

Management of Pediatric ME/CFS: Lessons from the Johns Hopkins Clinic



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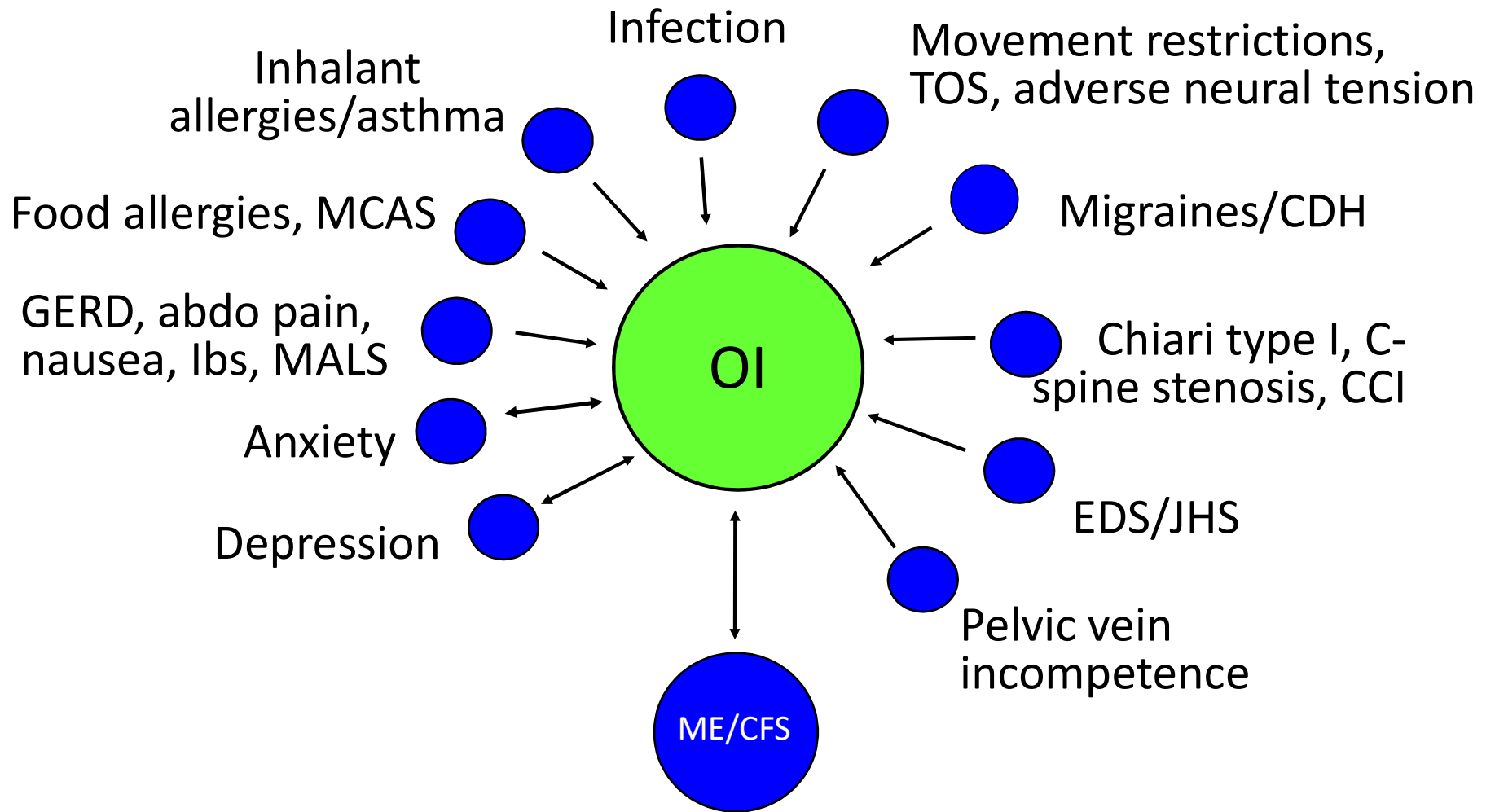
Division of General Pediatrics and Adolescent Medicine
Johns Hopkins University School of Medicine

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.

Topics for discussion

- Orthostatic intolerance
- Joint hypermobility, EDS, and other overlapping comorbid conditions in pediatric ME/CFS
- Neural strain
- A word on outcomes
- Considerations in refractory cases



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

Syncope

Diminished concentration

Headache

Blurred vision

Fatigue

Exercise intolerance

Dyspnea

Chest Discomfort

Palpitations

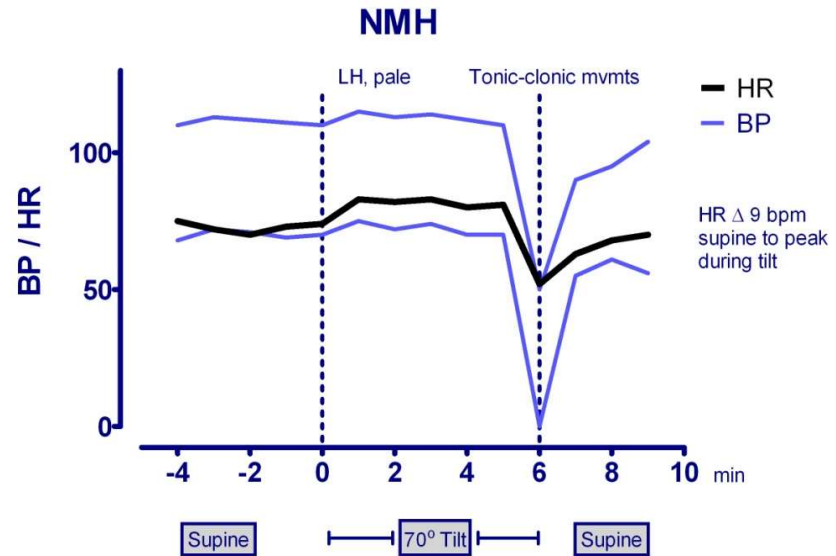
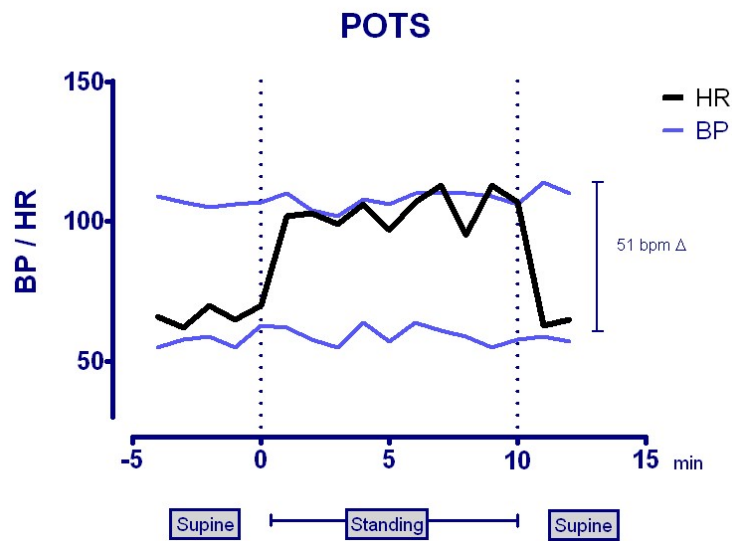
Tremulousness

Anxiety

Nausea

Nocturia

Common forms of orthostatic intolerance



POTS: 40 bpm \uparrow in HR in adolescents (30 bpm in adults) in first 10 min of standing/HUT, with OI symptoms, without OH in first 3 minutes.

NMH: 25 mm Hg \downarrow in SBP, with OI symptoms

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 during stage 1 tilt

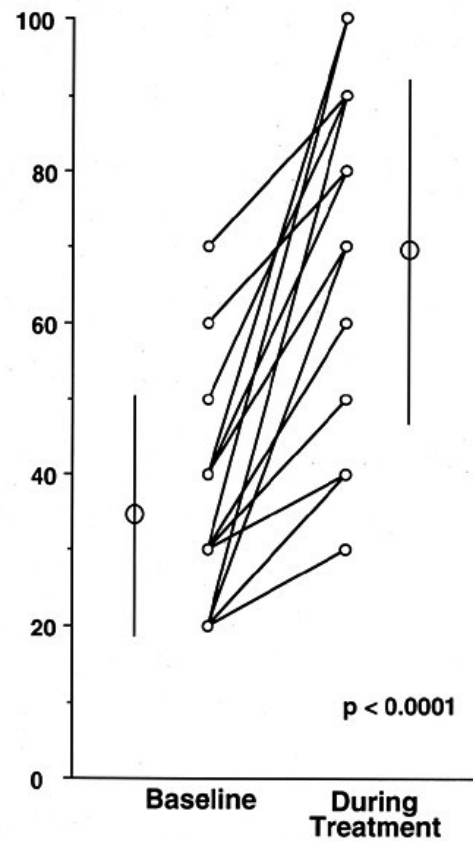
	<u>ME/CFS</u>	<u>CONTROLS</u>
Worse fatigue	23	0
Lightheadedness	20	0
Warmth	20	0
Nausea	16	0
Diaphoresis	4	0

Acrocyanosis is common in ME/CFS



Response of CFS subjects to open treatment of orthostatic intolerance

General Sense of Well Being



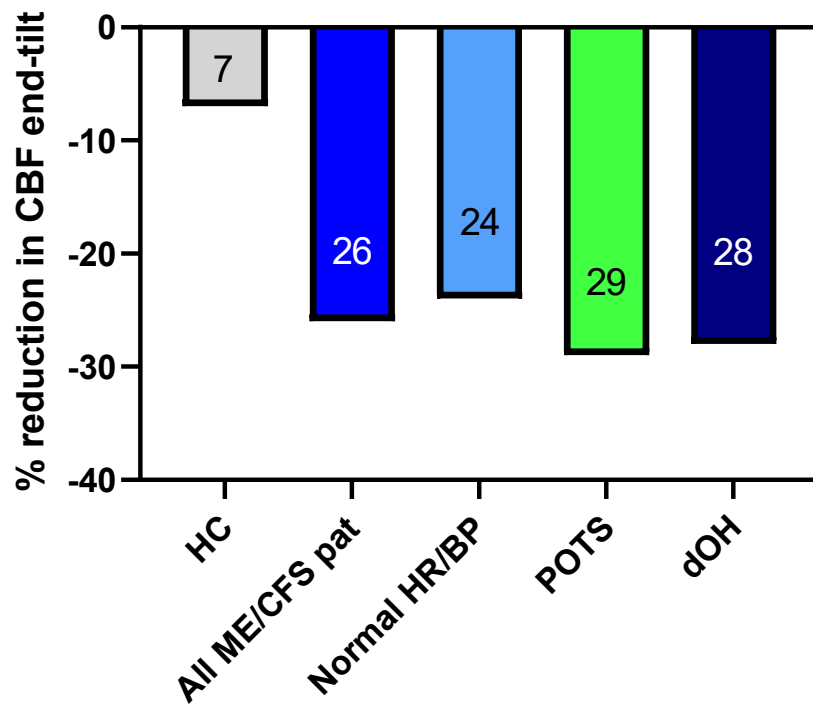
JAMA
1995;274:961-7.

Orthostatic Intolerance in Pediatric ME/CFS

Author	Yr	Country	Method	Findings
Rowe	1995	US	HUT 70° Max 70 min	7/7 NMH
Stewart	1999	US	HUT 80° 45 min	18/26 POTS, 22/26 NMH Overall, 96% with OI Acrocyanosis in 18/26
Tanaka	2002	Japan	7 min of active standing	Delayed recovery of cerebral oxygenation in 21/28 CFS vs. 2/20 controls
Wyller	2007	Norway	HUT 20° Max 15 min	HR, DBP higher in CFS Higher sympathetic tone
Galland	2008	NZ	HUT Max 30 min	More OI in CFS vs controls 13/26 vs 5/26; P =.04

Rowe PC, et al. Lancet 1995; 345:623-4; Stewart JM, et al. Pediatrics 1999; 103:116-121; Tanaka H, et al. J Pediatr 2002;140:412-17; Wyller VB, et al. Am J Cardiol 2007;99:997-1001; Galland B et al; Pediatr Res 2008;63:1-7.

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

Fukuda and OI symptoms in 55 ME/CFS (ages 10-23) & 55 healthy controls. Roma M et al. Frontiers Pediatr 2019	ME/CFS %	HC %	P
Fatigue (several X/wk or more)	100	5	<0.001
Unrefreshing sleep (most/all of time)	98	18	<0.001
PEM (at least once in 2 wks)	95	7	<0.001
Cognitive impairment (several X/wk or more)	82	2	<0.001
Headache (several X/wk or more)	76	18	<0.001
Lightheadedness (several X/wk or more)	76	15	<0.001
Myalgias (several X/wk or more)	69	20	<0.001
Sore throat (≥ 1 /wk)	51	7	<0.001
Arthralgias (several X/wk or more)	44	20	0.01
Tender glands (≥ 1 /wk)	40	2	< 0.001

Operationalizing Orthostatic Intolerance in a cohort of 55

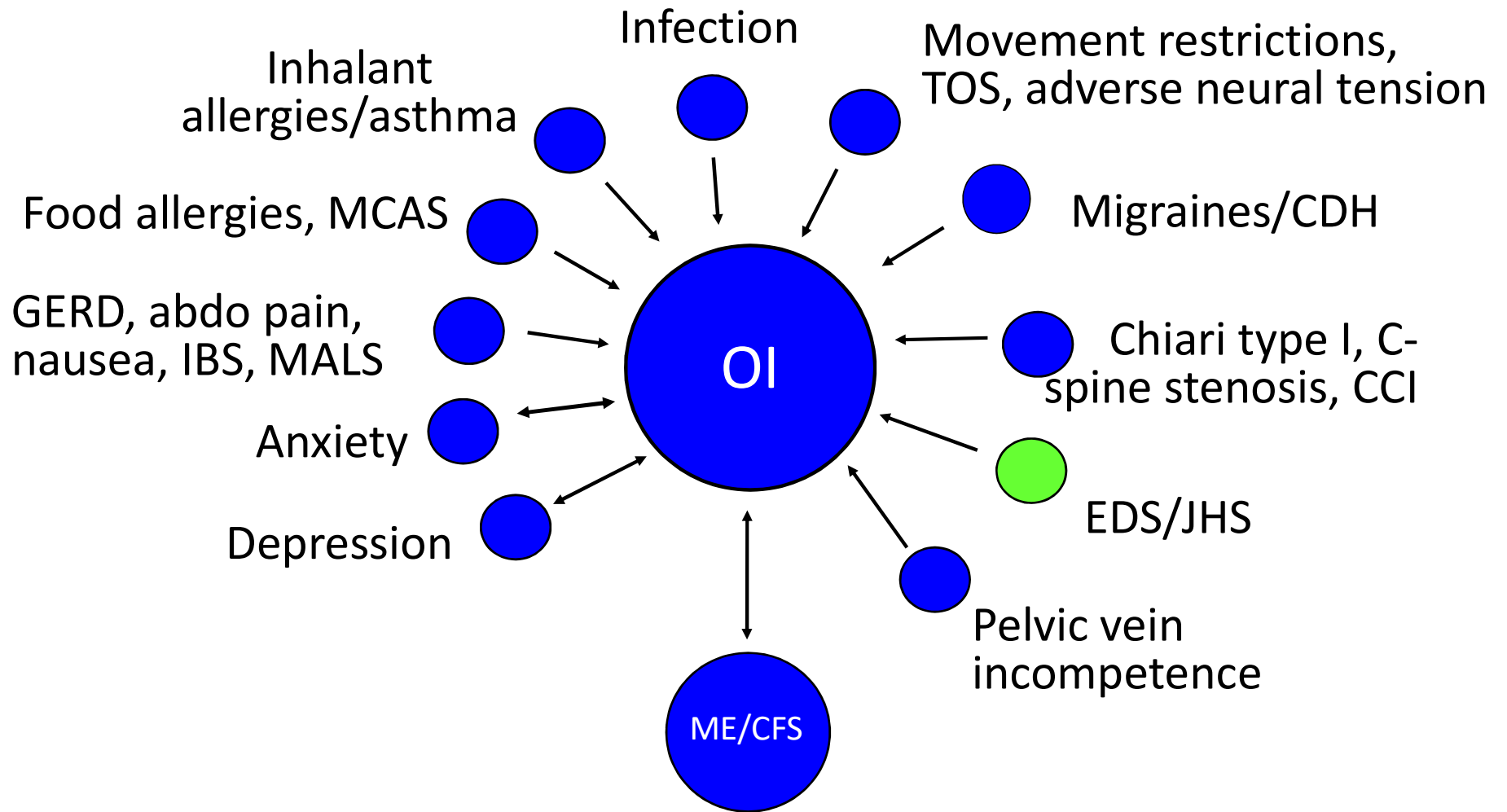
	N	Cumulative %
LH at least several X/wk	42	76
Pre-study Dx or Rx of OI	5	84
POTS or NMH on Passive Standing Test	6	96
Worse OI and ME/CFS symptoms on PST	2	100

Impaired HRQOL in Adolescent ME/CFS: Impact of Core Symptoms

*Maria Roma, Colleen L. Marden, Marissa A. K. Flaherty, Samantha E. Jasion,
Erica M. Cranston and Peter C. Rowe**

 **frontiers**
in Pediatrics

Feb 2019



Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome

Peter C. Rowe, MD, Diana F. Barron, MS, Hugh Calkins, MD, Irene H. Maumenee, MD, Patrick Y. Tong, MD, PhD, and Michael T. Geraghty, MB, MRCPI

J Pediatr 1999;135:513.

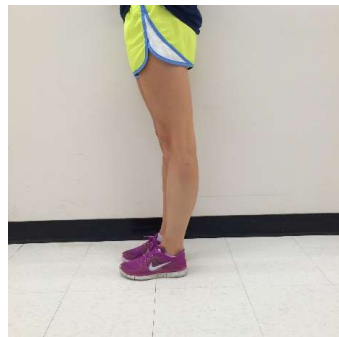
Of 100 adolescents seen in the CFS clinic at JHH over a 1 year period, we identified 12 subjects with EDS (P < .01, binomial test)

6 classical-type, 6 hypermobile-type EDS

11 females, 1 male

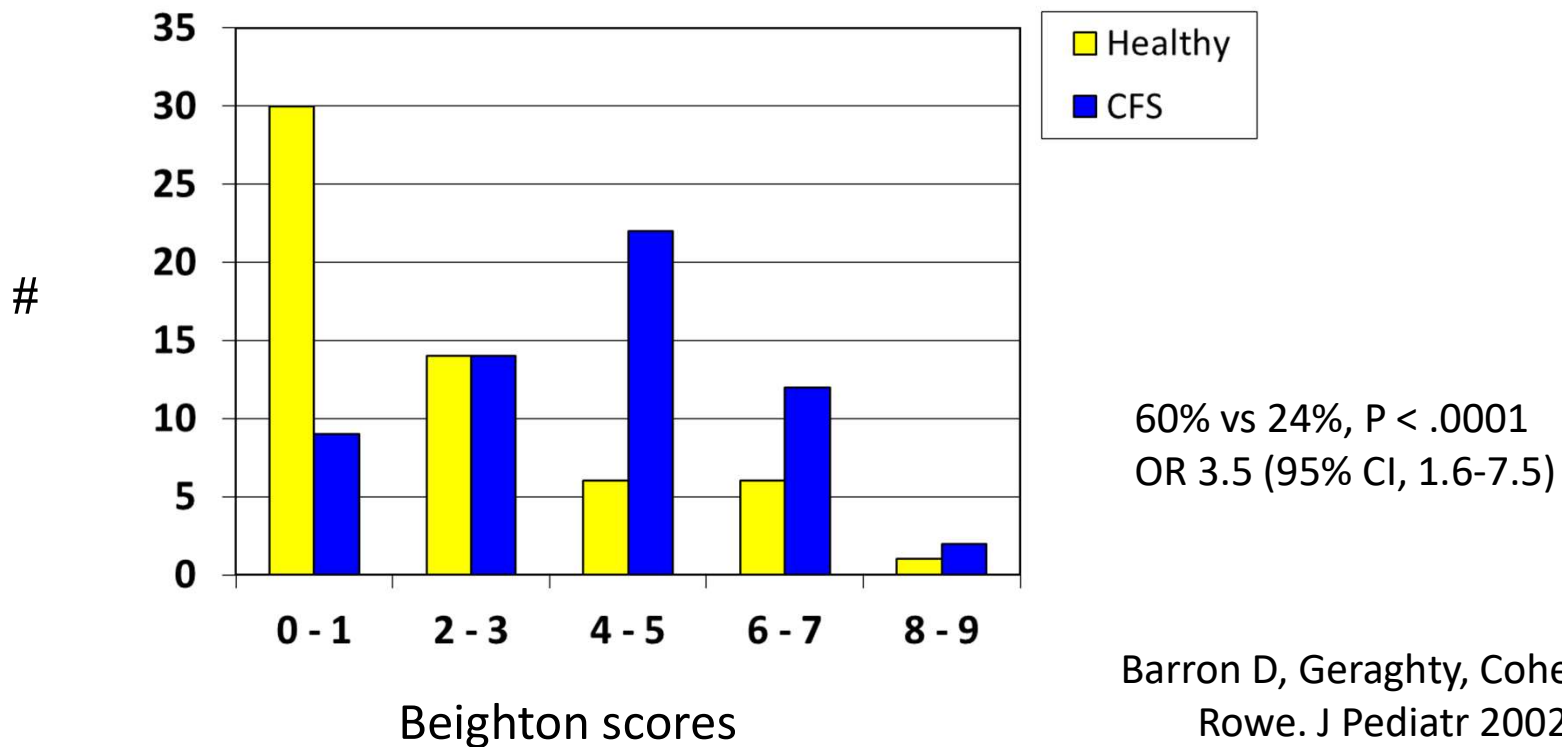
12 with chronic OI symptoms. All with either NMH alone (N=2), POTS alone (N=3), or both (N=7). All had increase OI symptoms upright.

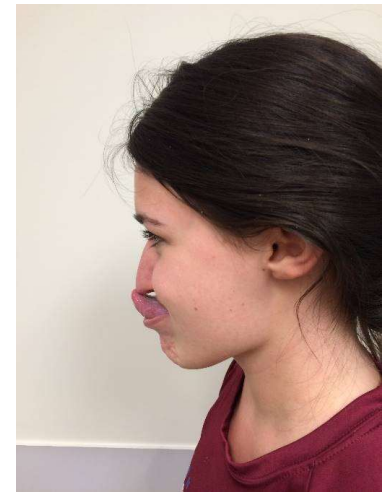
Beighton Score



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







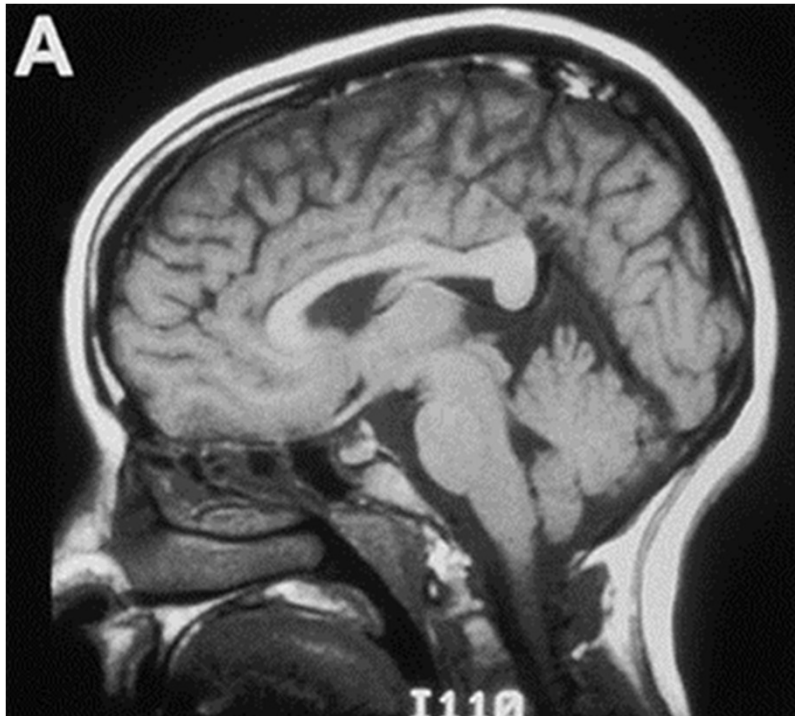
Non-articular disorders associated with JH

Anxiety	Headache due to CSF leaks
Carpal tunnel syndrome	Hiatal hernia
Chiari malformation	Mitral valve prolapse
Cervical spine instability	Pelvic congestion syndrome
CFS/FMS	Pelvic organ prolapse
Chronic pain syndromes	POTS and NMH
Constipation	Scoliosis/kyphosis
Fecal incontinence	TMJ dysfunction
GI motility disorders	Vulvodynia

Adapted from Castori M. ISRN Dermatology 2012

Syndrome of occipitoatlantoaxial hypermobility, cranial settling, and Chiari malformation Type I in patients with hereditary disorders of connective tissue

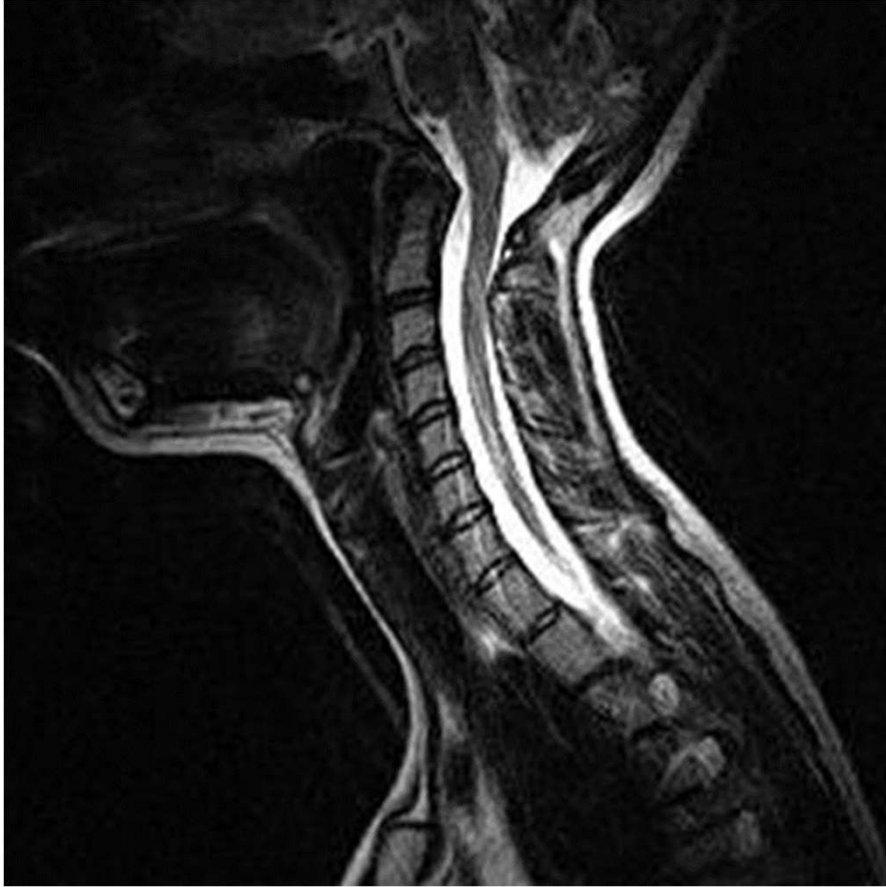
**THOMAS H. MILHORAT, M.D.,¹ PAOLO A. BOLOGNESE, M.D.,¹ MISAO NISHIKAWA, M.D.,¹
NAZLI B. McDONNELL, M.D., PH.D.,² AND CLAIR A. FRANCOMANO, M.D.³**



Normal brain MRI



Chiari and basilar impression



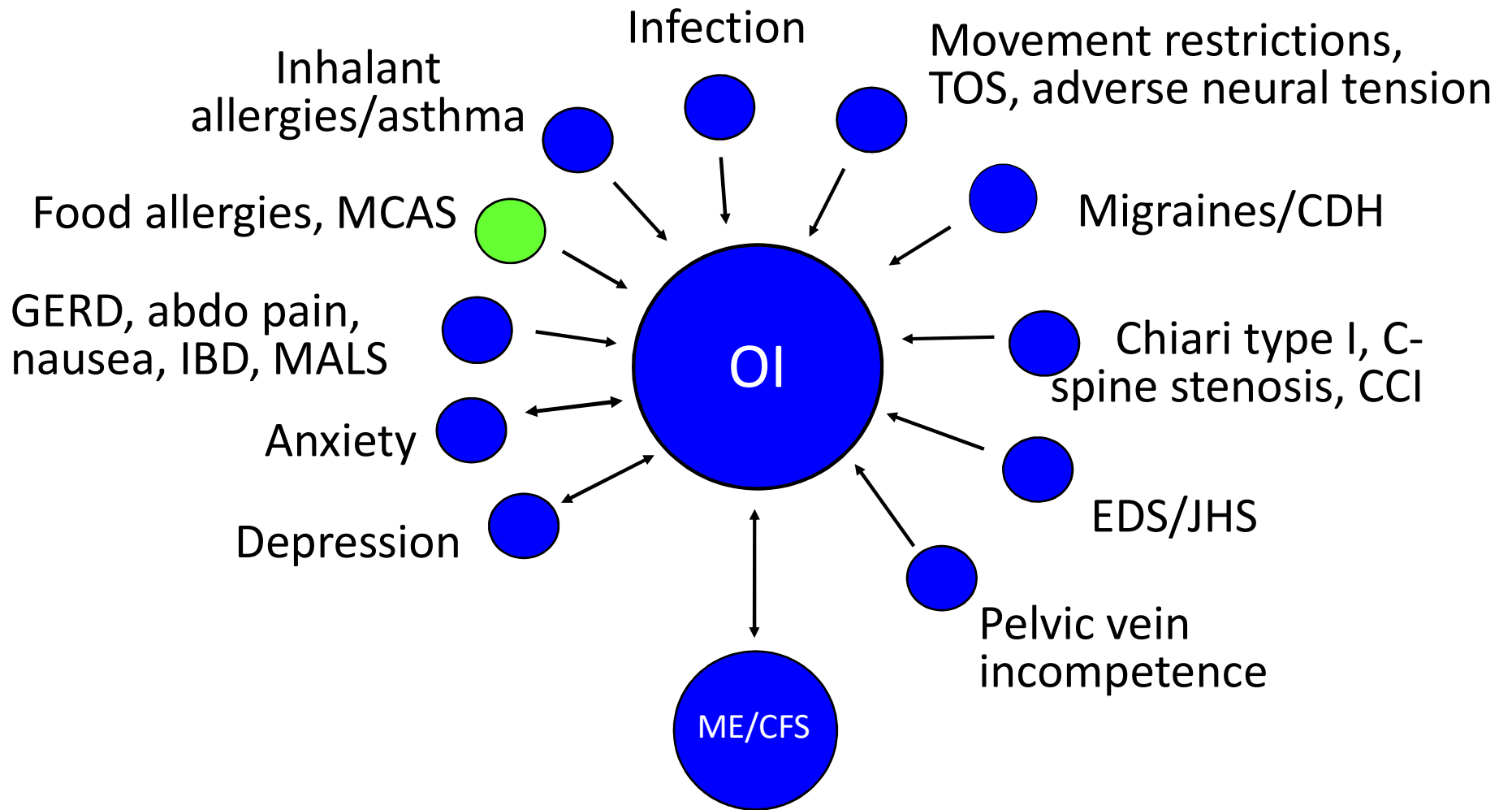
Students who can do these tricks with their hands ...



... can have pain when writing.



Silver or plastic ring splints, wrist braces, keyboarding options might help.

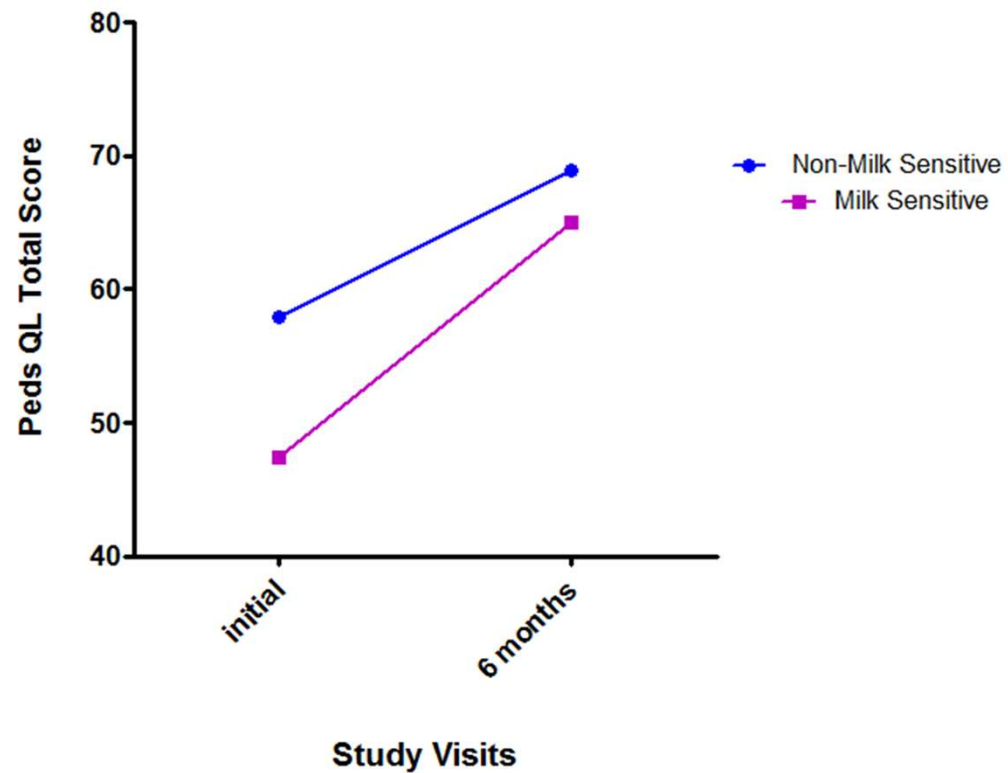


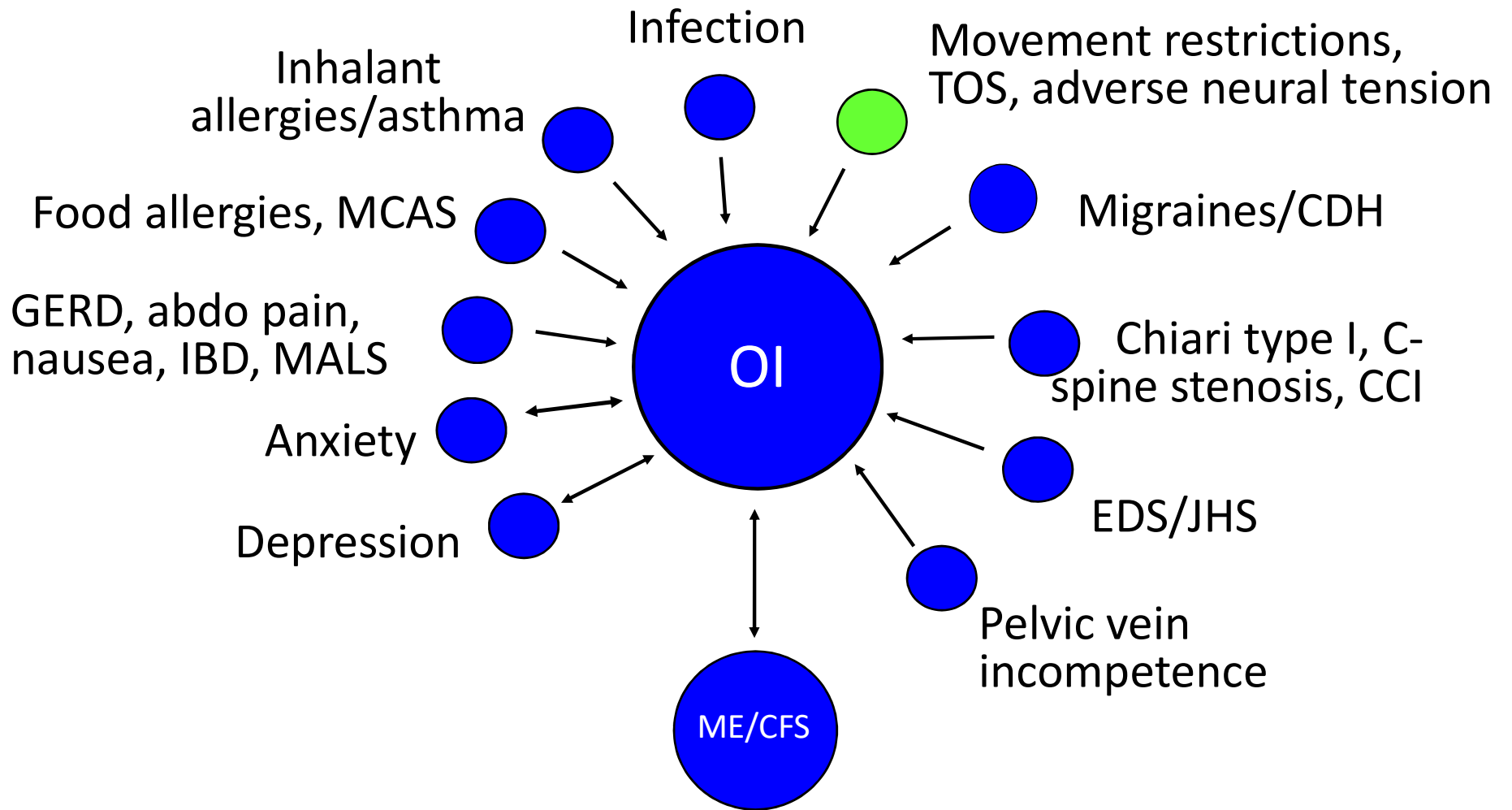
Cow's milk protein intolerance in adolescents and young adults with chronic fatigue syndrome

Peter C. Rowe (prowe@jhmi.edu)¹, Colleen L. Marden¹, Samantha E. Jasion¹, Erica M. Cranston^{1,2}, Marissa A. K. Flaherty^{1,2}, Kevin J. Kelly³

- 17/55 (31%; 95% CI, 19–43%) met study criteria for cow's milk protein intolerance:
 - (a) no immediate anaphylactic reactions to milk, (b) ≥ 2 of epigastric pain, reflux, early satiety), (c) improvement in UGI symptoms on milk-free diet, (d) ≥ 2 recurrences of UGI symptoms > 2 hours after open re-exposure to milk
- Compared to the milk-tolerant, milk-sensitive participants had significantly worse HRQOL at baseline but not at 6 months (after institution of the milk-free diet).

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





Observations in Adolescents with ME/CFS

Increased prevalence of postural abnormalities and movement restrictions



Observations in Adolescents with ME/CFS

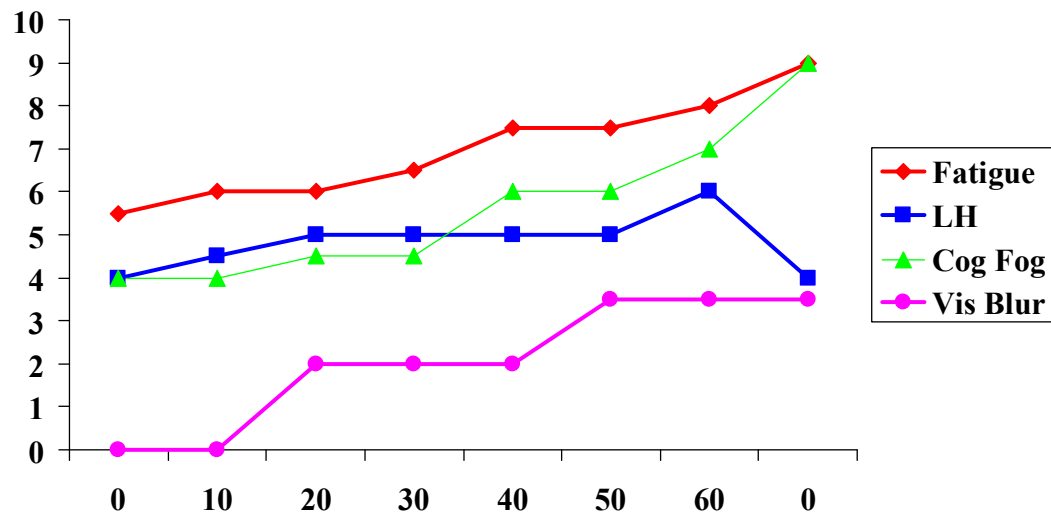
Increased prevalence of postural abnormalities and movement restrictions

ME/CFS symptoms could be reproduced by selectively placing mechanical tension on the neural tissues



Passive SLR over 12 minutes in adolescent with ME/CFS

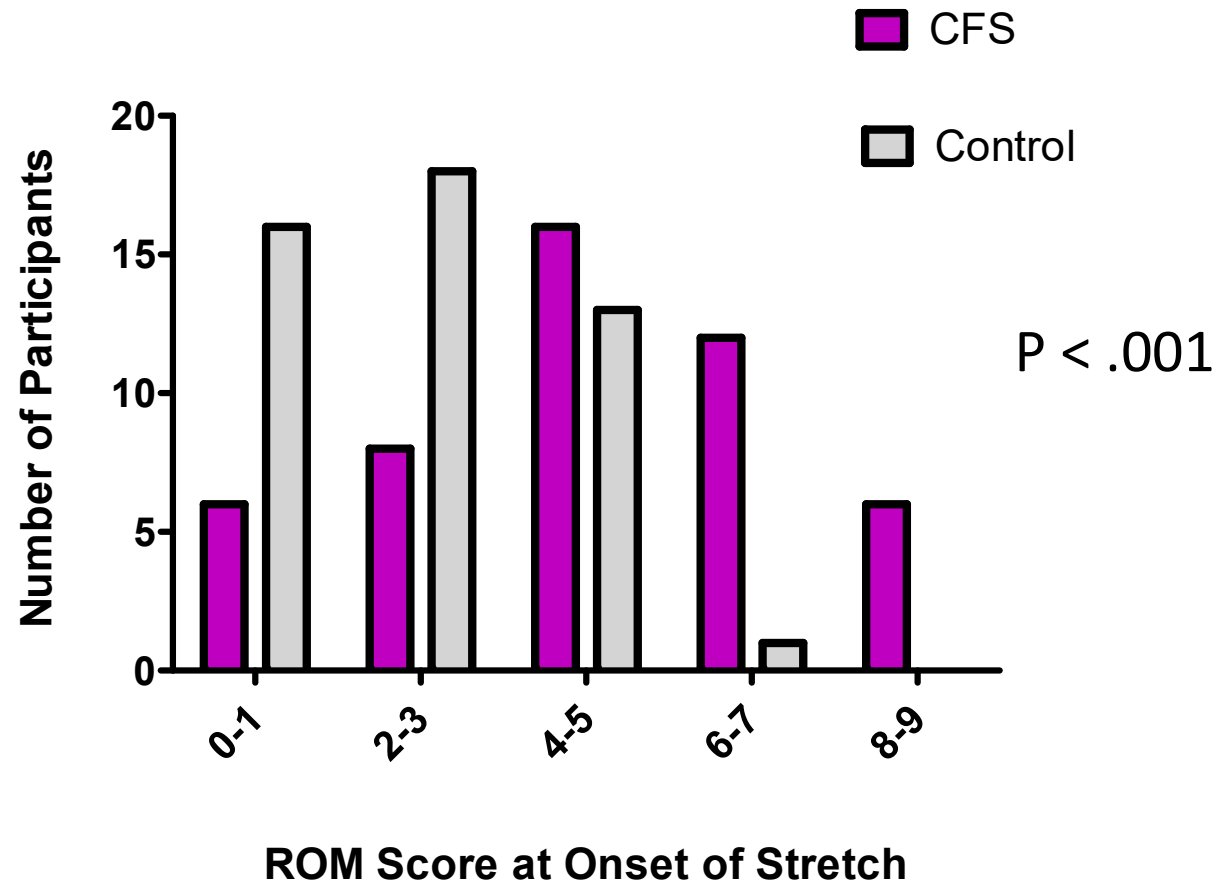
Severity



Degrees of SLR

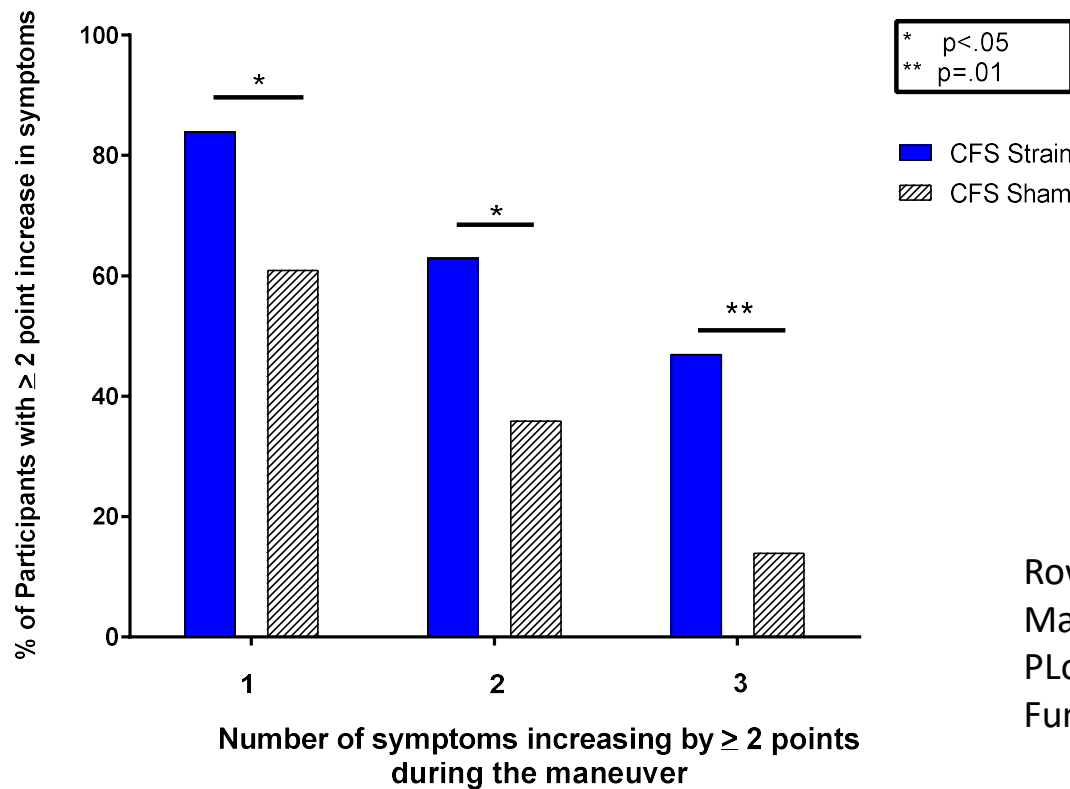
Rowe PC, Fontaine KR, Violand RL. Neuromuscular strain as a contributor to cognitive and other symptoms in chronic fatigue syndrome. *Frontiers in Integrative Physiology* 2013; 2013;4:115.

INDIVIDUAL EXAM MANEUVERS	CFS	Controls	Odds Ratio	P
Slump L leg < 170	13%	8%	1.7	.48
Slump R leg < 170	10%	2%	5.0	.10
ADF L < 95	15%	0%	15.0	<.01
ADF R < 95	13%	0%	13.0	<.02
SLR L < 45	69%	38%	6.0	.001
SLR R < 45	71%	31%	7.3	<.001
ULNT1 L < 170	71%	56%	2.0	.13
ULNT1 R < 170	65%	31%	5.0	.001
PKB L < 130	46%	35%	1.6	.30
PKB R < 130	38%	33%	1.2	.66
Pr. press-up abn.	52%	17%	3.8	.002



Rowe PC, 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

Neuromuscular Strain Increases Symptom Intensity in Chronic Fatigue Syndrome



Rowe PC, Fontaine KR, Lauver M, Jasion SE, Marden CL, Moni M, Thompson C, Violand RL. PLoS ONE 2016; 11(7): e0159386. Funded by the CFIDS Association of America/SMCI

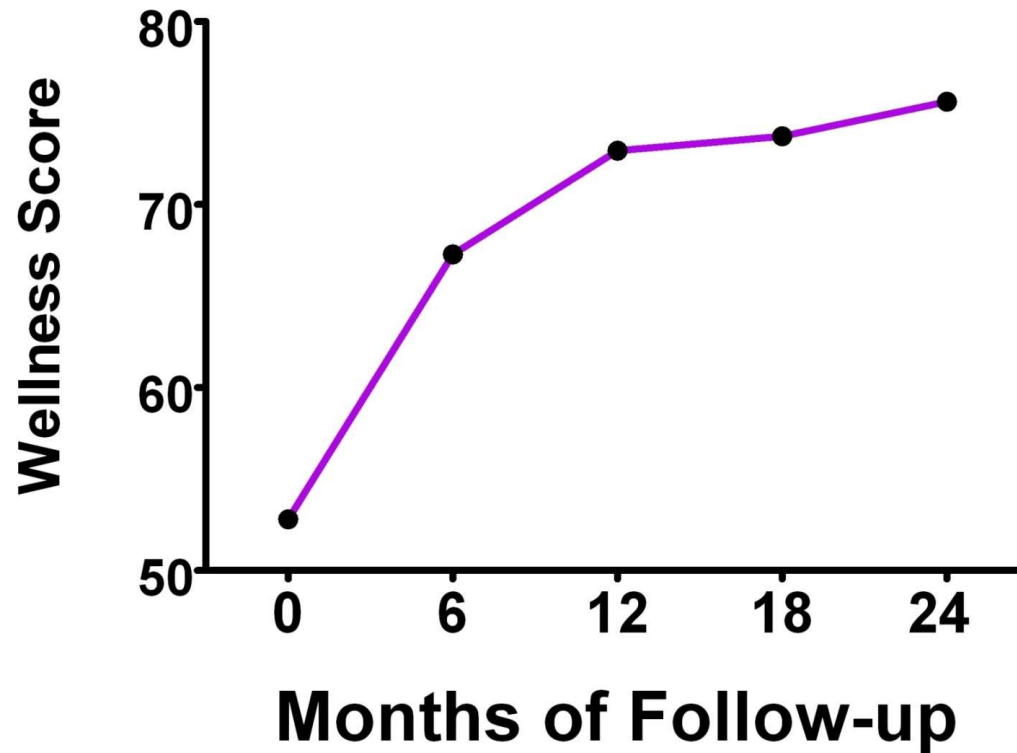
Speculation

- If a simple and relatively brief passive SLR strain can provoke symptoms, then prolonged, repetitive, or excessive strain beyond the usual range of motion in daily life might be followed by a similar exacerbation
- Treating these areas of movement restriction—before advancing to more aerobic exercise—might improve the ability of ME/CFS patients to tolerate activity better.

Topics for discussion

- Orthostatic intolerance
- Joint hypermobility, EDS, and other overlapping comorbid conditions in pediatric ME/CFS
- Neural strain
- **A word on outcomes**
- Considerations in refractory cases

Johns Hopkins ME/CFS Cohort Study 2008-2014:
Outcomes with individualized treatment



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ME/CFS is a heterogeneous condition.

We need to continually ask: MECFS due to what?

Rowe et al. *J Transl Med* (2018) 16:21
<https://doi.org/10.1186/s12967-018-1397-7>

Journal of
Translational Medicine

RESEARCH

Open Access



Improvement of severe myalgic encephalomyelitis/chronic fatigue syndrome symptoms following surgical treatment of cervical spinal stenosis

Peter C. Rowe^{1*}, Colleen L. Marden¹, Scott Heinlein² and Charles C. Edwards II³



The severe end of the spectrum: 25 yr old with ME/CFS

- Onset at age 9 with gradual decrease in stamina, worse following sinus infection at 13
- Unable to attend school after grade 8 due to symptoms; now mostly housebound
- Multiple co-morbid conditions:

POTS ↓ IgG Low carnitine Migraines Urticaria (MCAS?)	Gallstones IBS Tachygastria Brachial plexus movement restrictions
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Conclusions

- Pediatric ME/CFS is a serious, chronic, complex, multisystem disease that often can profoundly limit the health and activities of affected patients
- The physical examination is often abnormal
 - Acrocyanosis
 - Tachycardia or hypotension [$>95\%$]
 - Joint hypermobility [60%]
 - Movement restrictions
- Many symptoms of the illness are amenable to established therapies
- Effective treatment for severe ME/CFS is a critical need

Resources



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

Peter C. Rowe¹, Rosemary A. Underhill^{2}, Kenneth J. Friedman³, Alan Gurwitt⁴,
Marvin S. Medow⁵, Malcolm S. Schwartz⁶, Nigel Speight⁷, Julian M. Stewart⁸,
Rosamund Vallings⁹ and Katherine S. Rowe¹⁰*

Open Access, so available to all free of charge

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

http://www.youtube.com/watch?v=YnCcEoFSgvc&feature=youtu.be&utm_source=getresponse&utm_medium=email&utm_campaign=research_1st&utm_content=Research+1st+News+%7C+October+2014

- A Clinical Approach to ME/CFS in Adolescents and Young Adults, 16 March 2017

https://www.youtube.com/watch?v=_WqGmHpL6MI

- Orthostatic intolerance in EDS, 19 December 2018

https://www.youtube.com/watch?v=7lA3Vcbz_w8

- 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/>

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- Summer students (John Fan, Alli Johns, Marissa Flaherty, Jocelyn Ray, Samantha Jasion, Erica Cranston, Megan Lauver, Maria Roma)
- Many families and patients:
 - Special thanks to the following families:
Boies, Bowen, Caldwell, Cornell, Ellen, Fox-Penner, Kelly, Kiely, Lauver, McFerron, Newbrand, Scheidlinger, Smith, and Vogel.