Joint hypermobility/EDS in ME/CFS

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Presenter Disclosure Information

Peter C. Rowe, MD

- No financial relationships to disclose
- No commercial products will be discussed

Joint hypermobility/Ehlers-Danlos Syndrome in ME/CFS

- Background on EDS and joint hypermobility
- Association between JH/EDS and ME/CFS
- Reasons to assess for JH in the clinical care and research studies of ME/CFS

Ehlers-Danlos Syndrome

- Heterogeneous disorder of connective tissue
- Characterized by varying degrees of:
  - Skin hyperextensibility
  - Joint hypermobility
  - Cutaneous fragility
- Most forms result from mutations in genes encoding fibrillar collagens or the collagen-modifying enzymes

de Paepe A, Malfait F. The Ehlers-Danlos syndrome, a disorder with many faces. Clin Genetics 2012;82:1-11.

Ehlers-Danlos Syndrome

- Because fibrillar collagen provides strength and structure to essentially all tissues and organs, EDS has widespread clinical manifestations
- Early varicose veins, easy bruising
- Easy fatigability and widespread pain common

Royce PM, Steinmann B, Superti-Furga A. The Ehlers-Danlos syndrome.
In: Connective Tissue and its Heritable Disorders. New York: Wiley-Liss, 1993: 351-407.

Earlier Classifications of EDS

Berlin Nosology 1988

Type I

Type II

Type III

Type IV

…

Villefranche 1997

Classical (formerly EDS I and II)

Hypermobility (formerly EDS III)

Vascular (formerly EDS IV)

Kyphoscoliosis

Arthrochalasia

Dermatosparaxis

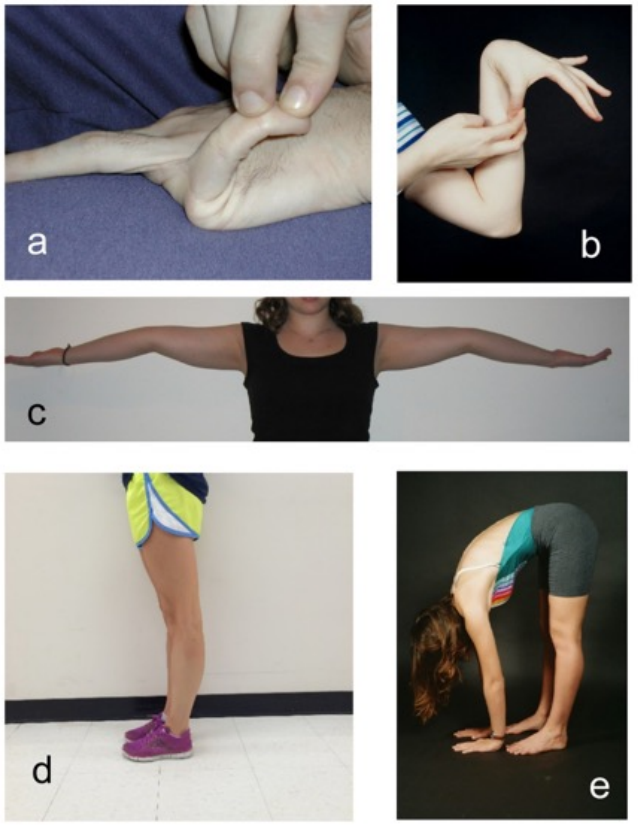
2017 International Classification of the Ehlers-Danlos Syndromes

(Malfait F, et al. Am J Med Genet Part C Semin Med Genet 175C:8–26).

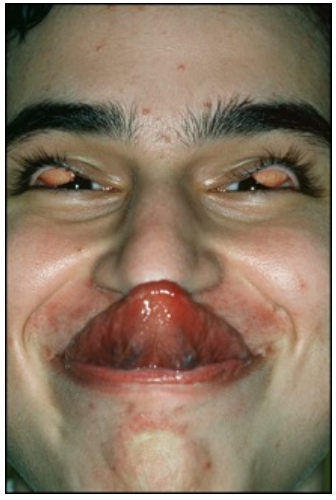
In view of the vast genetic heterogeneity and phenotypic variability of the EDS subtypes, … the definite diagnosis relies for all subtypes, except hEDS, on molecular confirmation with identification of (a) causative variant(s) in the respective gene.

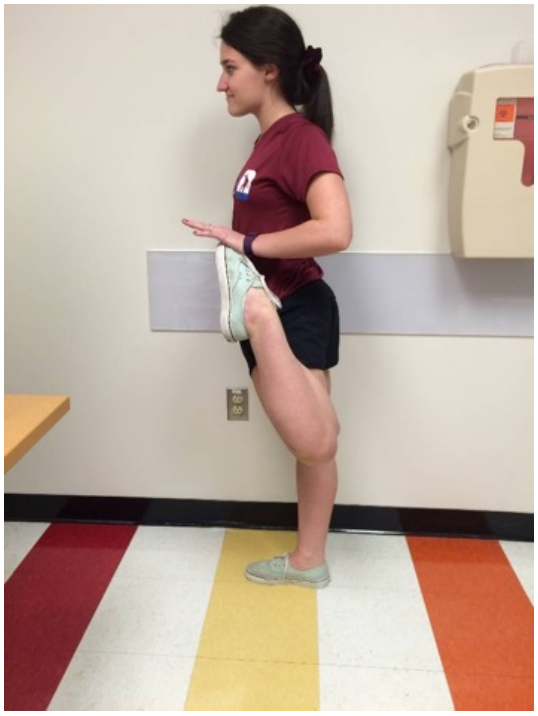
Beighton Score

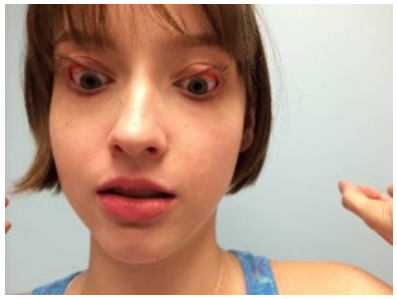
Maneuver (1 point for each positive)	L	R	Score
a. Passive dorsiflexion of the fifth finger at the metacarpophalangeal joint > 90°			
b. Passive apposition of the thumb to the flexor aspect of the forearm			
c. Hyperextension of the elbow > 190°			
d. Hyperextension of the knee > 190°			
e. Forward flexion of the trunk with the knees straight so the palms rest flat on the floor			
Beighton score (maximum score=9)			

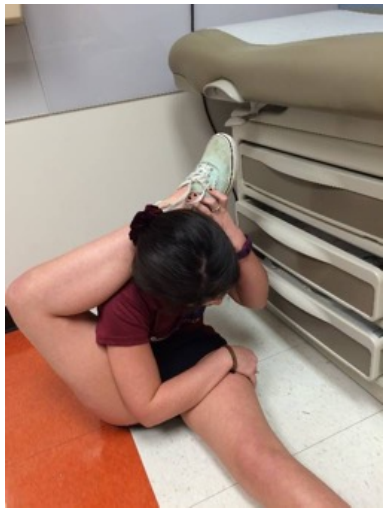


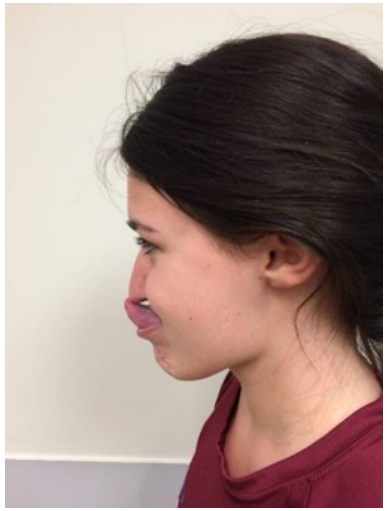
Hypermobility (2017): ≥ 6 in pre-pubertal children, ≥ 5 in pubertal children & adults up to age 50, ≥ 4 over 50 yrs

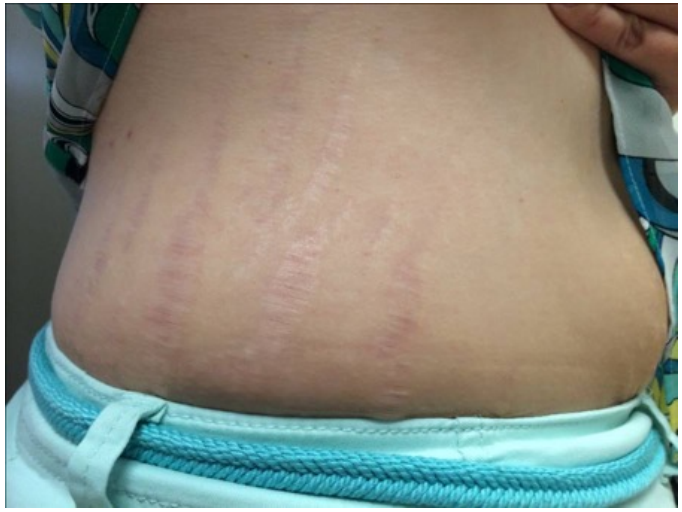


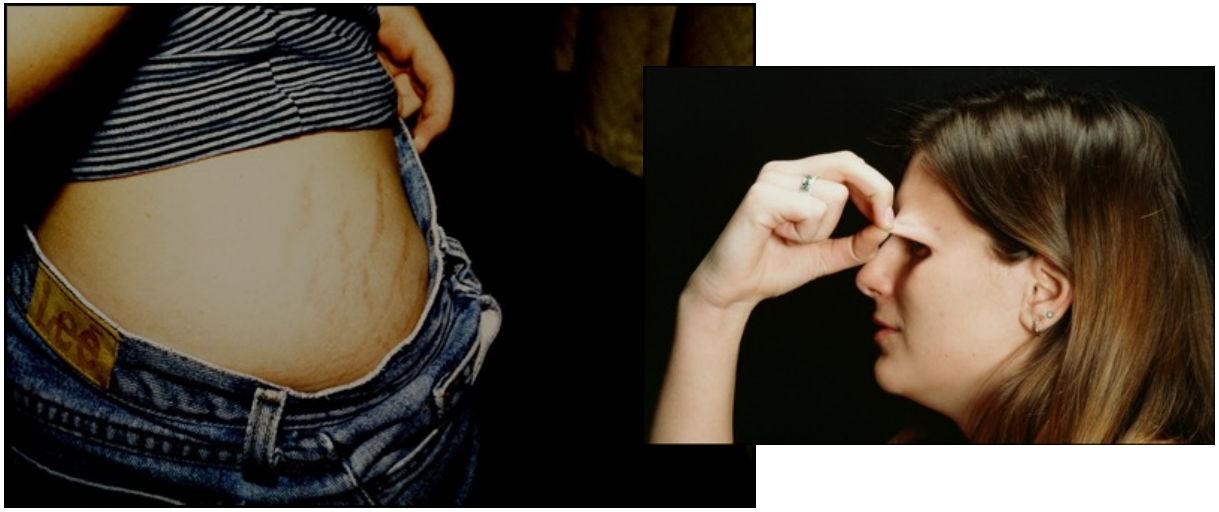


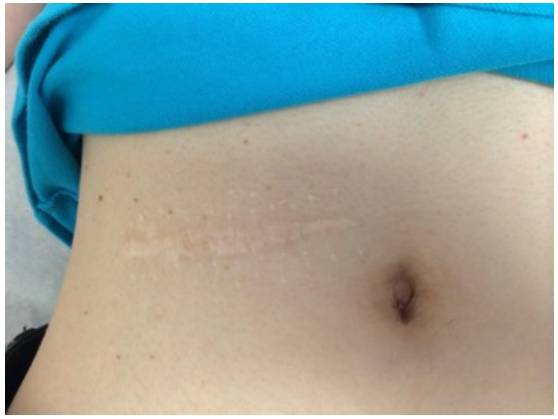


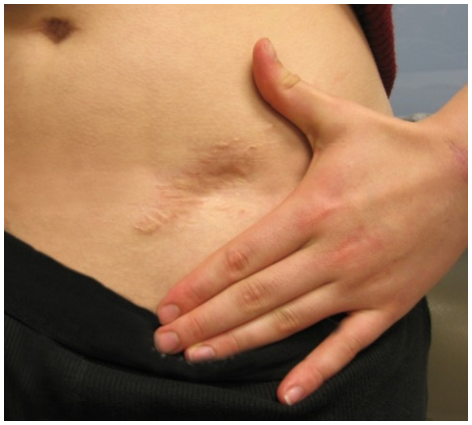


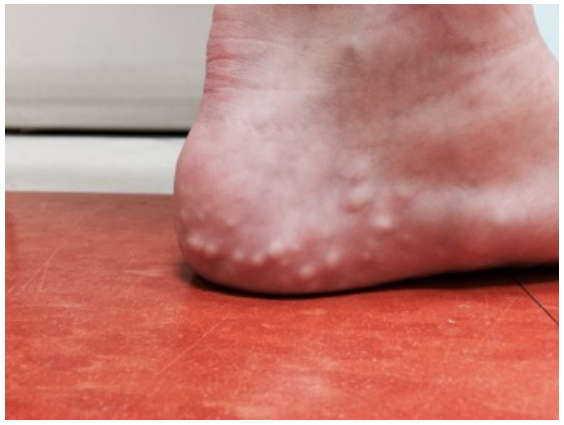





Lee





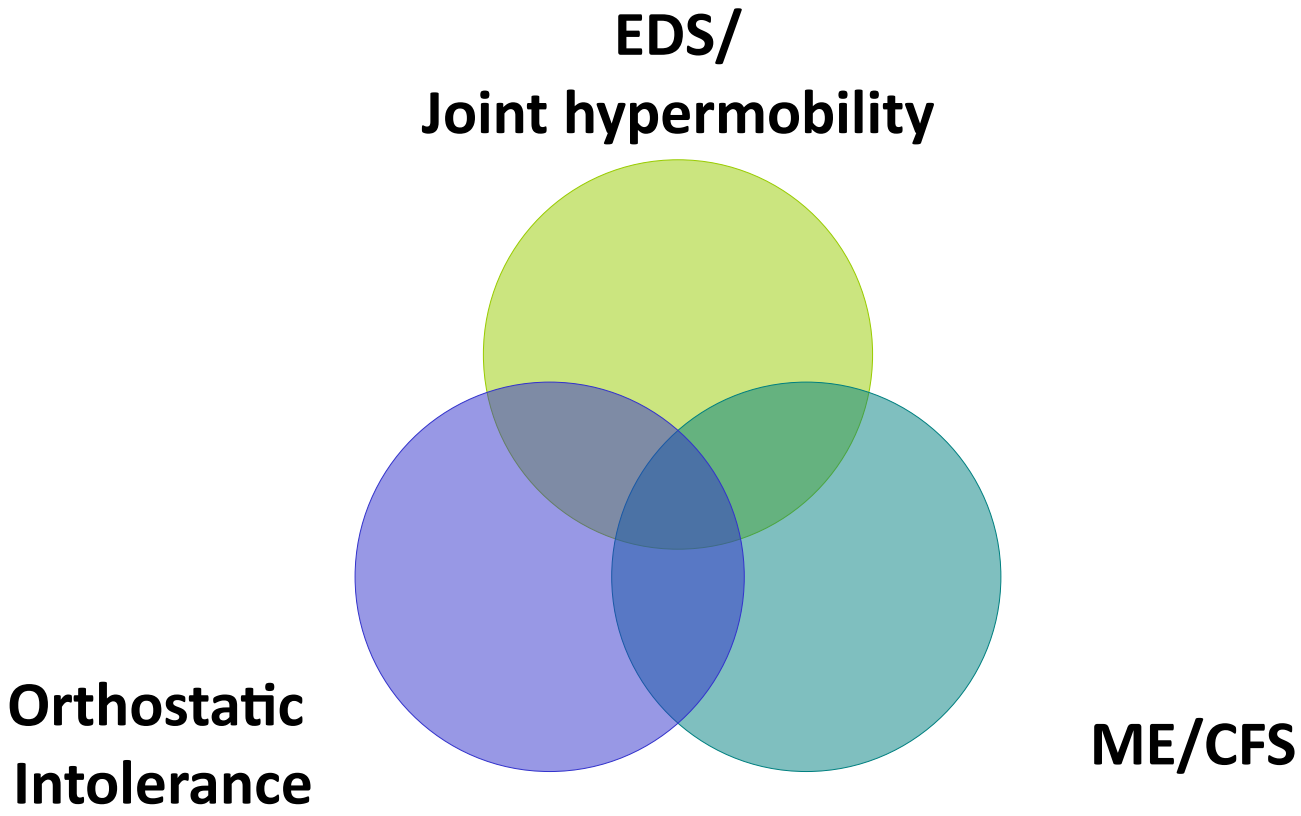


Sex and joint hypermobility

Country	Ages	Males	Females	P
USA (1987) N=260	5-17	7%	18%	<.005
Israel (1991) N=429	6-14	8%	18%	< .005
USA (1997) N=264 athletes	12-19	6%	22%	<.001
Iceland (1999) N=267	12	13%	41%	<.001

"*The striking preponderance of affected women vs. men in EDS-HT is presently unexplained.*"

de Paepe A, Malfait F. The Ehlers-Danlos syndrome, a disorder with many faces. Clin Genetics 2012;82:1-11.


EDS/
Joint hypermobility
Orthostatic
Intolerance
ME/CFS

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

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

J Pediatr 1999;135:513.

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

6 classical-type, 6 hypermobile-type EDS

11 females, 1 male

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

EDS features in 12 patients with ME/CFS

Median Beighton score = 7 (range 5-9)

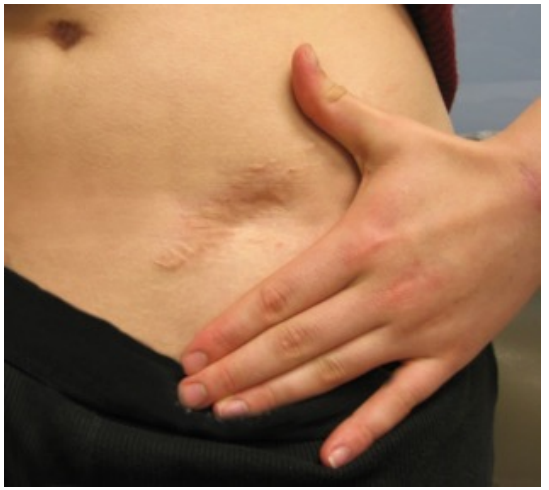
Joint dislocations in 12/12

Joint surgery in 3/12

Acrocyanosis in 12/12

Localized skin hyperextensibility (most commonly eyelid) in 12/12

Papyraceous scars in 6/12



Joint hypermobility is more common in children with chronic fatigue syndrome than in healthy controls

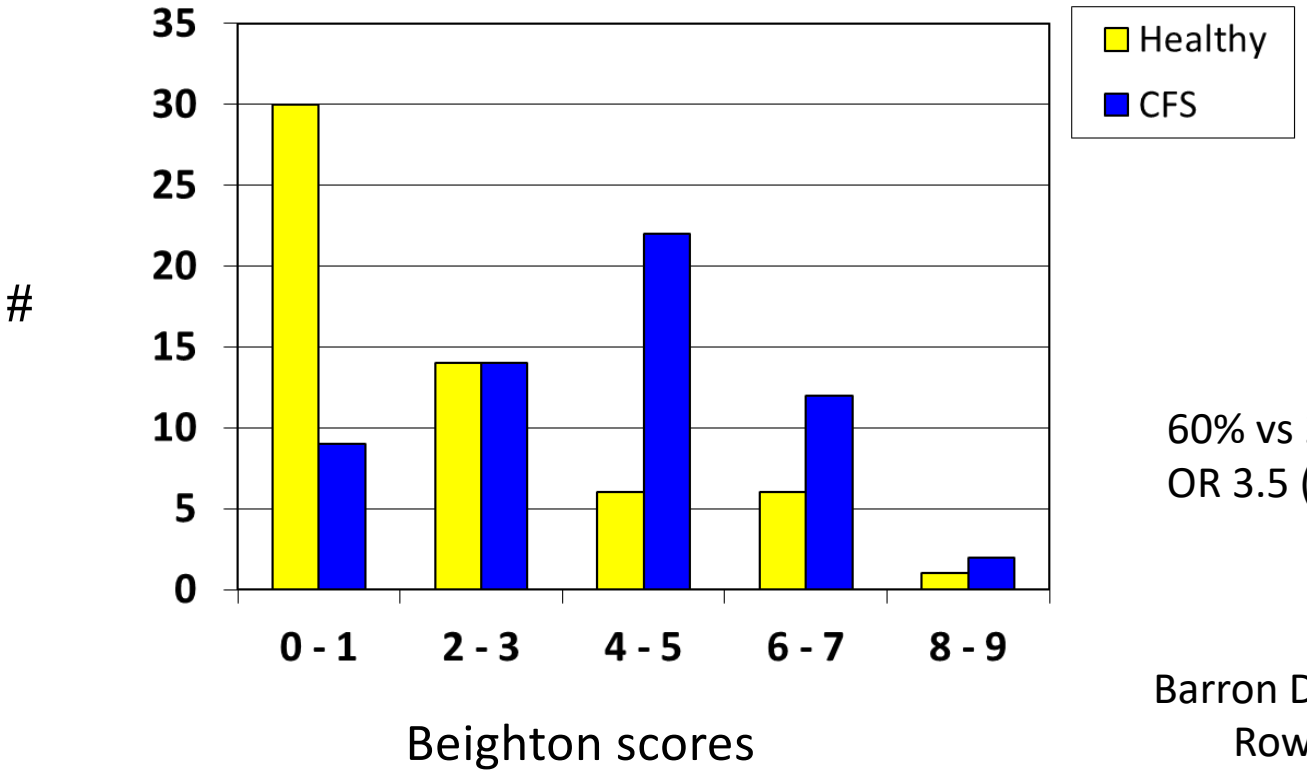
Diana F. Barron, MS, CPNP, Bernard A. Cohen, MD, Michael T. Geraghty, MB, MRCPI
Rick Violand, PT, and Peter C. Rowe, MD

Study question: do children with CFS have a higher prevalence of joint hypermobility?

Beighton scores obtained in 58 new & 58 established CFS patients, and in 58 controls

J Pediatr 2002;141:421-5

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

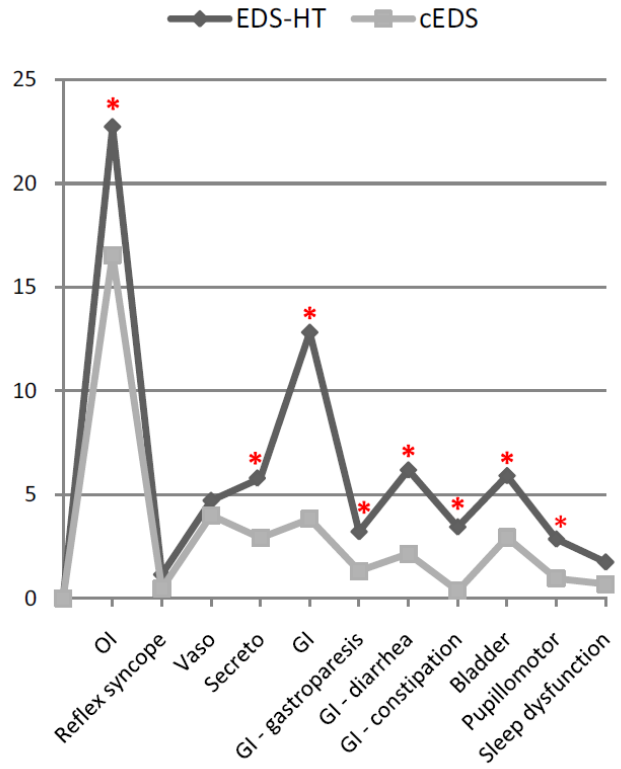


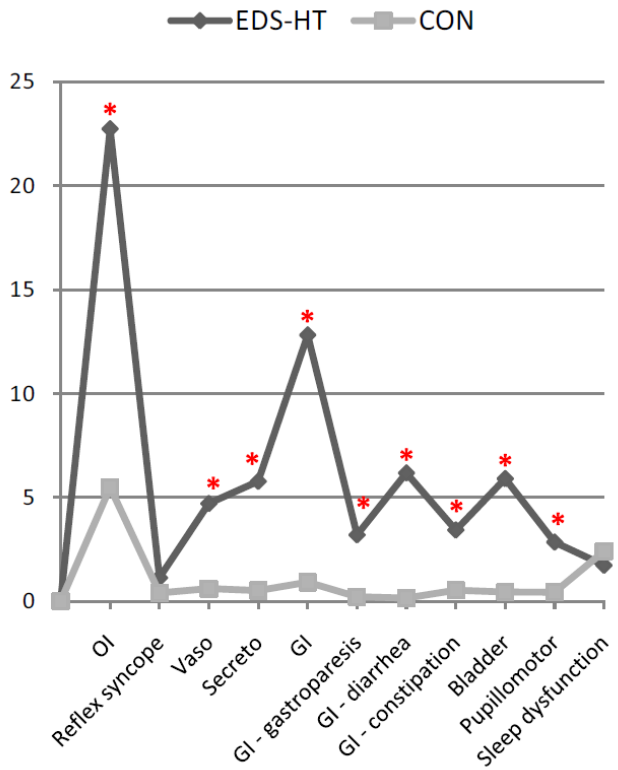
60% vs 24%, P < .0001
OR 3.5 (95% CI, 1.6-7.5)

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

Autonomic symptom profile scores in EDS

De Wandele I, et al. Seminars Arth Rheum 2014;44:353-61





Further evidence of the association between JH and ME/CFS

- Nijs J, et al. J Manipulative Physiol Ther 2006;29:32- 39)
  - Compared with the healthy volunteers (4.3%, 3/68), significantly more patients with CFS (20.6%, 14/69) fulfilled the criteria for generalized joint hypermobility (Fisher exact test, $P < 0.004$).
- Eccles JA, et al. Clinical Medicine 2021 Vol 21, No 1: 53–8
  - Among 63 adults meeting criteria for ME/CFS or Fibromyalgia, endorsing hEDS criterion 1 (age/sex adjusted Beighton score) significantly predicted presence of ME/CFS as defined by Canadian criteria (p=0.045; OR 3.07; 95% CI 1.01–9.28) and the Fukuda criteria (p=0.031; OR 3.70; 95% CI 1.12–12.18).

Proposed mechanisms for the association of JH/EDS and OI

1. Connective tissue laxity in blood vessels allows increased vascular compliance, promotes excessive pooling during upright posture, leading to diminished blood return to the heart, and thus to OI symptoms.

   (Rowe PC, et al. J Pediatr 1999;135:494-9)

2. Physical inactivity as a result of joint dislocations and pain "may be disabling due to associated anxiety, depression, and a somatosensory amplification state; this may lead to secondary hypersympathetic responses triggered by fear of pain on standing." (Benarroch EE. Mayo Clin Proc 2012;87:1214-25)
3. Peripheral neuropathy (Gazit et al. Am J Med 2003;115:33-40)
4. Could the excessive mobility of the cervical cord lead to transient, dynamic compression and autonomic symptoms? (Holman AJ. Fibromyalgia Frontiers 2012)
5. Mast cell activation syndrome (MCAS) is more common in JH/EDS
6. Other shared factor

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

The Presentation of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Is Not Influenced by the Presence or Absence of Joint Hypermobility

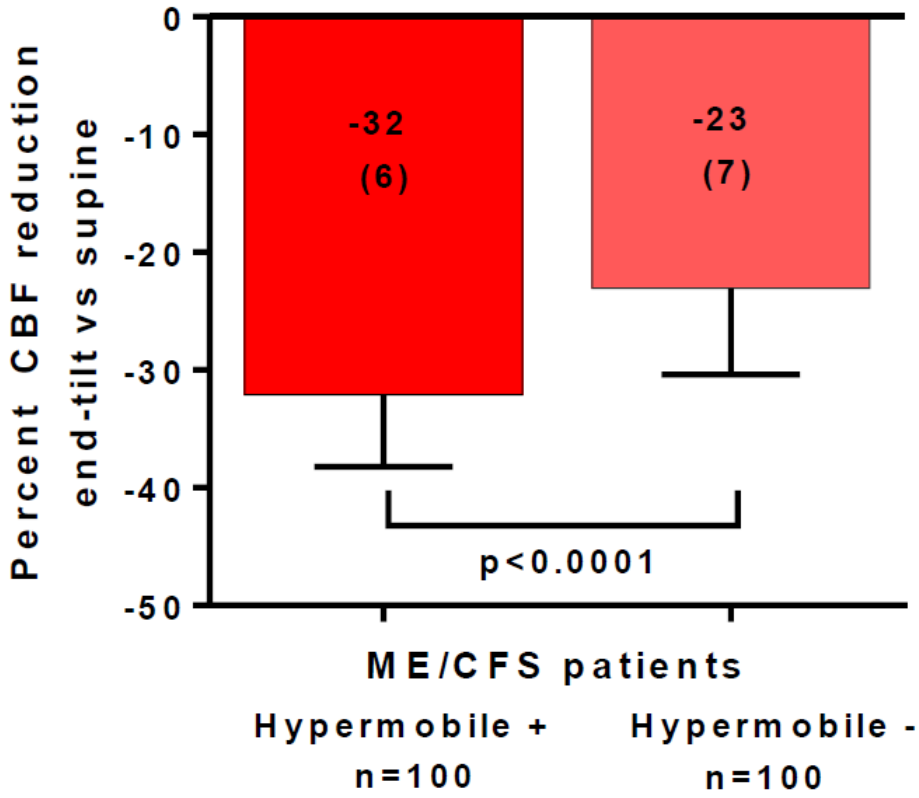
Sarah K. Vogel, BSc[1,*], Isabelle R. Primavera[1,*], Colleen L. Marden, BA[1], Samantha E. Jasion, OT[1], Erica M. Cranston, MD[1], Marissa A. K. Flaherty, MD[1], Richard L. Violand, PT[2], and Peter C. Rowe, MD[1]

55 with ME/CFS, divided into 2 groups, 27 JH neg, 28 JH pos (BS $\geq$ 4)

No significant difference in:

- Age at onset of ME/CFS
- Type of onset (abrupt vs gradual)
- ME/CFS symptoms
- Presence of orthostatic intolerance
- Co-morbid conditions
- HRQOL

Maybe not the end of the story …



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

Reasons to look for EDS and JH in the clinical care of those with ME/CFS

1. To improve general clinical management
2. To detect rare forms of EDS (Vascular EDS)
3. To ensure provision of appropriate physical therapy care
4. To provide a unifying diagnosis for patients

Modified from: Maria Roma, Colleen L. Marden, Inge De Wandele, Clair A. Francomano, Peter C. Rowe. Postural tachycardia syndrome and other forms of orthostatic intolerance in Ehlers-Danlos syndrome. Autonomic Neuroscience: Basic and Clinical 2018; 215: 89-96.

Non-articular disorders associated with JH

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

Adapted from Castori M. ISRN Dermatology 2012

Received: 4 October 2021 | Accepted: 16 October 2021
DOI: 10.1002/ajmg.c.31949

REVIEW ARTICLE

AMERICAN JOURNAL OF medical genetics PART C Seminars in Medical Genetics WILEY

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

Wilhelm Sandmann[1] | Thomas Scholbach[2] | Konstantinos Verginis[3]

[1]Section of Vascular Surgery, Clinic Bel Etage, Duesseldorf, Germany

[2]Outpatient Clinic for Children and Adolescents, Unit for Special Functional Examination with Ultrasound Duplex Sonography, Leipzig, Germany

[3]EVK Mettmann, Academic Teaching Hospital, University of Duisburg-Essen, Mettmann, NRW, Germany

Hypermobility associated with:
MALS
Nutcracker syndrome
SMA syndrome
May Thurner
Pelvic congestion syndrome

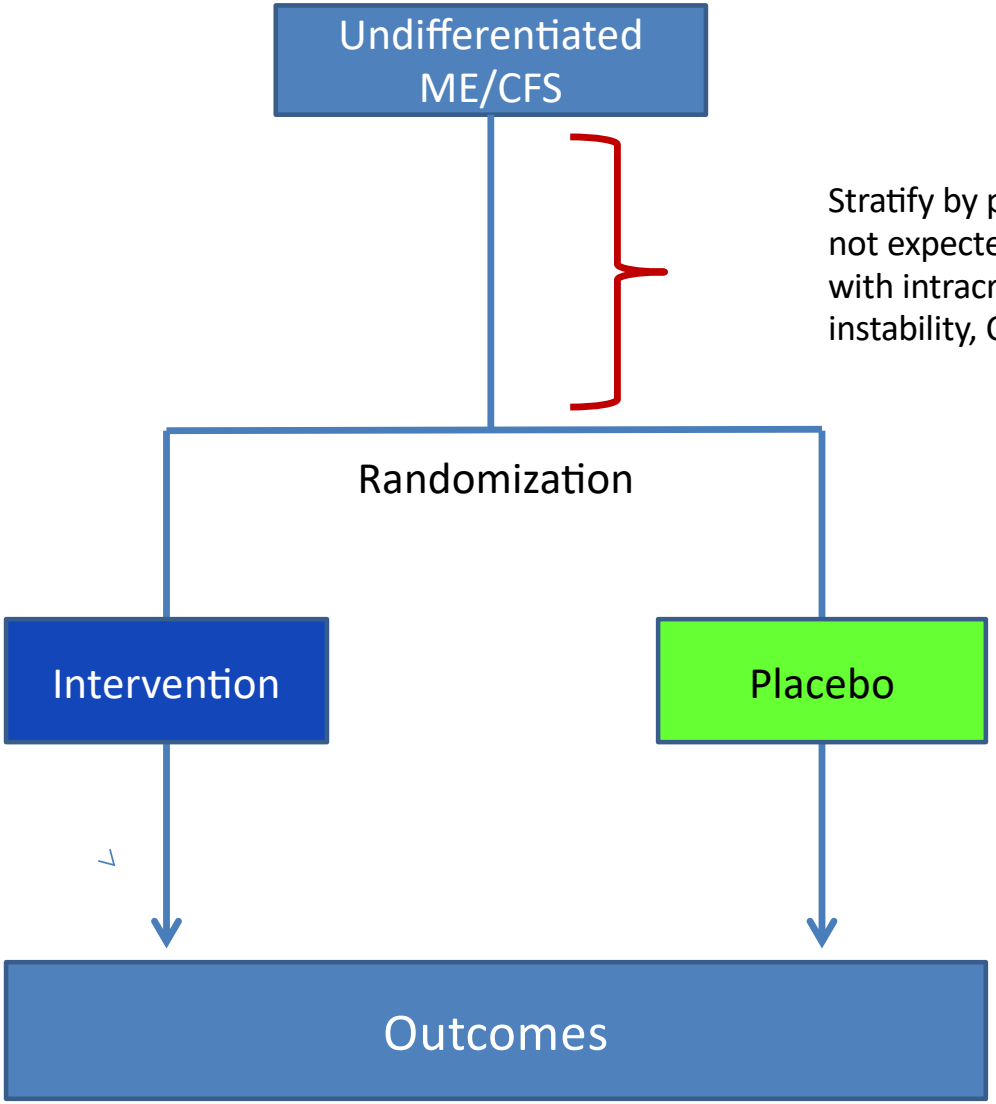
Reasons to look for EDS and JH in the clinical care of those with ME/CFS

1. To improve general clinical management
2. To detect rare forms of EDS (Vascular EDS)
3. To ensure provision of appropriate physical therapy care
4. To provide a unifying diagnosis for patients

Reasons to look for EDS and JH in research studies of ME/CFS

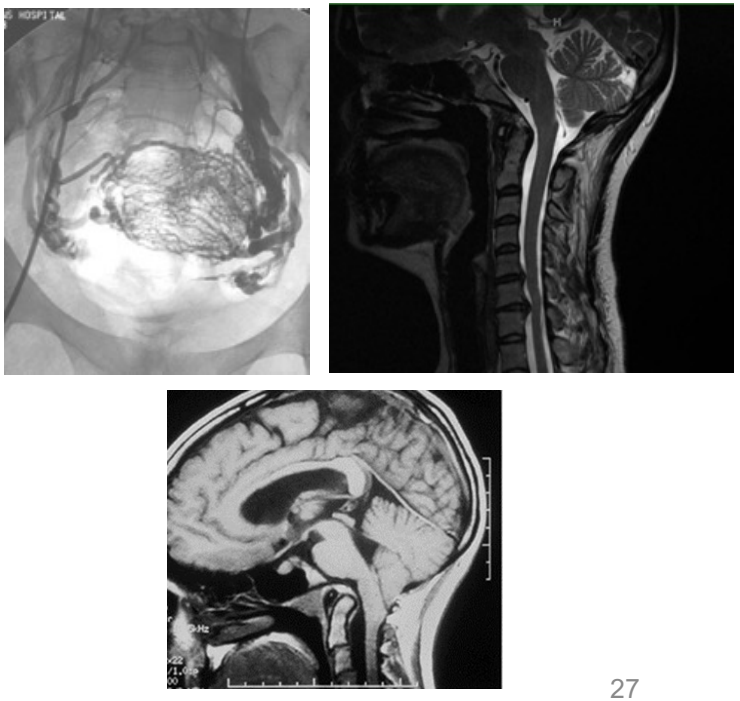
1. To accurately describe the clinical features of study populations
2. To reduce biased assignment to subgroups in pathophysiology studies
3. To reduce enrollment of potential non-responders in treatment studies
4. To prevent incorrect causal inferences

Modified from: Maria Roma, Colleen L. Marden, Inge De Wandele, Clair A. Francomano, Peter C. Rowe. Postural tachycardia syndrome and other forms of orthostatic intolerance in Ehlers-Danlos syndrome. Autonomic Neuroscience: Basic and Clinical 2018; 215: 89-96.



Enrichment approaches

Stratify by presence or absence of hEDS. Exclude sub-groups not expected to respond to the study intervention (e.g, those with intracranial hypotension, pelvic varicosities, cranio-cervical instability, Chiari, MCAS, etc)



Resources

- EDS Ehlers-Danlos Society
  http://ehlers-danlos.com/
- EDS Awareness for webinar talks on various topics of importance to EDS
  http://www.chronicpainpartners.com/
- Am J Med Genet C (Semin Med Genet). 2017;175C (entire issue on the 2017 classification and management of specific problems)

THANK YOU

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- Research Coordinator Colleen Marden and Nurse Renee Swope
- Summer students (John Fan, Alli Johns, Marissa Flaherty, Jocelyn Ray, Samantha Jasion, Erica Cranston, Megan Lauver, Maria Roma)
- Rowe's Research Runners
- Many, many families and patients