

Update on Orthostatic Intolerance in EDS

Metro DC EDS and HSD Support Group, July 9, 2023



Peter C. Rowe, M.D.
 Professor of Pediatrics
 Sunshine Natural Wellbeing Foundation Professor of Chronic Fatigue and Related Disorders
 Division of General Pediatrics and Adolescent Medicine
 Johns Hopkins University School of Medicine

Update on Orthostatic Intolerance in EDS

- Overview of orthostatic intolerance: what is it, what symptoms, how do we diagnose it
- Common forms: OI is not just POTS ...
- New work on reductions in cerebral blood flow during tilt
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- Management of orthostatic intolerance
- Illustrative cases emphasizing new targets of therapy: venous insufficiency, cervical stenosis and CCI, & MCAS

Orthostatic Intolerance

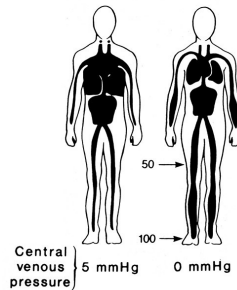
“Orthostatic” means “upright.”

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.

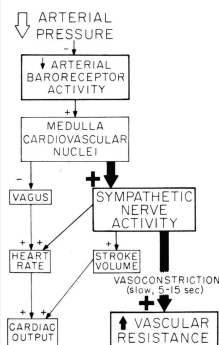
Supine Standing



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

The normal response is a 10-20 beat increase in heart rate and better blood vessel constriction to return blood to the heart and brain.

Low PA



Normal physiological response to upright posture

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 |

Due to reduced cerebral blood flow

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

Due to 2° hyperadrenergic response

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

- Have you ever fainted?
- Do you feel lightheaded or unwell when you stand for more than 5 minutes?
- 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 study in a reclining position, with knees to chest, or feet under you?
- Do you fidget and move around when standing?

Diagnostic testing

- Orthostatic vital signs—HR and BP measured supine, sitting, and standing—often measured over < 2 minutes: insufficient to identify most forms of chronic orthostatic intolerance. Prolonged testing of ≥ 10 minutes usually needed.
- Standing test (usually 10 min after a variable time supine):
 - Passive Stand Test
 - Active Stand Test

Passive Standing Test

Supine: 5 min with BP and HR every minute

Standing: 10-15 min with feet positioned 6 inches apart, 6 inches from a wall, leaning slightly backwards against the wall.

HR & BP measured each minute

Symptoms recorded every 1-2 minutes

Hyatt KH, Jacobson LB, Schneider VS. Comparison of 70° tilt, LBNP, and passive standing as measures of orthostatic tolerance. *Aviat Space Environ Med* 1975;46:801-8.

Head-up tilt table testing

Supine: Obtain baseline HR and BP values



Stage 1: head-up tilt to 70° for ~ 45 min

Stage 2 (optional): return to supine for 10 minutes, then head-up tilt for 15 minutes with isoproterenol (1-2 mcg/kg/min).

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Common Forms of OI

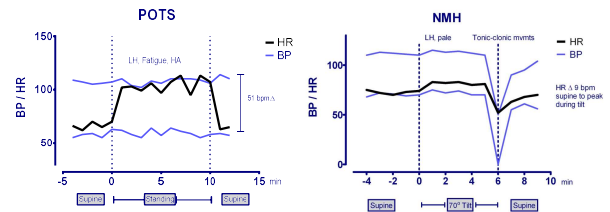
- **Initial Orthostatic Hypotension (IOH):**
 - transient ↓ of 40 mm Hg in SBP or 20 mm Hg DBP within 15 sec of standing, lasting < 60 seconds (more common in adolescents)
- **Orthostatic Hypotension (OH):**
 - sustained ↓ of 20 mm Hg in SBP or 10 mm Hg in DBP within 3 min of standing or HUT (more common in older adults)
- **Delayed OH**
 - OH occurring after 3 minutes upright

Freeman R, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res 2011;21:69-72; 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;12:e41-63.

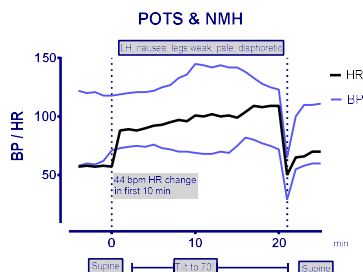
Common Forms of OI

- **Postural tachycardia syndrome (POTS):**
 - ≥ 40 bpm ↑ in HR in adolescents (≥ 30 bpm in adults) in first 10 min of standing or head-up tilt, with chronic OI symptoms, with no OH
- **Neurally mediated hypotension (NMH):**
 - ≥ 25 mm Hg drop in BP during standing or HUT, often associated with a reduction in HR
- **Inappropriate sinus tachycardia (IST):**
 - Sinus rhythm with a HR > 100 bpm at rest; similar symptoms to POTS
- **Low orthostatic tolerance:**
 - Orthostatic symptoms in the absence of HR and BP changes; Many of these individuals have reduced cerebral blood flow.

Common forms of orthostatic intolerance

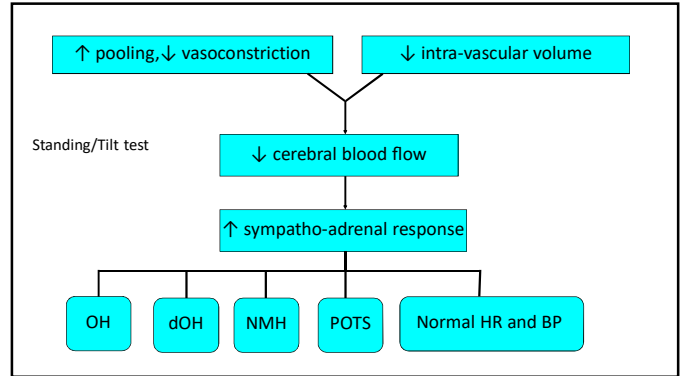
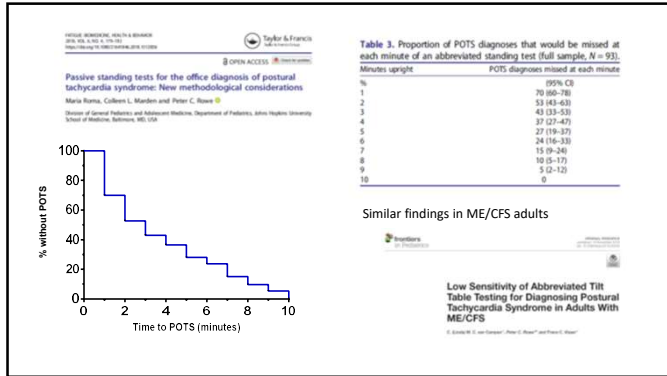


POTS and NMH can occur together



Acrocyanosis is common in OI





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What does it mean if you have lots of symptoms with standing, but the formal tests of heart rate and blood pressure are normal during a passive standing test or a head-up tilt table test?

Does this mean nothing is wrong?

What does it mean if you have lots of symptoms with standing, but the formal tests of heart rate and blood pressure are normal during a passive standing test or a head-up tilt table test?

Does this mean nothing is wrong?

NO!

Clinical Neurophysiology Practice 5 (2020) 50-58

Contents lists available at ScienceDirect

Clinical Neurophysiology Practice

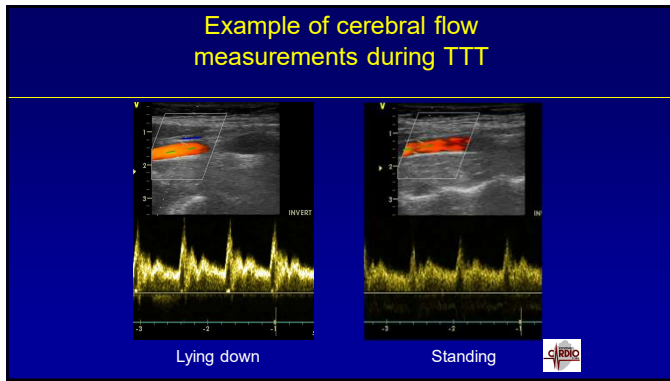
Journal homepage: www.elsevier.com/locate/cnp

Research paper

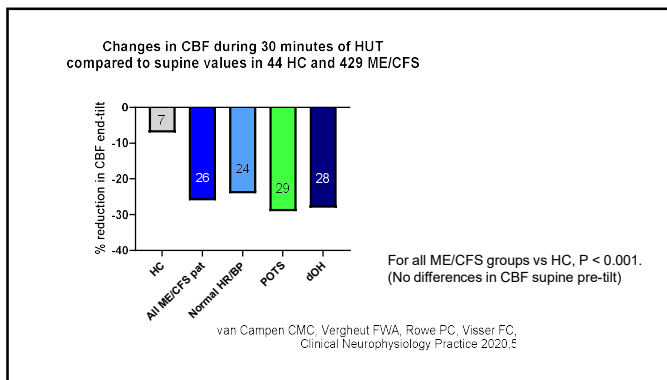
Cerebral blood flow is reduced in ME/CFS during head-up tilt testing even in the absence of hypotension or tachycardia: A quantitative, controlled study using Doppler echography

C. (Linda) M.C. van Campen^{a,b}, Freek W.A. Verheugt^b, Peter C. Rowe^c, Frans C. Visser^a

^aStichting CardioZorg, Pluimvzweg 5, 2132 HN Hoofddorp, The Netherlands
^bDepartment of Cardiology, Onze Lieve Vrouwe Ziekenhuis (OLVZ), Oosterpark 9, 1091 AC Amsterdam, The Netherlands
^cDepartment of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA



Tilt results	ME/CFS N=429	Control N=44	P
Normal HR and BP	58%	100%	<0.0005
dOH	14%		
POTS	28%		



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

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

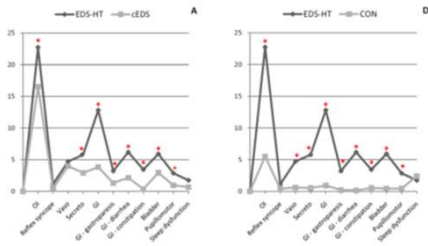
11 females, 1 male

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.

- ### Autonomic symptoms in EDS and controls
- De Wandele I, et al. Seminars Arth Rheum 2014; 44:93-100 and 353-61;
- 75/80 (94%) with EDS-HT reported symptoms of OI
 - Mean (SD) Autonomic Symptom Profile total score higher in EDS-HT than controls:
57.9 (21.57) vs 12.3 (10.73), $P < 0.001$
 - OI during tilt more common in EDS-HT:
74% vs 34%, $P = 0.001$
 - POTS most common form of OI in hEDS (41% vs 11% in HC)

Autonomic symptoms in EDS and controls

De Wandele I, et al. Seminars Arth Rheum 2014

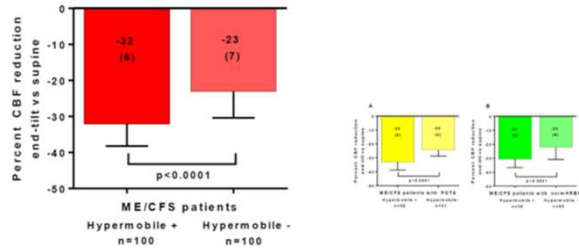


Prevalence of Orthostatic Intolerance in EDS:

No population based studies

In clinic-based reports, 41-100% with JH/EDS report orthostatic symptoms on a regular basis

HR and BP abnormalities are identified in 56–80% of JH/EDS patients in published studies



Van Campen C, et al. Medical Research Archives vol 9 issue 7. July 2021

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Management of Orthostatic Intolerance

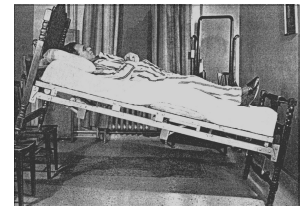
- Step 1: Non pharmacologic measures
- Step 2: Treat contributory conditions
- Step 3: Medications
 - Monotherapy
 - Rational polytherapy

Step 1: Non-pharmacologic measures

Raising the head of the bed has an anti-diuretic effect and preserves blood volume at night

MacLean AR, Allen EV. Am Heart J 1944; 27:145

Ten Harkel ADJ, et al. J Int Med 1992; 232:139-145.



Step 1: Non-pharmacologic measures

Compression garments

- Support hose
(20-30 better tolerated than 30-40 mm Hg)
(waist high > thigh high > knee high)
- Body shaper garments
- Abdominal binders



Step 1: Non-pharmacologic measures

Use postural counter-measures

- standing with legs crossed
 - squatting
 - knee-chest sitting
 - leaning forward sitting
 - elevate knees when sitting (foot rest)
 - clench fists when standing up
- [Use the muscles as a pump]**



Postural countermeasures



Step 1: Non-pharmacologic measures

- Fluids:** Minimally 2 L per day
 Drink at least every 2 hours
 Need access to fluids at school
 Avoid sleeping > 12 hrs/day
 Cooling garments in hot weather
- Salt:** Increase according to taste (up to 10 g daily)
 Supplement with salt tablets, ORS

Step 1: Non-pharmacologic measures

Cooling garments

- Neck wraps
- Cooling hats
- Towels
- Vests



<http://www.mscooling.com/>
<https://glaciertek.com/>
<http://www.mycoolingstore.com/>

Oral rehydration products



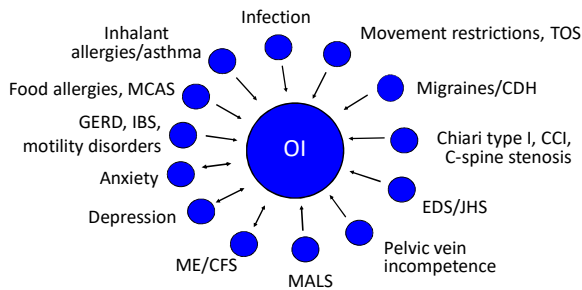
Step 1: Non-pharmacologic measures: Exercise

Avoid excessive bed rest/sleeping
 For most impaired, start slowly, increase gradually
 Recumbent exercise may help at outset
 Beware rigid advancement of graded exercise
 Exercise might not be tolerated before orthostatic intolerance is treated
 Manual forms of PT may be a bridge to better tolerance of exercise

[Complete inactivity is the enemy]

Management of Orthostatic Intolerance

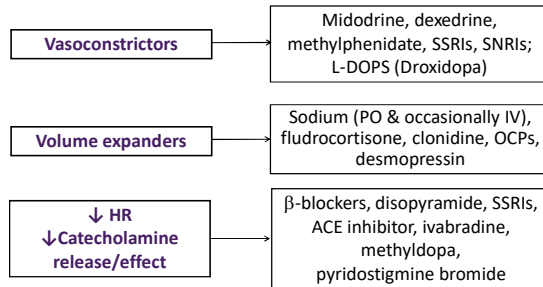
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Management of Orthostatic Intolerance

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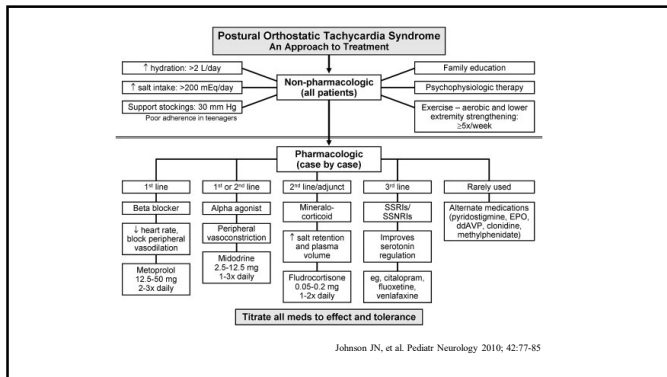
Pharmacologic Therapy



How to select initial therapy?

Algorithm vs. individualized approaches

Caveat: we have *no* clinical trial data to support the primacy of one therapy over another for managing OI. Most advice is based on the experience of individual clinicians.



Individualized approach

- **SBP < 110:** fludrocortisone, midodrine
- **Increased HR at baseline:** β-blocker, ivabradine if HR > 100 bpm
- **Based on other clinical clues**
Increased salt appetite: fludrocortisone
HA: β-blocker
Dysmenorrhea/worse fatigue with menses: OCP, Depo
Anxiety/low mood: SSRI, SNRI, clonidine
Myalgias prominent: SNRI
Hypermobility: stimulant, midodrine

Management of orthostatic intolerance

- requires careful attention by the patient and the practitioner to the factors that provoke symptoms
- requires a willingness to try several medications before a good fit is achieved
- requires a realization that meds often can treat symptoms but do not necessarily cure OI
- management of OI is one part of a comprehensive program of care

Selected OI References

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- Grubb BP. Neurocardiogenic syncope. *N Engl J Med* 2005;352:1004-10.
- Stewart JM, Boris JR, Chelmsky G, Fischer PR, Fortunato JE, Grubb BP, et al. Pediatric disorders of orthostatic intolerance. *Pediatrics* 2018;141:e20171673
- 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.
- *Autonomic Neuroscience* 2018 (entire issue on POTS)
- Vernino S, et al. Postural orthostatic tachycardia syndrome (POTS): State of the science and clinical care from a 2019 National Institutes of Health Expert Consensus Meeting - Part 1. *Autonomic Neuroscience* 2021.
- Raj SR, et al. Postural orthostatic tachycardia syndrome (POTS): Priorities for POTS care and research from a 2019 National Institutes of Health Expert Consensus Meeting - Part 2. *Autonomic Neuroscience* 2021.

OI in EDS references

- Barron, D.F., et al., 2002. Joint hypermobility is more common in children with chronic fatigue syndrome than in healthy controls. *J Pediatr*. 141, 421-5.
- De Wandele, I., et al., 2014a. Autonomic symptom burden in the hypermobility type of Ehlers-Danlos syndrome: A comparative study with two other EDS types, fibromyalgia, and healthy controls. *Semin Arthritis Rheum*. 44, 353-61.
- De Wandele, I., et al., 2014b. Dysautonomia and its underlying mechanisms in the hypermobility type of Ehlers-Danlos syndrome. *Semin Arthritis Rheum*. 44, 93-100.
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- Rowe, P.C., et al., 1999. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. *J Pediatr*. 135, 494-9.

Web Resources

- CFS - SolveMECFS Initiative <http://solvecfs.org/>
- International Association for CFS/ME.org iacfsme.org
- OI - Search “Dr. Peter Rowe” on YouTube for webinar on “Managing Orthostatic Intolerance.”
- Dysautonomia International is a non-profit www.dysautonomiainternational.org
- EDS - Ehlers-Danlos Society <http://ehlers-danlos.com/>

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Case: 24 yr old with fatigue, LH, warmth

L hip dislocation at birth; Rx Pavlik harness for 3 months
Active in gymnastics and dance
Headaches in early adolescence, q 2weeks in high school, typically worse through school day and better after nap
No difference with propranolol

24 yr old with fatigue, LH, warmth

HA less common in college on OCPs; daily during the week off active hormone pills. Now off them.

Aggravating factors for HA: any upright posture, inadequate hydration, skipping meals, warm environments, summer weather

LH since early HS years, especially after rising from seated position, standing in one place, anatomy lab in Physician Assistant school

24 yr old with fatigue, LH, warmth

No syncope, but vision goes black, hearing distant
Brings knees to chest when seated; studies lying down; stays in motion when standing
Hands and feet often appear purple
Sensation of warmth or heat when upright for long periods

24 yr old with fatigue, LH, warmth

Worried about having to stand for long periods of time for clinical rotations in PA school

Energy fairly good

Shoulders sublux easily

HR 60 supine in early AM, 90s during day

Normal mood; laid-back disposition

24 yr old with fatigue, LH, warmth

O/E: Tall, thin young woman

Wt 62 kg; ht 180.2 cm (>97th); BMI 19.1

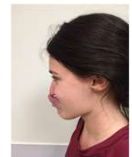
Easy eversion of lids; + Gorlin's sign; can touch tongue to elbow, place leg behind head

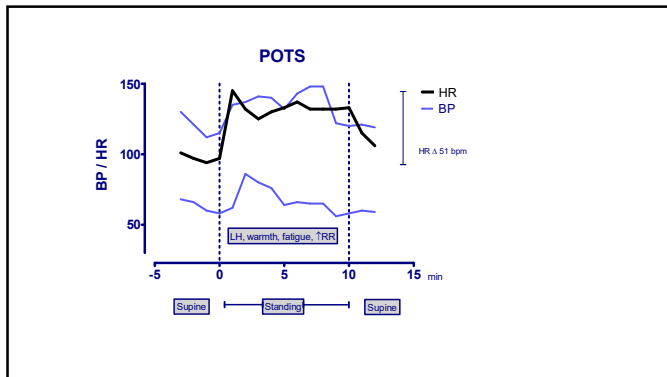
BS = 7/9; no arachnodactyly

Lordotic posture

Cardiac exam normal

Echo and labs normal





What would you do next?

- Midodrine
- Methylphenidate
- Beta blocker
- Mestinon
- Resume oral contraceptives
- Desmopressin acetate
- ARB/ACE inhibitor

What would you do next?

- Midodrine
- Methylphenidate
- Beta blocker
- Mestinon
- Resume oral contraceptives (stopping them associated with ↑symptoms)
- Desmopressin acetate
- ARB/ACE inhibitor

Course

“The 12.5 mg atenolol dose seems to be working well. My upright HR has remained lower, ranging from 60-95. Hot flashes are significantly less frequent, no headaches, much easier time with exercising as well. My resting HR has usually been in the high 50s. No side effects. BP 105/70. Do you recommend I stay at 12.5 mg or is it OK to go to 25mg?”

Course

- Increased LH and fatigue as temperatures rise
- Adds midodrine, with benefit for energy.
- Tries dexedrine as an alternative (sib on this)
- On dexedrine with atenolol, feels 100%.
- Appetite suppression on dexedrine; now uses it only on days when upright longer, taking midodrine on other days

Medical student with chronic fatigue

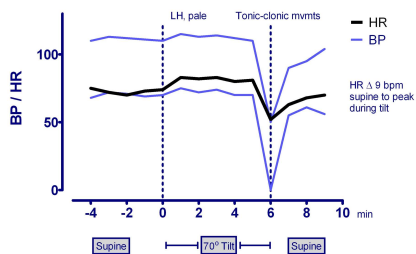
- Onset of persistent fatigue, unrefreshing sleep, exercise intolerance, myalgias, cognitive difficulties at entry to SOM
- PMH: Syncope since age 11; usually twice a yr, often after standing or after showers
- Frequent knee dislocations, 4 spont. pneumothoraces

Medical student with chronic fatigue

- In medical school, much more lightheaded, now 2 episodes of presyncope/week, LH several times/day
- Worse fatigue after syncopal episodes
- Symptoms thought due to atypical depression, although mood reported as OK. Worse syncope on sertraline 150 mg/day.
- Had to repeat year 1



Medical student with chronic fatigue



Medical student with chronic fatigue

- Joint and skin laxity noted by tilt staff
- Echo: aortic root normal, mild MVP
- Dx: Ehlers-Danlos syndrome

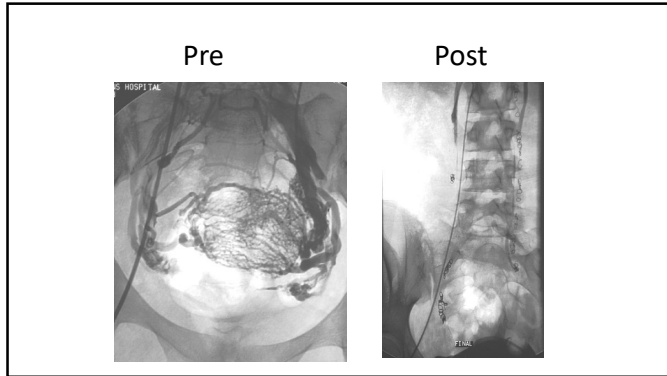
Medical student with chronic fatigue

- Syncope resolved with increased salt, fluids, midodrine
- Persistent non-cyclic pelvic heaviness and low back pain with standing; concerned about ability to tolerate surgical clerkship

Pelvic Congestion Syndrome

Venbrux AC, Lambert DL. *Curr Opin Ob Gyn* 1999; 11:395

- Pelvic heaviness or pain with long periods of standing
- Worse at end of the day, during menses
- Associated symptoms: fatigue, dyspareunia, bladder urgency
- Strong association with varicose ovarian veins
- 89% have > 80% relief after embolization of ovarian vein varicosities




Medical student with chronic fatigue

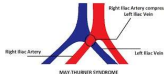
- Improved pelvic pain and orthostatic symptoms after embolization of ovarian vein varices
- Now able to stand for 7 hrs during surgical clerkship
- Wants to be a surgeon

Review Article

Phlebology

Imaging findings of pelvic venous insufficiency in patients with postural orthostatic tachycardia syndrome

Martha-Gracia Knutson¹, Kenneth S Zurcher² , Neil Mourani³, Iratzean Patel⁴, Amy Ross-Orenstein⁵, Lucinda A Harris⁶, Andrew Lawrence⁶, Francisco Aguilar⁶, Michael Schlaaf⁶, B. Holly Smith⁶ and Steven J South⁶



Received 7 October 2022 | Accepted 14 October 2022
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REVIEW ARTICLE

Surgical treatment of abdominal compression syndromes: The significance of hypermobility-related disorders

Wilhelm Sandmann¹ | Thomas Scholbach² | Konstantinos Verginis³

Case 3b: 20 year-old with recurrent syncope

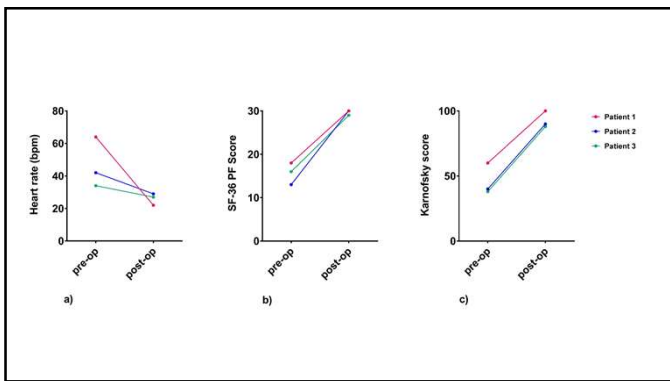
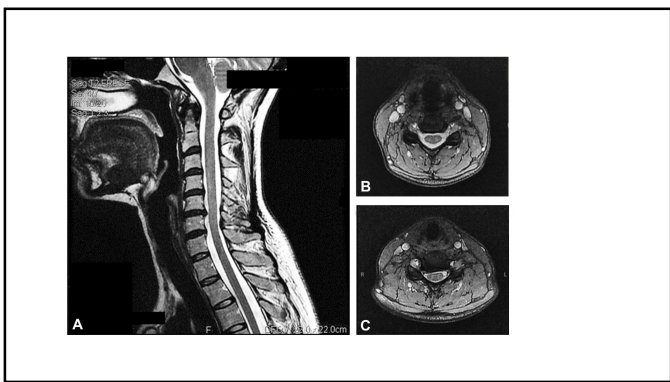
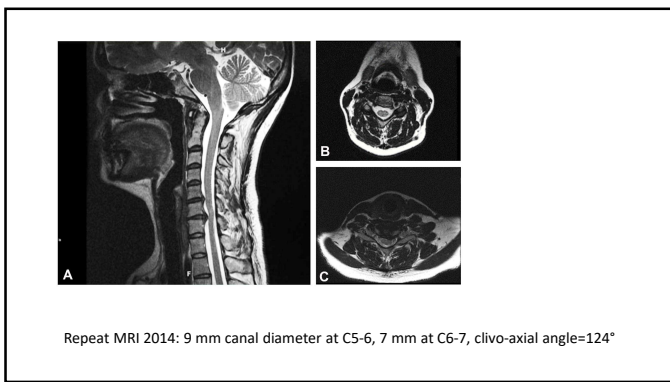
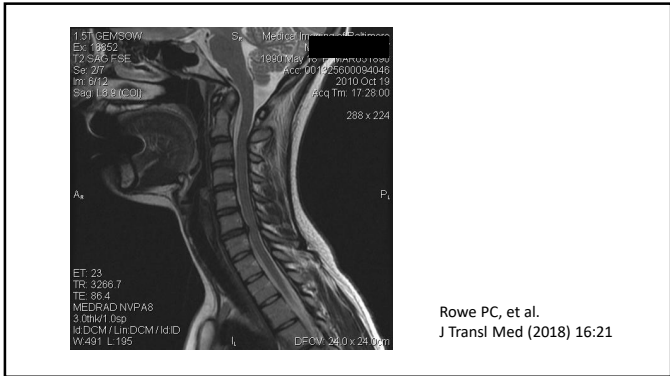
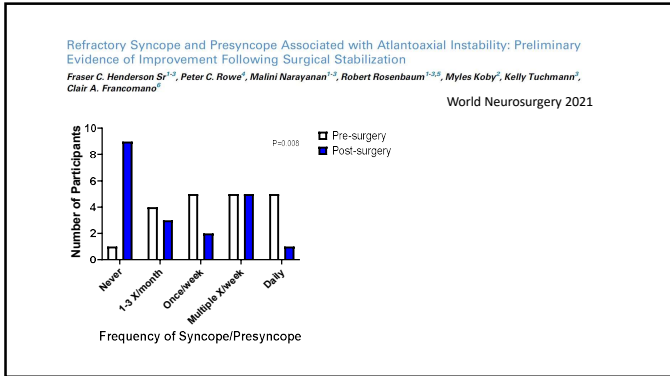
First of many shoulder dislocations at age 10
Age 18: multiple episodes of syncope without prodromal warning, associated with marked fatigue, 19 concussions

Treatments for syncope:

Fludrocortisone 0.1 mg daily, Methylphenidate 20 mg BID, Midodrine 7.5 mg q4h for three doses, OCPs, Mestinon

- papyraceous scars at the site of her prior shoulder surgery.
- Striae on the medial thighs. Piezogenic papules of the heel.
- Beighton score is 7/9. She has blue sclerae.
- Deep tendon reflexes were 2+ and symmetrical in the arms, brisk at 3+ at the knees, with spread of the reflexes to 5 cm of proximal to the patella.





Case 4: 22 year old with ME/CF5

- Onset of fatigue, sore throat, splenomegaly at 14 (associated with CMV)
- Co-morbid conditions at time of consultation:
 - Orthostatic intolerance
 - Joint laxity
 - Hypothyroidism
 - Raynaud's
 - Mild depression (after 2 years of illness)
 - Migraines
 - Reduced neurodynamic ROM on PT exam

22 year old with ME/CFS

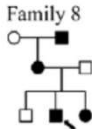
- Manages to complete high school and college in full-time program, but mainly on grit
- HA/pain remedies no Δ:
 - Riboflavin, CO-Q10, LDN, B12 injections
 - Topiramate, valproate, pregabalin, beta-blockers, verapamil, candesartan
 - Duloxetine, TCAs
 - Hydroxychloroquine
- Some benefit from increased salt and fluids, compression garments
- OI remedies no Δ:
 - Fludrocortisone,
 - Midodrine, stimulants
 - Propranolol, nadolol
 - Disopyramide
 - Pyridostigmine bromide
 - Clonidine
 - OCPs

22 year old with ME/CFS

- Develops resting tachycardia 104-140 bpm, with marked increase 2-3 minutes after trying to exercise (HR to 180, with exacerbation of migraines)
- Background mild allergies and asthma, but in 5th year gets urticaria after watermelon, abdo pain with apples, bananas, urticaria in reaction to detergents, hand sanitizers
- What is going on to explain the urticaria and allergies? What is left to try for the tachycardia?

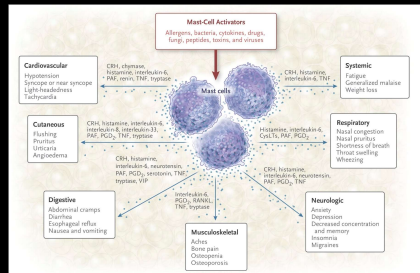
Mendelian inheritance of elevated serum tryp-tase associated with atopy and connective tissue abnormalities

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- Jonathan J. Lyons, MD*
- Guangping Sun, MEd
- Kelly D. Stone, MD, PhD*
- Celeste Nelson, CRNP*
- Laura Wisch, MSN*
- Michelle O'Brien, RN, BSN*
- Nina Jones, RN, BSN*
- Andrew Lindley, MD, PhD*
- Hirsh D. Komaroff, MD*
- Yun Bai, MS*
- Linda M. Scott, MS, CRNP*
- Daly Cantore, MSN*
- Irina Maric, MD*
- J. Pablo Abonia, MD*
- Marc E. Rothenberg, MD, PhD*
- Lawrence R. Schwartz, MD, PhD*
- Joshua D. Milner, MD*
- Todd M. Wilson, DO*

Clinically Relevant Mediators Released from Mast Cells and Putative Effects.



Theoharides TC et al. N Engl J Med 2015;373:163-172



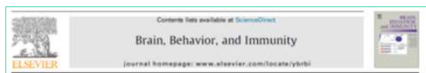
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A concise, practical guide to diagnostic assessment for mast cell activation disease

Lawrence B. Afari, Gerhard J. Holdings



Mast cell activation disease: An underappreciated cause of neurologic and psychiatric symptoms and diseases

Lawrence B. Afari¹, Dieter Pöhlau², Martin Raithe³, Britta Harmsch^{4,5}, Franz L. Dumoulin¹, Joergem Homann¹, Uwe M. Mauer¹, Sabrina Haezler¹, Gerhard J. Holdings^{1,6}

22 year old with ME/CFS

- Tryptase normal; already on loratadine
- Allergy symptoms start improving with meds directed at MCAS:
 - Ranitidine 300 mg BID helps sinus congestion
 - Montelukast helps migraines
 - Quercetin 1000 mg BID helps energy
- LH better with DDAVP 0.1 mg TID; HR still elevated

HR, exercise tolerance, cognition improve on Ivabradine

Dose	Resting HR	Exercise HR
0 mg	115	170-180 in 2 min, w/HA
2.5 mg BID	110	170-180 in 2 min, w/HA
5 mg BID	90	155, no HA
7.5 mg BID	80	140, no HA
10 mg BID	72	130s with 30-40 minutes on elliptical; no HA

“Made a weekend trip to Sedona, and did 10 miles of hiking in a day, with the last hike up to Devil’s Bridge.”



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