Treatable Co-morbid Conditions: Dysautonomia, Milk Protein Intolerance, and Adverse Neural Tension. Lessons from ME/CFS

April 30, 2017

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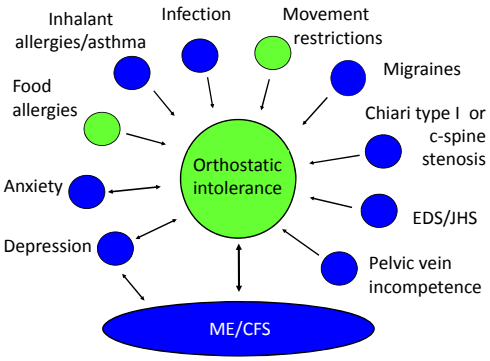

15 yr old with fatigue, LH, brain fog

Separation anxiety at age 6-7 yrs
Age 12: after a GI virus, develops fatigue, LH, tachycardia, cognitive problems, myalgias, rare HA. Meets criteria for CFS.

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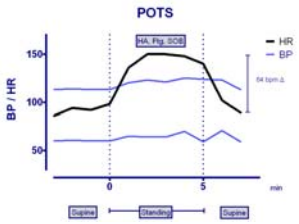


15 yr old with fatigue, LH, brain fog

By 15, part-time schooling. Unable to attend after 10th grade due to fatigue, anxiety, LH, brain fog.
Minimal response to OI and anxiety meds.
Adverse neural tension in upper limbs
Neck discomfort and tightness identified by PT
Age 19: neuro exam shows intermittently + Hoffman sign
FH: mother has congenital cervical stenosis, 2 fusions at 34 and 43 yrs for degenerative discs, TOS surg x2

Course

Elects to undergo conservative disc replacement at site of disc bulge at C 6-7

Within 2 months, working as dog walker & vet tech

Gradually able to exercise more, marked reduction in anxiety, POTS resolves; part-time univ. classes

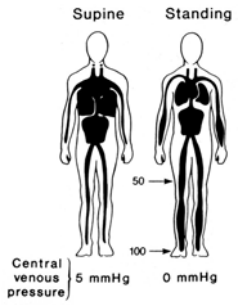
After 6 months, summer job as wrangler at dude ranch: arises at 6 AM to saddle horses, leads campers on horseback ride, cooks, active until late evening

5 yr F/U: completed BA, weekend photographer 12 hrs/day, now rock climbing, unrestricted activities

Orthostatic Intolerance

The term "orthostatic intolerance" refers to a group of clinical conditions in which symptoms worsen with quiet upright posture and are ameliorated (although not necessarily abolished) by recumbency.

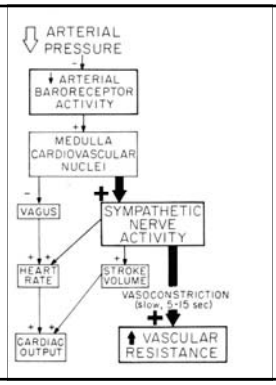
Modified from: Low PA, Sandroni P, Joyner M, Shen WK. Postural tachycardia syndrome (POTS). J Cardiovasc Electrophysiol 2009;20:352-8.



500-750 mL of blood pools in the lower half of the body on standing

Low PA

Normal physiological responses to orthostatic stress



Rowell LB

Human Cardiovascular Control, 1993

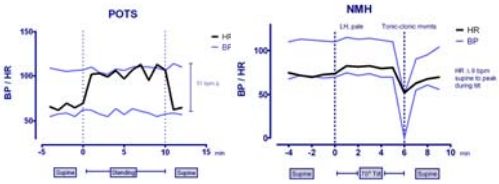
Symptoms of Orthostatic Intolerance

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

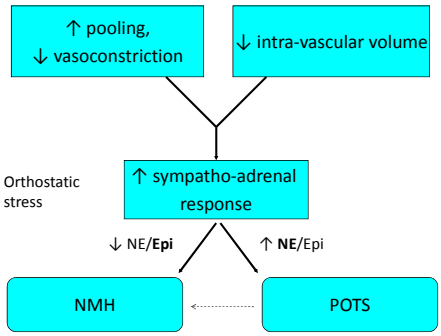
Historical questions with high yield in OI

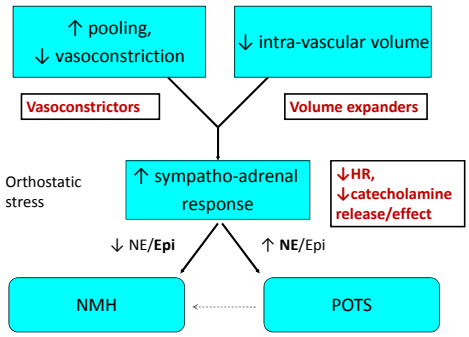
- How long can you stand still before feeling unwell?
- How do you feel in the following settings:
  - Waiting in line, shopping?
  - Standing at a reception, in chorus, at a service?
  - After taking a hot shower, bath, or sauna?
  - In a warm environment (in a hot room, on a hot day)?
- Do you feel lightheaded or unwell …
  - when you stand for more than 5 minutes?
- Have you ever fainted?
- Do you study in a reclining position, with knees to chest, or feet under you?
- Do you fidget and move around when standing?

Common forms of orthostatic intolerance



POTS: 40 bpm ↑ in HR in adolescents (30 bpm in adults) in first 10 min of standing/HUT, or HR > 120 bpm, with chronic OI symptoms, and in the absence of orthostatic hypotension
NMH: 25 mm Hg ↓ in SBP, often with chronic OI symptoms





Pharmacologic Therapy

Vasoconstrictors	Midodrine, Dexedrine, methylphenidate, SSRIs, SNRIs; L-DOPS (Droxidopa)
Volume expanders	Sodium (PO & occasionally IV), fludrocortisone, clonidine, OCPs, desmopressin
↓ HR, ↓catecholamine release/effect	β-blockers, disopyramide, SSRIs, ACE inhibitor, pyridostigmine bromide, ivabradine

Is neurally mediated hypotension an unrecognised cause of chronic fatigue?

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

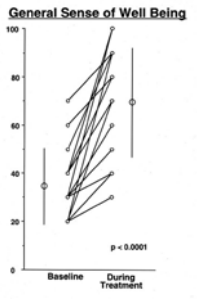
Lancet 1995; **345:** 623–24

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.

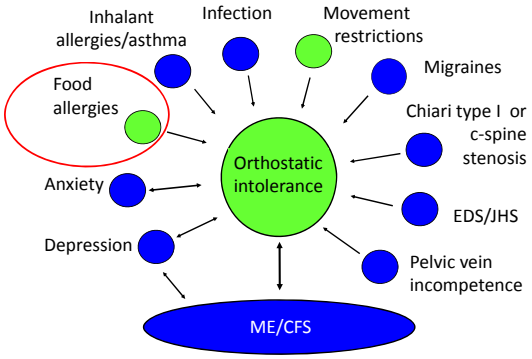
Caveats

- Orthostatic intolerance syndromes have heterogeneous precipitating and perpetuating factors
- We must continue to reassess for a primary cause of symptoms, not accepting POTS or NMH as the primary diagnosis, always asking:

"Orthostatic intolerance: due to what?"

OI References

- Raj SR. Postural tachycardia syndrome (POTS). Circulation 2013;127:2336-42.
- Grubb BP. Neurocardiogenic syncope. N Engl J Med 2005;352:1004-10.
- Stewart JM. Common syndromes of orthostatic intolerance. Pediatrics 2013;131:1–13.
- Sheldon RS, et al. 2015 Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Treatment of Postural Tachycardia Syndrome, Inappropriate Sinus Tachycardia, and Vasovagal Syncope. Heart Rhythm 2015.
- Search "Dr. Peter Rowe" on YouTube for webinar on "Managing Orthostatic Intolerance."
- Dysautonomia International (www.dysautonomiainternational.org)



An 18 yr old with fatigue & GI complaints

- Gradual onset of nausea, abdominal pain, early satiety, lightheadedness, and fatigue at age 15
- Tilt test: HR rises from 70 bpm supine to 96 bpm in 10 minutes, then continues gradually to 141 bpm at 40 min, associated with reproduction of nausea, abdo pain, fatigue, c/w dysautonomic response
- Rx: increased salt and fluid, fludrocortisone

An 18 yr old with fatigue & GI complaints

- Modest improvement in LH and fatigue with fludrocortisone
- Feels hungry, but after a couple of bites of food feels full
- Nausea usually present after eating, on most days
- Periumbilical burning on a constant basis

An 18 yr old with fatigue & GI complaints

- Reports GERD symptoms
  - acid taste for many years
  - metallic taste in mouth commonly
- No oral ulcerations
- Normal stools
- No weight loss
- Exam notable only for epigastric tenderness

An 18 yr old with fatigue & GI complaints

- Prior w/u:
  - Normal UGI and SBFT
  - Normal endoscopy and colonoscopy
  - WBC 4,000, but stable
  - Normal ESR
  - Negative ANA
- Improvement with a course of prednisone; symptoms recurred after prednisone stopped

Asking about foods

- Never liked milk
- Abdominal pain after milk on cereal
- Loves cheese, ice cream, sour cream

Course

Trial off milk protein
Returns in 3 weeks (glaring):

"I feel worse. This was like 3 weeks from Hell!"*

Course

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Returns in 3 weeks (glaring):

"I feel worse. This was like 3 weeks from Hell!"*

*Disqualified from Johns Hopkins Telethon appearance

Course

Impression: soy protein as co-allergen
Recommendation: trial of milk and soy protein elimination
Within a week: much improved
- less nausea, GER
- abdo pain and headache better
-recurrences only after inadvertent re-exposure to milk or soy

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

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, sinusitis, myalgias, fatigue, asthma

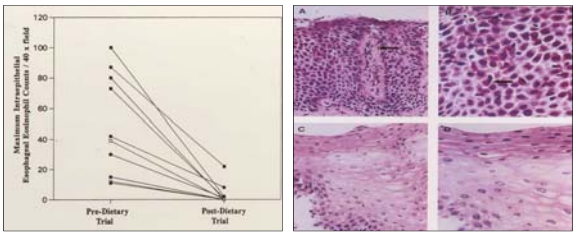
Kelly KJ et al. Gastroenterology 1995;109:1503-12

Treatment of non-IgE mediated food allergy

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

LTFU

At age 31, mother gives birth to infant who is intolerant of milk-based formula (loose stools, fussy), improved on Neocate.


ACTA PÆDIATRICA
NURTURING THE CHILD

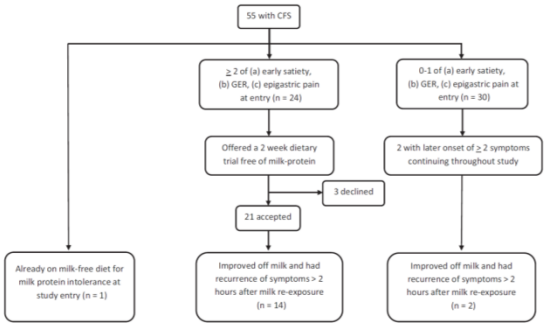
Acta Paediatrica ISSN 0803-5253

REGULAR ARTICLE

105, pp. e412–e418

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

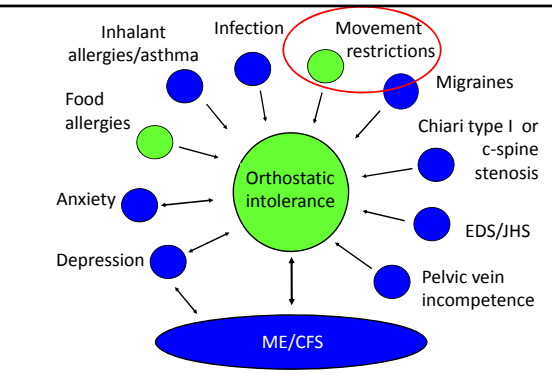
Peter C. Rowe (prowe@jhmi.edu)[1], Colleen L. Marden[1], Samantha E. Jasion[1], Erica M. Cranston[1,2], Marissa A. K. Flaherty[1,2], Kevin J. Kelly[3]



Aphthous ulcers and milk protein intolerance

	Milk intolerant	Milk tolerant
Aphthous ulcers	9	3
No aphthous ulcers	8	35

OR=13.1; 95% CI, 2.9-59.8; P<0.001



Neurodynamics: the interaction of nerve mechanics and nerve physiology

- As bones, muscles, joints, and connective tissues move in daily life, they impose forces on the neural tissues
- With dynamic change (movement) the nerve tissues must elongate, slide, angulate around joints, and undergo compression
- Mechanical stresses to nerves evoke physiologic responses (changes in nerve blood flow, electrical conduction, and axonal transport)
- Abnormal neurodynamic interactions initially were termed "adverse neural tension," later "neurodynamic dysfunction" or "neural tension dysfunction"

Shacklock M. Neurodynamics. Physiotherapy 1995; Manual Therapy 2005

Neurodynamic dysfunction

- Neuroanatomic studies have emphasized that the nervous system must adapt mechanically as we move
  - Vertebral canal length increases 5-9 cm from full backbend (extension) to full forward bend (flexion)
  - Median nerve must adapt to a 20% length difference between arm flexion and extension

Ref: Butler D. Mobilisation of the nervous system. 1999

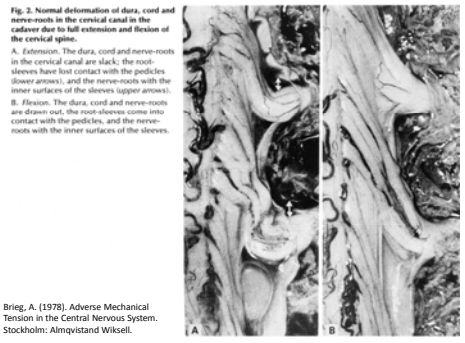


Fig. 2. Normal deformation of dura, cord and nerve-roots in the cervical canal in the cadaver due to full extension and flexion of the cervical spine.
A. *Extension.* The dura, cord and nerve-roots in the cervical canal are slack; the root-sleeves have lost contact with the pedicles (*lower arrows*), and the nerve-roots with the inner surfaces of the sleeves (*upper arrows*).
B. *Flexion.* The dura, cord and nerve-roots are drawn out, the root-sleeves come into contact with the pedicles, and the nerve-roots with the inner surfaces of the sleeves.

Brieg, A. (1978). Adverse Mechanical Tension in the Central Nervous System. Stockholm: Almqvistand Wiksell.

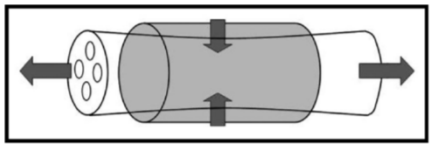


Figure 4.
Physical stresses placed on peripheral nerve. Tensile stress applied longitudinally to peripheral nerve creates an elongation of the nerve (an increase in strain). The transverse contraction that occurs during this elongation is greatest at the middle of the section undergoing tensile stress.

Structure and Biomechanics of Peripheral Nerves: Nerve Responses to Physical Stresses and Implications for Physical Therapist Practice. Phys Ther. 2006;86:92–109

An illustration of neurodynamics

(you may want to wait until afterwards to try this if you have CFS: it might provoke symptoms including brain fog)

Consequences of abnormal mechanical tension within the nerve

- ↓d intraneural blood flow and ↓electrical conduction, intraneural edema (swelling)
- release of inflammatory neuropeptides
- Protective increase in resting muscle tone (which in turn increases the energy expenditure and reduces the ease of movements)
- ↑d mechanical sensitivity
- Autonomic responses (sweating, altered blood flow to peripheral tissues)

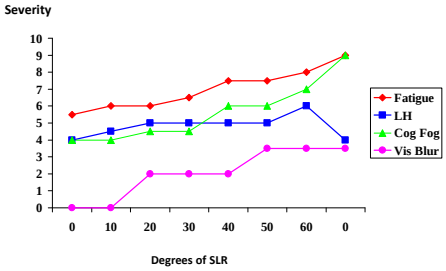
Ref: Butler D. Mobilisation of the nervous system. 1999

Observations in Adolescents with ME/CFS

Increased prevalence of postural abnormalities and movement restrictions

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

Passive SLR over 12 minutes in adolescent with ME/CFS



ORIGINAL ARTICLES

www.jpeds.com • The Journal of Pediatrics

Impaired Range of Motion of Limbs and Spine in Chronic Fatigue Syndrome

Peter C. Rowe, MD[1], Colleen L. Marden[1], Marissa A. K. Flaherty, MD[1], Samantha E. Jasion[1], Erica M. Cranston[1], Allison S. Johns[1], John Fan, MD[1], Kevin R. Fontaine, PhD[2], and Richard L. Violand, PT[3]

(J Pediatr 2014;165:360-6).

[1]Department of Pediatrics, JHUSOM, Baltimore, MD;
[2]Department of Health Behavior, University of Alabama School of Public Health, Birmingham, AL;
[3]Violand and McNerney, PA, Ellicott City, MD.

Methods: main study measures

ROM measures:*

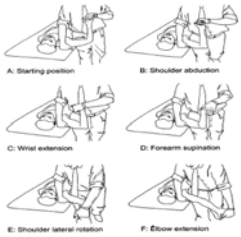
- Seated slump test
- Ankle dorsiflexion
- Passive straight leg raise
- Upper limb neurodynamic test 1
- Prone knee bend
- Prone press-up

*Performed with minor modifications according to the methods of Butler DS, Mobilisation of the Nervous System, 1999

From: Walsh J, et al. Slump Test: Sensory Responses in Asymptomatic Subjects. The Journal of Manual & Manipulative Therapy 2007; 15:231–8

Rick Violand conducting a passive straight leg raise test

Upper Limb Neurodynamic Test



From: Butler DS, The Sensitive Nervous System 2000

Prone press-up

Results: subject recruitment

CFS N=55

Controls N=69

48 pairs matched by sex and Beighton score category*

* Matching performed by research assistant blinded to ROM score

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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
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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**

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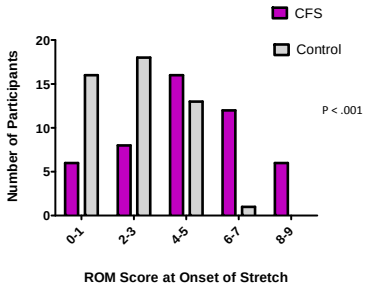

Rowe PC, Marden CL, Flaherty M, Jasion SE, Cranston EM, Johns AS, Fan J, Fontaine KR, Violand RL. Impaired range of motion of limbs and spine in chronic fatigue syndrome. J Pediatrics 2014

Results:

- Median ROM score higher in CFS:
  5 vs 2; P < .001
- CFS subjects more likely to have > 3 areas of impaired ROM:
  OR=6.0 (95% CI, 2.1-17.3); P < .001

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;165:360-6

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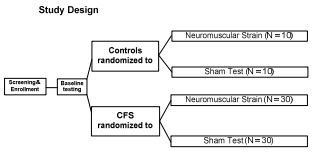
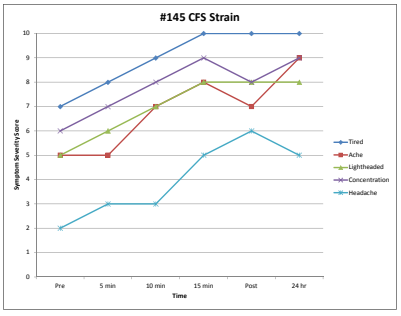
PLOS ONE | Neuromuscular Strain Increases Symptom Intensity in Chronic Fatigue Syndrome



Rowe PC, Fontaine KR, Lauver M, Jasion SE, Marden CL, Moni M, Thompson C, Violand RL. PLoS ONE 2016; 11(7): e0159386.



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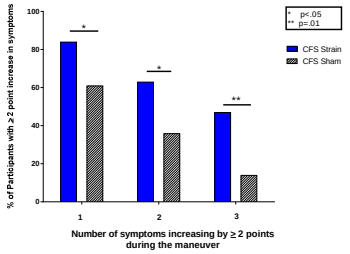

Rowe PC, Fontaine KR, Lauver M, Jasion SE, Marden CL, Moni M, Thompson C, Violand RL. PLoS ONE 2016; 11(7): e0159386.

Study Conclusions

- These novel findings are consistent with reduced compliance of the neuromuscular system in CFS and with the hypothesis that increased mechanosensitivity of muscles, fascia, connective tissue, and nerves is a contributor to the generation and exacerbation of CFS symptoms*

*Rowe PC, Fontaine KF, Violand RL. Front Physiol 2013;4:115.

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Conclusions

- The mechanisms of the impaired ROM remain to be determined (but are neutral with regard to etiologic hypotheses)
  - Intra-neural edema following infections?
  - Immune-mediated changes in nerves?
  - Stretch-induced mast cell activation in the nervous system?
  - Excessive mechanical strain of nerves across hypermobile joints?
  - Deformative stress on the spinal cord and peripheral nerves?

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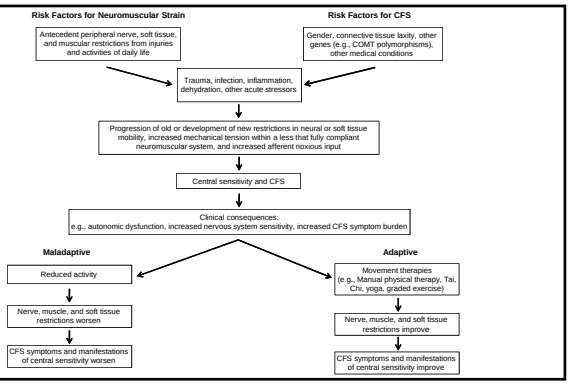

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- Many families and patients:
  - Special thanks to the following:

    Berger, Boies, Bowen, Caldwell, Cornell, Ellen, Fox-Penner, Kelly, Kiely, Lauver, McFerron, Newbrand, Scheidlinger, Smith, and Vogel families.

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