# Ehlers-Danlos Syndrome and the Overlap with Orthostatic Intolerance

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## Ehlers-Danlos Syndrome

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

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

## Presenter Disclosure Information

Peter C. Rowe, MD

- No relationships to disclose

## Ehlers-Danlos Syndrome

- Prevalence unknown, estimated at 1:5000
- 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.

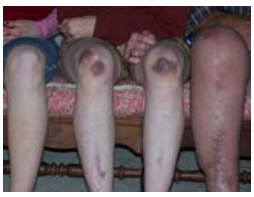
## EDS, JH, and Orthostatic Intolerance

Overview of Ehlers-Danlos Syndrome
Illustrative case
Orthostatic intolerance in EDS and JH
Challenges

## Classification of EDS

Beighton P, et al. Am J Med Genetics 1998;77:31-7.

Classical
(formerly EDS I and II)
Hypermobility
(formerly EDS III)
Vascular
(formerly EDS IV)
Kyphoscoliosis
Arthrochalasia
Dermatosparaxis



3 generations with Classical EDS. Note hemosiderin deposition in knees and shins, varicose vein stripping on R

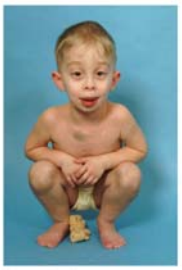


*Fig. 5.* Patient with Ehlers–Danlos syndrome, dermatosparaxis type. Note the typical facial appearance with epicanthic folds, downslanting palpebral fissures, blue sclera, micrognathia, prominent lips and facial scars especially around the mouth. There is a large bruise on the thorax from minor trauma.

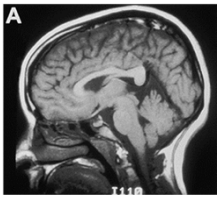
*Fig. 8.* Patient with Ehlers–Danlos syndrome, musculocontractural type, showing craniofacial dysmorphism with malar hypoplasia, downslanting palpebral fissures, blue sclera and microcornea, long philtrum with thin upper lip and protruding jaw with pointed chin.

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

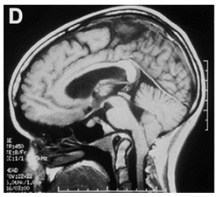
J Neurosurg Spine 7:601–609, 2007

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

Thomas H. Milhorat, M.D.,[1] Paolo A. Bolognese, M.D.,[1] Misao Nishikawa, M.D.,[1] Nazli B. McDonnell, M.D., Ph.D.,[2] and Clair A. Francomano, M.D.[3]




Normal brain MRI




Chiari and basilar impression

## Updated EDS Classification

| EDS subtype | Inheritance pattern | Protein | Gene |
|---|---|---|---|
| Classic | AD | Procollagen type V | *COL5A1/COL5A2* |
| | | Procollagen type I | *COL1A1* |
| | AR | Tenascin-X | *TNX-B* |
| Cardiac-valvular | AR | Deficiency of α2(I) collagen chain | *COL1A2* |
| Hypermobility | AD | Unknown | ? |
| | | (Tenascin X) | *TNX-B* |
| Vascular | AD | Procollagen type III | *COL3A1* |
| Vascular-like | AD | Procollagen type I (R-to-C) | *COL1A1* |
| Kyphoscoliotic | AR | Lysyl hydroxylase-1 | *PLOD1* |
| Musculocontractural | AR | Dermatan-4-sulfotransferase-1 | *CHST14* |
| Spondylocheirodysplastic | AR | ZIP13 | *SLC39A13* |
| Brittle cornea syndrome | AR | ZNF469 | *ZNF469* |
| | | PRDM5 | *PRDM5* |
| Arthrochalasis | AD | Procollagen type I (deletion of N-propeptide cleavage site) | *COL1A1/COL1A2* |
| EDS/OI overlap | AD | Procollagen type I (delay in N-propeptide cleavage) | *COL1A1/COL1A2* |
| Dermatosparaxis | AR | Procollagen-I-N-proteinase | *ADAMTS2* |

AD, autosomal dominant; AR, autosomal recessive; EDS, Ehlers–Danlos syndrome.

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

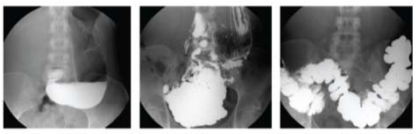


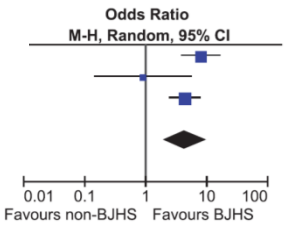

Figure 4: Visceroptosis of the gut in a 40-year-old woman with severely debilitating gastrointestinal functional complaints. Note marked gastroptosis (a) and pelvic localization of the small bowel (b) and transverse colon (c).

## Presentations suggestive of EDS

| | |
|---|---|
| Joints: | Hypermobility, Dislocations, Pain |
| Skin: | Bruising, Hyperextensibility, Atrophic scars, Striae |
| Vessels/hollow organs: | Rupture, Sudden death |
| Other features: | GI dysmotility, Kyphoscoliosis, Chiari, Pneumothorax, Organ ptosis or prolapse |

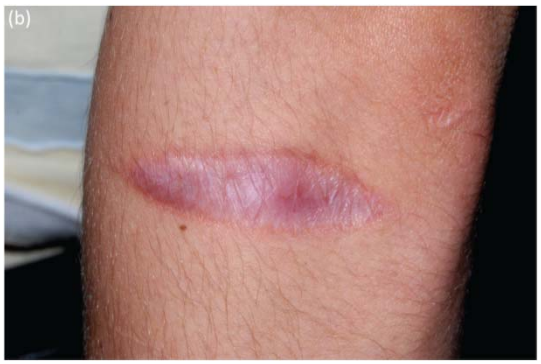
Sobey G. Clinical Medicine 2014;14:432; Castori M. ISRN Dermatology 2012

## BJHS and psychological distress: a systematic review and meta-analysis.




OR for anxiety 4.39
(95% CI 1.92, 10.40)

Smith TO et al. Rheumatology 2013




Sobey G. Clinical Medicine 2014;14: 432

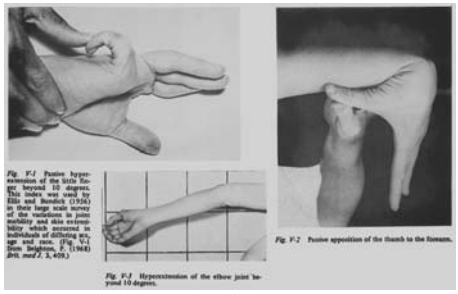
## Gender and EDS

*"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.

Beighton score (possible scores 0-9):

On each side, 1 point for > 90° hyperextensibility of 5th finger, 1 point for thumb to forearm, and 1 for > 10° hyperextensibility at elbow



## Gender 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 |

On each side, 1 point for >10° hyperextensibility at knees; 1 point for palms to floor

**TABLE I. The 1998 Brighton Criteria for a Diagnosis of Benign Joint Hypermobility Syndrome [Grahame et al., 2000]**

Major criteria
- (1) Beighton score of ≥4/9
- (2) Arthralgia for >3 months in >4 joints

Minor criteria
- (1) Beighton score of 1–3
- (2) Arthralgia in 1–3 joints
- (3) History of joint dislocation
- (4) Soft tissue lesions >3
- (5) Marfan-like habitus
- (6) Skin striae, hyperextensibility, or scarring
- (7) Eye signs, lid laxity
- (8) History of varicose veins, hernia, visceral prolapse

For a diagnosis to be made either
- Both of the major criteria must be present
- OR one major and two minor
- OR four minor
- AND other disorders of connective tissue need be excluded

AMERICAN JOURNAL OF medical genetics

## The Lack of Clinical Distinction Between the Hypermobility Type of Ehlers–Danlos Syndrome and the Joint Hypermobility Syndrome (a.k.a. Hypermobility Syndrome)

Brad T. Tinkle,[1]* Howard A. Bird,[2] Rodney Grahame,[3] Mark Lavallee,[4] Howard P. Levy,[5] and David Sillence[6]

Am J Med Genet Part A 149A:2368–2370.

It is our collective opinion that BJHS/HMS and EDS hypermobility type represent the same phenotypic group of patients that can be differentiated from other HCTDs but not distinguished from each other. Clinically, we serve this population better by uniting the two diagnostic labels.

## 24 yr old with fatigue, LH, warmth

No syncope, but vision goes black, hearing distant

Brings knees to chest when seated; studies lying down; stays in motion when standing

Hands and feet often appear purple

Sensation of warmth or heat when upright for long periods

## EDS, JH, and Orthostatic Intolerance

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Challenges

## 24 yr old with fatigue, LH, warmth

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

Energy fairly good

Shoulders sublux easily

HR 60 supine in early AM, 90s during day

Normal mood; laid-back disposition

## 24 yr old with fatigue, LH, warmth

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

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

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

## 24 yr old with fatigue, LH, warmth

O/E: Tall, thin young woman

Wt 62 kg; ht 180.2 cm (>97$^{th}$); BMI 19.1

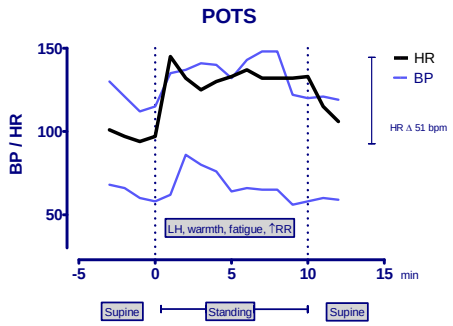
Easy eversion of lids; + Gorlin's sign; can touch tongue to elbow, place leg behind head

BS = 7/9; no arachnodactyly

Lordotic posture

Cardiac exam normal

Echo and labs normal




## Course

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

## Possible treatments

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

## Course

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

## What we tried:

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

## EDS, JH, and Orthostatic Intolerance

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**Is neurally mediated hypotension an unrecognised cause of chronic fatigue?**

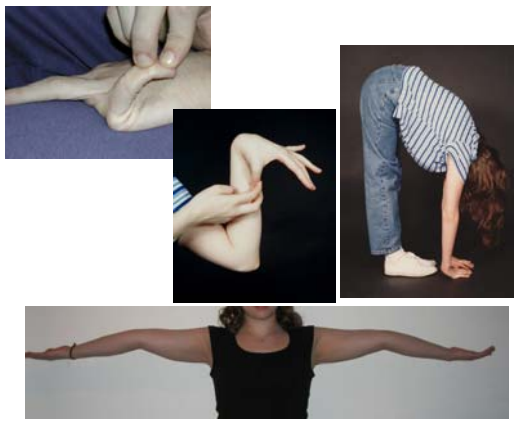
*Peter C Rowe, Issam Bou-Holaigah, Jean S Kan, Hugh Calkins*

*Lancet* 1995; **345:** 623–24

The Relationship Between Neurally Mediated Hypotension and the Chronic Fatigue Syndrome

Issam Bou-Holaigah, MD; Peter C. Rowe, MD; Jean Kan, MD; Hugh Calkins, MD

*JAMA* 1995;274:961-7



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

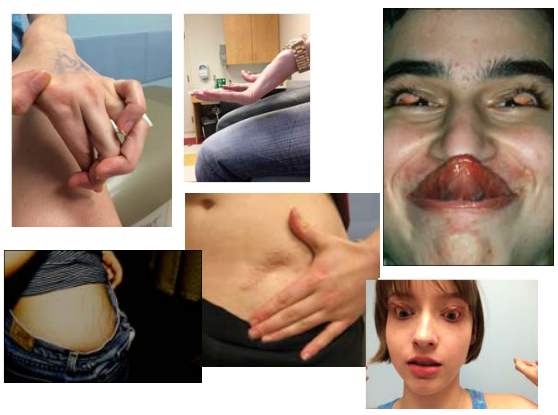
*Peter C. Rowe, MD, Diana F. Barron, MS, Hugh Calkins, MD, Irene H. Maumenee, MD, Patrick Y. Tong, MD, PhD, and Michael T. Geraghty, MB, MRCPI*

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

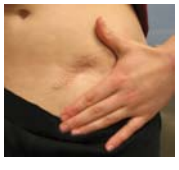
11 females, 1 male

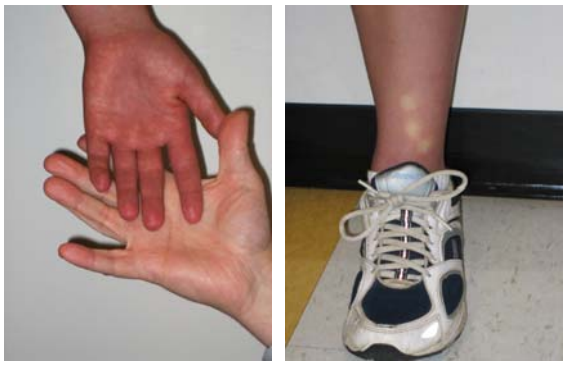
J Pediatr 1999;135:494-9



EDS features in 12 patients with 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





## EDS In CFS Patients With Orthostatic Intolerance

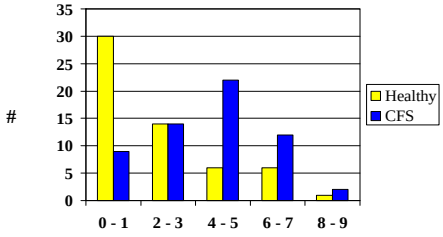
5 had at least 3 episodes of syncope

7 had lightheadedness, but no syncope

NMH in 9/12, POTS in 10/12

Rowe PC, Barron DF, Calkins H, Maumanee IH, Tong PY, Geraghty MT. J Pediatr 1999;135:494-9

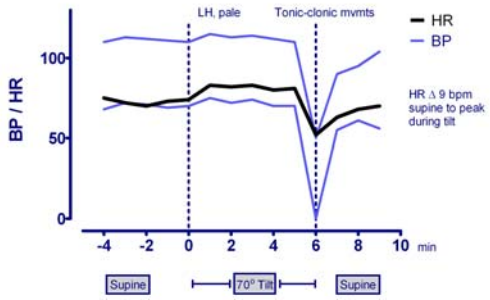
## Beighton Joint Hypermobility Scores in 58 Adolescents With CFS And 58 Healthy Controls




Beighton scores

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

## Young adult with EDS (patellar dislocations, pneumothoraces, CFS, recurrent syncope)




## Dysautonomia in Adult JHS

- Subjects:
  - 48 consecutive patients with joint hypermobility syndrome
  - 30 healthy controls
- Methods
  - Questionnaire of symptoms
  - Autonomic testing in a subset

Gazit et al. Am J Med 2003;115:33-40

## 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

Median Beighton scores higher in CFS (4 vs. 1)

Beighton score $\geq$ 4 higher in CFS (60% vs. 24%)

J Pediatr 2002;141:421-5

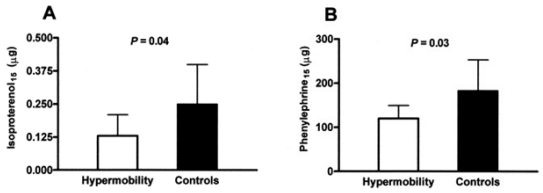
## Dysautonomia in JHS: Results

- OI symptoms more common in JHS patients
  - LH, syncope, palpitations, fatigue, impaired concentration, dyspnea, tremulousness, nocturia
- OI more common
  - 78% of JHS vs. 10% of controls had OI
    - Mix of OH, POTS and uncategorized OI
  - Standing time: 14.5 (6) vs. 19 (3.5) min

Gazit et al. Am J Med 2003;115:33-40

## Dysautonomia in JHS

Gazit et al. Am J Med 2003;115:33-40




**Dose to increase HR 15 bpm**

**Dose to increase SBP 15 mm Hg**

## Dysautonomia in EDS and controls

De Wandele I, et al. Seminars Arth Rheum 2014

| | Control | EDS-HT | p |
|---|---|---|---|
| Orthostatic grading scale | | | |
| Frequency | 0.6 ± 0.69 | 1.9 ± 1.14 | <0.001[a,c] |
| Intensity | 0.8 ± 0.51 | 2.2 ± 1.00 | <0.001[a,c] |
| Standing time | 0.1 ± 0.56 | 1.6 ± 1.12 | <0.001[a,c] |
| Other conditions (heath and exercise) | 0.1 ± 0.23 | 1.6 ± 1.12 | <0.001[a,c] |
| Daily life interference | 0.0 ± 0.19 | 1.8 ± 0.93 | <0.001[a,c] |
| Total score | 1.6 ± 1.44 | 9.0 ± 3.63 | <0.001[a,c] |

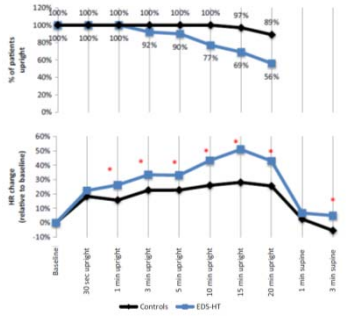
## Differences between POTS+JH vs POTS alone

| Feature | POTS+JH N=26 | POTS alone N=39 | P |
|---|---|---|---|
| Age (yrs) | 30±13 | 40±11 | .01 |
| Female gender | 100% | 90% | .07 |
| Migraine | 73% | 28% | .001 |
| Syncope | 62% | 30% | .04 |
| Viral onset | 0% | 15% | .07 |

From: Kanjwal K, et al. Indian Pacing and Electrophysiology J. 2010;10:173-8

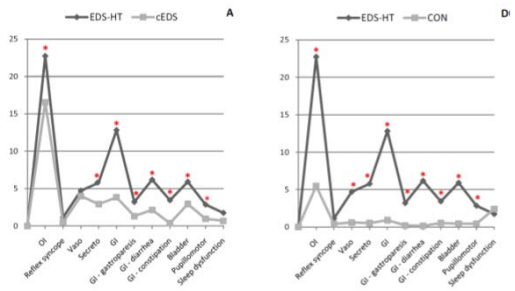
## Response to tilt

De Wandele I, et al. Seminars Arth Rheum 2014




## Autonomic symptoms in EDS and controls

De Wandele I, et al. Seminars Arth Rheum 2014




## Proposed mechanisms for the association of JH/EDS and OI syndromes

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. Other shared factor

**Mendelian inheritance of elevated serum tryptase associated with atopy and connective tissue abnormalities**

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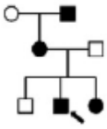

## Conclusions

- Females have a higher prevalence of JH and EDS-hypermobile type than males
- CFS patients with OI have an increased prevalence of EDS and JH
- Dysautonomia and OI are more common in those with EDS/JH
- Subjects with POTS + JH present earlier
- The mechanisms for the association between JH/EDS and OI syndromes are not known
- Improvement is common and recovery can occur

## What about prognosis in EDS with POTS?

- 16 yr old who had been a healthy dancer and swimmer, develops LH at 12.
- HR 78 to 125, SBP 104 to 84 with presyncope at 7 min of HT
- Beighton score=7/9
- Blue sclerae, Gorlin sign, snapping scapula.
- Wellness score in 2010=40/100

## ACKNOWLEDGEMENTS

- Grants from NIAID, DoD, CFIDS Association of America
- Sunshine Natural Wellbeing Foundation (endowed Chair)
- Volunteer RA Colleen Marden
- Summer students (John Fan, Alli Johns, Marissa Flaherty, Jocelyn Ray, Samantha Jasion, Erica Cranston)
- Many families and patients:
  - Special thanks to the following:
    Boies, Bowen, Caldwell, Cornell, Kelly, Kiely, McFerron, Newbrand, Smith
  - Megan Lauver, Hannah Vogel

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## Recovery in EDS,CFS, POTS

With PT, extra salt and fluids, meds, gradually improves over 2 years.

Able to resume dance, hikes 6-7 miles.

Joins ROTC, (72 sit-ups in 2 min., 38 push-ups in 2 min., 2 mile run)

Off all meds by 2 ½ yrs.

Approved for military.