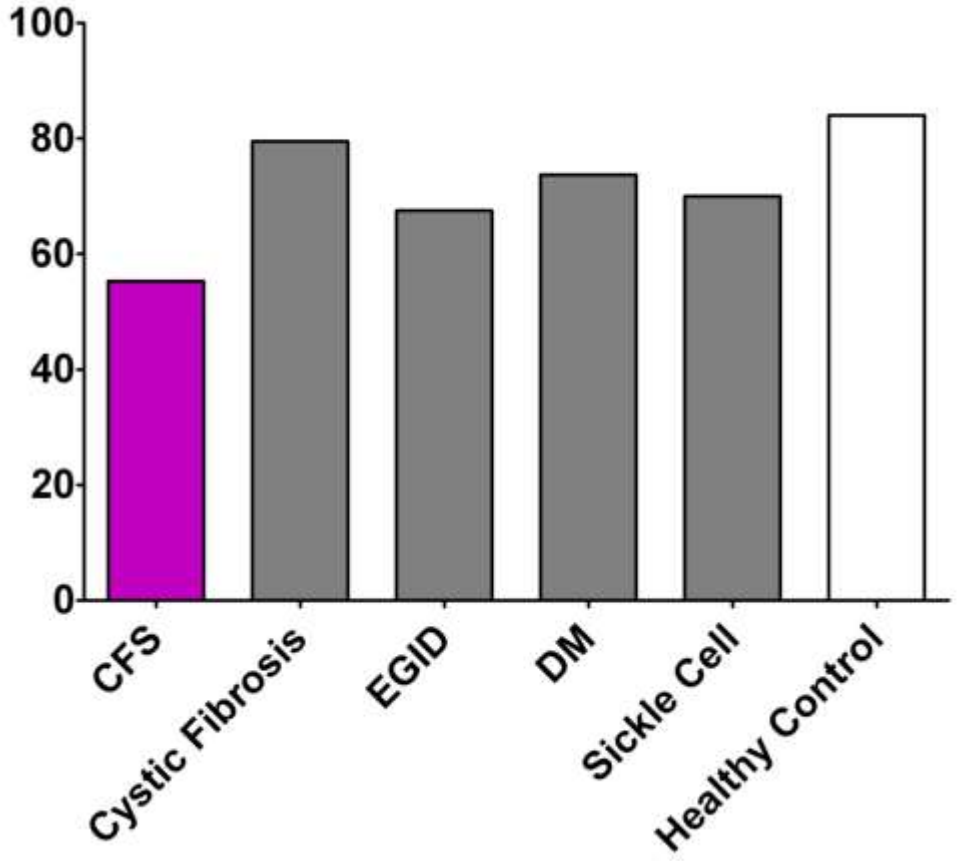
CFS

- Affects previously active individuals in all SES strata
- Female to male ratio 2:1 to 5:1
- Uncommon before 10 yrs; peaks at 40-49
- Prevalence estimated at 4/1,000 adults
- Heterogeneous precipitating & perpetuating factors
- More common in MZ than DZ twins
- Proven treatments are limited: CBT and graded exercise help, but effects are modest
- Severity in adults comparable to MS, CHF; common cause of prolonged school absence in adolescents
- Estimated $24 billion in losses annually

Health-related QOL:
CFS vs. other pediatric chronic conditions



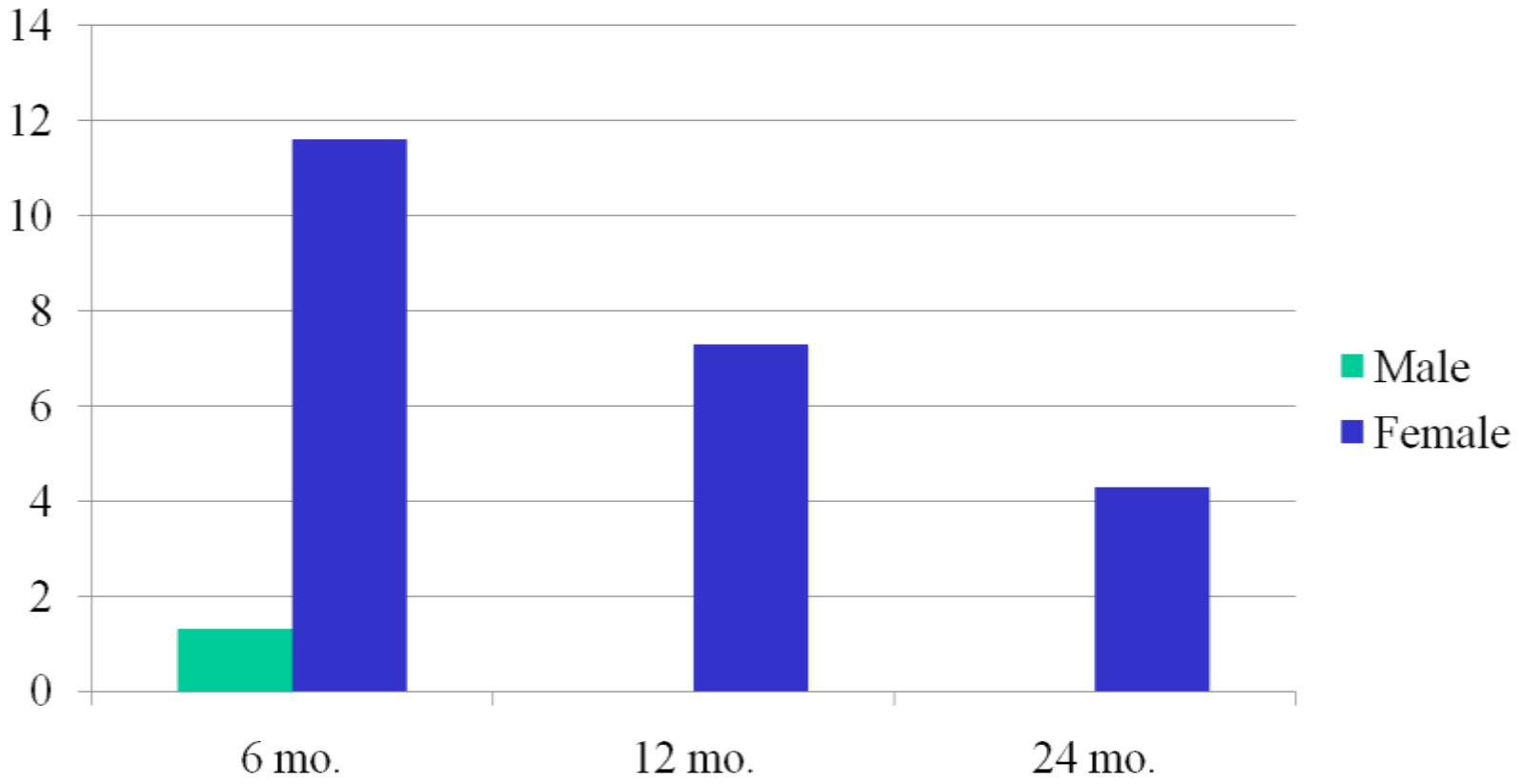
CFS data from Johns Hopkins Pediatric CFS Cohort Study; other conditions from Ingerski LM, et al., J Pediatrics 2010;156:639-44

Infection and Immunity

- Debate about whether infection acts as a “hit and run” phenomenon, triggering some other physiologic dysfunction but not directly causing symptoms, or whether persistent symptoms are due to active infection
- After EBV, Q-fever, other illnesses, ~10% get CFS; main risk factor is severity of the initial infection
- Evidence of active infection thus far not detected in chronic state

301 adolescents with infectious mono: % with CFS over time

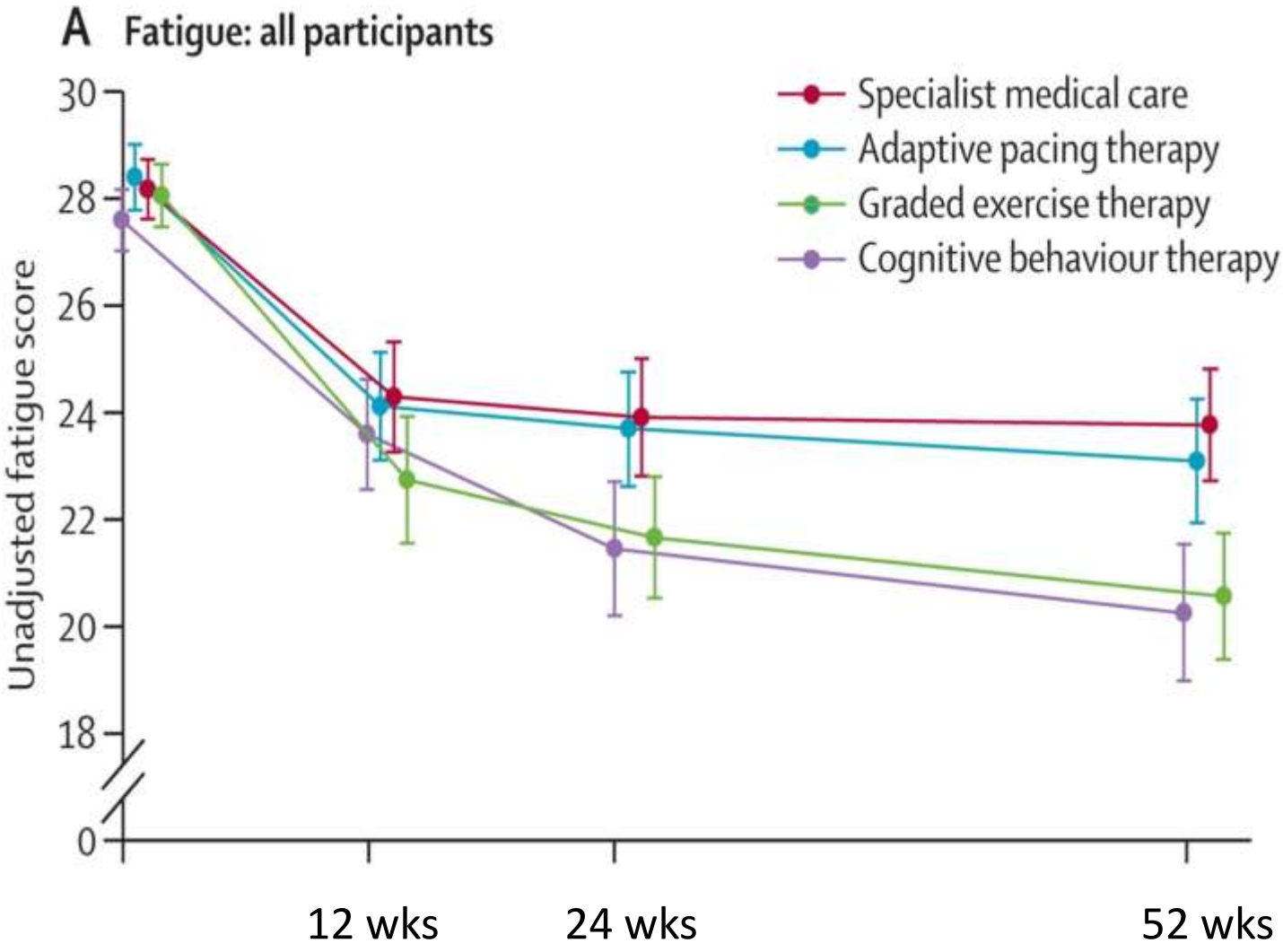
Katz BZ, et al. Pediatrics 2009;124:189-93.



Pediatric CFS Impact: School Attendance

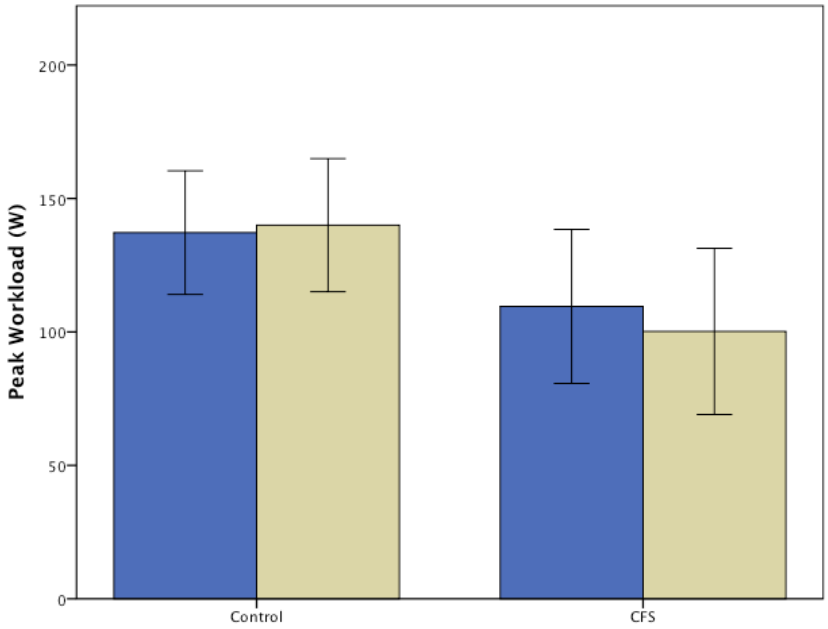
Crawley E, Sterne JAC. Arch Dis Child 2009;94:752-6

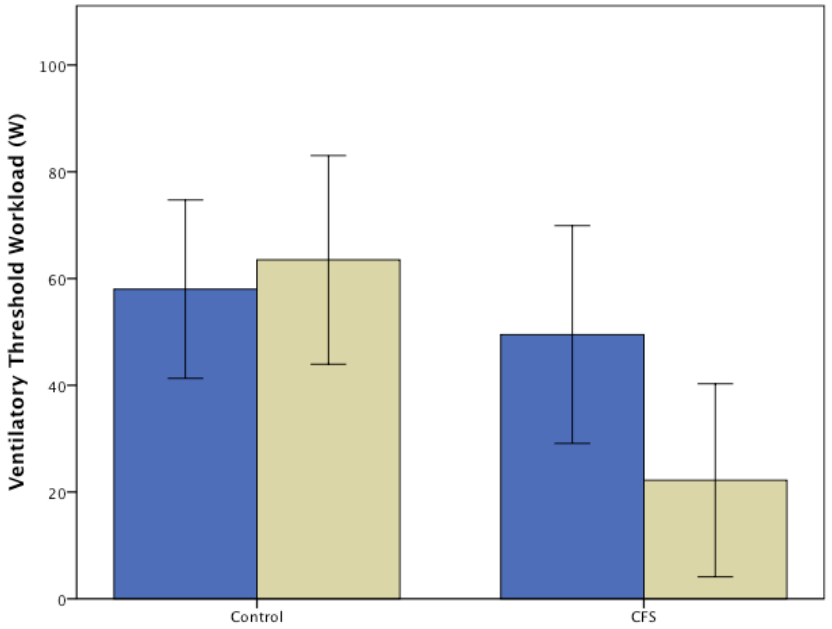
- 211 with CFS, 69% F, median age 14.6
- Evaluated in CFS specialist clinic in UK
- 56.9% attended school 20% or less
- Those with better physical function were more likely to attend school (OR 1.70; 95% CI, 1.36-2.13)
- No association between attendance rates and anxiety, gender, age, FH of ME/CFS



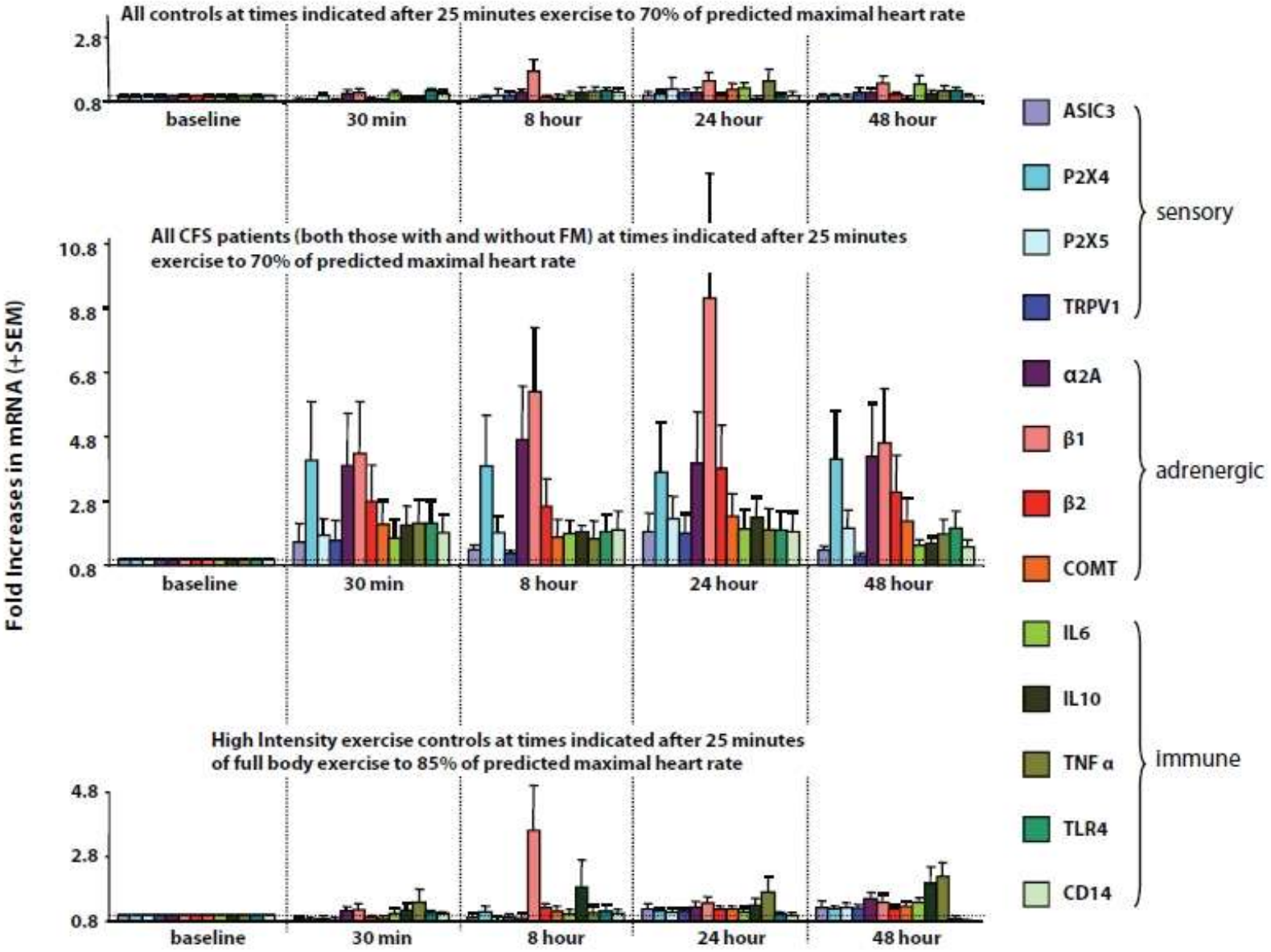
White PD et al. PACE trial. Lancet 2011

Measurements of workload at peak exercise (A) and at the ventilatory threshold (B) in individuals with CFS and control subjects obtained during cardiopulmonary exercise test #1 (blue bars) and cardiopulmonary exercise test #2 (gold bars).





Snell CR, Stevens SR, Davenport TE, Van Ness JM. Physical Therapy 2014



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.

CFS and its related disorders

- CFS definition and epidemiology
- Recent research findings of note
- Treating related disorders
  - Orthostatic intolerance
  - Joint hypermobility and the paradox of movement restrictions
  - Delayed milk protein intolerance

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

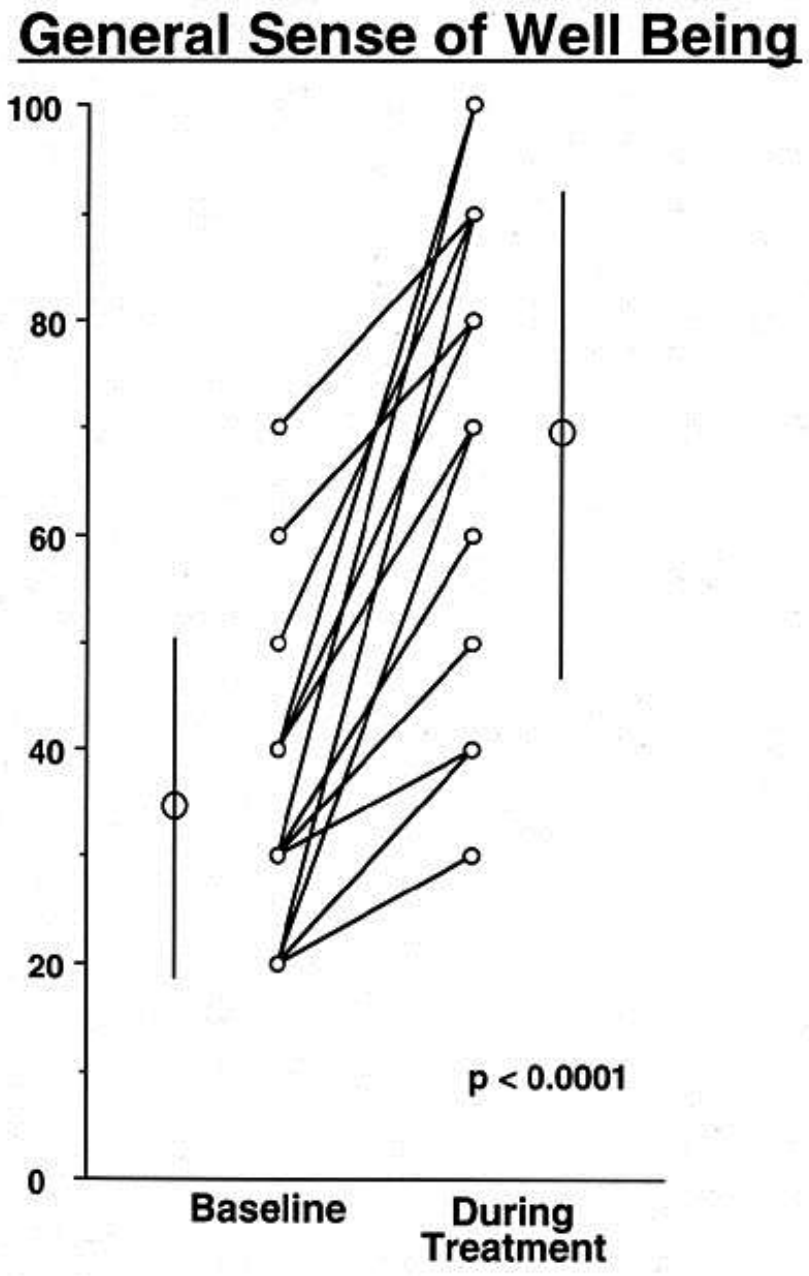
JAMA 1995;274:961-7

Symptoms of Orthostatic Intolerance

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

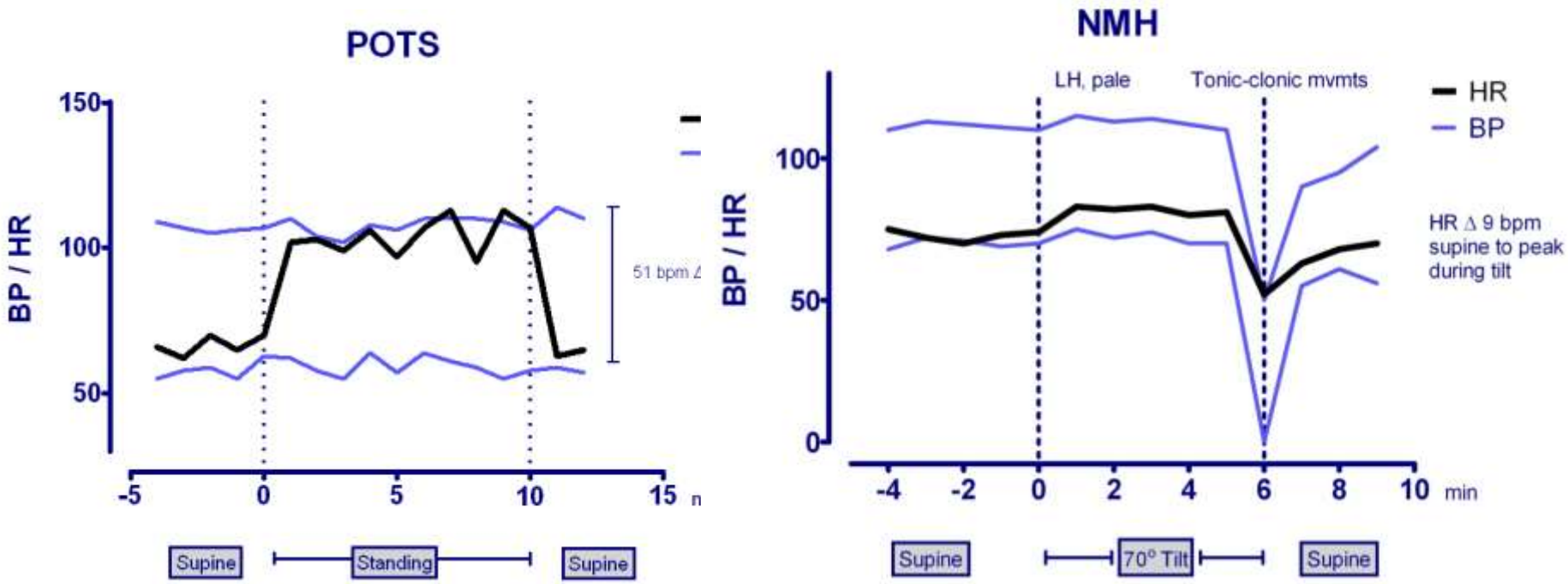
Dependent acrocyanosis

Response of CFS subjects to open treatment of orthostatic intolerance



JAMA 1995;274:961-7.

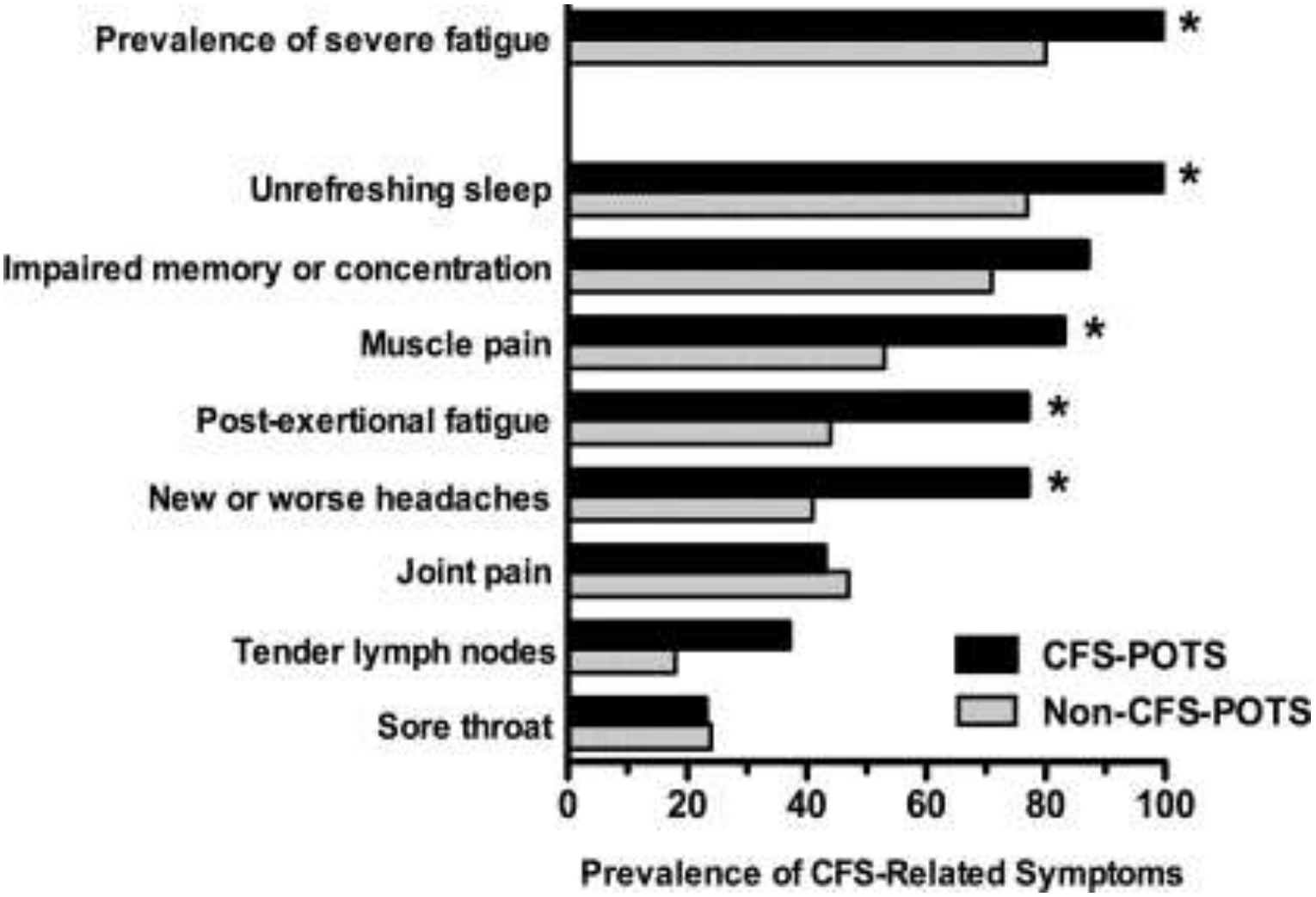
Common forms of orthostatic intolerance in pediatric CFS



POTS: 30 bpm increase (40 bpm in adolescents) in HR with symptoms, or HR > 120 bpm, in first 10 min of standing or HUT

CFS and POTS in adults

Okamoto LE, et al. Clin Sci 2012;122:183-92



Clinical SCIENCE

www.clinsci.org

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

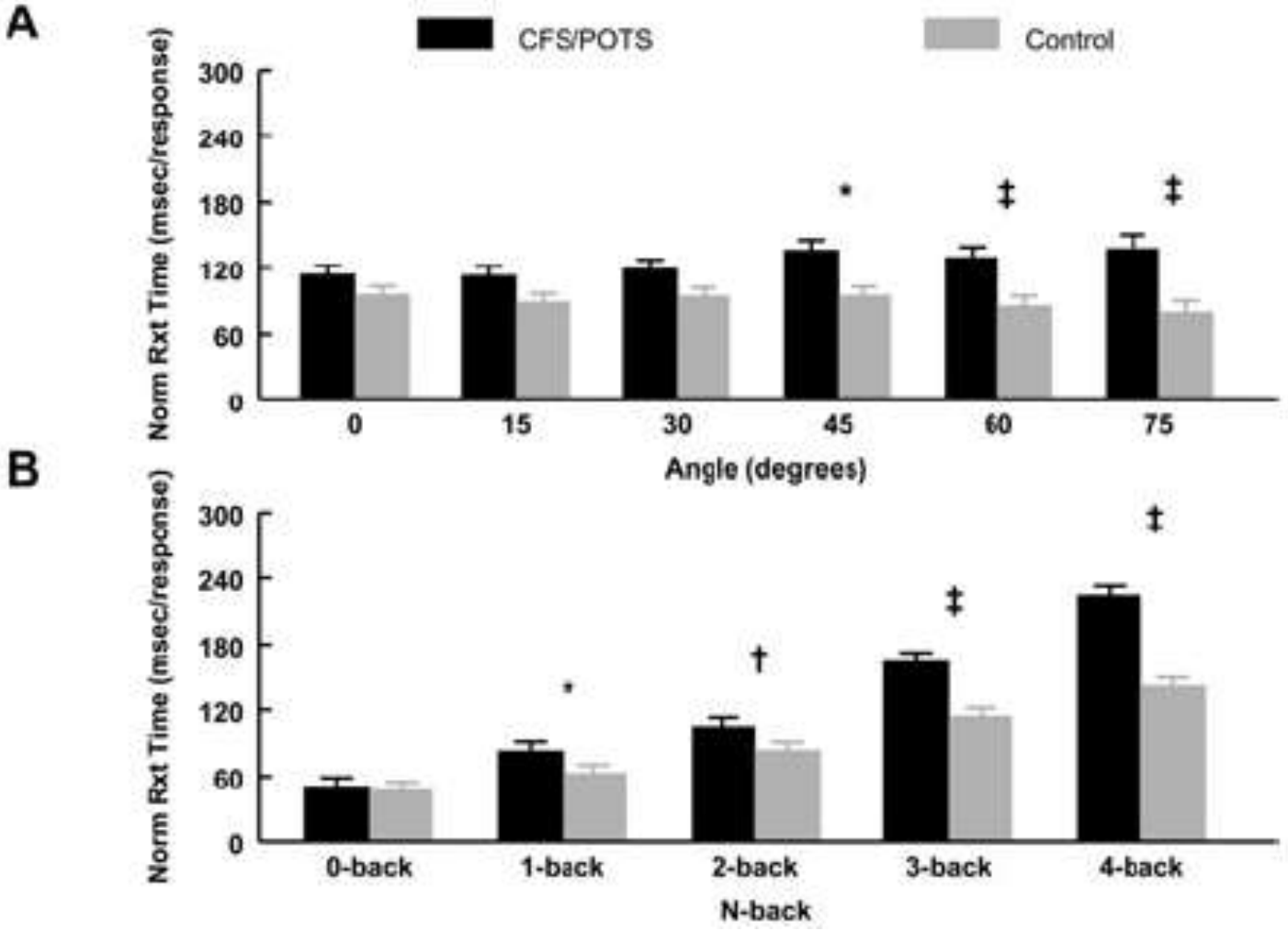
Increasing orthostatic stress impairs neurocognitive functioning in chronic fatigue syndrome with postural tachycardia syndrome

Anthony J. OCON*, Zachary R. MESSER†, Marvin S. MEDOW*† and Julian M. STEWART*†‡

*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.

N-back testing

- Tests working memory, concentration, attention, information processing
  - 0-back: subject responds if the character on screen is the one they were told to expect
  - 1-back: subject responds when the current character is the same as displayed “1” back
  - 2-back: same character as was displayed 2 characters back


A
CFS/POTS
Control
Norm Rxt Time (msec/response)
300
240
180
120
60
0
*
‡
‡
0
15
30
45
60
75
Angle (degrees)
B
Norm Rxt Time (msec/response)
300
240
180
120
60
0
*
†
‡
‡
0-back
1-back
2-back
3-back
4-back
N-back

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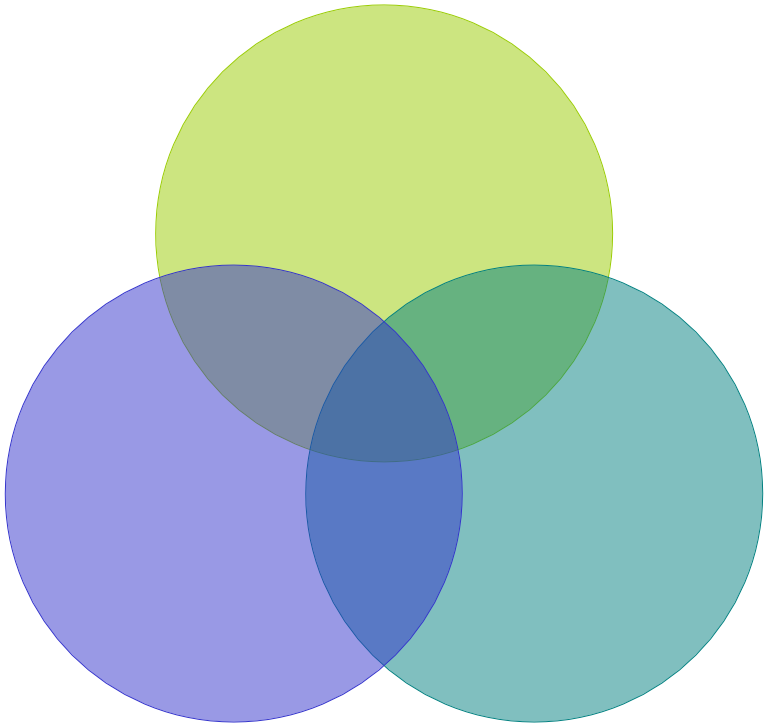
EDS/
Joint hypermobility



Orthostatic Intolerance

CFS

CFS Associated With EDS and Orthostatic Intolerance

Among 100 adolescents in the CFS clinic at JHH over a 1 year period, we identified 12 with EDS ($P < 0.01$)

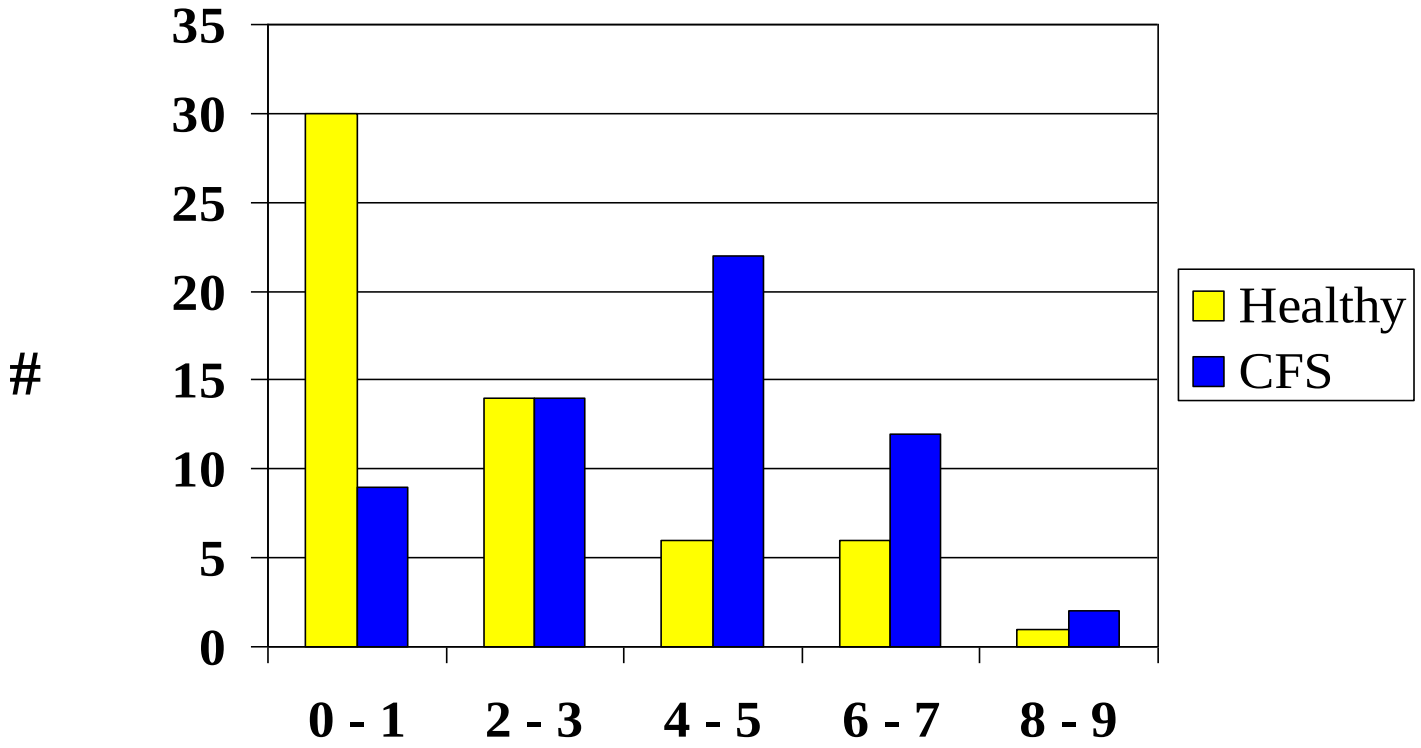
6 classical-type, 6 hypermobile-type EDS

12/12 with OI (9 NMH, 10 POTS)

Rowe PC, Barron DF, Calkins H, Maumanee IH, Tong PY, Geraghty MT.

J Pediatr 1999;135:494-9

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



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

Observations in Adolescents with CFS

- Increased prevalence of postural abnormalities and movement restrictions

Abnormal postures

Restricted Ankle Dorsiflexion

Healthy

CFS

Restricted Prone Knee Bend

Healthy

CFS

Restricted Straight Leg Raise

Healthy

CFS

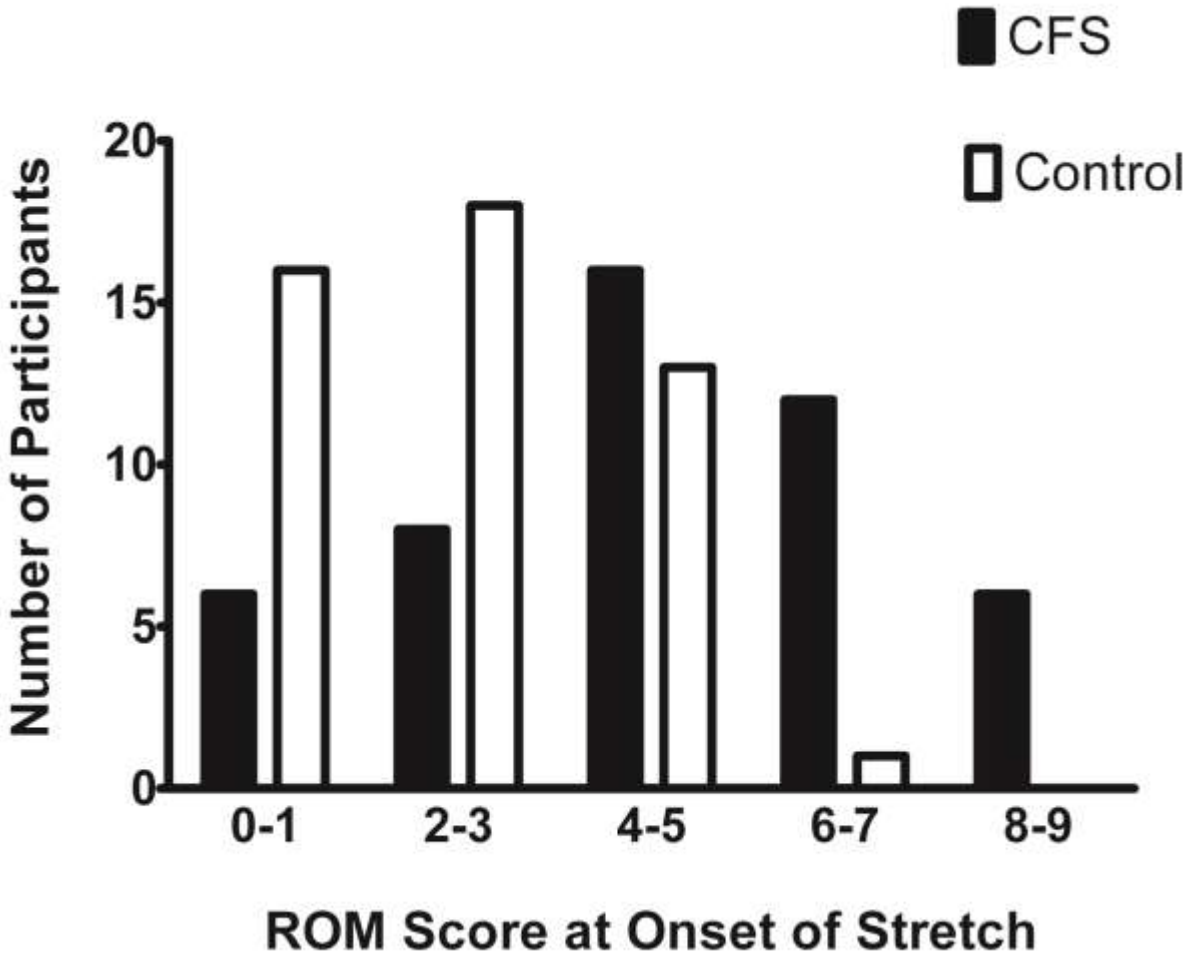
ROM in 48 CFS subjects 10-23 yrs old matched on sex and Beighton score (Rowe PC, et al. J Pediatrics 2014)

Maneuver	CFS %	Controls %	P Wilcoxon signed ranks
Slump Left Leg < 170	13	8	.48
Slump Right Leg < 170	10	2	.10
ADF Left < 95	**15**	**0**	**<.01**
ADF Right < 95	**13**	**0**	**<.02**
SLR Left < 45 onset	**69**	**38**	**.001**
SLR Right < 45 onset	**71**	**31**	**.001**
ULTT Left < 170 onset	71	56	.13
ULTT Right < 170 onset	**65**	**31**	**.001**
PKB Left < 130 onset	46	35	.41
PKB Right < 130 onset	38	33	.66
Prone press-up	**52**	**17**	**.002**

Abnormal ROM in 48 pairs matched on gender and joint hypermobility score

(Composite score range: 0-11)

ROM score	CFS, median score (range)	Controls, median score (range)	P Wilcoxon signed ranks
At onset of stretch	5 (0-9)	2 (0-7)	<.001
At end-range	2 (0-7)	0 (0-3)	<.001



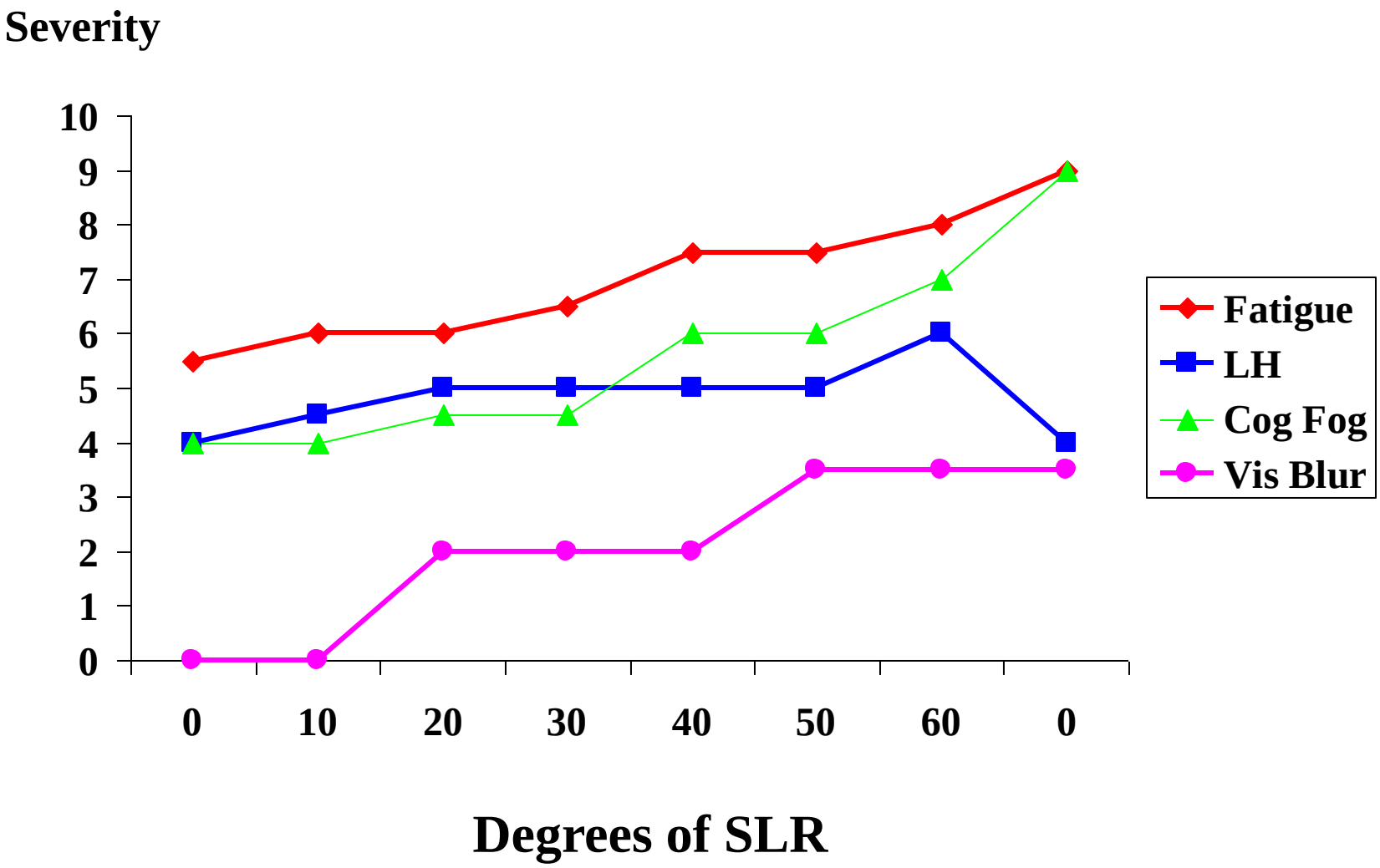
Marden CL, Flaherty M, Jasion SE, Cranston EM, Johns AS, Fan J, Fontaine KR, Violand RL. Impaired range of motion of limbs and spine in chronic fatigue syndrome. J Pediatrics 2014

Observations in Adolescents with CFS

- Increased prevalence of postural abnormalities and movement restrictions

- CFS symptoms can be reproduced by selectively placing mechanical tension on the neural tissues

Symptom Changes with SLR over 12 minutes in Adolescent with CFS



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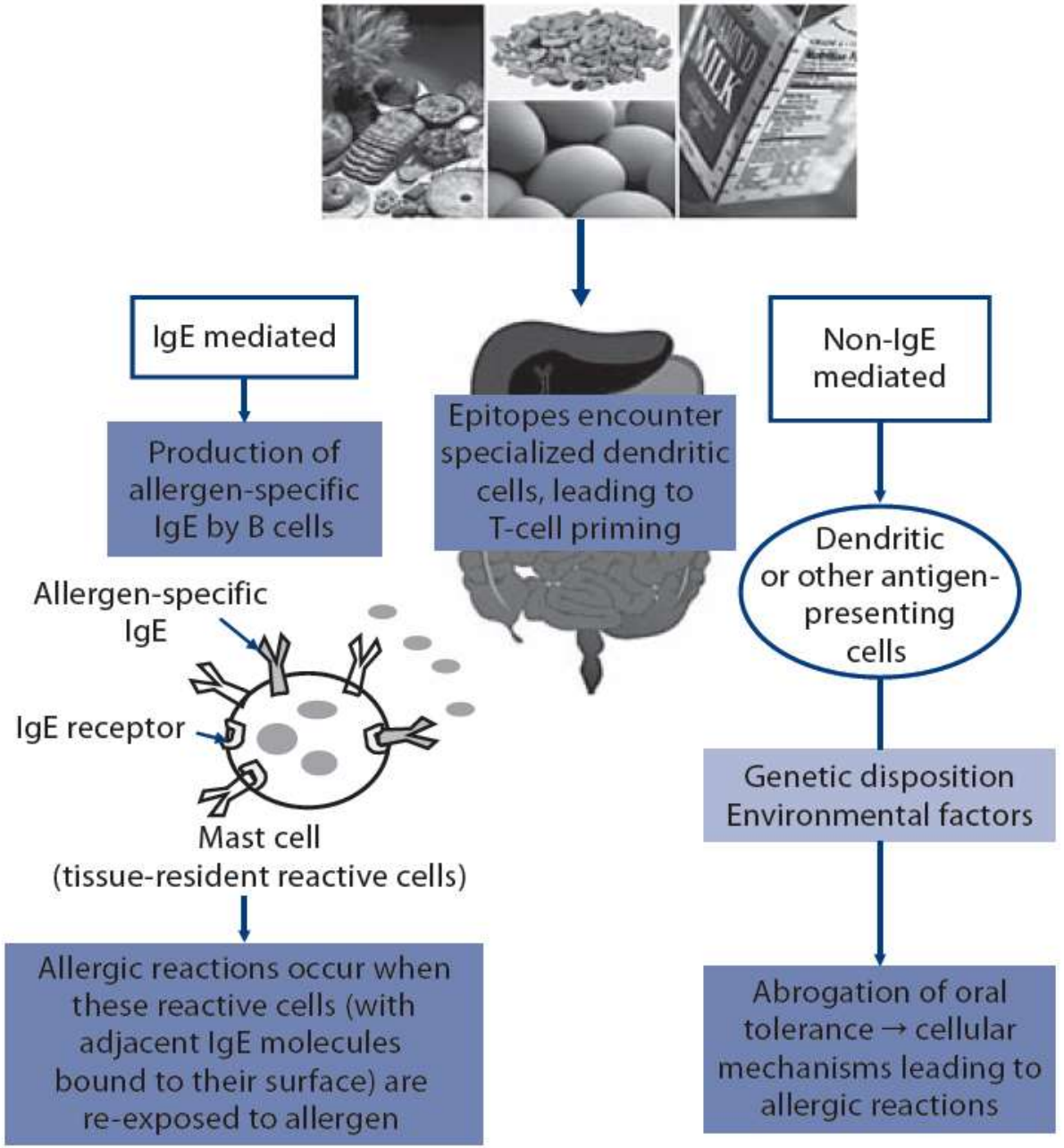


Ann Nutr Metab 2011;59(suppl 1):8–18
DOI: 10.1159/000334145

Non-IgE mediated food allergy : 3 cardinal features

1. Recurrent vomiting or GER
2. Recurrent epigastric or abdominal pain
3. Food refusal, picky eating, early satiety

Other: aphthous ulcers, unexplained fevers, diarrhea or constipation, headache, myalgias, fatigue, asthma

Kelly KJ et al. Gastroenterology 1995;109:1503-12

Non-IgE mediated food allergy

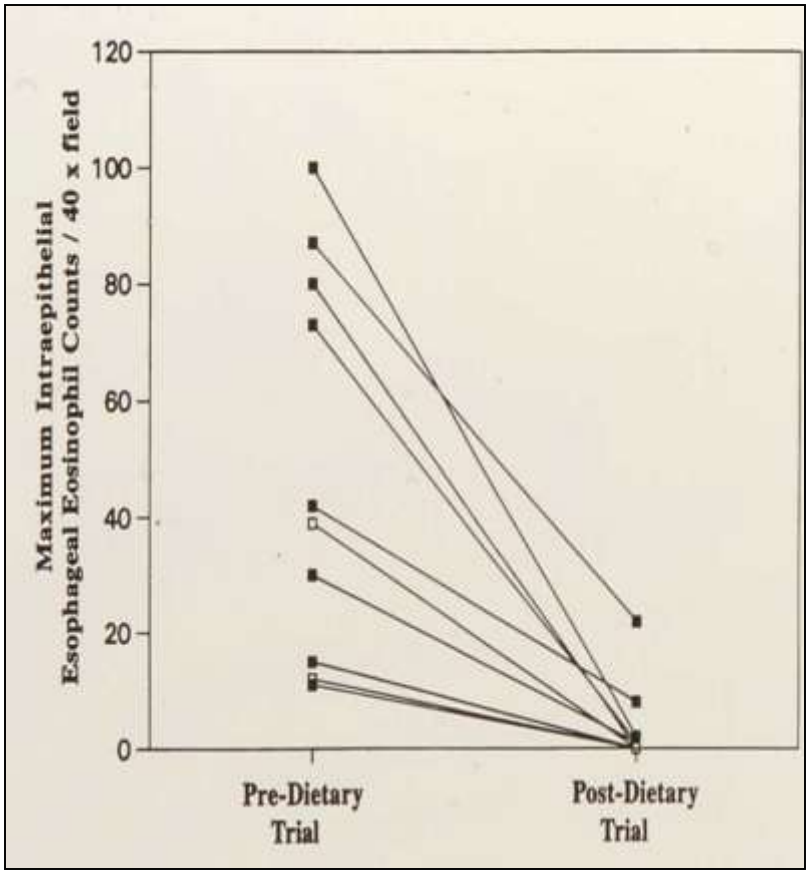
- Reaction to suspected food usually delayed by 2-6 hours
- IgE level, prick skin tests, RAST tests often negative
- Eosinophilic colitis or esophagitis only the tip of the iceberg

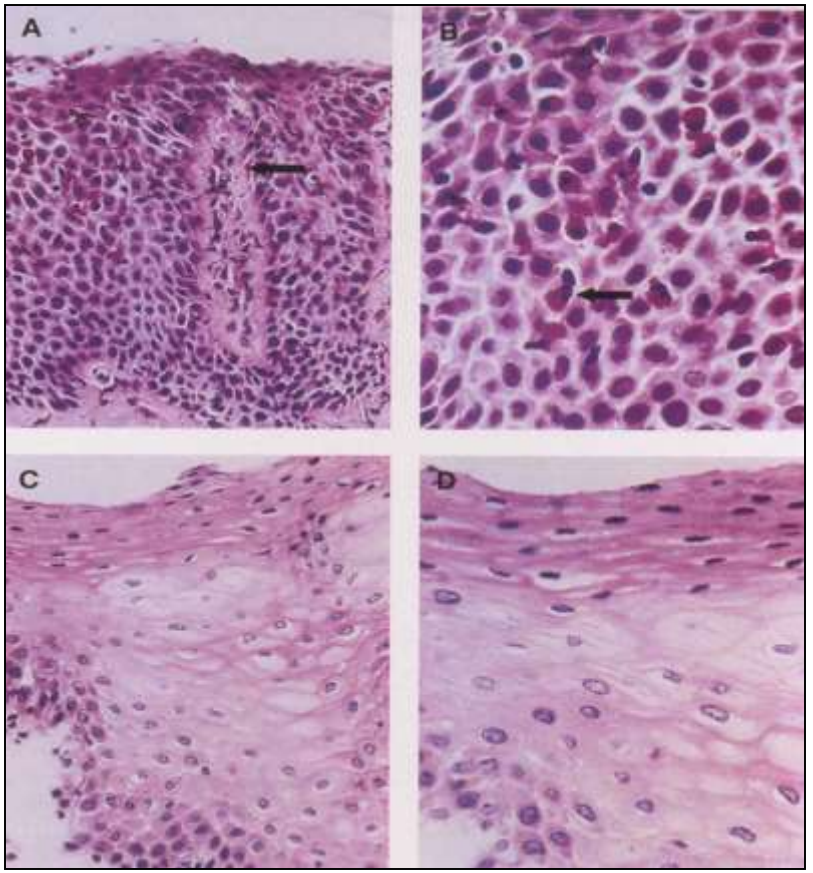
Treatment of non-IgE mediated food allergy

1. Strict avoidance of offending food proteins (Milk > soy > egg)
2. Amino-acid formula (Neocate, EO28, Elecare) sometimes needed for infants, those with many allergies
3. Multivitamins, Ca supplements

Improvements in esophageal eosinophils after amino acid formula diet

Kelly KJ et al. Gastroenterology 1995;109:1503-12





Non-IgE mediated food allergy

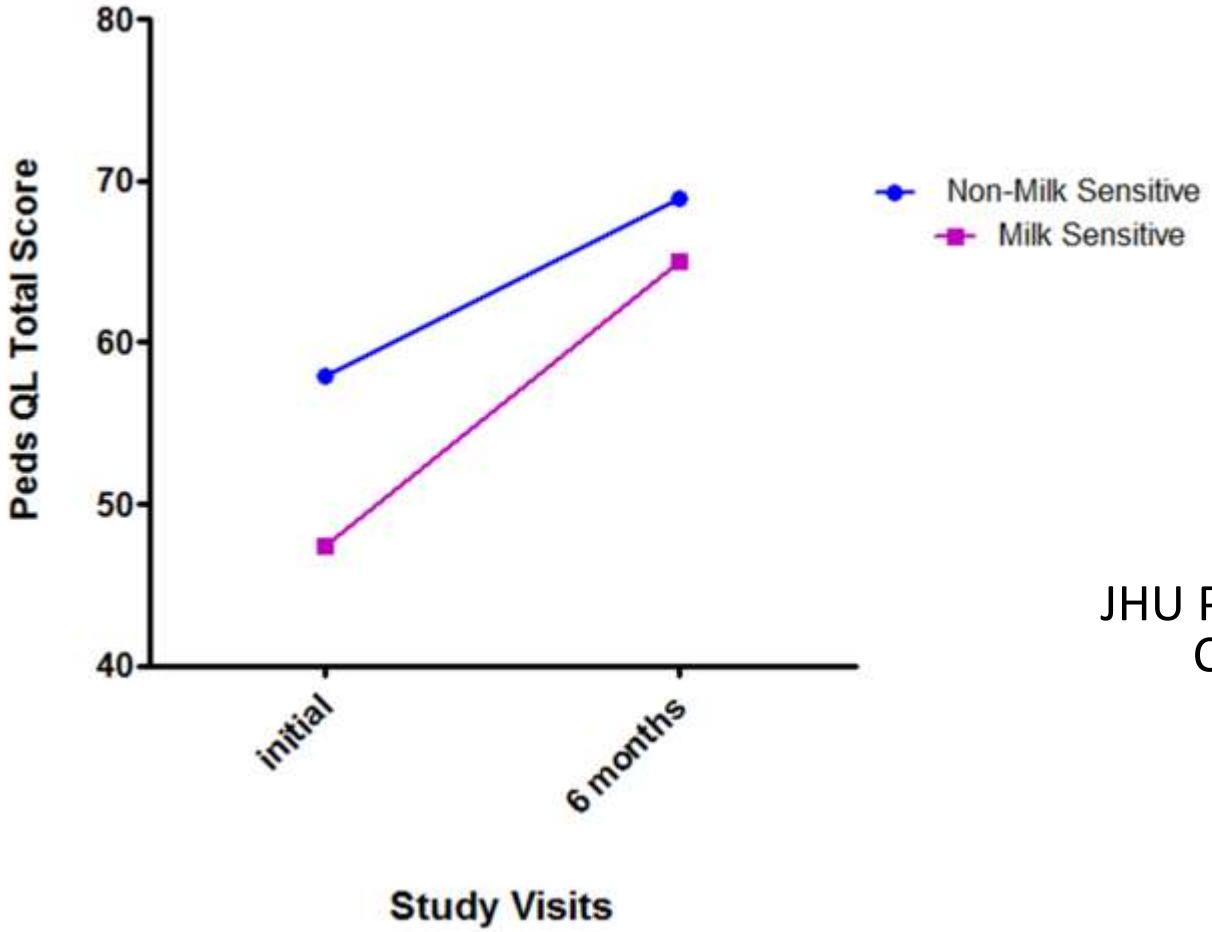
Diagnosis supported by clinical response to diet, recurrence of symptoms 2-6 hours after inadvertent dietary challenge, confirmed by DBPCOFC

Delayed milk protein hypersensitivity: data from the Johns Hopkins CFS cohort

- 55 subjects with CFS
- Followed for 2 years and treated with multimodal therapy
- Subjects with delayed hypersensitivity to milk protein compared to those without milk sensitivity on history, current symptoms, and quality of life

Baseline feature	Milk sensitive (N=17)	Not milk sensitive (N=38)	P
Increased vomiting in infancy	47%	13%	.01
Early satiety	69%	26%	<.01
Epigastric pain	75%	26%	<.01
GER	69%	29%	<.01
Aphthous ulcers	56%	8%	<.001
Worse with milk	43%	10%	.01
Peds QL score	47.4	58.0	.01

Response to multi-modal therapy (including milk-free diet in those with milk sensitivity)



JHU Pediatric CFS Cohort Study

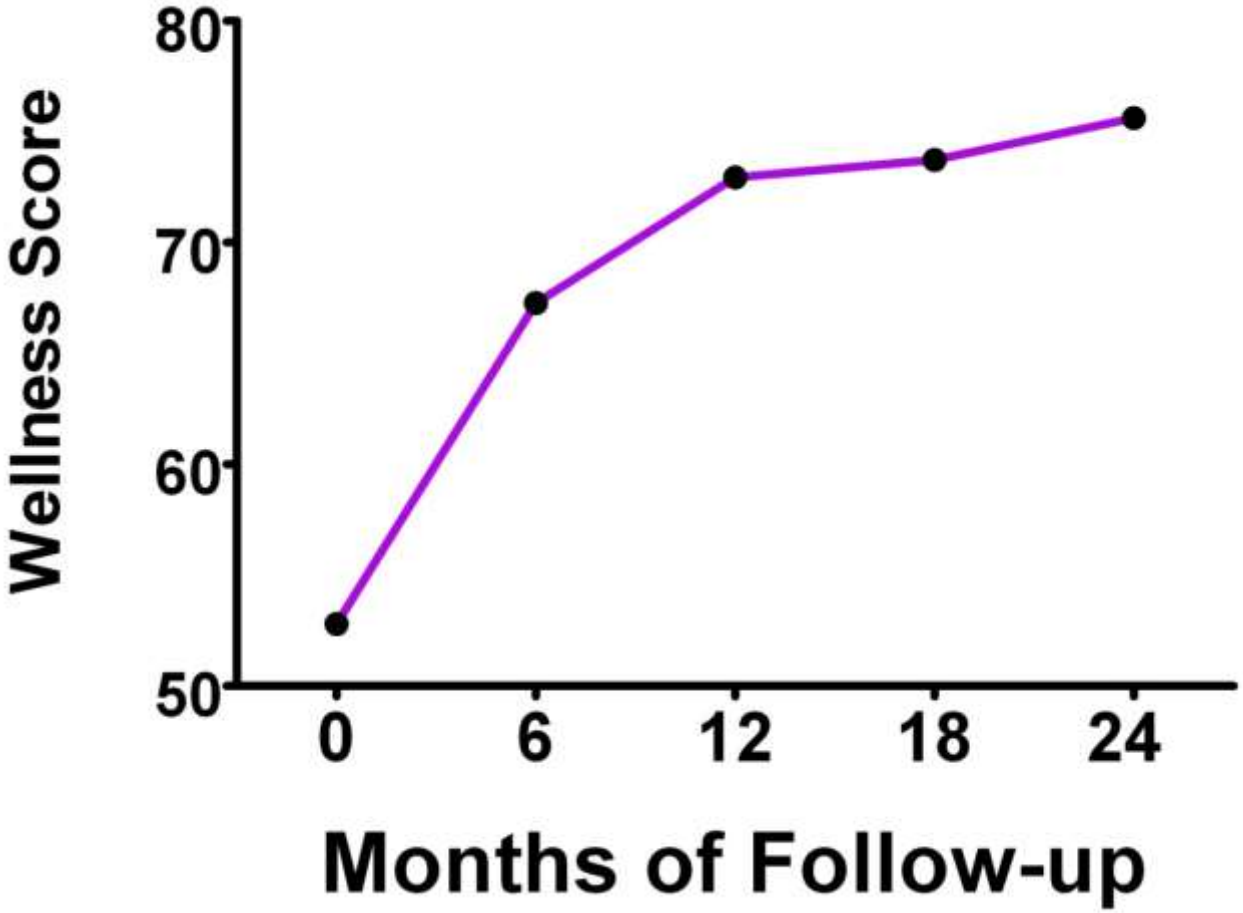
Conclusions

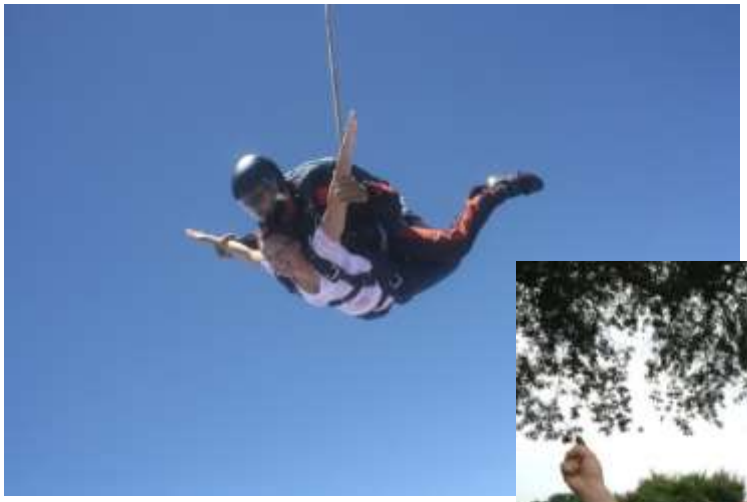
- Adolescents and young adults with CFS have a higher than expected (31%) prevalence of DMPH
- Specific symptoms significantly more common among those with DMPH include reflux, aphthous ulcers, early satiety, and abdominal/epigastric pain

Conclusions

- DMPH contributes to worse health-related QOL in those with CFS
- Treatment with a milk-free diet and multi-modal CFS therapy was associated with improvement in the magnitude of differences in HRQOL after 6 months
- DMPH thus deserves further attention as a treatable contributor to CFC symptoms and HRQOL in CFS

Johns Hopkins CFS Cohort Study: Outcomes with individualized treatment



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RUN FOR THEIR LIVES
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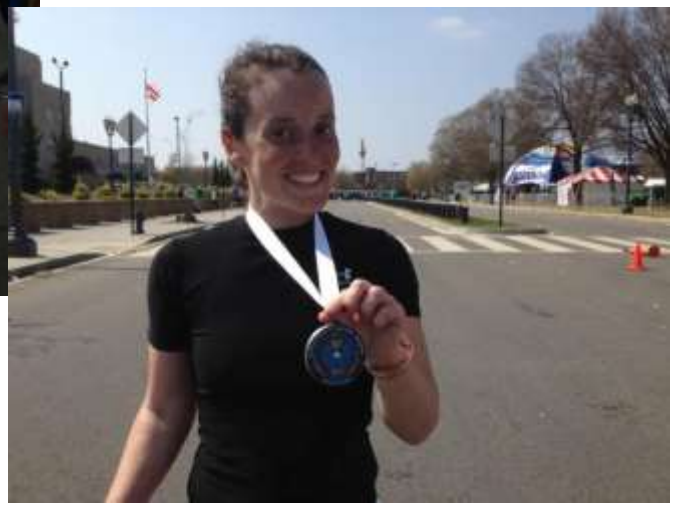

Resources

- ME/CFS: a primer for clinical practitioners, 2014: Downloaded from www.iacfsme/org
- The CFIDS Association webinars are an excellent source of information on various topics related to CFS: http://solvecfs.org/
- Search “Dr. Peter Rowe” on YouTube for webinar on “Managing Orthostatic Intolerance.”
- Dysautonomia International is a non-profit group. This site has fact sheets, exercise guides, and regular research updates. Talks from conferences are available: www.dysautonomiainternational.org
- Co-cure is a patient-run CFS information exchange: http://www.co-cure.org/

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- Summer students (John Fan, Alli Johns, Marissa Flaherty, Jocelyn Ray, Samantha Jasion, Erica Cranston)
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  - Special thanks to the following:

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  - Megan Lauver, Hannah Vogel