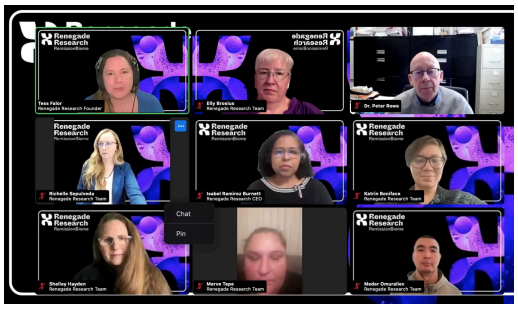
Renegade Research Event Transcript, with Slides

Peter Rowe, MD, Part 2, Feb 16, 2024.
Unlocking Mysteries in ME/CFS regarding…



- **Biomechanical issues including thoracic outlet syndrome**
- **Neuro-anatomic problems including cervical stenosis & CCI**
- **Mast Cell Activation**

Recording Link: **youtube.com/watch?v=WaM2mPzR64w**

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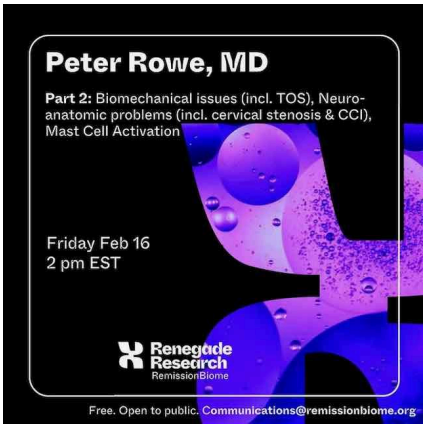
RemissionBiome GoFundMe: gofundme.com/f/Remissionbiome
Rowe's Research Runners: rowesresearchrunners.org

Links for host Renegade Research



renegade-research.org
twitter.com/renegaderes
twitter.com/remissionbiome

Dr. Rowe presented to Renegade Research Feb 9, 2024
Part 1: Orthostatic Intolerance, Brain Blood Flow, & Venous compression syndromes

Links for speaker Peter Rowe, MD

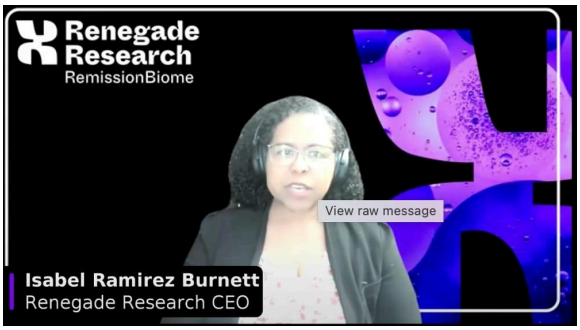
Chronic Fatigue Syndrome (CFS) and Related Disorder Program at Johns Hopkins
Dr. Rowe's Research on Chronic Fatigue Syndrome and Related Disorders
Pre-order: Dr. Rowe's book" Living Well with Orthostatic Intolerance: A Guide to Diagnosis and Treatment"
Dr. Peter Rowe, Is The Physical Examination Normal in CFS? [No!]
Part 1 (Orthostatic heart rate and blood pressure changes, Part 2 (Joint Hypermobility),
Part 3 (Postural dysfunctions and movement restrictions)
Manual Therapy in CFS: Part 1 of 2
Manual Therapy in CFS: Part 2 of 2
An ME/CFS Expert Helps a Long-COVID Patient Recover | April 2023
General Information Brochure on Orthostatic Intolerance and its treatment | March 2014 (most recent update)

Transcript: Introductions & Announcements

I'm Tess Falor. I am founder of Renegade Research group here that is a nonprofit that is studying ME/CFS and long covid. We're patient led and we are organizing community science projects to do distributed self-experiments and pool data to try to be able to do research that is difficult to do in standard systems. Our largest project Remission-Biome is one of the main things that we're working on right now. You

can go to the website remissionbiome.org [or Renegade-research.org] to sign up for our newsletter and be updated about RemissionBiome and Renegade Research and all the talks and everything we have happening. Our panel is part of our team. This is not everybody that's on our team, but I just wanted to recognize everybody that is here. And I'm going to have everybody wave. Elly suggested that so we'll wave to everybody.

I mentioned the upcoming talks. We have different types of talks and one of the new type that we're starting is the clinical roundtables, and I'll have Isabel give a little pitch about that.



1:30 Isabel Ramirez-Burnett: Yes, thank you everybody for being here. Our Clinicians RoundTable will start March 15th at 1PM Eastern will be the first one and you will have the link to register for that posted. The first one will be with Dr. Ruhoy and Dr. Kaufman, and the purpose of the Clinician's Roundtable is to give expert clinicians treating ME/CFS, long covid, and post infectious conditions an opportunity to explain their practice and how they approach the complex patients that we are and have other clinicians learn what they do and hopefully expand the pool of clinicians treating these conditions, as well as having patients learn as well and bring the information to their providers. And again, the purpose is to expand the pool of providers who are helping us and treating us as patients. So, welcome and we hope to see you there.

2:30 Tess Falor: I'll mention we have another roundtable in the works. We don't have the link for it yet but it is with Dr Gillette and Amy from Barcelona who Isabel and I just got to meet last week. They do work that's related to what Dr. Rowe is talking about. So that'll be another good one in April. So if you go to remissionbiome.org [or Renegade-Research.org] and sign up for our newsletter you'll get that link when it comes out to register for it.

The other type of talks that we'll have coming up are research roundtables, and these are ones that we had been doing internally within our team to discuss science mostly related to RemissionBiome and hypotheses of what might be happening during remission events. And it's been a really awesome meeting, bringing together researchers from all the different fields. It had been on invite only, but we're going to be opening these up to the public so look out for announcements about that. And it'll be fun to join for people who want to know more about the research and see some of the behind the scenes discussions.

3:35 I have a quick poll that I'm going to do before we jump in here. So the poll should pop up. Just kind of want to get a feel for who's in the audience right now. We have about half of the answers. So far a lot of patients again. We have a pretty knowledgeable audience, knowledgeable about these specific topics. So, almost to the end [of the poll]. Here, all right. I will end it now. Yeah, so we have 77% are patients. We have caregivers and friends and family. We have five clinicians here and 11 researchers. And for how much you know about these conditions we about 50/50 know a lot or some. We have a few people who know very little about it so we'll have a kind of wide range of questions at the end to try to make sure that everybody comes out of this with a lot of knowledge.

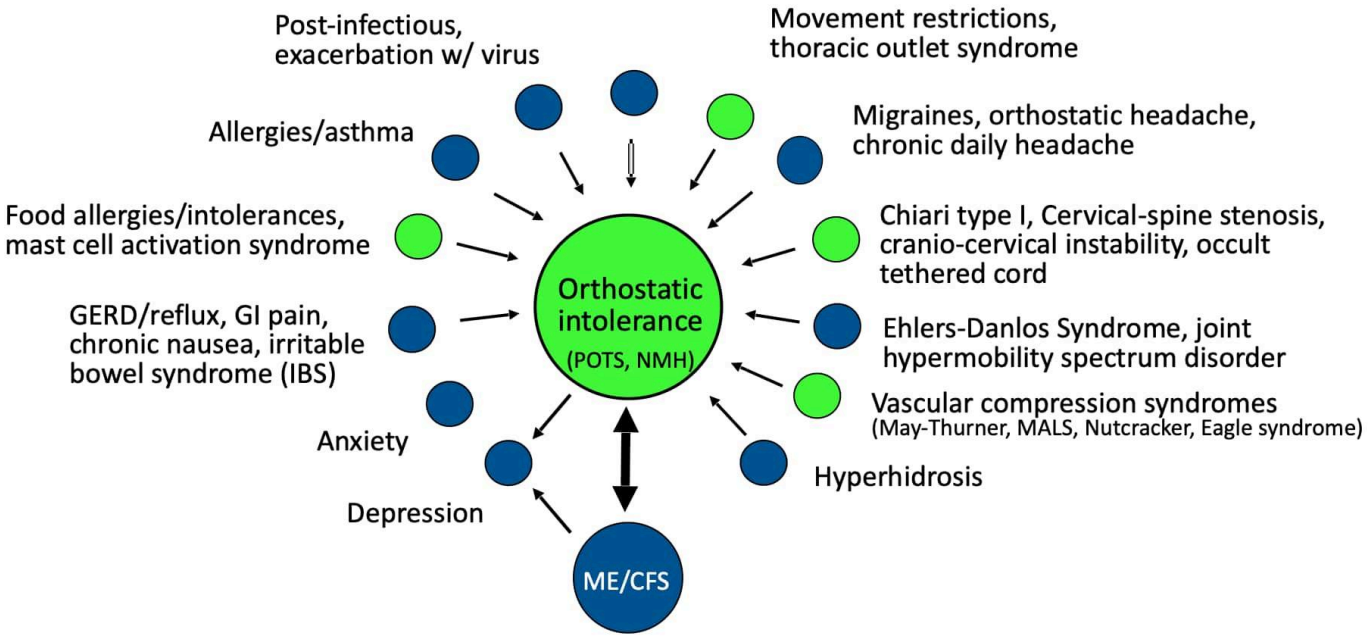
5:08 Okay. So, I will now introduce Dr Rowe. He is the director of The Johns Hopkins Children's Center Chronic Fatigue Clinic and a professor of pediatrics at Johns Hopkins University with research interest including ME/CFS, fibromyalgia Gulf War Illness, pelvic congestion syndrome, hypermobility syndromes including EDS, and orthostatic intolerance syndromes including POTS. SolveME honored Peter Rowe in April 2023 for his work as a provider, researcher, educator and advocate for ME/CFS and long covid communities. And if you were here last week, you will know that he is an excellent presenter. We're very grateful, fortunate to have you here. So we're looking forward to this and I'll pass it off to you Dr. Rowe.

5:55 Peter Rowe, MD.

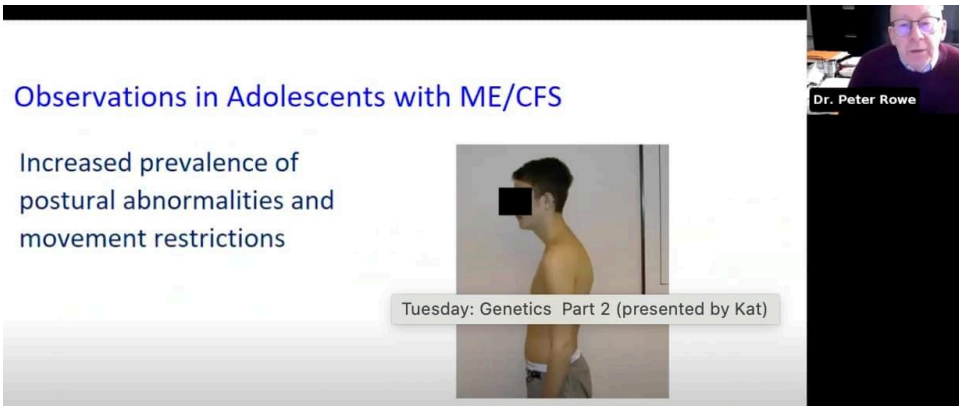
Great. Well thank you for having me back.

So we had the talk last week and that focused primarily on the issues of orthostatic intolerance and some of the vascular compression syndromes and how they contribute to orthostatic intolerance,, and today I'm going to spend most of the time on **movement restrictions and biomechanical factors** which are things that we've been interested in for about 20 years. These concepts have not caught on as much as I would have hoped with other ME/CFS researchers. I'll then turn to some comments about **neuroanatomic problems**. I mentioned that I'd be talking about **Mast Cell Activatio**n today but due to time constraints, it'll really be something we only touch on a little bit with each of the patient stories. I'll try to illustrate most of these problems with true patient histories.

Biomechanical issues that include thoracic outlet syndrome



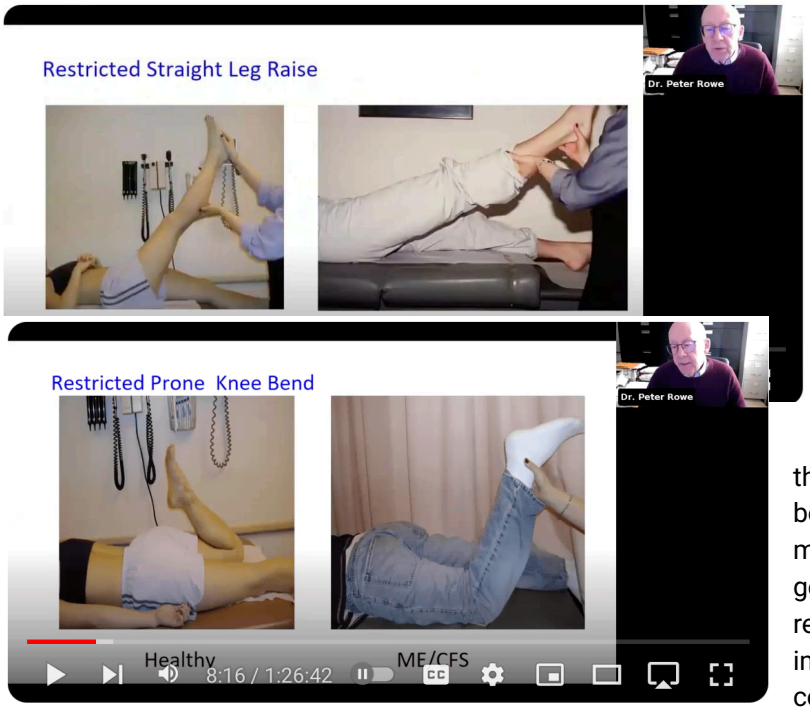
7:10 So let's start off with the biomechanical issues that include thoracic outlet syndrome. One of the things that we noticed a long time ago is that many of our adolescent patients came in with postural



abnormalities and movement restrictions.

You can see in this picture that this young man had a lot of rounding of the back (kyphosis) and when you look at his head, he has a very head-forward posture that's not very conducive to proper ergonomic posture. The best position to be in is to have your head straight above the spine and well supported, and the further it's away from the spine, the more work is required to maintain the head position.

Straight Leg Raise (SLR)

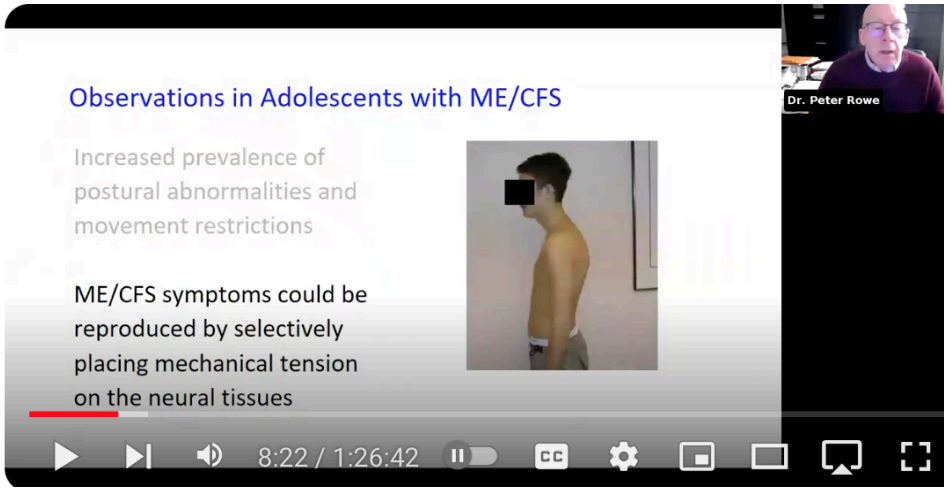


7:56 We also noticed that a lot of our patients would have limitations in range of motion and get stretch at an early point on maneuvers like straight leg raising (SLR), or bending their ankle backwards, or lying flat and bringing their leg up.

And the boy on the right was unable to get his leg any further than this on prone knee bend without getting anterior thigh stretch.

And then, when we would send people to the physical therapists that we worked with, it was interesting that the patients would call us the next day or two and ask: "am I supposed to be this tired?" We knew by that point that these manual physical therapists were doing very gentle forms of physical therapy, and treat these restrictions in a way that led to some improvements after a few sessions, but the first couple of visits would stir up their symptoms.

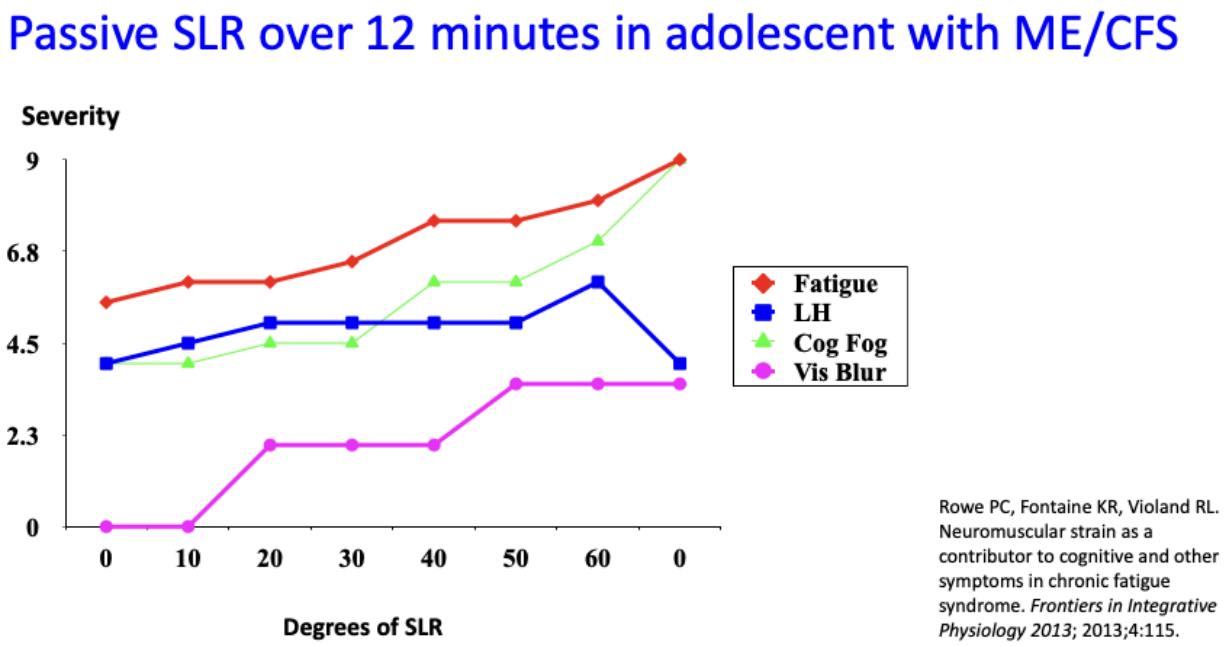
So we started wondering what was going on, because this ability to provoke symptoms with movements of the limbs and spine seemed really important as a potential clue to understand the pathogenesis of symptoms of ME/CFS. In their initial assessments, the PTs were just doing range of motion tests.



9:04 [Slide of a graph with no data yet: Passive SLR over 12 minutes in adolescent with ME/-CFS. Severity vs degrees of SLR.]

So we thought let's bring in a couple of patients. Our initial thought was that what the PTs were doing was somehow disturbing their orthostatic blood pressure and cerebral blood flow control. So we thought maybe these range of motion tests like the straight leg raise are causing some kind of change in heart rate or blood pressure like we were seeing on the tilt test. So we said let's bring somebody in and we're going to lift their leg to 10 degrees for 2 minutes, measure heart rate, blood pressure, pulse

oximetry, skin temperature, and symptoms; then go to 20 for 2 minutes, 30 for two minutes, and so on. So the whole test was 12 minutes, and the patient wasn't really doing any work.



9:48 So what happened? Well, here you can see one of these patients who had only mild to moderate ME/CFS. He was still able to attend college. He came in with a fatigue score of about 5.5 out of 10. As we went raised his leg gradually, by the 30° point he was having increased fatigue, he was having some further cognitive fogginess, really much more by 40 degrees. At the 60 degree point we brought his leg down and this young man could not leave the physical therapy office for another hour. It really sort of flattened him. And notice that lightheadedness in the blue got worse as well, even though lifting somebody's leg ought to improve the amount of blood getting back to their heart and actually reduce the lightheadedness. **So, we saw cardinal features of ME/CFS being reproduced.**

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
- Abnormal neurodynamic interactions initially were termed “adverse neural tension,” later “neurodynamic dysfunction” or “neural tension dysfunction”

Shacklock M. Neurodynamics. Physiotherapy 1995; Manual Therapy 2005

10:45 And this introduces a concept that's well known in physical therapy called **neurodynamics**. It refers to the interaction of the nerve mechanics and nerve physiology. The point being that as we move in daily life, the bones

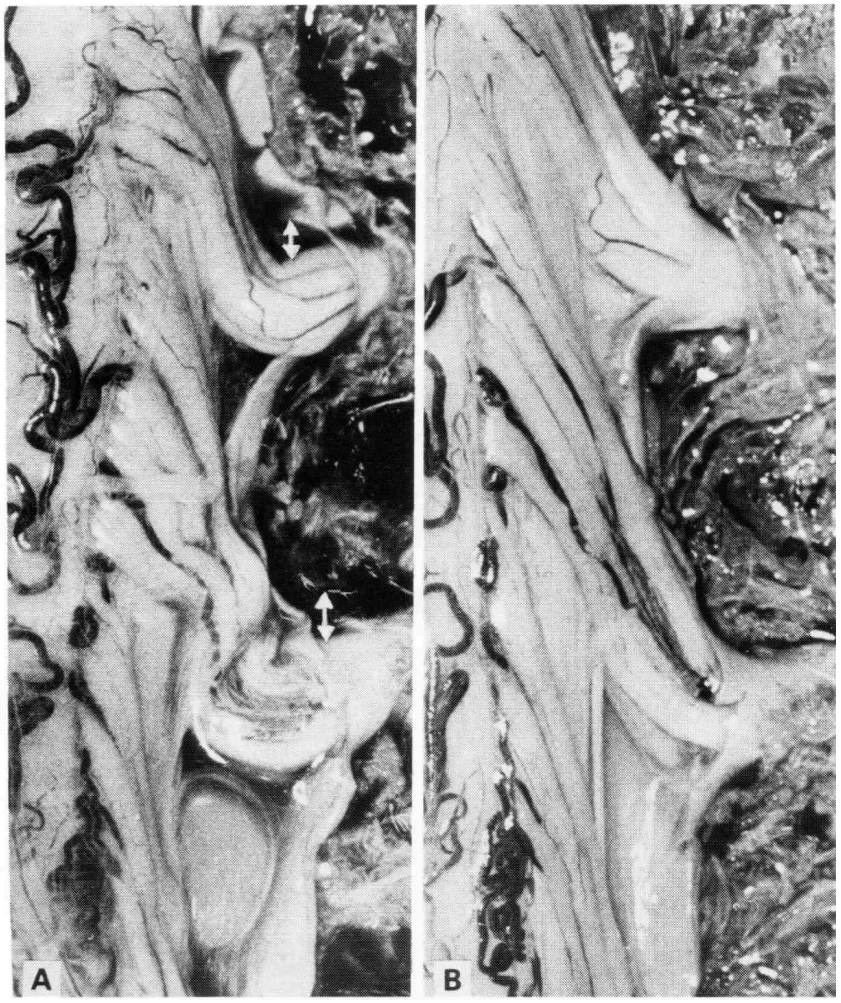
and the muscles and the joints and the connective tissues impose forces on the nerves. And with movement, the nerve tissues have to elongate, they have to slide and angulate around joints. And, as part of the elongation, they undergo some compression with mechanical stress to the nerves, which then causes other physiologic responses. When this is happening in an abnormal way, the abnormal neurodynamic interactions first were called adverse neural tension, which is a term you'll sometimes see in the physical therapy literature. Later people said, well you don't really know if it's true nerve dysfunction. Let's call it neurodynamic dysfunction or neural tension dysfunction.

There's still a bit of argument about these terms. But to give you an idea about this, people who have done a variety of anatomic studies have also shown that the nervous system has to adapt mechanically as we move. So if you go from a full back bend position to a full forward flexion, the spinal cord and the spinal canal length has to increase 5 to 9 centimeters [!]. If you look at the median nerve in the arm when we have our arm in a position of flexion it takes 20% of a length difference and elongation to get to full extension of that of that median nerve.

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.

12:33 This is a picture by a neurosurgeon, Alf Breig from Scandinavia. They were doing cadaver studies. On the left is a dissection of the spinal cord and the nerve roots in an extension posture. You can see they're sort of slackened, and then with flexion [on right] where the spinal cord has to elongate, you can see things are much

tighter and taught, including the blood vessels. So there's a lot of change that goes on in the spine just from flexion to extension.

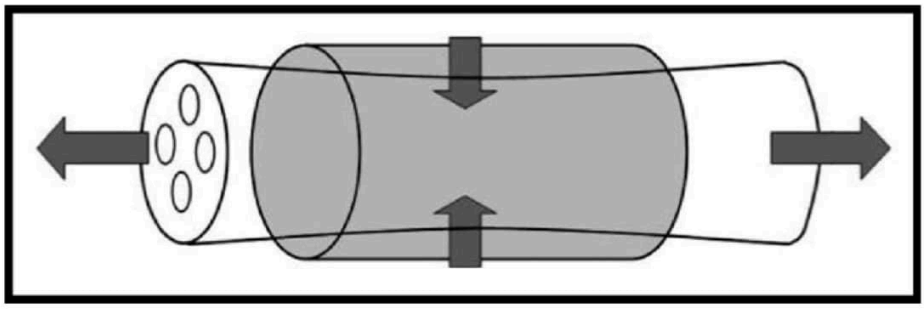


Figure 4.
Physical stresses placed on peripheral nerve. Tensile stress applied longitudinally to peripheral nerve creates an elongation of the nerve (an increase in strain). The transverse contraction that occurs during this elongation is greatest at the middle of the section undergoing tensile stress.

Reference: Topp KS, Boyd BS. Structure and Biomechanics of Peripheral Nerves: Nerve Responses to Physical Stresses and Implications for Physical Therapist Practice. Physical Therapy. 2006;86:92–109

13:07 This is a slide showing that when you elongate that nerve you're also getting this kind of effect that you'd get with one of those little finger puzzle toys [toy example], so you're getting some compression midway through that nerve.

An illustration of neurodynamics

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

And so I thought it might be helpful for people to get a sense of what we mean by **neurodynamics**. And if you have ME/CFS you might want to NOT do this, but the next few slides… if you're feeling okay you might want to participate.

My wife was kind enough to do the modeling for this and if you start with your arm like this and then extend it

most of us will get a bit of pulling across the top of the elbow here, reflecting some neural tightness. If you then lean your neck over towards the area that's tight, often that lessens the degree of stretch.

14:05 And if you go the other way and take more slack out of that system, it usually increases the stretch and you can increase that further by turning your wrist down. So that illustrates the fact that we all have a certain degree of neural tension. The nerves are not just rubber bands that can stretch infinitely.

14:27 What happens is if you've got abnormal tension within the nerves is that the muscles around those nerves will tighten up and contract to stop you from stretching the nerves beyond where they are under strain and tension. That, in turn, increases the amount of energy expenditure required, because you're working against your own muscle contraction.

Consequences of abnormal mechanical tension within the nerve

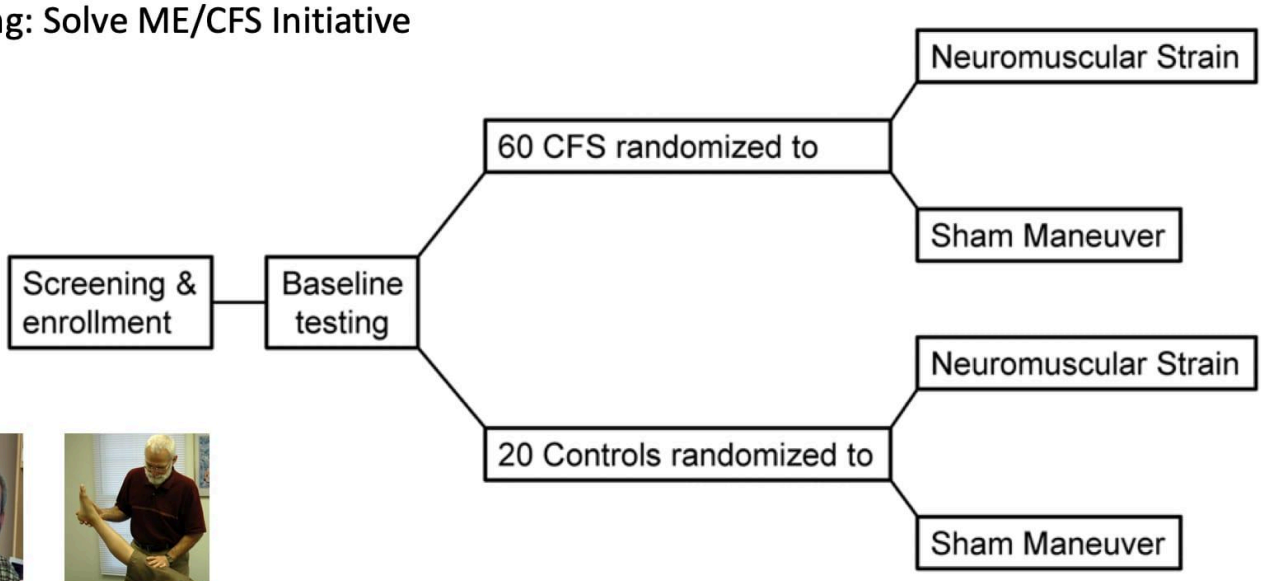
- Protective increase in resting muscle tone (which in turn increases the energy expenditure and reduces the ease of movements)
- ↓d intraneural blood flow and ↓electrical conduction, intraneural edema (swelling)
- ↑d mechanical sensitivity
- Autonomic responses (sweating, altered blood flow to peripheral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

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

14:49 You can see reductions in blood flow to the nerves and changes in electrical conduction of the nerves as well as swelling in the nerves. And, all of those changes can lead to more sensitivity of the nerve to different stimuli. **We also know from the literature that you can get increased autonomic nervous system responses** so people with abnormal tension within the nervous system can get **sweating**. They can get altered blood flow to the tissues that those nerves are supervising, and it's very important to note that this can lead to **neuroinflammation** and the release of inflammatory neuropeptides. All of these are familiar terms in the ME/CFS pathophysiology literature.

Neuromuscular Strain in CFS

Funding: Solve ME/CFS Initiative



15:37 We wanted to study this a bit more systematically. And, so with Kevin Fontaine, who's shown on the bottom and Rick Violand, who's my physical therapist collaborator for the last 25 years, we began a study that was funded by the Solve ME/CFS Initiative. We randomized 60 patients to a neuromuscular strain or a sham maneuver and 20 controls to the same things.

Outcomes

- Symptom intensity difference between baseline and during or 24 hours after the study maneuver for 5 cardinal features on a 0-10 scale:
  - Fatigue
  - Body pain
  - Concentration difficulties
  - Lightheadedness
  - Headache
- Scores summed to create a combined symptom score
- Secondary outcome: the proportion reporting a 2-point symptom intensity increase for any symptoms

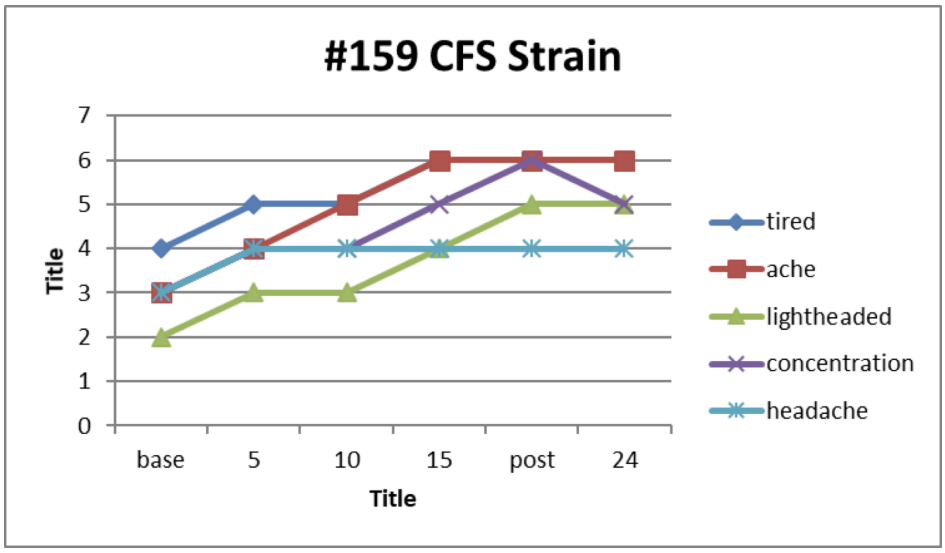
16:08 We were looking at the symptom intensity differences between baseline supine posture (before we did the maneuver) and after 15 minutes of straight leg raise, as well as 24 hours after the maneuver. And we were looking at five symptoms on a 0 to 10 scale: fatigue, body pain, concentration problems, lightheadedness, and headaches. We

summed those individual symptoms scores to create a combined symptom score, and we also looked at the proportion who reported at least one symptom increase in intensity of two points. So, what did we find?

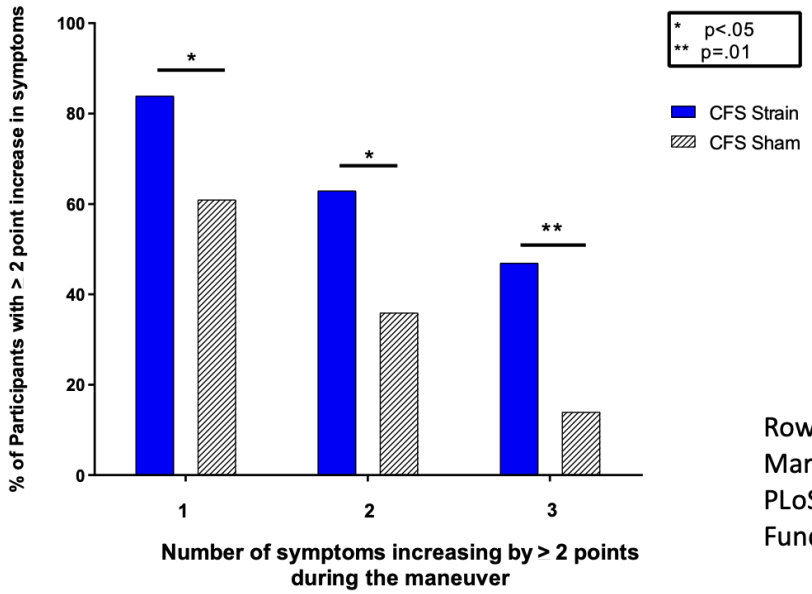
CFS strain minus CFS sham				
	During 15 minute strain or sham		**24 hours after strain or sham**	
Symptoms	**Difference (95% CI)**	**P-value**	**Difference (95% CI)**	**P-value**
Fatigue	0.72 (-0.01, 1.45)	0.05	0.86 (-0.05, 1.78)	0.07
Pain	**0.94 (0.07, 1.81)**	**0.04**	0.76 (-0.21, 1.74)	0.12
Lightheadedness	0.63 (-0.48, 1.74)	0.26	**1.75 (0.78, 2.72)**	**0.001**
Difficulty with concentration	**1.13 (0.17, 2.08)**	**0.02**	0.66 (-0.35, 1.67)	0.20
Headaches	-0.23 (-1.1, 0.64)	0.60	0.04 (-1.03, 1.12)	0.94
Total symptom score	**3.52 (0.41, 6.62)**	**0.03**	**4.30 (1.32, 7.27)**	**0.005**

16:48 Well, when we compared the CFS strain group –remember they're having a true straight leg raise, positioned so that each individual would have a slightly different but individualized strain, halfway between the point at which they reported stretch initially and the point at which they were at end range for that straight leg raise, so it was a good stretch but not painful. And when we subtracted the scores of the strain from the sham group, who had only a towel under their legs, so not more than a five degree elevation of their leg, what we saw acutely during the 15 minutes of straight leg raise was increased pain and problems with concentration in the ones who had the true straight leg raise. And, their total symptom score was much higher than that of the sham group. Then we called them 24 hours later and said, "What's the difference now?" And, 24 hours later they had increases in lightheadedness and in the total symptom score suggesting that **this simple maneuver was capable of triggering post-exertional malaise**.

17:57 Here's an example of somebody who's rating their symptoms on a 0 to 10 scale. Here's lightheadedness [green/ triangle], baseline, then supine 5 minutes into the straight leg raise the score is going up. It goes up at 15 [minutes] and is even a bit higher in a few minutes after the test. Headache [light blue/ square] went up one point, body pain [red/square] went up about three, and fatigue [dark blue/ diamond] went up two points. So this person had a number of symptoms that were aggravated by this maneuver.



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

18:31 When we looked at the number of people who had a symptom that increased in intensity by more than two points or more during the maneuver, 80% of the true strain patients had at least one symptom get worse, about 60% had two symptoms get worse, and about 45% had three symptoms get worse. Now, some of the people in the sham group also had increases in symptoms. We think this occurred in part because they had had to come in from their cars to the research setting and so we were provoking some day-to-day increases in symptoms as well.

19:10 One of the patients who was a PhD student said a week after the study maneuver …. [Dr. Rowe reads from **Slide: Comments about prolonged symptoms after 15 minutes of SLR**]

> "Today is the first day I'm feeling better from the study but I'm still not feeling great. I was in a lot of pain all weekend. My whole body hurt. I was exhausted but couldn't sleep. I wasn't capable of holding a coherent conversation or making decisions all weekend. Friday [the day after the study visit] I was emotionally unstable and cried a lot, also nauseated and couldn't eat. I'm still having more brain fog than usual."

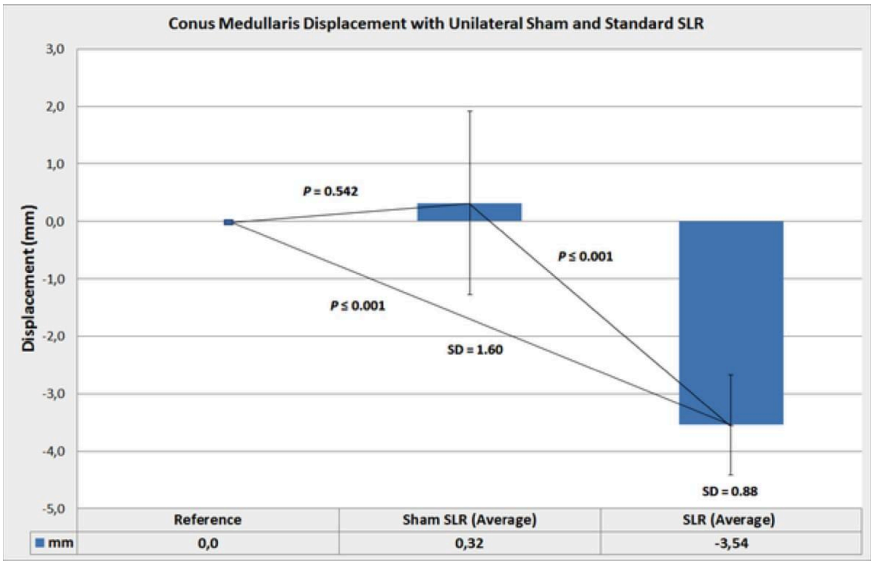
So we didn't formally study the one week outcomes of this straight leg raise, but clearly some patients had quite prolonged symptoms afterwards. We concluded that a longitudinal strain applied to the nerves and the soft tissues around around those nerves in the lower limb was capable of increasing symptom intensity in people with ME/CFS for at least up to 24 hours, confirming our preliminary observations in the college students that increased mechanical sensitivity is a contributor to symptoms in this disorder.

Conclusions

- A longitudinal strain applied to the nerves and perineural soft tissues of the lower limb is capable of increasing symptom intensity in individuals with ME/CFS for up to 24 hours.
- These findings confirm our preliminary observations that increased neural mechanical sensitivity is a contributor to the provocation of symptoms in this disorder.

20:18 What might have been happening to cause symptoms? Because they were so immediate, there was a bit of a help from this paper from 2016 where the investigators did a sham straight leg raise and then a normal straight leg raise. They measured where the lower part of the spinal cord was on an MRI machine. With the sham straight leg raise you get no real change in where that spinal cord is located, but with a true straight leg raise, the spinal cord goes down three and a half centimeters. So the straight leg raise transmits a stretch to the spinal cord and that could have been somehow implicated in the increase in symptoms

Fig 5. Conus medullaris displacement with unilateral Sham SLR and standard SLR.



Rade M, Könönen M, Marttila J, Shacklock M, Vanninen R, et al. (2016) In Vivo MRI Measurement of Spinal Cord Displacement in the Thoracolumbar Region of Asymptomatic Subjects with Unilateral and Sham Straight Leg Raise Tests. **PLOS ONE** 11(6): e0155927.

https://doi.org/10.1371/journal.pone.0155927
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0155927

20:58 The mechanism for the translation of strain into symptoms is unknown, but my feeling is that whatever it is, is neutral with regard to the hypotheses about the causes of ME/CFS. You could, for example, have a lot of swelling of the nerves after an infection, or if there's an immune response you could get changes in the nerves or the brain. The mast cells we know respond to stretch of the skin and maybe the mast cells in the nervous system were responding and releasing products that caused symptom exacerbation. It could be that the nerves are not as stretchy as the ligaments, so when they're going across hypermobile joints, they're over stretched. And there could be some other stress on the spinal cord and the peripheral nerves. We really don't know the answer to this question.

The mechanisms for transduction of neuromuscular strain into increased symptoms are unknown (but are neutral with regard to etiologic hypotheses)

- Intra-neural edema following infections?
- Immune-mediated changes in nerves/brain?
- Mast cells responding to stretch?
- Excessive mechanical strain of nerves across hypermobile joints?
- Deformative stress on the spinal cord and peripheral nerves?

21:52 We next tried to look at how prevalent these problems were in our adolescents with ME/CFS. And this was a cohort study we did with doctors Fontaine and Rick Violand as well as a number of summer students that worked with us.

ORIGINAL ARTICLES

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

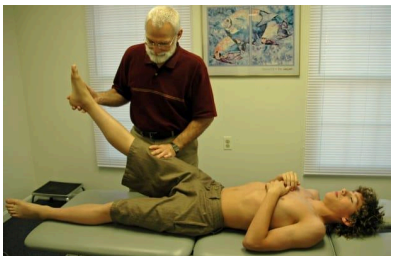
Peter C. Rowe, MD[1], Colleen L. Marden[1], Marissa A. K. Flaherty, MD[1], Samantha E. Jasion[1], Erica M. Cranston[1], Allison S. Johns[1], John Fan, MD[1], Kevin R. Fontaine, PhD[2], and Richard L. Violand, PT[3]

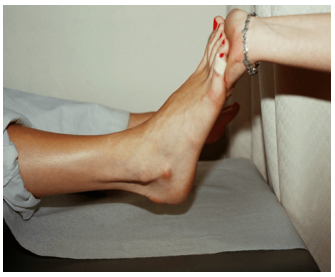
Reference: (J Pediatr 2014;165:360-6).

We developed an 11-point assessment of a range of motion that added the ankle dorsiflexion on each side of the body, passive straight leg raised on each side, prone knee bend, and seated slump test,
and the Upper Limb neurodynamic test, and then also a prone press up like you see in the bottom right.

Methods: main study measures

ROM score (0-11):*
Ankle dorsiflexion
Passive straight leg raise
Prone knee bend
Prone press-up
Seated slump test
Upper limb neurodynamic test 1

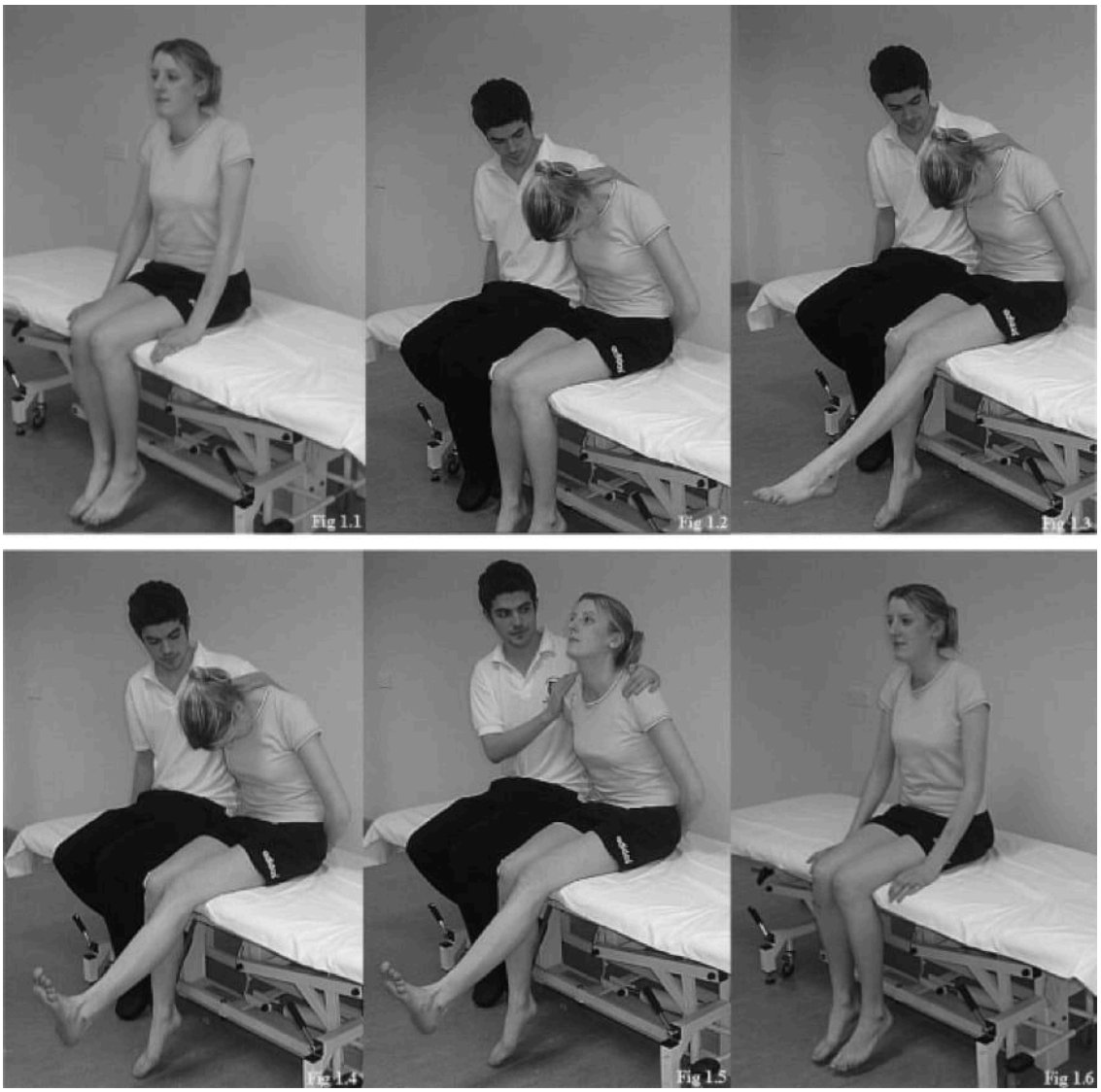




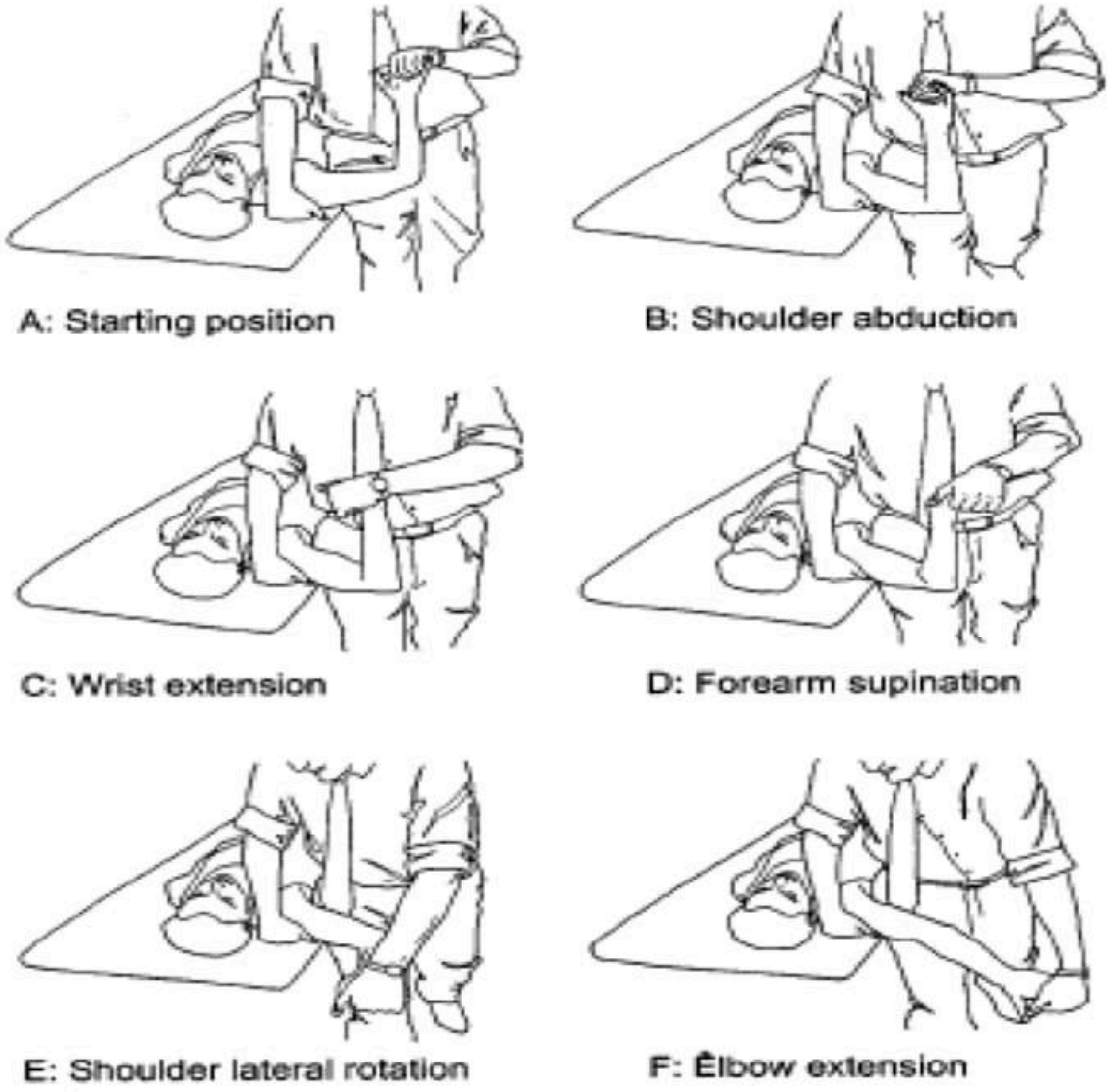
*Performed with minor modifications according to the methods of Butler DS, Mobilisation of the Nervous System, 1999

Seated slump test

22:30 Here's the seated slump test. This is a test that actually takes the slack out of the nervous system. You sit straight up and then you slump, which rounds the spine and elongates the spinal cord. You then bring the head down and then the patient tries to bring the leg up to horizontal. And an abnormal test is when they can't bring the leg fully horizontal, or when they start getting symptoms from this.



Slide: Upper Limb Neurodynamic Test



Reference: From: Butler DS, The Sensitive Nervous System 2000

22:57 The upper limb neurodynamic test is something that's used to evaluate the brachial plexus of nerves that come out of the neck and down into the arms, so it puts strain primarily on the median nerve in this picture.

Here's what we found in this cohort study that had about 48 matched patients and controls. We found that on every single one of these individual examination maneuvers, our ME/CFS patients had a higher prevalence of an abnormal result than the controls.

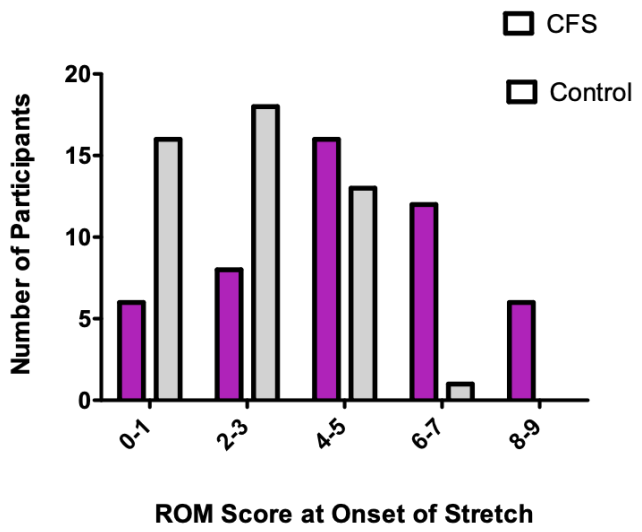
INDIVIDUAL EXAM MANEUVERS	ME/CFS	Controls	Odds Ratio	P
Slump L leg < 170	13%	8%	1.7	.48
Slump R leg < 170	10%	2%	5.0	.10
ADF L < 95	15%	0%	15.0	<.01
ADF R < 95	13%	0%	13.0	<.02
SLR L < 45	69%	38%	6.0	.001
SLR R < 45	71%	31%	7.3	<.001
ULNT1 L < 170	71%	56%	2.0	.13
ULNT1 R < 170	65%	31%	5.0	.001
PKB L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

On the next slide, I've just outlined the ones where the difference was statistically significant. So we saw limited ankle dorsiflexion in about 15%, limited straight leg raise in about 70% compared to 30 some percent in the controls. Upper Limb tension testing was abnormal. The prone press up was abnormal. And these are really highly significant differences in most instances.

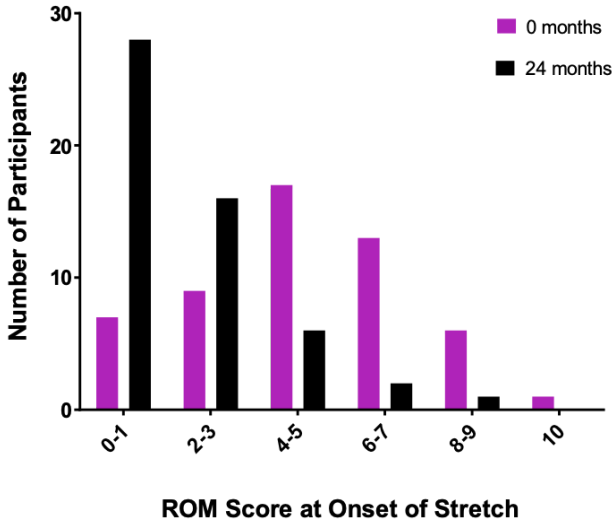
INDIVIDUAL EXAM MANEUVERS	CFS	Controls	Odds Ratio	P
Slump L leg < 170	13%	8%	1.7	.48
Slump R leg < 170	10%	2%	5.0	.10
ADF L < 95	**15%**	**0%**	**15.0**	**<.01**
ADF R < 95	**13%**	**0%**	**13.0**	**<.02**
SLR L < 45	**69%**	**38%**	**6.0**	**.001**
SLR R < 45	**71%**	**31%**	**7.3**	**<.001**
ULNT1 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

23:56 This slide shows you that range of motion score from 0 to 11 at the onset of when we caused stretch. And you can see that it's as if the ME/CFS population was an entirely different group than the controls.

Impaired range of motion of the limbs and spine in ME/CFS: initial comparison with controls, and 2-year follow-up



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



(J Pediatr 2018;200:249-53)

24:15 Again these were highly significant differences in the scores. Fortunately on the right, you see the range of motion score just in our patients, and the violet was their score at baseline and the black is what where they were 24 months after being in this cohort study, during which they received treatment of their orthostatic intolerance, their allergic inflammation, and probably 90%, received some form of physical therapy. So these are not fixed range of motion restrictions. They improve in concert with the person getting better overall. And we don't know how much relieving the range of motion restrictions causes the improvement, but they're certainly correlating.

Speculation

- If a simple and relatively brief neural 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 movements—might improve the ability of ME/CFS patients to tolerate activity.

24:56 One of the ideas from this work is that if a simple and relatively brief neural strain like a straight leg raise can provoke symptoms, then having that same range of motion on a prolonged basis, a repetitive basis, or an excessive basis beyond their usual range of motion in daily life might be followed by the same exacerbations and symptoms.

25:20 Our experience over the last 20 years has been that if we treat these areas before advancing to any kind of more active exercise or activity, that improves the ability of patients to tolerate activity. So, we have not tested that formally, but that's certainly been a consistent observation.

Thoracic Outlet Syndrome (TOS)

Syndrome caused by compression of the neurovascular bundle as it passes through the space posterior to the clavicle and over 1st rib

3 main forms: - Neurogenic - Venous- Arterial

Causes: congenital (cervical rib), fibrous anomalies, clavicle fx, repetitive trauma, overuse (e.g., overhead athletes)

25:40 Let me mention a bit about thoracic outlet syndrome, which we've been paying more attention to in our current cohort study. This is a disorder where you get compression of the neurovascular bundle as it passes through the space behind the clavicle and over the first rib to get down into the arm. There are three main types: the neurogenic form accounts for about 95% of them. There are venous and arterial forms as well, and these are distinguished by the fact that the arm turns ruddy and purple and swollen, often associated with clotting in these vessels.

The main causes of thoracic outlet syndrome are crowding in this space as the nerves are coming out of the neck. So that can be caused by an extra cervical rib, by fibrous abnormalities, and thickening of fibers that can compress the nerves. You can get the same crowding of this space if you've had recurrent clavicle fractures or repetitive trauma. TOS is common in athletes who are using their arms for overhead activities like pitchers or volleyball players.

This [Fig 1] is a picture from the right side of the spine and then the scalene muscles that come out posteriorly in the neck and the yellow represents the nerves that are coming down and competing for space because sometimes the scalene muscles are too plump and they compress the nerves in the scalene triangle, or the clavicle can be compressing the nerves, and the neurovascular bundle can get compressed by the area under the pectoralis minor muscle.

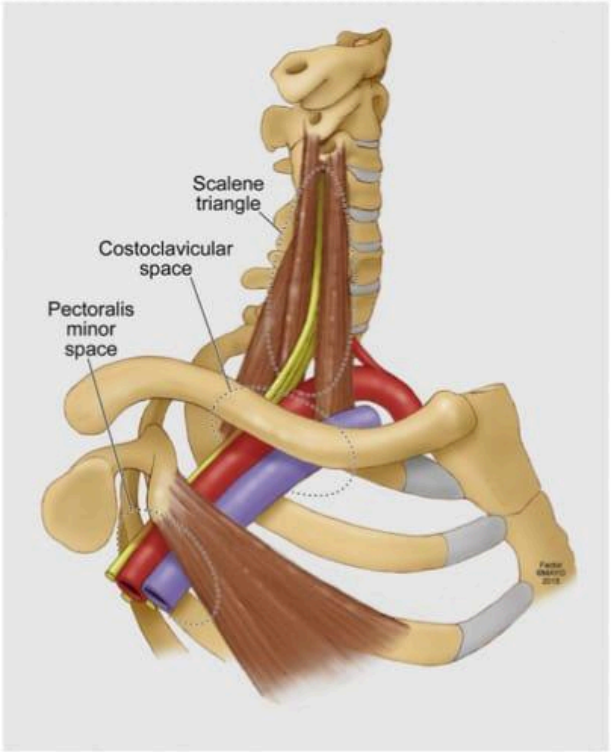


Fig 1. An overall view of the right thoracic outlet (J Vasc Surg 2016;64:e23-e35.)

Here's the same view from the front. [See Fig 2.]

27:30 The symptoms you get if you've got compression of the nerve are you get paresthesias, a term that means numbness or tingling, and you can get weakness in the arm, so that chopping food is harder, taking the lids off things is more difficult, and most people get arm fatigue with their arms overhead. They can get some associated pain in the head and neck or in

the shoulder or arm.

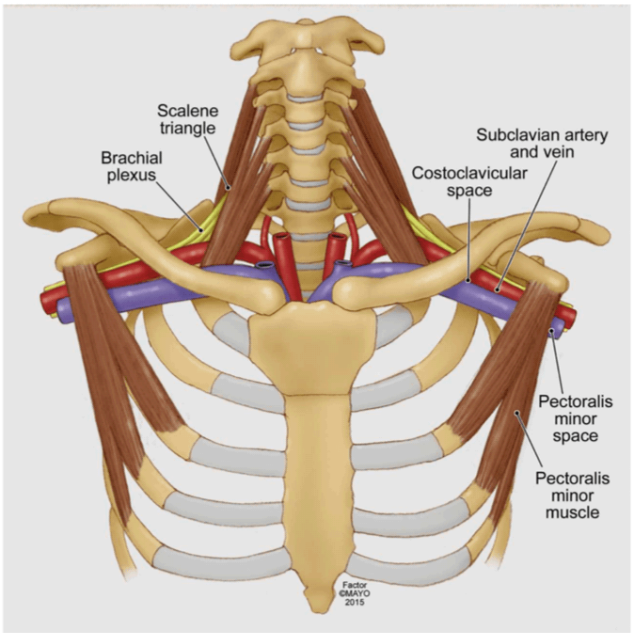


Fig 2. Anterior view of the upper chest showing bilateral thoracic outlets, scalene triangles, and pectoralis minor spaces involved in compression of the brachial plexus.

We test for this with a Roos test (also called an elevated arm stress test). Sometimes, an injection of lidocaine into the scalene muscles or an injection of Botox can be helpful to diagnose it and to treat the problem.

Neurogenic TOS (27:30)

Symptoms

• Paresthesias or weakness in the arm

• Associated pain in head, neck, shoulder, arm

Tests

• No single maneuver accurate, but Roos test (elevated arm stress test) may be most helpful

• Lidocaine scalene block, botox helpful diagnostically and therapeutically

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Elevated arm stress test (Roos)

From Watson LA, et al. Manual Therapy 2009; 14:586-95

Roos Test

28:11 Here's the elevated arm stress test that we're using in our current study. This is a three minute test where the person just stands in this Candlestick position opening and closing the hands slowly. If you've got thoracic outlet syndrome people usually recommend physical therapy as the first step in management, but if that isn't successful, they move on to botox injection to the scalenes. And, if that leads to improvements but Botox only lasts three months or so, and the symptoms keep coming back, then many vascular surgeons will remove the first rib to make more room for the nerves and blood vessels.

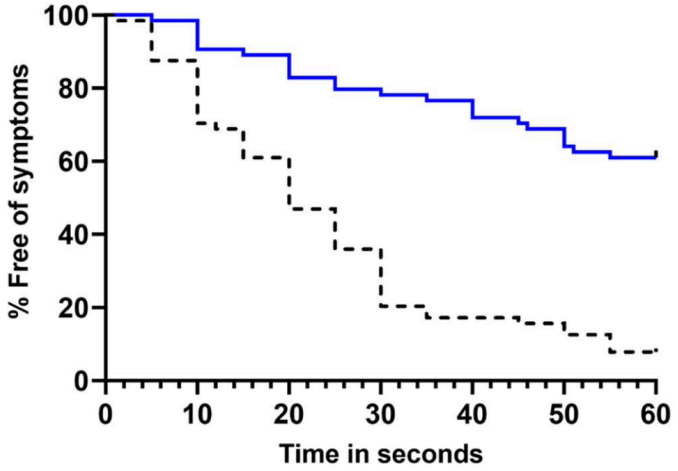
Thoracic outlet syndrome

• PT recommended as a first step in management
• For neurogenic TOS, surgical treatment involves first rib resection and scalenectomy

Ref: Brooke BS, Frieschlag JA. Contemporary management of TOS. Curr Opin Cardiol 2010;25:535-540

28:52 We started being intrigued by the fact that when we asked specifically if patients with ME/CFS had difficulty with their arms overhead, often they didn't report this to us spontaneously because they thought everybody had the same problem. These patients would report that when they were shampooing their hair (at least if they had a little bit more hair than me) their arms would get tired and they'd get numbness and tingling. As we started employing the elevated arm stress test in the clinic we noticed that people weren't just getting arm symptoms.

Provocation of local and systemic symptoms during the elevated arm stress test in individuals with ME/CFS or idiopathic chronic fatigue (JHH ME/CFS Clinic).



Local symptoms provoked in 61/64 (95%) within a median of 20 seconds.
Systemic symptoms in 30/64 (47%) including LH, Ftg, HA.

I'm showing in this slide a life table analysis of people who had endorsed having problems with the arms overhead.We only tested that group, but 61 out of 64 developed some kind of arm fatigue or paresthesias within a median time of **20 seconds of arms up** on this test.

29:50 The other thing we were intrigued by is that this test could bring on systemic symptoms of lightheadedness, fatigue, and headaches. So we're now investigating the elevated arm stress test in all of our new patients in this study to get a sense of the overall prevalence at least among the adolescents and young adults. TOS can be a cause of persistent fatigue so it's important to look for it.

30:15 Neuro-anatomic Problems

Let me move on to the neuroanatomic problems. We had published a case series six years ago reporting three people with moderate to severe ME/CFS symptoms in whom no treatments were working. Once we recognized that they had single- or two-level areas of cervical spinal stenosis, and treated them surgically, we saw huge improvements in their overall function. We don't intend to suggest that this is a common phenomenon that applies to most with ME/CFS, but it is something that can occur and needs to be recognized and treated differently.

Case Series of 3

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. Marden[1], Scott Heinlein[2] and Charles C. Edwards II[3]

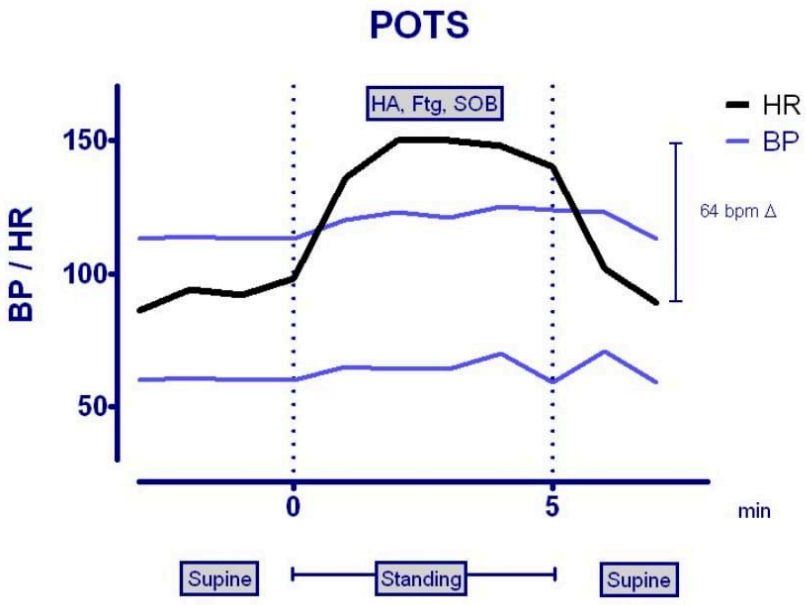
30:57 Let me tell you about one of these patients, the first of these three individuals. This was a 15-year-old who had fatigue, lightheadedness, and brain fog. Her past history was notable for some separation anxiety when she first started in school, but she actually was a very good student, liked school, and the anxiety had disappeared. At age 12, she developed a rotavirus viral gastroenteritis infection, after which she developed fatigue, lightheadedness, a fast heart rate, cognitive problems, myalgias, and infrequent headaches. She was unable to attend school after the 10th grade despite being a good student who only wanted to be in school advancing her education.

15 yr old with fatigue, LH, brain fog

Separation anxiety at school entrance (age 6-7)

Age 12: after a GI virus, develops fatigue, LH, tachycardia, cognitive problems, myalgias, rare HA.

By 15, part-time schooling. Unable to attend after 10th grade due to fatigue, anxiety, LH, brain fog



31:39 She also had some free floating anxiety that she knew was kind of irrational, but she couldn't make it go away. She had lightheadedness and brain fog. We did a just a five minute standing test in her because of the intensity of her symptoms. Her heart rate rose to 150 just standing still, leaning against the wall, ,associated with headaches, fatigue, and shortness of breath. We were concerned that if we kept her up longer she would faint.

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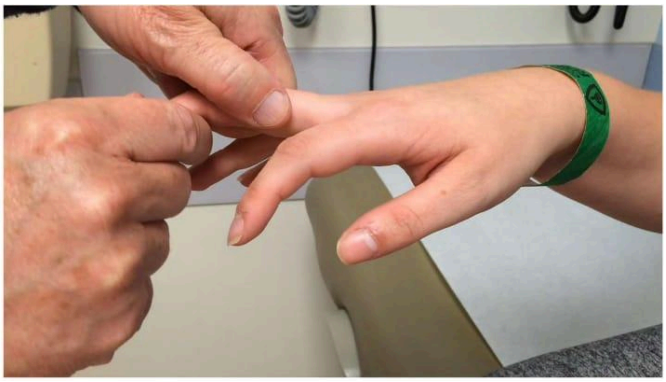
15 yr old with fatigue, LH, brain fog

Minimal response to OI and anxiety meds
PT notes tension in posterior neck muscles
Age 19: neuro exam shows intermittently positive Hoffman sign

FH in mother:
congenital cervical stenosis
2 fusions at 34 & 43 yrs for degenerative discs Thoracic Outlet Syndrome surgery x 2

32:06 She had a minimal response to the entire list of orthostatic intolerance medications and didn't respond to the things her psychiatrist tried for the anxiety. Her physical therapist noted that she had some tightness in the back of her neck and asked us to take another look at her. We had been seeing her for neurologic examinations every six months. And at this point, she had a new finding known as a positive Hoffman sign.

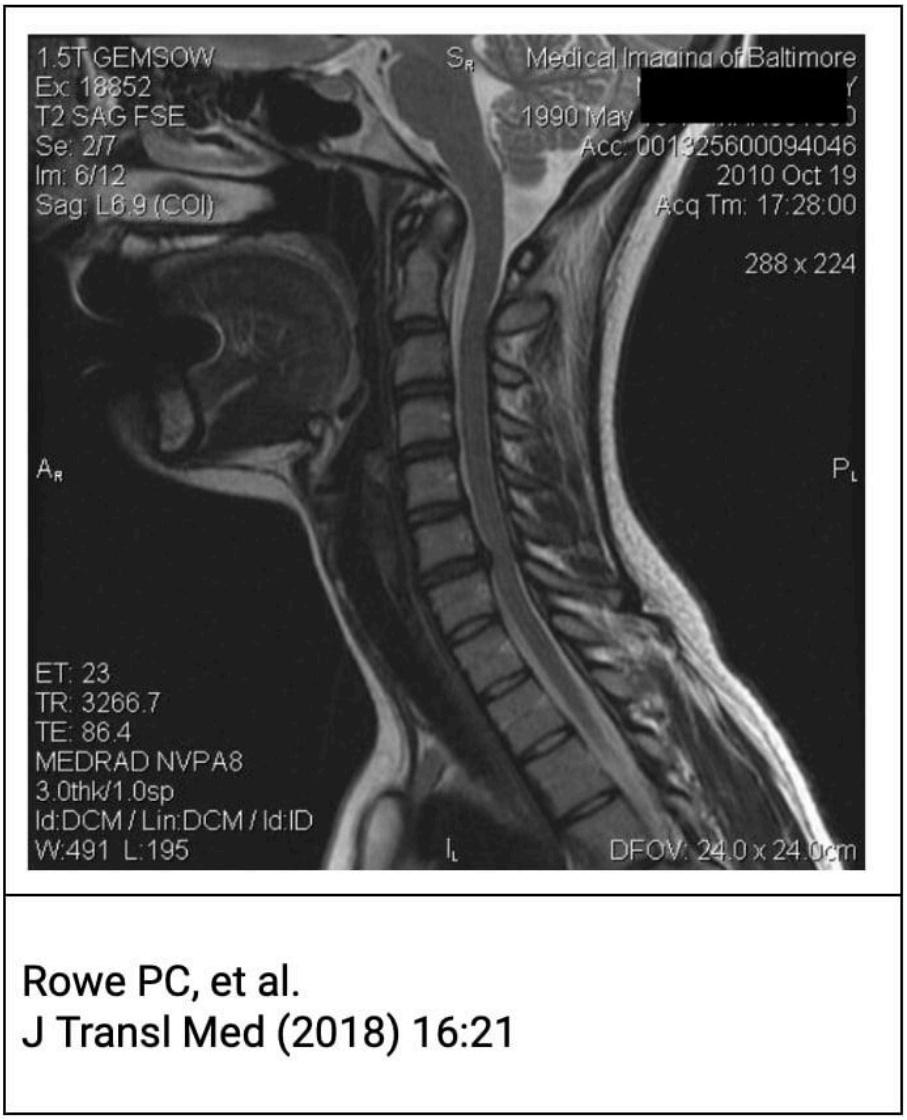
Here I'm showing how you elicit this sign. You support the distal part of the middle finger, you bend it down, and then you flick it. And what you're looking for is an abnormal contraction of the fingers, typically the thumb and the first finger. And that can be a sign of some sort of neurologic irritability in the neck. Often if you see asymptomatic people with a positive Hoffman sign they have on MRI some kind of bulging disc in the neck. It doesn't mean that they need surgery, but this physical finding is another one of the physical findings that can be abnormal in ME/CFS patients.



Eliciting Hoffman

the Sign

33:10 So we then looked at the family history, and frankly that's probably what we should have paid more attention to, her mother had a congenital cervical stenosis, and she'd undergone surgical fusions of the vertebrae in her neck at 34 and 43, so at a very early age for degenerative disc disease. And she'd had thoracic outlet syndrome surgery on each side as well.



Her daughter's MRI, which we obtained after we elicited the Hoffman sign, showed a number of abnormalities. One was that, normally you'd see spinal fluid that's in white on this picture – you'd see spinal fluid on either side of the spinal cord. Notice that by the time you get down to this third cervical vertebrae there's hardly any spinal fluid cushioning the spinal cord from being up against bones. As you follow this down you see that at the C6 to C7 vertebral interface, this disc is bulging out. Because the spinal cord is so narrow, there's no space to accommodate the disc bulge as might occur in someone with a normal spinal canal diameter. The spinal canal diameter should be 13 millimeters (mm) or more. Cervical stenosis is defined as 10 mm or less. This young woman's spinal canal diameter was 8 mm up in this range, reduced to about 6 or 7 mm at the C6-7 disc bulge. The parents had found a spine surgeon that they knew from their church, Dr. Charles Edwards at Mercy Hospital in Baltimore, and he said something to the effect of: "Well, I don't know how this relates to the tachycardia and fatigue, but this disc bulge is going to cause neurologic damage if you happen to get into a car accident and have a whiplash injury."

34:57 She elected to undergo a conservative artificial disc replacement without fusion. This individual had been essentially housebound for at least three years. Within two months of the surgery, she took a job as a dog walker. She was able to exercise more without anyone encouraging her. She had a big reduction in the anxiety and tachycardia and she started doing a part-time classes. After six months she was asking us is she could take a summer job in Colorado

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, tachycardia, LH; part-time univ. classes

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

LTFU (5 yrs): full-time college student, part-time retail job, weekend wedding photographer 12 hrs/day

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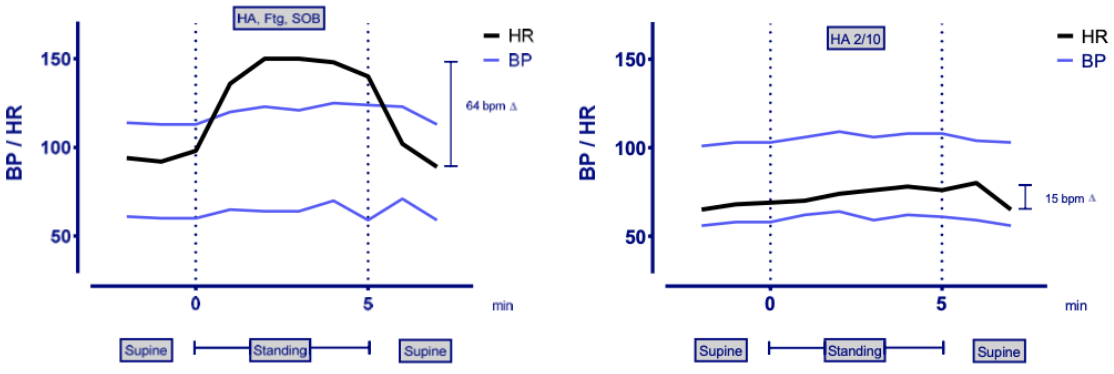
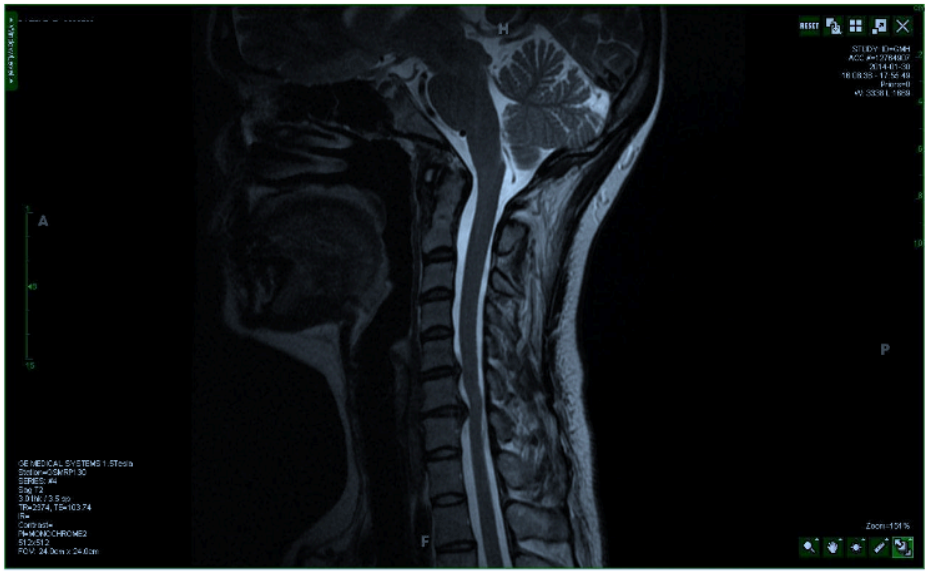
35:30 I was a little apprehensive, but she she went out there and her job was to get up at 6:00 in the morning and saddle the horses so that she could take people out on a Colorado Mountain trail ride bring them back, unsaddle the horses help, clean them up, help with the cooking. So she was physically very active from dawn to dusk, and by September, 10 months after the original surgery, she enrolled in college, graduating in four years while working one night a week in a retail job and doing wedding photography on the weekends for a day. So she did really well just from this surgery.



36:08 On the right is her standing test after surgery which showed resolution of her POTS. She has now been symptom-free for about six years working in an international aid charity in Baltimore.

Young woman, brisk reflexes

SB 2014, with 9 mm canal diameter at C5-6,
7 mm at C6-7, and 124° clivo-axial angle

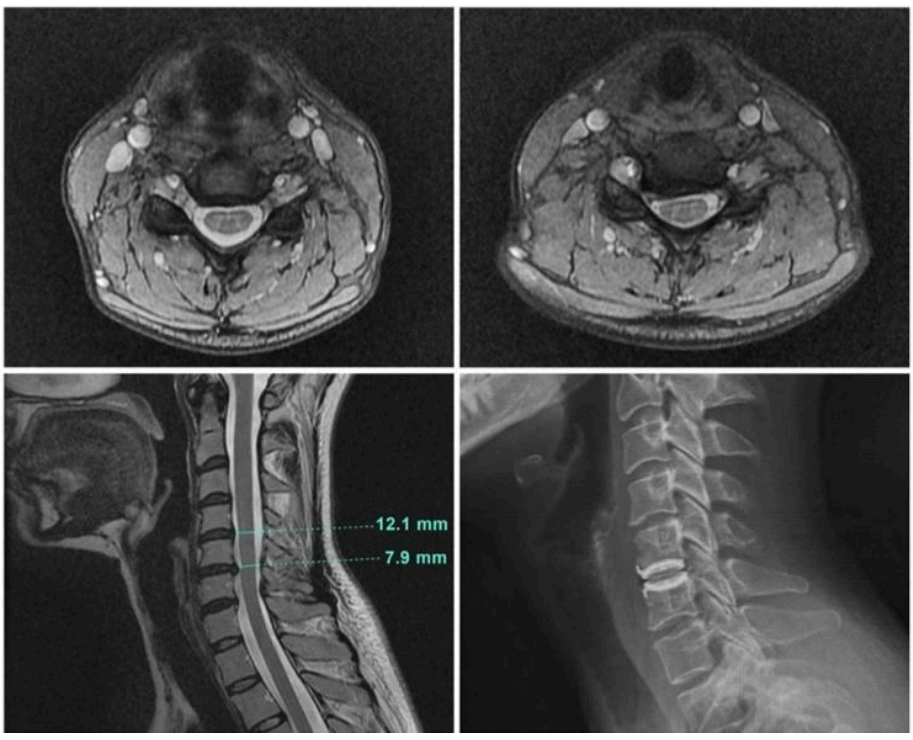


36:24 That led to the next person in that series coming in. This young woman had been thought to have brisk reflexes by the neurologists that were due to her psychiatric medications and that she had a functional or basically made-up gait disorder. We thought she had very brisk reflexes. The MRI showed that she had two bulging discs which you can see here.

It looks like the spinal cord is being pushed away and it's thinned in the area of the disc bulges. So she was down to a 7 mm spinal canal diameter at C 6-7. She had two discs replaced and that area was fused. She had been at home needing a wheelchair to go to her doctors' offices, with two weeks of PEM after each appointment.

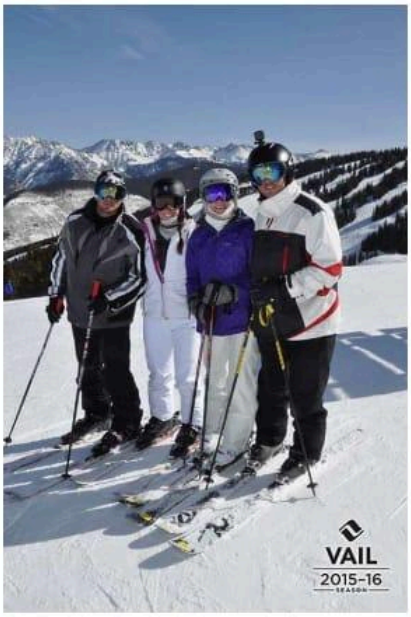
37:18 She called me a week after the surgery and said "I don't think it's working."
I said, "Well, what do you mean?" She said, "Well, I went home on day two after surgery, and on the third day my mother and I took a 30 minute walk." And I thought, "Oh perfect. We nailed it!" [*pumps fist*] "On the fourth day we took a 45 minute wall." "Uh huh." "And the fifth day we went for an hour-long walk, but today I'm really exhausted." So you know she was just advancing her activity way too fast. We had her pump the brakes and work up on her stamina gradually. She's now able to live independently again.

37:50 The third patient had just one level of disc protrusion leading to about an 8 mm canal diameter. Whereas right above it, she had a nice 12 M millimeter diameter. Here's the 12 millimeter section on the elft. On the right is the area where the disc (in black) was pressing asymmetrically on the spinal cord.



She had a disc replacement. And about four months later, here's a picture of she and her husband and a couple of friends skiing in Vail, Colorado.

38:27 The next slide she sent me was her being carted off the mountain by the ski patrol people because she'd torn her ACL (anterior cruciate ligament in the knee). And we often joke that anyone in our clinic who can tear their ACL skiing has done very well from the standpoint of their ME/CFS.



38:43 This young woman did well for about four years, with really good activity, and then the symptoms started creeping back in. We were a little puzzled, but finally got repeat imaging. We wrote this paper up with Dr. Edwards II, who's the surgeon, and his son Charlie, who spent the summer working with us on research projects. Charlie's a senior at Vanderbilt University, hoping to go into medicine. He did a great job on this report.

frontiers Frontiers in Neurology

TYPE Case Report
PUBLISHED 30 November 2023
DOI 10.3389/fneur.2023.1284062

OPEN ACCESS

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RECEIVED 27 August 2023
ACCEPTED 10 November 2023
PUBLISHED 30 November 2023

Case report: Recurrent cervical spinal stenosis masquerading as myalgic encephalomyelitis/ chronic fatigue syndrome with orthostatic intolerance

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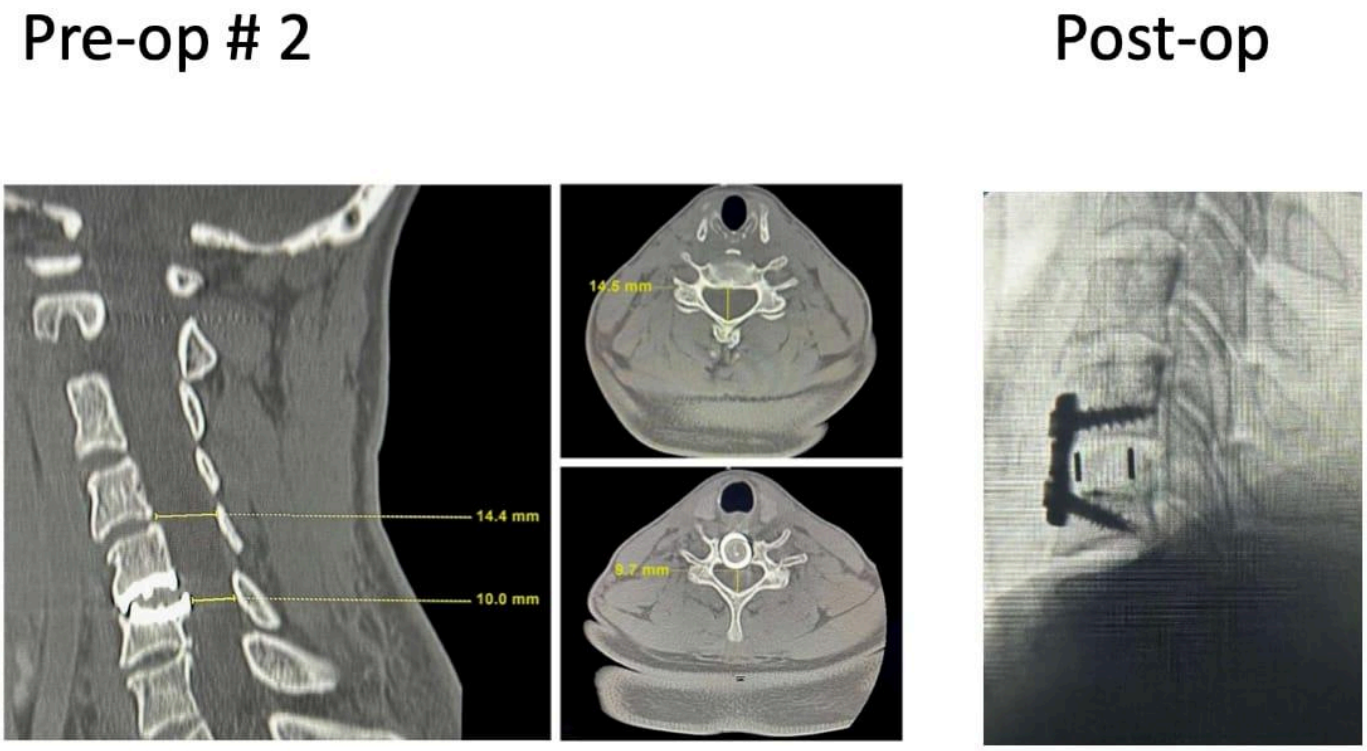
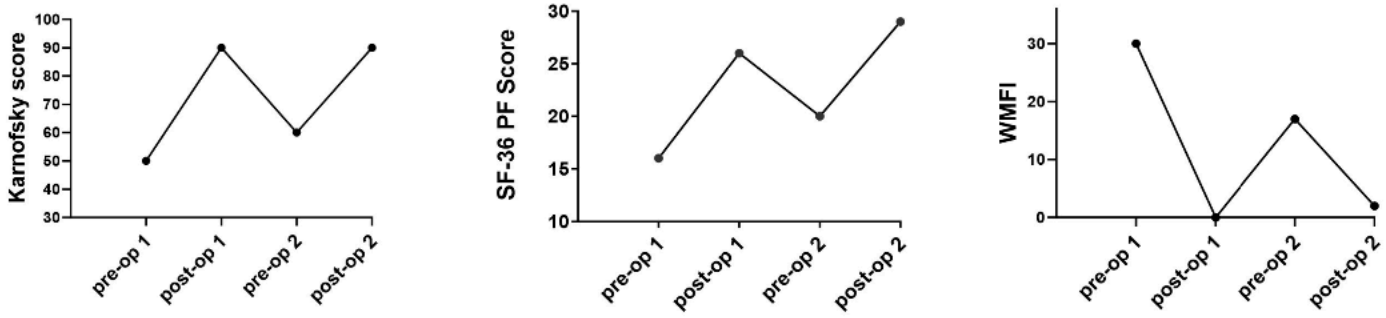
39:11 This paper was published in November 2023. What we found on the repeat Imaging is here she's got a normal canal diameter above the area of the artificial disc, but look what's happened to the lower part of the disc.



This metallic component of the artificial disc had shifted, probably during one of her falls skiing, and now it was recapitulating not only the symptoms, but also the spinal stenosis. She had the area repaired, and this time, she had a fusion shown by these screws on the far right. She has again had a marked improvement in her overall function which we measured using the Karnofsky score, where 100 is as good as you could imagine feeling, the SF36 physical function score, and the Wood Mental Fatigue Inventory score, where higher scores indicate worse function. But just looking at the Karnovsky, here she is pre-op, here she is after the first operation, here she is when the symptoms return, and here she is after the second operation.



40:11 We were leaning on work that had already been done by Dr. Dan Heffez. Dan had been a Neurosurgical trainee at Hopkins when I was an intern, and he's practiced out in Milwaukee and Chicago. He realized that some people sent to him with the diagnosis of fibromyalgia and chronic fatigue syndrome actually had neurologic examination evidence consistent with some sort of cervical myelopathy, some damage to the cord.

40:39 He had a huge series of 270 with fibromyalgia, 20% of whom had Chiari malformation where the cerebellar tonsils descend into the foramen magnum, the hole at the base of the skull. 46% of them had a narrowing of their spinal canal diameter at c5-6, so they had cervical stenosis.

Eur Spine J (2004) 13 : 516–523
DOI 10.1007/s00586-004-0672-x

ORIGINAL ARTICLE

Dan S. Heffez
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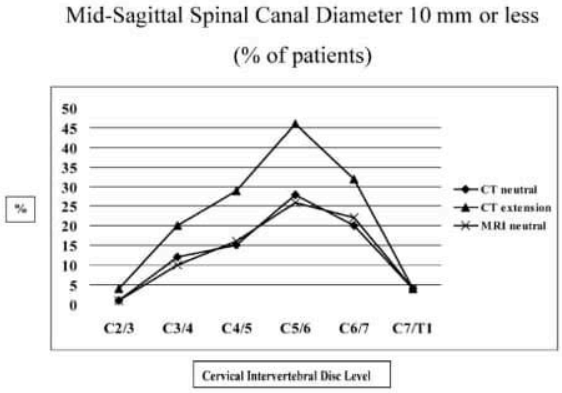
Robert Gottschalk
Dean A. Elias
Alan Shepard
Sue E. Leurgans
Charity G. Moore

Clinical evidence for cervical myelopathy due to Chiari malformation and spinal stenosis in a non-randomized group of patients with the diagnosis of fibromyalgia

- N=270 with FM
- Cerebellar tonsillar ectopia in 20%
- 46% with AP Canal diameter at C5/6 of < 10 mm



41:00
He then took a group of these patients who had agreed to surgery and compared them to a group that didn't have surgery either because they were milder or Insurance wouldn't cover it or they just were apprehensive. And you can see very clearly that on measures of improvement in fatigue, exertion, concentration, headache, pain, dizziness, and nausea, the ones who had surgery, who were probably sicker in the first place, had better improvements at the one-year point than the people who had not had surgery.

Treatment of cervical myelopathy in patients with the fibromyalgia syndrome: outcomes and implications

Symptom	% Improved at 1 yr Surgical group	% Improved at 1 yr Non-surgical group	P
Fatigue	59	10	<0.001
Ftg on exertion	50	6	<0.001
↓concentration	79	13	<0.001
Headache	72	15	<0.001
Body pain	61	16	<0.001
Dizziness	81	17	<0.001
Nausea	100	43	0.003

Heffez DS, et al. Eur Spine J 2007;16:1423-33

[A patient with Mast Cell Activation overlapping with Structural Problems]

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25 yr-old female with fatigue

- Unathletic as a child, poor depth perception
- Flexible, able to do a lot of limber tricks (such as putting her legs behind her head lying prone with feet going past her head)
- Tachycardia in adolescence (EKG and ECHO both normal)
- Seasonal allergies; at 22 started immunotherapy
- Developed itching, congestion, and throat closing requiring a 5-7 day course of Medrol with each increase in the dose of immunotherapy.
- At 18 mo. into this course, she was only at 1/2 of the full dosage

---

41:35 Let me bring this towards a close by talking about a 25 year old that we saw during the COVID pandemic. This young woman described herself as unathletic as a child. She had a lot of clumsiness and poor depth perception. She was very flexible. She was able to do a lot of tricks, for example lying on her belly and her legs would come up behind her head so the feet would go past her head. She's super flexible.

42:04 She developed tachycardia as an adolescent. She had some seasonal allergies, and started immunotherapy (allergy shots) at 22, but had a mast cell type of reaction with each injection, characterized by itching, congestion, and throat closing, needing a week of prednisone or something like it with each increase in the dose of immunotherapies. By 18 months into the immunotherapy she was only at half of her usual full dose.

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25 yr-old female with fatigue (cont'd)

- Working full-time as a BMT nurse at onset of main ME/CFS symptoms in March of 2019, age 23
- Gradual progression over the next 18 months, with marked exacerbations every 1-2 months, lasting 4-14 days
- Unable to continue working by July 2020

She was working full-time as a bone marrow transplant nurse when she started getting ME/CFS symptoms in March of 2019 at age 23. These symptoms progressed over the next 18 months. I'll show you them on the next slide. She would get big flare-ups every one or two months that would last up to two weeks. And these were becoming so frequent that she was unable to work by 2020 in July.

42:56 So these were her initial symptoms. She had fatigue that was present on a constant basis, worse with activity, awakening un-refreshed - everybody is familiar with that. She had headaches at an 8 out of 10 level. She had neck pain, she had lightheadedness with a heart rate that reached 140 beats per minute at work, brain fog. She had arm fatigue with arms overhead, consistent with thoracic outlet syndrome [TOS]. She couldn't braid her own hair. She

had many other symptoms like night sweats, and some right-sided numbness and tingling. And when she went to the ER at Emory to get the right-sided symptoms evaluated,, they diagnosed a probable conversion disorder.

Symptoms at initial evaluation via telemedicine August 2020

- Fatigue always present, worse after activity (e.g, working), despite sleeping 12-16 hours/day, awakening unrefreshed. Could work two nursing shifts, then needed 2 days to recover.
- Headaches were bilateral and frontal, occurring qOD, 8/10, with retro-orbital pressure and throbbing, associated with nausea, lightheadedness, and numbness and tingling.
- Neck pain daily, worse with flexion, improving when she used a neck traction device. With lateral rotation she felt crepitus in the neck. Head and neck feel unsupported.
- Lightheadedness daily, usually with postural changes. She felt heavy and weak when she was upright and had associated nausea. HR ~ 140 bpm at work, SBP at times in the 80's.
- Brain fog daily and gradually worsened over the preceding 4 months. Difficulty with concentration, memory, word finding, and processing, especially in stressful situations
- Myalgias widespread. Arms overhead postures elicited numbness, so she avoided these (e.g., washing her hair). Unable to carry heavy objects, such as a gallon of milk.
- Itching, facial flushing
- Others: photophobia, night sweats, dysphagia, right-sided numbness and tingling, SOB, constipation, TMJ dysfunction, unusual sensation of overstimulation, new panic

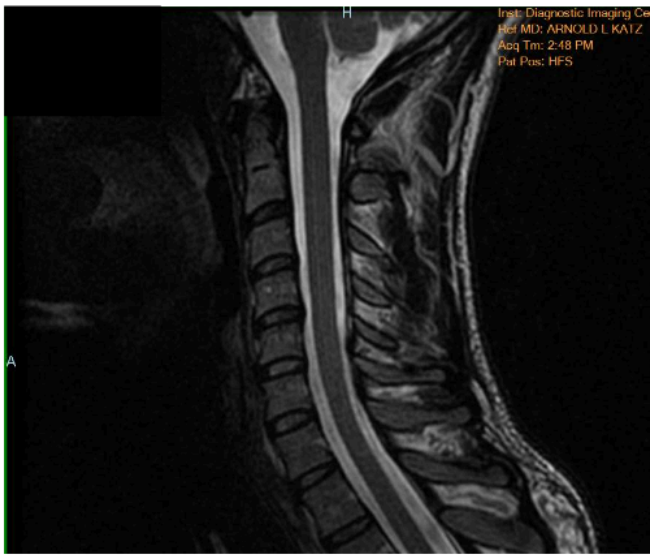
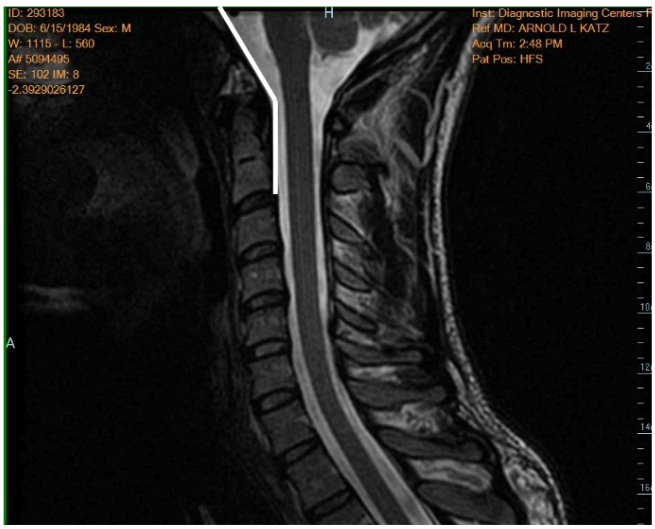
---

43:39 She had a lot of other problems including a new sense of overstimulation that she didn't understand. The symptom that really caught our attention was that her neck pain was worse with neck flexion. She had used a neck traction device that you put over the door frame, and pulling upward on her neck, she felt better. Anytime she rotated her neck to the side she felt a crepitus or grinding in the neck, and, most importantly, her head and neck felt heavy and unsupported. Those are features that we see with **ligamentous instability** at the skull base.

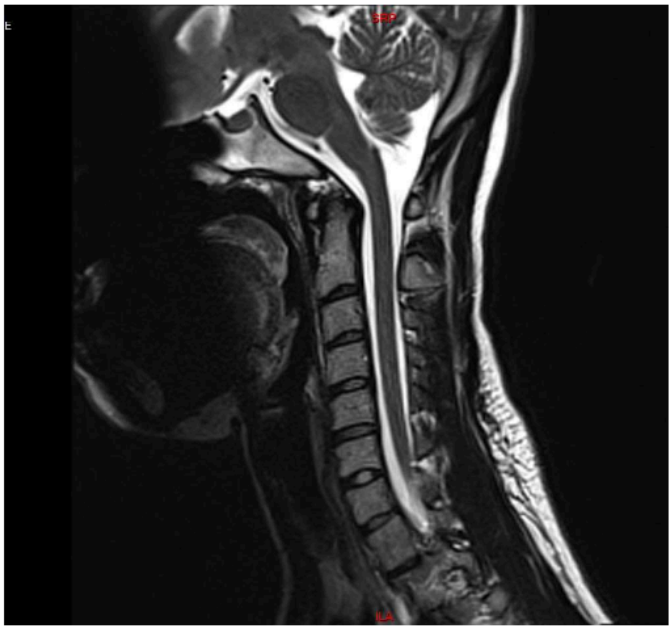
44:15 We met with her by tele-medicine and we thought she probably had hypermobile Ehlers-Danlos Syndrome. She certainly mets ME/CFS criteria. She has well diagnosed POTS. She had some irritable bowel syndromes. She had all these allergies and Mast Cell Activation Syndrome [MCAS]. She had evidence of neurogenic thoracic outlet syndrome. Based on her neck symptoms, we suspected cranio-cervical or atlanto-axial instability.

Problem formulation:

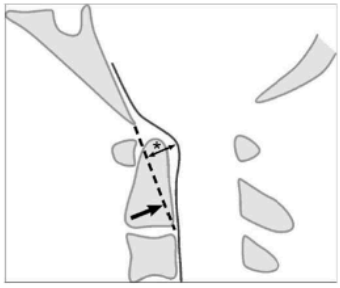
• Hypermobile EDS
• ME/CFS
• POTS
• Irritable bowel syndrome/dysmotility
• Seasonal allergies and MCAS
• Neurogenic TOS
• TMJ dysfunction
• Suspected cranio-cervical or Atlanto-axial instability
• Anxiety

	
Different patient to show almost normal appearance of the base of the skull (except for loss of normal cervical lordosis)	Same image, now with white lines outlining the clivo-axial angle of approximately 150 degrees

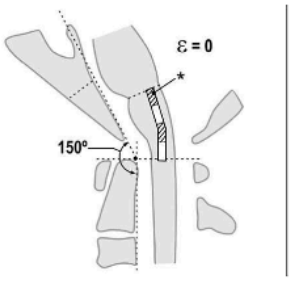
44:41 Here's a picture of another patient with a nearly normal appearance at the skull base. On the next slide, I've drawn in the clivo-axial angle, which is one of the metrics that we look for. That angle should be about 150 to 170 degrees. Here's her MRI that she sent us.



Prior supine MRI:
Clivo-axial angle ~130°; Grabb-Oakes 9.2 mm



Grabb-Oakes measurement; Nl < 7 mm



Clivo-axial angle (Nl is 150-170)

Henderson FC, et al. *Surg Neurol Int* 2010; 1:30

She had a very unusual clivo-axial angle at 130 degrees, and her brain stem was oriented forward which probably added some neural strain to this part of the brain stem. The other thing that jumped out was she had an abnormal Grabb-Oakes measurement, which is drawn from the base of the clivus to the back of C2 and you draw a perpendicular to where the tissue stops. Normal is less than 7, she had a 9 mm distance. The area behind the odontoid shows a pannus formation that tends to occur in people with loose ligaments.

Plan:

- Continue trials of meds for POTS
- See allergist for MCAS evaluation
- Trial of a hard cervical collar
- Schedule in-person visit

Hard cervical collar as a diagnostic and therapeutic trial

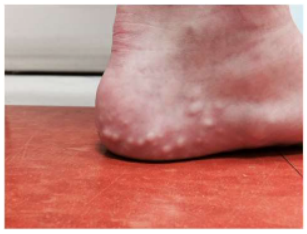
- Immediate resolution of headaches and neck pain
- More energy, able to do consecutive hours of activities and errands
- 50% improvement in lightheadedness
- More restorative sleep
- More fluent speech
- Improvement in photophobia and a sense of sensory overstimulation
- Better temperature regulation at night

- Within 2 days or removing collar, experiences a return of all symptoms

---

45:38 We thought, well, until we get a chance to examine her, let's at least put her in a **hard cervical collar** like the one shown in this picture. And with the hard collar on, as a diagnostic trial, she had immediate resolution of her headaches and neck pain. She had enough energy to do consecutive hours of activity and errands. Lightheadedness was better, sleep was better, her speech was clear, the sensation of light sensitivity and sensory overstimulation was better. She misunderstood our instructions and took her collar off two days before we saw her in clinic, but this was helpful because it confirmed that she had a return of all of those symptoms.

Physical exam findings:



- Alert, composed young woman
- Beighton score was 5/9. Striae over the hips, hyperextensible upper eyelids, velvety skin, pes planus, piezogenic papules at the ankles.
- DTRs 3+ and brisk at the triceps; increased spread of patellar reflexes to > 10 cm above the patella bilaterally.
- Hoffman positive bilaterally (R > L).
- Absent gag reflex.
- Sensation to light touch & pinprick reduced on the R side of her face
- Arm symptoms with EAST (Roos)

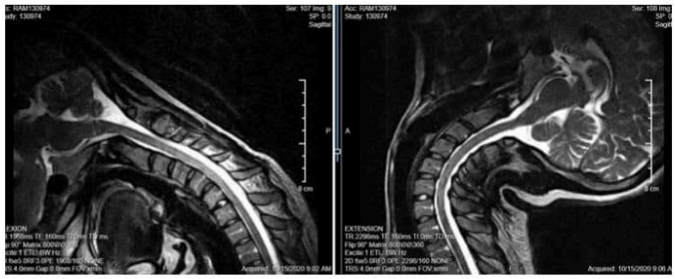
46:20 When we examined her, she did have evidence of joint hypermobility. Her Beighton score was elevated. She had a number of other things we see, including these piezogenic papules at the heels. Her reflexes were super brisk, her Hoffman sign was also positive, and she didn't have a gag reflex, which indicates some problem in the upper cervical spine or skull base with compression of the nerves there. She had the thoracic outlet syndrome test that was positive.

Dynamic imaging:

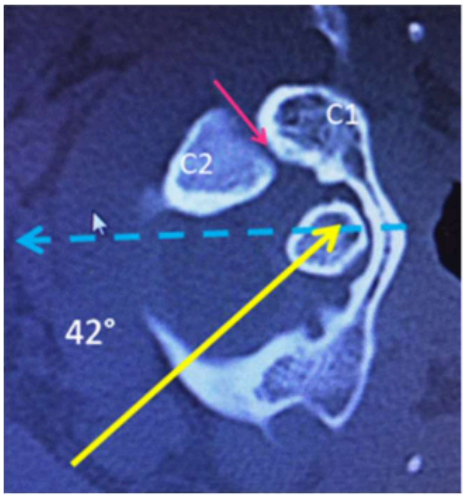
Supine c-spine CT scan in flexion, extension, lateral rotation:

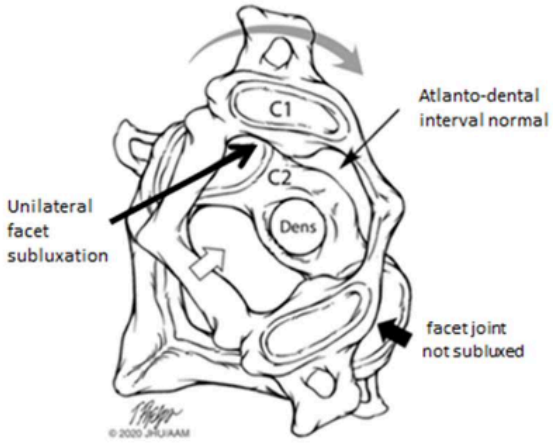
- 5 mm of A-P movement (translation) at skull base (normal < 1 mm)
- 43^{o} of right and 45^{o} of left rotation of C1 on C2 (normal < 38^{o})

Seated C-spine MRI in flexion and extension



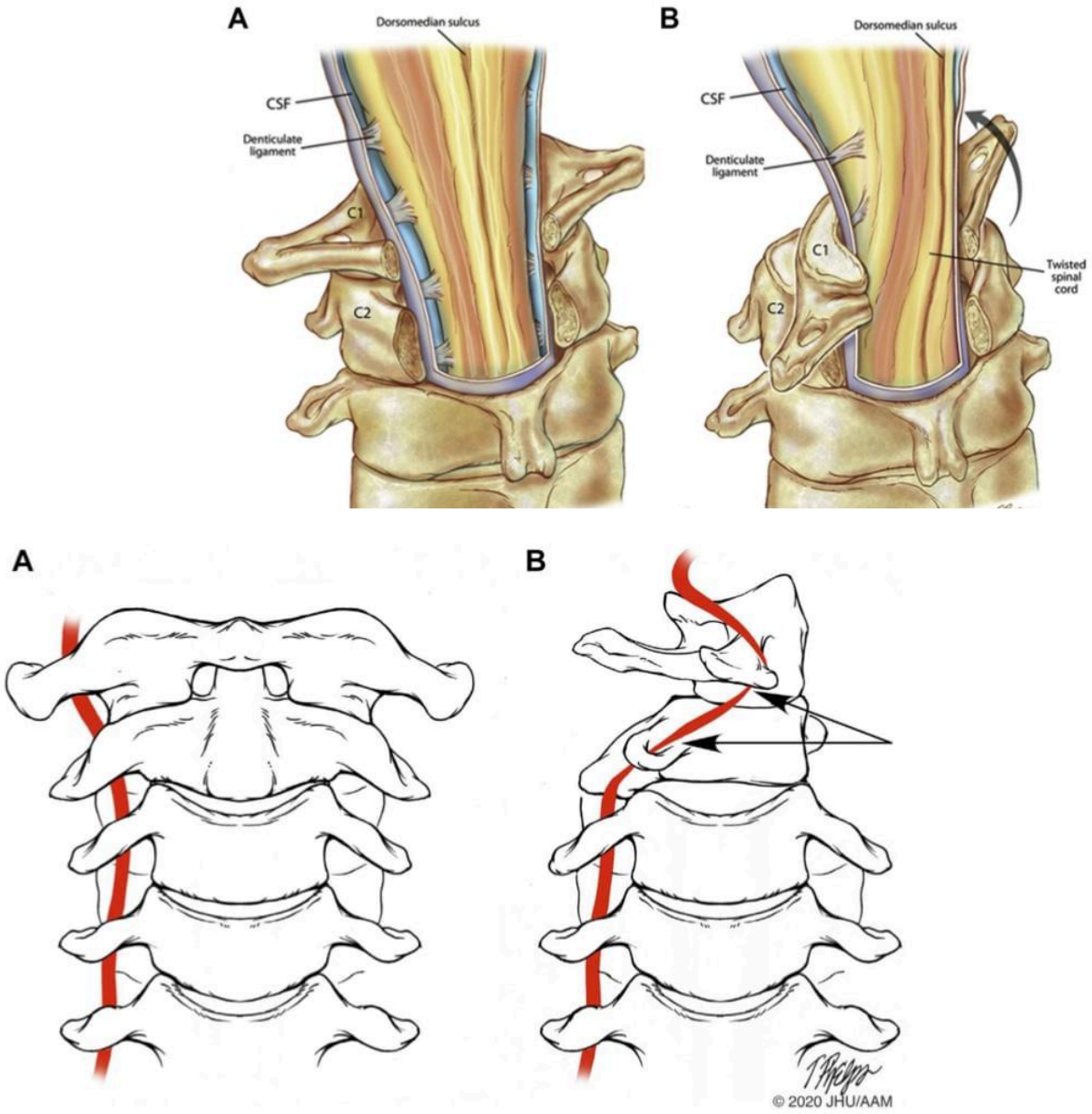
When we suspect this instability, we do dynamic Imaging. You can't pick it up with a plain CT or plain MRI where you're just lying in the scanner. So with the supine dynamic c-spine CT scan, the technician rotates the patient's neck to either side, and they do flexion and extension. She had 5 millimeters of movement in the frontal plane at the skull base when normal is less than one millimeter. She had excessive rotation of C1 on C2 – normally that should be less than 38 degrees–she had 43 and 45 degrees of instability so that confirmed with radiologic objective findings what we suspected.





Henderson FC, et al. Atlanto-axial rotary instability (Fielding type 1): characteristic clinical and radiological findings, and treatment outcomes following alignment, fusion, and stabilization. Neurosurgical Review 2020. https://doi.org/10.1007/s10143-020-01345-9

47:38 What's probably contributing to symptoms when you can turn your C1 too far on C2, as you narrow the space within which the spinal cord is sitting, you probably are wrenching it like a wet dish rag. That interferes with neural transmission through this area.



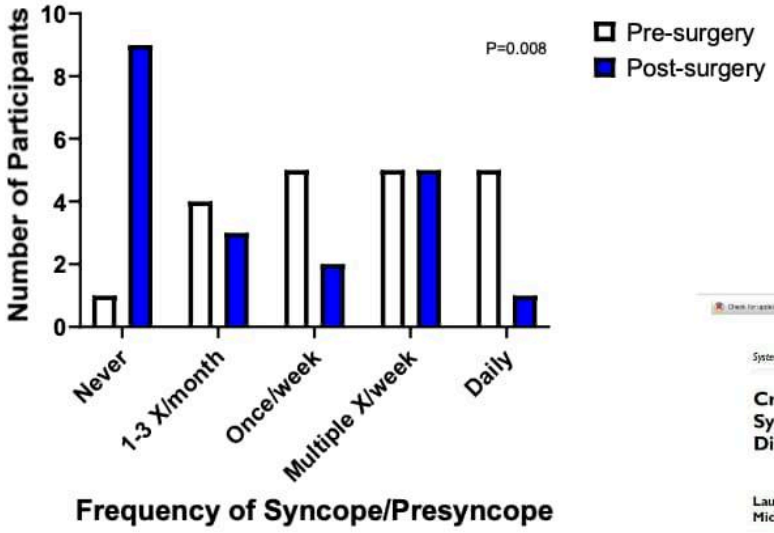
Henderson Sr FC, et al. Refractory Syncope and Pre-syncope Associated with Atlanto-axial Instability: Preliminary Evidence of Improvement Following Surgical Stabilization. World Neurosurg 2021; doi.org/10.1016/j.wneu.2021.01.084.

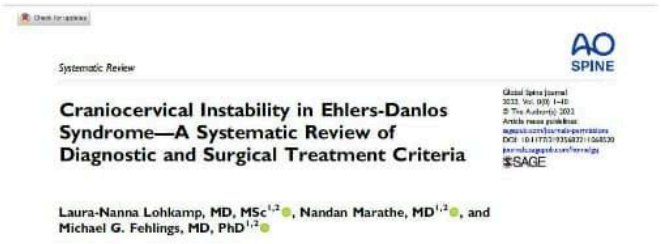
And another potential problem is, we've drawn in the vertebral artery which comes up through a hole in the lateral aspect of each vertebrae. There's a vertebral artery on each side, but we didn't put it in this illustration. If you can turn C1 too far on C2, you can see that you can pinch off blood supply, usually thought to occur beyond 41 or 42 degrees of rotation.

Refractory Syncope and Presyncope Associated with Atlantoaxial Instability: Preliminary Evidence of Improvement Following Surgical Stabilization

Fraser C. Henderson Sr[1-3], Peter C. Rowe[4], Malini Narayanan[1-3], Robert Rosenbaum[1-3,5], Myles Koby[2], Kelly Tuchmann[3], Clair A. Francomano[6]

World Neurosurgery 2021





48:19 Dr. Frasier Henderson in the Washington DC suburbs has been a leader in looking at these problems especially in the group that have Ehlers-Danlos Syndrome [EDS]. In one of the papers where we looked at the frequency of syncope or pre-syncope (near-fainting), in white is the frequency before surgery, with fainting once a week, multiple times a week, or daily. In blue you can see the shift in the frequency of those problems after stabilization surgery.

48:49 Dr Henderson published a recent paper on craniocervical instability [CCI] where he did occiput to C2 fusions. This young woman had the occiput to C2 fusion and everything improved. She was back to working part-time as a research nurse. She still had some leg heaviness because she had one of the problems we talked about last week [in Part 1], May Thurner syndrome – with compression of the common iliac vein, but she just had that stented about two months ago. We're awaiting feedback on how she's improved.

Treatment and 5 month outcomes:

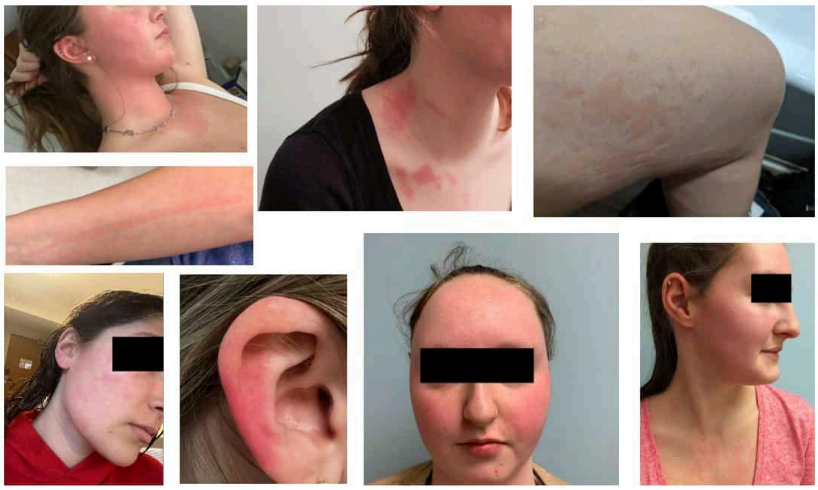
- Occiput to C2 fusion March 2021.
- Headache, neck pain resolved; head now feels supported
- Much better energy and tolerance of activity and shopping
- No longer lightheaded with standing despite elevated HR
- Improved nocturia, clumsiness, grip strength
- Cognition and processing improved
- Working part-time, increasing gradually
- Still has leg heaviness from May-Thurner
- Still has MCAS, EDS, but functioning better

49:25 So these neurosurgical problems can't be expected to fix everything that might be wrong with the patients. She still has Mast Cell Activation and Ehlers Danlos Syndrome, but now has much much better functioning. There was nothing psychological about her problems.

I want to make sure people don't think we're recommending these surgical procedures for everybody with ME/CFS. I just think that these problems can occur in our patients. They mimic the ME/CFS symptoms and they ought to be looked at in those who have no responses to any of the standard medical therapies, and especially if they have abnormalities on their neurologic exam.

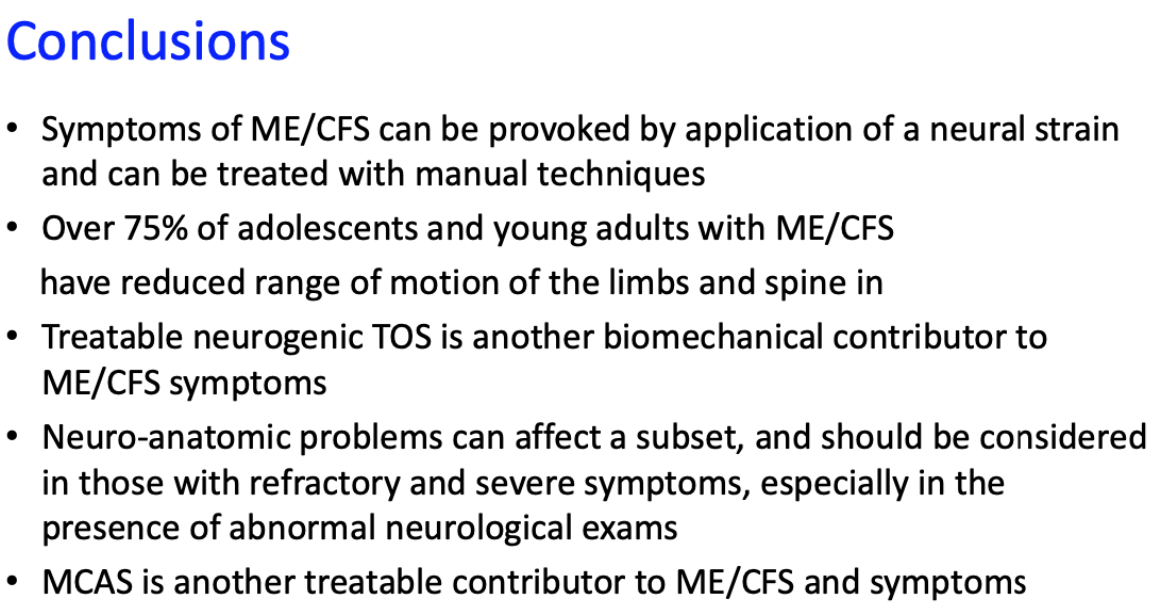
Mast Cell Activation

49:57 I mentioned I'd say a little bit about Mast Cell Activation. This is just a picture of some of the facial flushing that we'll see in our patients. You can see in this girl that her whole face is bright red and she's got a rash on the chest, blotchy rashes where people scratch themselves, hives, erythema affecting the ears and the face. These are the things that we're paying much more attention to these days on the physical examination. The mast cell treatments are often very helpful in getting people more stable.



In Conclusion

50:34 In conclusion for today's session, we know the symptoms of ME/CFS can be provoked by application of a neural strain to the limbs and can be treated with manual therapy techniques. Over 75% of adolescents and young adults with ME/CFS have reduced range of motion of the limbs and spine, and that can even occur when they're hypermobile, in which case they get focal areas of restricted range of motion. Treatable neurogenic thoracic outlet syndrome is another biomechanical contributor to ME/CFS symptoms. These neuroanatomic problems that I mentioned can affect the subset of patients and probably should be considered in those who have refractory or severe symptoms. And lastly, Mast Cell Activation is another treatable contributor to ME/CFS symptoms. We think the same conclusions apply to Long Covid, at least among the patients we've evaluated. It's just that many of the long Covid researchers have not been applying the lessons of ME/CFS to their patients.



I'm going to just end with acknowledgement of the groups that have helped us do this work over the last 30 years. The Sunshine Natural Wellbeing Foundation donated enough to endow a professor's chair that has allowed me to see patients without the usual time constraints in modern medicine. The Boies and Caldwell families have contributed to endowed funds that have helped us hire more physicians and helpers. We've had a really great team of physicians and nurses and research assistants, some fantastic summer students, a number of others who do fundraising like Emily Steffensmeier, and really many of the families and patients in our clinic have sort of kept this process alive. We're incredibly grateful to everybody who has contributed.

THANK YOU

- Grants from NIAID, DoD, Solve ME/CFS Initiative
- Sunshine Natural Wellbeing Foundation (Endowed Chair)
- Boies Family Endowed Fund
- Allison Caldwell Endowed Fund
- Our team: Renee Swope, RN, and Dr. Camille Broussard, Dr. Alba Azola, Meghan Swope, Rick Violand, Colleen Marden
- Summer students (John Fan, Alli Johns, Marissa Flaherty, Jocelyn Ray, Samantha Jasion, Erica Cranston, Megan Lauver, Maria Roma, Vik Siberry, Lindsay Petracek, Charlie Edwards)
- Rowe's Research Runners--thanks to Emily Steffensmeier
- Many, many families and patients

I'm going to stop there and see if we've got time for questions and we can go another half hour, Tess, if that's the case.

Wrap Up

52:40 Tess Falor, PhD, Renegade Research Founder: Yeah that would be great. We're … So first of all, that was great. Our team behind the scenes was joking around that you were showing some of my MRIs because I have a lot of these conditions. I'm actually going to be getting surgery next Wednesday in artificial disc replacement and I'm going to be very curious to see what happens after that.

Peter Rowe, MD
So that's an interesting point.The first patient I showed had a very abnormal clivo-axial angle, she had the congenital cervical stenosis, and she had one disc bulge … we wondered initially: Do we have to open up the entire cervical spinal canal? Do we have to fix that abnormal clivo-axial angle? Dr. Edwards elected to do the least invasive procedure first. And that was all she needed ….

and she's five or six years out from the surgery and doing beautifully.

Tess Falor: Yeah, yeah that's my plan …. thinking about all the different pieces of it. Start with the easiest and then go from there.

Peter Rowe: I should call out that patient because I think she tried to give me a heart attack. She decided that her two activities after surgery would be salsa dancing with her husband and rock climbing. **Be good to your doctors**.

End of Peter Rowe Presentation Part 2 of 2. Keep reading for the Q&A.

Peter Rowe, MD, Part 2, Feb 16, 2024.
Unlocking Mysteries in ME/CFS regarding…

- **Bio-mechanical issues including thoracic outlet syndrome**
- **Neuro-anatomic problems including cervical stenosis & CCI**
- **Mast Cell Activation**

Recording Link: **youtube.com/watch?v=WaM2mPzR64w**

If the information in this transcript with slides helps you, and you can afford to, please consider donating to either Renegade Research / Remission Biome or Dr. Rowe's work or both. Minimum GoFundMe donation is $5.

RemissionBiome GoFundMe: gofundme.com/f/Remissionbiome
Rowe's Research Runners: rowesresearchrunners.org

53:56 Q&A with Peter Rowe, MD. Feb 16, 2024

Tess Falor: Okay. So we're going to do the Q&A a little bit differently this time. We are splitting up by topics and we're going to have our team members jumping in here to ask questions from a certain topic. We'll start off with Richelle talking about some of the first topics of the talk.

54:23 Richelle Sepulveda: Okay so I'm trying to make sure I'm reading off the ones that were kind of marked to start off with. So there's one on here that I think is going to be somewhat relevant for a lot of us, especially with long covid. She says, "I've lost a good amount of my use of my hands, since having covid and long covid. My long covid is fairly severe. I'm extremely limited in what I'm able to do now.

Q. TOS: Is it possible to develop thoracic outlet syndrome as a result of this without any of the repetitive repetitive motion issues so can it be acquired?

Peter Rowe: Yeah, that's a great question. We don't know why thoracic outlet syndrome symptoms start happening at a certain point, but they can, and who knows what leads to that change. Something changes as the nerves are traversing from their exit point in the cervical spine down under the clavicle and into the arm. Maybe it's the position that people are in when they're sick. Who knows, but if you've got those problems with arms overhead…. a lot of the patients feel that these things have come on so gradually that they don't tell us.

I had one girl who we suspected might have this and I asked: how do you do with activities that involve reaching up … and it was around Christmas time… like putting the ornaments on the Christmas tree? Her parents were

across the room, and they almost fell off their chairs laughing, and I was a bit puzzled, because I hadn't said anything funny. Does she not like decorating the Christmas tree? They laughed even harder, because this girl orchestrated everybody in the family to decorate the tree. She loved doing it, but she knew that every time she put her arm up, she'd be tired for half a day, so she just gave the orders to others. But she didn't even mention this to her physicians.

Others have problems holding their arms on the steering wheel at 10 and 2 and they typically hold the steering wheel at the bottom at 6 o'clock because anything that involves arm extension like emptying the dishwasher, putting the clothes up on the rack, those things will cause symptoms. A lot of the girls who have longer hair will bend over in the shower rather than reaching up to shampoo their hair, to avoid provoking these symptoms, so we think it's a big problem. We think it's highly prevalent, and it's just another example of how the physical examination can be quite abnormal in patients with ME/CFS. It's baffling to me how anyone in the early 90's said, "Yeah. These are all people with a normal exam." Nonsense.

57:01 Richelle Sepulveda: There's also a couple that are questions that are somewhat related to each other, and so I'll kind of like group them together. [I] won't read the questions specifically, but for things like neurogenic thoracic outlet syndrome with issues traveling alongside with issues of instability and versus stenosis, but also things like our..

Q. Is scoliosis a risk factor for that, as it's, you know, part of the overall structural issues, that could lead to suspected thoracic outlet?

57:32 Peter Rowe: The one thing we suspect, and this has been written about – but there's not a lot of information directly about it, is everybody who deals with Ehlers-Danlos Syndrome suspects that neurogenic thoracic outlet syndrome is much more common in that population. So there must be some connection between instability in the spine and thoracic outlet syndrome, but it hasn't been a topic that people have spent a lot of time on unfortunately. We're trying to get another paper on TOS with Charlie Edwards into print, drawing attention to the need to look for TOS in the ME/CFS population.

58.17: Richelle Sepulveda: And then one last one in here, that's again grouping several kind of together:

Q. Spontaneous Improvement: The possibility of children growing out of ME/CFS? and the possible long COVID? and
Q. Is surgery always going to be something that is recommended m when it starts to be like intransient? And
Q. How much is that Improvement spontaneous? And how much of it is going to require intervention?

58:45 Peter Rowe: Let me make a couple of comments about that. We are not recommending surgery as a non-specific treatment of ME/CFS. Surgery really has to be for confirmed, standardly defined instability, with obvious radiologic metrics, concordant symptoms that have been unresponsive to conservative measures of medication treatment and PT, and ideally you often want some sense that you're going to see improvement when you stabilize the neck with a hard collar.

We do have a number of patients that get better spontaneously. I think Kathy Rowe in Australia has the largest series of some over 700 adolescents that she followed over time, but the average duration of illness was something like eight years among those who improved eventually. So it's not a brief illness.

You know, when I first got involved in this field, the received wisdom was that all one needed to do was wait two years, and they'll all be better. And that's clearly nonsense as well.

0:59:59 Tess Falor: Was that the last one, Richelle, your topic? Okay.
1:00:03 Richelle Sepulveda: For now, at least. We'll see if more come up.

1:00:07 Tess Falor: and come back around. Okay, so then the next topics were the cervical stenosis and CCI. One of the questions that came up is:

Q. Spinal Stenosis: Do you have ideas about the mechanism whereby this spinal stenosis causes ME?

1:00:23 Peter Rowe: So we don't know exactly. But in each of the patients that we saw with spinal stenosis, it was the front part of the cord that was being compressed. And, if you've got something pressing on your spinal cord, you had better have some kind of major alert message to the brain stem centers that control physiologic responses, because if you don't there's something really wrong. You've got a major threat to the organism if you've got something poking on the spinal cord directly. So it's likely that symptoms are caused by some combination of abnormal nerve messages caused by that compression. In all of the patients that we reported, everybody had some improvement in anxiety, at least it was what they called anxiety. I think it was a heightened fight or flight response that was being generated by pressure on the spinal cord. How that then dovetails with all of the ME/CFS symptoms I think is a little unclear, but we think that a big factor is that if you can improve the orthostatic intolerance, one way or the other, people generally feel better.

1:01:37 Tess Falor: Another set of questions was about

Q. Treatments that don't involve surgery. So do you have any….

1:01:48 Peter Rowe: So we have some patients who have excessive rotational angulation of C1 on C2 up to 49 degrees but their function is pretty good. We've generally treated them with physical therapy. They might wear a collar at night to stop them from moving their neck excessively during sleep. There are reports of clinics around the country where they use Prolotherapy which is an injection of some kind of substance that tightens up the ligaments. The problem is that most of these are for-profit clinics and none of them have been interested in measuring carefully whether these treatments work or not. So all we've got there is anecdotes and it would be good if one of these approaches was used in a study in an academic center where the academicians have no vested financial interest in whether it works or not, but they could assess it properly. So I think that's what we'll need in order to know whether one of these less invasive techniques might work great.

1:02:53 Tess Falor: Yeah. Actually I live in Denver, a few miles away from the Centeno Schultz Clinic that does the Prolotherapy, but I haven't seen research into outcomes.

1:03:06 Peter Rowe: And, by the way, we need, in more conventional academic sites, we also need to do better with looking at the outcomes of our patients who've undergone these surgeries.

1:03:26 Tess Falor: So, kind of a broad question. For people on the webinar who think that they might have these conditions, but they don't know where to get started. Or, you know, maybe their clinician doesn't know about any of these conditions.

Q. How could people get started? Is there, you know, certain things that you can ask your doctor for?

1:03:57 Peter Rowe: If you just get the plain MRIs supine, you might be able to see a bulging disc or a Chiari malformation, but they don't pick up these more subtle things that are only picked up by excessive motion. So you have to find somebody that has a seated upright MRI. We do an MRI with flexion and extension and then we have a

couple of radiologists in the Baltimore/Washington area that do the dynamic CT scans properly. But I can't even get those done at Hopkins.

So you have to show that you've got a lot of interest in this patient population and that you're willing to take the time to do all the detailed radiologic measurements. So, it is difficult for people to access this kind of care. Once you've identified somebody as having instability and they haven't responded to the conservative measures and their pain and functional disturbance is significant enough, there are only a handful of surgeons who are willing to do these procedures around the country. So, these are early days and medicine is often a very conservative profession where people want to see randomized trial evidence that the surgery is warranted. People are sometimes unwilling to operate on those with lax connective tissue because they have such poor healing. So there are a number of factors that lead to this being a little bit tougher than it should be I think to get access to care. But I think it's changing. I think as we're all trying to publish more information to bring this to everybody's attention, we're seeing more papers come out on what are the proper radiographic metrics for considering surgery, what, how symptomatic should people be and what are the things to do technically during the procedure to make sure it comes out right.

1:05:57 Tess Falor Great. I think I'm going to pass it off to Shelley to ask a few questions.

1:06:04 Shelley Hayden:: All right. Awesome. This has been so great, Dr. Rowe. I have three questions having to do with mast cells. Okay. They're kind of similar. The first one is what I'm going to give you, the first two together.

Q. MCAS: What do you suggest for mast cell stabilization aside from pharmaceuticals, and then someone asked for your general medication recommendations for mast cells.

1:06:30 Peter Rowe: I've learned a lot from our colleague, Larry Afrin, who's a hematologist oncologist who's led a lot of the efforts to better understand Mast Cell Activation. He does a tremendous amount of teaching of his colleagues. And Larry's first, second, and third point are … ***find out what's triggering the mast cells***. Is it specific foods? If so, eliminate those. Is it odors? We had one patient who had for a long time had a lot of trouble every time she took a shower. She just felt miserable in the shower. We thought, "Oh it's because the hot water aggravating your orthostatic intolerance." Then she read something in the New York Times about plastics and she took out the plastic shower liner and replaced it with a linen one, and for the first time in about 10 years she had major improvements in her ability to tolerate the shower. It wasn't the orthostatic intolerance alone, it was the fact that her mast cells were being stirred up by some off-gassing from the plastics, and that process of identifying triggers can be quite different for each person.

Some people with Mast Cell Activation get very symptomatic with leftovers because the leftovers that are put in the fridge, the bacteria on those foods can generate histamine. Others are very intolerant of high histamine foods or anything that's fermented, or red wine, or chocolate. There are websites for low histamine diets. They're really quite complicated, but if you can identify specific foods that really stir up symptoms, and eliminate those from the diet without nutritional problems, that is a good first step.

The medications we use for Mast Cell Activation are actually quite benign, and I want to come back to the issue of definition, but the main medicines are what are called H1 antihistamines, things like Claritin and Zyrtec and Allegra. And then, the H2 antihistamines are drugs like Pecpid or famotidine, which bind to other histamine receptors. And another class of antihistamines are the older tricyclic antidepressants like doxepin, nortriptyline, amitriptyline. Sometimes, they're a bit tough to use, but sometimes they can be really good. Cyproheptadine is a particularly sedating antihistamine with strong antihistamine effects. We often use that at night. Then you can pick drugs that

somehow prevent the mast cells from dumping out all their contents which include histamine but hundreds of other substances. The big mast cell stabilizer is cromolyn, oral cromolyn. But others like montelukast or Singulair, and some of the other drugs can help reduce mast cell degranulation.

Different supplements can be helpful, like quercetin. Aspirin for some people in low doses is helpful. Vitamin C can be helpful. You have to spend a lot of time seeing what each person will respond to. Some people are trying N-acetylcysteine, another drug that might have mast cell controlling effects. Some are investigating it for both fatigue and brain fog as well. So there are a number of things that are available to people, often without prescription, that people can play with, in conjunction with their physicians.

The diagnostic question is a tough one because the academic allergy community has followed very strict rules for diagnosing Mast Cell Activation. They want to see a 20% increase above the basal tryptase level during a flare. Well that means that if that's the only way you get diagnosed, most people in the underdeveloped world can't get a tryptase level, can't get diagnosed, and then can't get treated.

Dr. Afrin and a number of us have written a counter argument to the consensus view of Mast Cell Activation which says you need to have a consistent clinical story and a response to one of these medications I just mentioned, plus or minus some biological evidence of an elevation in histamine or one of the other mast cell byproducts. It's a much more patient-friendly approach that doesn't restrict the number of people who could potentially be treated the way that the academic consensus-1 definition does.

1:11:14 Shelley Hayden: All right. Thank you so much. That was super helpful. I really appreciated the anecdotal story about the woman with plastic shower liner. I think all of us are going to be thinking about anything that could be triggering us.

Q. Mast Cells: The next question about mast cells was just – can you share a little bit more about how it relates and may be aggravating some of these spinal issues.

1:11:37 Peter Rowe: The mast cells - they're really a part of the primitive immune system. They're what we use to tackle some organism that we haven't seen before. So if you don't have antibodies to something, the mast cells can sense that there's an invader. They dump out their contents. The histamine brings other white blood cells to that region, and they can possibly gobble up the infection. If you've got a lot of Mast Cell Activation, if they've been stirred up already, and then you get something like COVID, Dr. Afrin has proposed that that is a trigger to the hyperimmune response that the mast cells can orchestrate in response to a new infection.

1:12:21 They also seem to play a role in long COVID as well. So we use a lot of antihistamines and similar type medications in our long COVID patients, especially if they have a strong allergic type history. *One of the theories that's out there and I don't know how much credence to give this, is that because the mast cells have enzymes in them that can break down proteins, some people have speculated that you can go from not being hypermobile to being hypermobile due to the effect of mast cell degranulation and these enzymes on the ligaments. So that's an interesting question. It would be nice to have better data, but there are some strong opinions that this must be how some people become worse and worse over time.*

1:13:13 Shelley: Yeah. I think that is an important question for a lot of us trying to figure out where we are on our diagnostic journey. Thank you so much. Really appreciate that. Tess, what's next?

1:13:25 Tess: We will go to Elly next.

1:13:30 Elly Brosius: Hi there. This is a comment from Dr. Hassan Abdallah. I think you know him, Dr Rowe. He says great presentation, and

Q .CCI surgeons: Can you tell us about your experience with neurosurgeons differing inputs about cervical instability and the effect of Chiari type on CCI.

1:13:57 Peter Rowe: I think this is another area where the people are at different points of adoption of and in their agreement with the new data. As we talked about before, some people are super skeptical. They want to see around seven randomized trials before they'll change their practice. Others of us see some reasonably coherent information, and we're trying to help our patients at an early point. We don't have people at Hopkins for example who do this kind of surgery for our patients with cranio-cervical instability. At least they don't do a lot of it. Maybe they do it when they see certain patients, but not because they have ME/CFS or Ehlers-Danlos Syndrome. It's been a big problem finding people who can properly evaluate and carefully treat them. I think Hassan knows some of the individual players in the region, but these guys are really very brave in tackling this problem when much of the neurosurgical profession is criticizing them for doing surgeries that are too aggressive.

1:15:14 Elly Brosius: Okay We have a question about

Q. scoliosis. Is that a predisposing factor? Can you explain that a little bit more?

1:15:26 Peter Rowe: So it may be that the people who have laxity of their ligaments are much more likely to have scoliosis, so it may that it's the it's the underlying connective tissue laxity that predisposes them to both scoliosis and spinal instability. We don't have a lot of our cranio-cervical or Chiari patients who have bad scoliosis, and that may just be a sampling error. But Ehlers-Danlos Syndrome can predispose you to Chiari malformation as well as to spinal ligamentous instability.

Tess: Do you have any more questions, Elly?
Elly: No.
Tess: Okay. We'll go to Michael. Do you have any questions?

1:16:14 Michae Natt: I've got a few that I picked up from the chat. Excellent talk. Thank you very much for doing this for us. The first one is,

Q. LDN: is there a role for low dose naltrexone [LDN] in these populations?

1:16:29 Peter Rowe: We use a lot of low dose naltrexone, especially in our EDS patients because it's often very helpful for their pain. Chronic pain is a big problem in that population, maybe because the ligaments are so loose that their joints are excessively movable. Low dose naltrexone has been studied more formally in fibromyalgia patients. I think we all find that it's quite safe to use. It's one of the drugs where you don't expect major side effects.

There are debates about how we should start it. Some people suggest starting at one and a half milligrams nightly, and in two weeks you can go to three milligrams, and then in another two weeks four and a half milligrams. Others feel that such a rapid advancement races past effective doses that are often quite low. So some people start at 0.5 milligrams and go up weekly in 0.5 mg increments until they see a benefit. The sweet spot for dosing might be between 1.5 and 3 mg per night. So again, those are differences of opinion that we could settle with better studies and more coordinated randomized trials. But for now, it's safe enough to try using either dosing regimen. We find that it can occasionally give a nice overall benefit for general function, not just for pain, and we've used it in our Lovg COVID patients as well.

1:17:57 Michael Natt:: Okay and the next one is….

Q. Are muscle biopsies ever useful in the diagnosis of ME?

1:18:07 Peter Rowe: We haven't used them. I think they're more of a research tool as we try to understand what's going on, and whether there might be mitochondrial metabolic activity that's abnormal, but we have not typically seen any evidence of true muscle fiber abnormalities in the ME/CFS patients.

1:18:30 Michael Natt: There was this recent study by Rob Wüst in the Netherlands which showed some interesting findings in the long COVID population.

Q. Lymph Drainage: So does any of your research hint as to why lymphatic drainage techniques like the Perrin Technique might be benefiting some patients?

1:18:53 Peter Rowe: Yeah. It's unclear how much you can separate the lymphatics from the fascial tissues from other areas of muscle tightness. I think if you're doing lymphatic massage you're doing more than just targeting the lymphatics. You have to be touching other tissues and so as the osteopaths say, “to touch is to treat,” so you're not quite sure what you're doing but you're probably changing more than just your target tissue. But Ray Perrin’s techniques have been effective for some and we just need more study of that and comparison studies to see which techniques help people get better in a faster manner.

1:19:40 Micheal Natt: Happy for me to continue. I've got several more questions if we've got time.

Peter Rowe: I'm good.
Tess Falor: Let's do maybe two more.

1:19:48 Michael Natt:

Q. Endothelial meds: .Is there a role of drugs that support endothelial function such as diosmin, hesperadin, sulodexide, and statin, things that support vascular tone and which may be dysfunctional in people with POTS, ME, and long COVID?

1:20:05 Peter Rowe: I think people have started to look at those. And it makes sense that if you got something that could cause some vascular constriction that ought to make people with orthostatic intolerance a bit better, but I'm not aware of too many formal studies of those items. The statins can have an anti-inflammatory effect on some people so we have the occasional patient who gets put on a statin for their hyperlipidemia and they notice some other Improvement like in their cognitive function or their general energy. So, again, it would be lovely to have big coordinated trial networks like they have in pediatric cancer or in HIV with hundreds of ME/CFS clinicians around the country doing these formal studies so we could get to a more effective treatment faster.

1:20:59 Michael Natt: Okay. Thank you. And probably the last one is

Q. Glucose: What's the role of glucose sensitivity in the worsening of POTS and is there a role for ketogenic diets or the use of Metformin.

1:21: 15 Peter Rowe: I'm not sure about the glucose question. I'm no expert on that. We have occasional anecdotes about patients who feel better on a ketogenic diet, but it's a bit of a struggle to adhere to that diet, and again it probably ought to be studied more carefully. What was the last bit of that question?

Michae Natt: It's whether metformin might be of use in, given this sense of some sort of glucose sensitivity.

1:21:50 Peter Rowe: There was the report recently of Metformin as a way of preventing long COVID. It didn't do it for everybody, but it was a statistically significant difference. So we've been using it in some patients who have acute infection for 10 days to try and limit the likelihood of long COVID. And anything that works in the acute phase, you'd wonder if it would work in the long-term phase to also do something beneficial. So that's a good candidate for another trial.

1:22:21 Michael Natt: All right. Thank you very much.
1:22:24 Tess Falor: All right. I'm gonna pass to Richelle, and then if there's a little bit more time we'll come back for a few more from Michael. But we had to point out that if you want to see what MCAS looks like, that Richelle has gotten red throughout the webinar. We're noticing that she's a little bit more pink now. I'll pass off to Richelle to ask a question.

1:22:47 Richelle: Yeah, I'm definitely blotchy and I'm trying really hard not to itch because I don't just get hives all down me in …and yeah got other things going on too so, but, which made me also….

A question that popped up here towards the end and it was asking about

Q. Idiopathic intracranial hypertension

and its relation to any of these patients. In the question they also say it's been found in MS, but there's also other possible like signs of it that are you know sometimes often dismissed on MRI's but are not, they're, just like, oh well, ….it's a partially empty cell, unless they have other symptoms don't worry about it and you're like well why do you think I got an MRI, or also like giant aroid granulations which they're like, " well we don't really know what they do so it's probably fine." If you've any comments on any of those kinds of findings, especially with the IIH [idiopathic intracranial hypertension].

1:23:44 Peter Rowe: With idiopathic intracranial hypotension – so low pressure, it's often associated with a tear in the dura that is a membrane that keeps the spinal fluid in place. If you get a tear in the dura –which is much more common if you have Ehlers-Danlos Syndrome – that can spontaneously leak spinal fluid. Then as spinal fluid leaks out faster than it's being made in the brain, then the brain is no longer well suspended by spinal fluid, and the brain sinks down against bone. Typically people with bad intracranial hypotension feel miserable when they stand or when they sit upright for more than a few minutes, and they get a just progressively worse headache the longer they are upright. Lying down relieves the headaches, and they generally feel better lying flat. That's the opposite of intracranial *hyper*tension where those people need their bed elevated. They need their head up because when they lie flat they get an excruciating headache. So, we can see both types of intracranial pressure abnormalities. The low pressure is much more common in those with Ehlers-Danlos Syndrome. The high pressure is common in people who have some sort of obstruction to outflow of blood from the brain. There's more work by our neuroradiology colleagues on that all the time. One of the leaders in that field is Dr. Ferdinand Hui who's a former Hopkins neuro radiologist who saw the light and moved out to Hawaii.

1:25:22 Richelle Sepulveda: So yeah that was kind of like trying to, like try, you know, look in on some of the questions on that and trying like the intermittent effect of like going back and forth between the hypo and hyper is also that fun little balance that is always trying to find that right spot, but I think that's all …. I'm losing focus myself. Otherwise, I would start getting into the glucose question, my thing, that's kind of kind of my jam, but I wouldn't be coherent. I don't think right now, kind of like I'm, my my

1:25:55 Peter Rowe: Yeah, I've got a hard stop in about two minutes, too.

1:25:58 Tess Falor: Okay. Great. So. yeah. Good time to wrap up then. But, we did chat with Dr. Rowe before this and he said that we will find a way to answer more of the questions that people have put into the chat for part one and

part two. So, look out for that.

remissionbiome.org [or Renegade-Research.org . Sign up for the newsletter and we'll include that with one of the future newsletters. I would like to thank Dr. Rowe for another excellent presentation. We really appreciate you spending your time with us.

Peter Rowe: Great, love doing this. Anytime.

Tess Falor: Great. Take care. All right. Bye everyone, bye.

End of

Peter Rowe, MD, Part 2, Feb 16, 2024.
Unlocking Mysteries in ME/CFS regarding…

- **Bio-mechanical issues including thoracic outlet syndrome**
- **Neuro-anatomic problems including cervical stenosis & CCI**
- **Mast Cell Activation**

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