Too Tired
EDS and Fatigue

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Fatigue by any other name

- Tired
- Bushed
- Listless
- Exhaustion
- Beat
- Pooped

- **THE ENEMY**

Defining fatigue

Fatigue

- Being overtired
- Temporary
- Usually has an identifiable cause and remedy
- Not the same as sleepiness
- May be physical and/or mental

Chronic Fatigue

- Lasts longer and is more profound
- Constant
- Develops over time
- Diminishes your energy and mental capacity
- Impacts emotional and psychological well-being

Chronic fatigue syndrome

- **Severe chronic fatigue for 6 or more consecutive months** and the fatigue is not due to ongoing exertion or other medical conditions associated with fatigue
- **The fatigue significantly interferes with daily activities and work**
- The individual concurrently has 4 or more of the following 8 symptoms:
  - **post-exertion malaise lasting more than 24 hours**
  - **unrefreshing sleep**
  - **significant impairment of short-term memory or concentration**
  - **muscle pain**
  - **pain in the joints without swelling or redness**
  - headaches of a new type, pattern, or severity
  - tender lymph nodes in the neck or armpit
  - a sore throat that is frequent or recurring
- *These symptoms should have persisted or recurred during 6 or more consecutive months of illness, and they cannot have first appeared before the fatigue.*

Box 1: Diagnostic criteria for chronic fatigue syndrome

Chronic fatigue lasting > 6 mo
plus at least 4 of the following:

- Subjective memory impairment
- Tender lymph nodes
- Muscle pain
- Joint pain
- Headache
- Unrefreshing sleep
- Postexertional malaise (> 24 h)

Scope of chronic fatigue

- May account 10-20% of the general population
- May account for ~1% of school absenteeism
- Affects people of any age
  - More common in adolescents than children
    - 31% of American adolescents experience significant morning tiredness more than one day a week [Ghandour et al., 2004]
- Affects females more often than males
- One of the leading causes of traffic accidents

Ghandour RM, Overpeck MD, HuangZJ, Kogan MD, Scheidt PC. Headache, stomachache, backache, and morning fatigue among adolescent girls in the United States: associations with behavioral, sociodemographic, and environmental factors. Arch Pediatr Adolesc Med 2004;158(8):797–803.

Symptoms of chronic fatigue

Physical

- Post-exertional
  - May be delayed several (up to 24) hours
- Non-refreshing sleep
- Aching/sore muscles
  - Widespread (Nishikai et al., 2001)
- Abdominal symptoms
- Painful lymph nodes
- Decreased immune response

Neurologic and psychological

- Moodiness
- Lack of motivation or apathy
- Impaired coordination
- Difficulty concentrating
- Short-term memory impairment
- Headaches
- Hallucinations

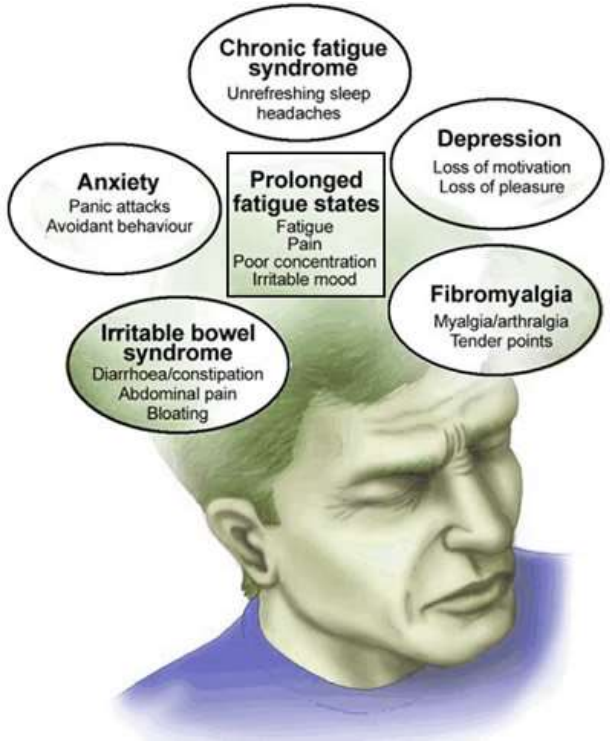
Causes of fatigue

- **Depression**
- Drug or alcohol abuse
- **Chronic sleep deprivation**
- Despair
- **Anxiety**
- **Electrolyte problems**
- Kidney disease
- Diabetes
- *Hypothyroidism*
- **Medications**
- Liver disease
- Asthma/lung disease
- Heart disease
- Infectious (e.g. TB, HIV, etc.)
- *Vitamin deficiencies*
- *Anemia*

Self-reported Use of Medication With Possible Sedative Side Effects	Number of EDS Patients
One or more analgesics with sedative side effects	62
Tramadol	14
Opiates/other opiate agonists	39
Codeine	22
Anti-epileptic drugs	3
Baclofen	2
One or more anti-depressive drugs with possible sedative side effects	38
One or more benzodiazepines	39
One or more β-blockers	6

Disorders associated with fatigue

- **Fibromyalgia**
- Rheumatoid arthralgia
- Multiple sclerosis
- Diabetes
- Cancer
- **Chronic pain**
- Lupus
- **Irritable bowel syndrome**
- **Anxiety**

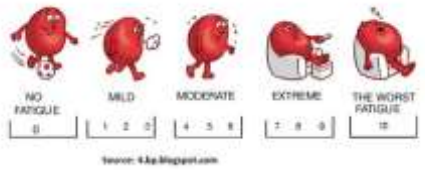


Double-dogged tired!!

- Connective tissue disorders *including* **EDS**

Evaluation

- History
  - Time of day
  - Effect of sleep
  - Alcohol or drug use
  - Exposures (TB, HIV, ticks)
- Medication review
- Fatigue questionnaire
  - e.g. Brief Fatigue Inventory
- Disability survey
- Quality of Life questionnaire



- Complete metabolic profile
  - CBC, liver, renal, calcium, thyroid, sed rate, c-reactive protein, random glucose, iron stores (ferritin), urinalysis, creatine kinase
- AM and PM cortisol levels
- Autonomic testing
- Formal sleep study
- *Myasthenia screen*
- *Infectious (TB skin test, mononucleosis, Lyme disease, HIV, etc.)*
- *Spinal tap*

Castori M, et al. Management of pain and fatigue in the joint hypermobility syndrome (a.k.a. Ehlers–Danlos syndrome, hypermobility type): Principles and proposal for a multidisciplinary approach. Am J Med Genet Part A 2012;158A:2055–70.

Mathias CJ, Low DA, Iodice V, Owens AP, Kirbis M, Grahame R. Postural tachycardia syndrome–current experience and concepts. Nat Rev Neurol 2011;8:22–34.

Increased injury rates in fatigue

- Muscle weakness [Sparto et al., 1997; Voermans and Knoop, 2011]
- Increased injury rate
  - Knee laxity [Skinner et al., 1986; Ortiz et al., 2010]
  - Knee and ACL injury [Gehring et al., 2009]
  - Postural sway/stability [Sparto et al., 1997; Dickin and Doan, 2008]
  - Decreased proprioception and falls [Celleti et al., 2012]

Celletti C, Galli M, Cimolin V, Castori M, Albertini G, Camerota F. Relationship between fatigue and gait abnormality in Joint Hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type. Research in Developmental Disabilities 2012;33:1914–18.
Dickin DC, Doan JB. Postural stability in altered and unaltered sensory environments following fatiguing exercise of lower extremity joints. Scand J Med Sci Sports 2008;18:765–72.
Ortiz A, Olson SL, Etnyre B, Trudelle-Jackson EE, Batlett W, Venegas-Rios HL. Fatigue effects on knee joint stability during two jump tasks in Women. J Strength Cond Res. 2010 April ; 24(4): 1019–1027.
Sparto P, Parnianpour M, Reinsel TE, Simon S. The effect of fatigue on multijoint kinematics, coordination, and postural stability during a repetitive lifting test. JOSPT 1997;25:3-12.

EDS/JH and Fatigue

Rowe et al., 1999

- Described 12 EDS patients (6 Classic/6 HM) with CFS and orthostatic intolerance (NMH/POTS)

Feature	Percent with
Fatigue >6 months	100%
Post-exertional malaise	100%
Unrefreshing sleep	100%
Impaired memory or concentration	92%
Multi-joint pain	83%
New headache	83%
Muscle pain	58%
Sore throat	25%
Tender cervical or axillary nodes	25%

Rowe PC, Barron DF, Calkins H, Maumenee IH, Tong PY, Geraghty MT. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. J Pediatr 1999;135:494-9.

Barron et al., 2002

- Fifty-eight consecutive children with chronic fatigue syndrome
  - 71% were female
  - Assessed only generalized joint hypermobility by using Beighton scoring
  - Average Beighton scores were higher than in healthy controls (4 vs 1, $P < .001$)
  - More CFS cases had Beighton scores ≥4 (60% versus 24%, $P < .0001$)
  - Odds ratio for hypermobility in CFS versus healthy controls was 3.5 ($P < .001$; 95% CI, 1.6-7.5)

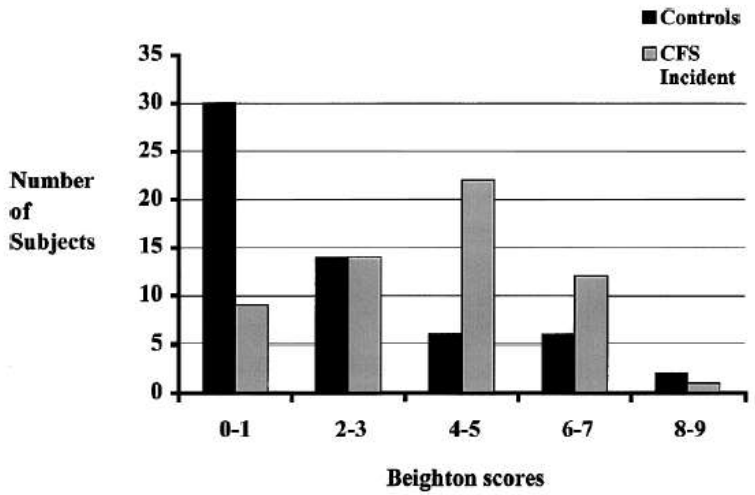


Figure. Distribution of Beighton joint hypermobility scores in 58 consecutive patients with CFS (incident cases) and 58 gender-matched controls with minor skin conditions. A score of 0 indicates no areas of joint hyperextensibility, and a score of 9 indicates a maximal number of hypermobile regions. Joint hypermobility is present if the Beighton score is ≥4.

Barron DF, Cohen BA, Geraghty MT, Violand R, Rowe PC. Joint hypermobility is more common in children with chronic fatigue syndrome than in healthy controls. J Pediatr 2002;141:421-5.

Gazit et al., 2003

- Forty-eight patients with JHS (hEDS)
- Underwent surveys and autonomic testing
  - Dizziness/lightheadedness 42 (88) v. 6 (20) controls ($p<0.001$)
  - Headache 36 (75) v. 17 (57) controls ($p<0.09$)
  - Impaired concentration 34 (71) v. 8 (27) controls ($p<0.001$)
  - Forgetfullness 24 (50) v. 7 (23) controls ($p<0.02$)
  - Irritability 29 (60) v. 7 (23) controls ($p<0.001$)
  - Confusion 14 (29) v. 1 (3) controls ($p<0.004$)
  - **Fatigue (physical) 34 (71) v. 10 (33) controls ($p<0.001$)**
  - **Fatigue (central) 32 (67) v. 6 (20) controls ($p<0.001$)**

Gazit Y, Menahem Nahir A, Grahame R, Giris Jacob G. Dysautonomia in the Joint Hypermobility Syndrome. Am J Med. 2003;115:33– 40.

Nijs et al., 2006

- Generalized joint hypermobility was more prevalent in patients with CFS than in matched healthy controls (21% versus 4%)
- 58.8% of CFS fulfilled criteria for JHS (hEDS)

- 56% of 402 patients in a chronic fatigue clinic had CFS and FM

Nijs J, Aerts A, De Meirleir K. Generalized joint hypermobility is more common in chronic fatigue syndrome than in healthy controls. Journal of Manipulative and Physiological Therapeutics 2006;29:32–9.

Nijsa J, Meeusa M, De Meirleira K. Chronic musculoskeletal pain in chronic fatigue syndrome: Recent developments and therapeutic implications. Manual Therapy 2006;11:187–91.

Tofts et al., 2009

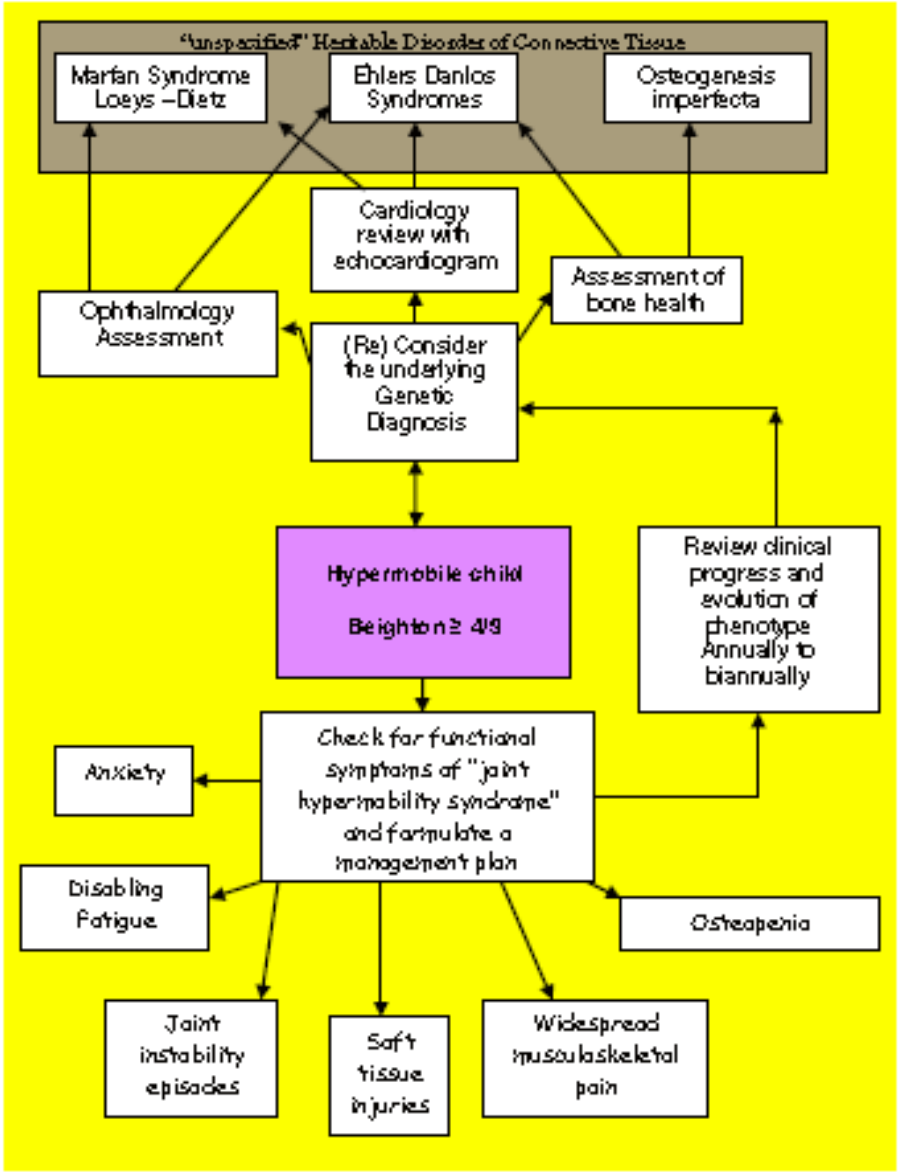


Figure 2
The connective tissue dysplasia clinic diagnostic approach to a child with hypermobile joints.

Tofts LJ, Elliott EJ, Munns C, Pacey V, Sillence DO. The differential diagnosis of children with joint hypermobility: a review of the literature. Pediatric rheumatology 2009;7:1.

Voermanns et al., 2010A

- Survey of 273 EDS patients
- Identified five possible determinants involved in **fatigue** in EDS predicting 38% of variance
  - Sleep disturbances
  - Concentration problems
  - Social functioning
  - Self-efficacy concerning fatigue
  - Pain severity

Table 1 Demographics of Ehlers-Danlos Syndrome Patients, Age and Sex Distribution of EDS Patients, and Distinction Between Nonseverely and Severely Fatigued Patients

Ehlers-Danlos Syndrome (EDS) Type	Number of Patients	Mean Age range (y)	Female n (%)	EDS Nonseverely Fatigued n (%)	EDS Severely Fatigued n (%)	Stat. Sign.[a] of Difference *P*
Classic (C)	45	43.1 (16 to 68)	35 (78)	14 (31)	31 (69)	C vs H 0.032
Hypermobility (H)	162	38.8 (16 to 74)	152 (94)	26 (16)	136 (84)	
Vascular (V)	11	33.6 (19 to 61)	9 (82)	5 (45)	6 (55)	
Kyphoscoliotic (K)	2	21.0 (16 to 26)	0 (0)	2 (100)	0 (0)	
Other/Type unknown	53	46.2 (19 to 89)	48 (91)	15 (28)	38 (72)	
Total	273	40.7 (16 to 89)	244 (89)	62 (23)	211 (77)	

[a]Fisher's exact test.

Voermans NC, Knoop H, van de KN, Hamel BC, Bleijenberg G, van Engelen BG. Fatigue is a frequent and clinically relevant problem in Ehlers-Danlos syndrome. Semin Arthritis Rheum 2010;40:267-74.

Voermans et al., 2010B

- Survey of 273 EDS patients
  - Chronic pain is highly prevalent
  - Pain is more prevalent and more severe in patients with the hypermobility type than in those with the classic type and vascular type
  - Pain severity is related to hypermobility, dislocations, and previous operations but not to other disease-related factors
  - Pain is related to sleep disturbances
  - Pain is related to functional impairment in daily life, independent of the level of fatigue
    - Pain and fatigue comprised 31% of the functional impairment

Table 3

Results of Multiple Regression Analysis of Pain and Fatigue, with Functional Impairment as Dependent Variable in all EDS patients ($n = 273$)

Dependent Variable: Functional Impairment (SIP Sum Score) in All EDS Patients			
Independent Variables		Beta	*P*
Pain	Most severe pain (VAS)	0.241	<0.001
Fatigue	CIS fatigue	0.392	<0.001
Enter: P in $= 0.05$; P out $= 0.1$; adjusted $R^2 = 0.309$			

Fatigue had a greater impact on functioning

Voermans NC, Knoop H, Bleijenberg G, van Engelen BG. Pain in Ehlers-Danlos syndrome is common, severe, and associated with functional impairment. Journal of Pain and Symptom Management 2010;40:370-8.

Kanjwal et al., 2010

All explained by POTS?

Kanjwal K, Saeed B, Karabin B, Kanjwal Y, Grubb BP. Comparative clinical profile of postural orthostatic tachycardia patients with and without joint hypermobility syndrome. Indian Pacing and Electrophysiology Journal 2010;10(4):173-8.

	POTS with JHS (N=26)	POTS without JHS (N=39)	*P*
Age(years)	30 ±13	40±11	**0.01**
Sex(Female)	26(100%)	35(90%)	**0.09**
Race (Caucasian %)	20(77%)	35(90%)	0.2
Comorbidity			
Migraine	19(73%)	11(28%)	**0.001**
Precipitating Event			
Trauma	0(0%)	2(5%)	0.5
Surgery	1(4%)	0(0%)	0.4
Pregnancy	3(12%)	2(5%)	0.4
Viral Infection	0(0%)	6(15%)	**0.07**
UTI	1(4%)	0(0%)	0.4
Symptoms			
Fatigue	15(58%)	23(59%)	1
Orthostatic palpitation	14(54%)	19(49%)	0.8
Dizziness/ presyncope	15(58%)	29(74%)	0.2
Syncope	16(62%)	13(30%)	**0.04**

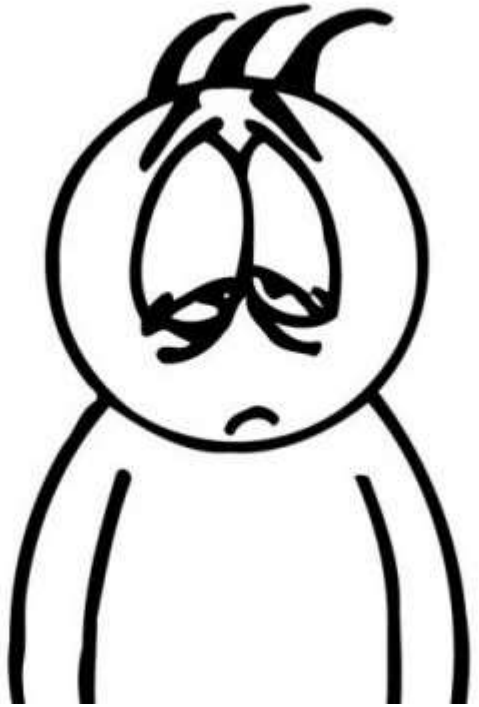
Voermanns et al., 2011

- Relationship of self-reported fatigue and muscle weakness
- 30 EDS patients
- Seventy-seven percent were severely fatigued (CIS fatigue score* ≥35)
  - Mean fatigue score was 41.5
    - Rheumatoid arthritis 34.2 (52% severe)
    - Healthy controls 17.3
- Fatigue severity was correlated with muscle weakness
  - $r = -0.408$ for manual muscle strength
  - $r = 0.461$ for hand-held dynamometry
  - $r = 0.603$ for self-reported muscle weakness
- Both muscle weakness and pain severity were significant predictors of fatigue severity

Voermans NC, Knoop H, Bleijenberg G, van Engelen BG. Fatigue is associated with muscle weakness in Ehlers-Danlos syndrome: an explorative study. Physiotherapy 97 (2011) 170–174.
*Fatigue severity subscale of the Checklist Individual Strength

Celletti et al., 2012

- Fatigue severity score mean score in our population shows a statistically significant difference if compared to those of normal healthy adults (6.2 0.9 versus 2.3 0.7; $p < 0.05$)
- Inability of muscles to generate or maintain force or power output during gait analysis
  - Loss of proprioception acuity

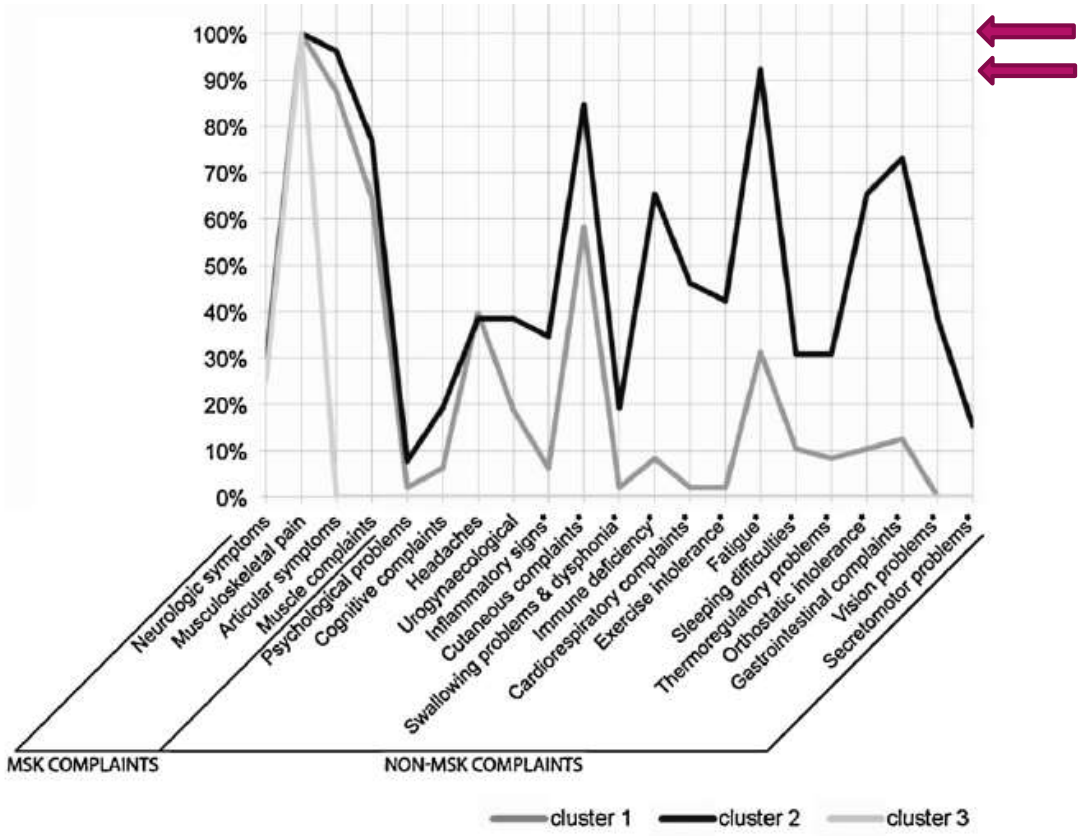


Celletti C, Galli M, Cimolin V, Castori M, Albertini G, Camerota F. Relationship between fatigue and gait abnormality in Joint Hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type. Research in Developmental Disabilities 2012;33:1914–18.

De Wandele et al., 2013

- Cluster analysis to look for hEDS subgroups
- Generated 3 clusters

- For those with other non-musculoskeletal complaints, fatigue was the most prevalent



Prevalence of all reported symptoms in each cluster.
*** Symptoms that are significantly more prevalent in cluster 2 than in cluster 1.**

De Wandele I, Rombaut L, Malfait F, De Backer T, De Paepe A, Calders P. Clinical heterogeneity in patients with the hypermobility type of Ehlers-Danlos syndrome. Research in Developmental Disabilities 2013;34:873–81.

Scheper et al., 2013

This suggests that despite greater physical fitness, those dancers with GJH had greater fatigue than controls

Does this argue against muscle weakness?

Does this argue for psychological factors?

Rombaut et al., 2012

- Forty-three women with hEDS compared to age- and gender-matched controls
- Showed substantial lower extremity muscle weakness
  - Significantly reduced knee extensor and flexor muscle strength and endurance parameters, with differences ranging from 30% to 49%
  - Reduced static muscle endurance time
  - Diminished functional performance
- **Lower extremity muscle mass was similar in both groups**
- Pain and fatigue dominated symptoms
- The hEDS group was physically impaired, especially in the functions of walking and bending

- Severely reduced quantitative muscle function and impairment in physical function in patients with hEDS compared to age- and sex-matched controls
  - The muscle weakness may be due to muscle dysfunction rather than reduced muscle mass

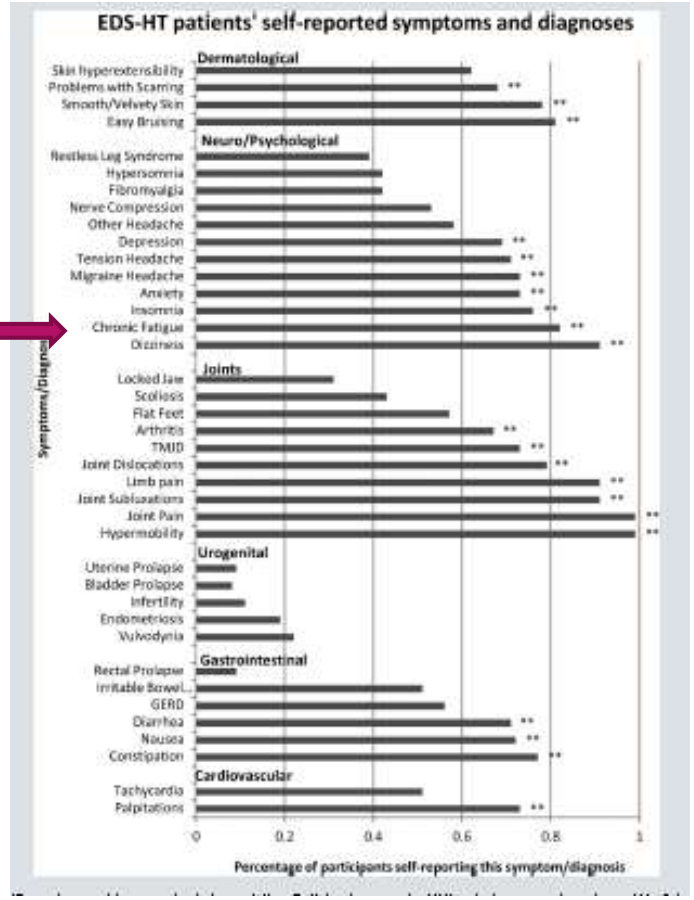
Rombaut L, Malfait F, De Wandele I, Taes Y, Thijs Y, De Paepe A, Calders P. Muscle mass, muscle strength, functional performance, and physical impairment in women with the hypermobility type of Ehlers-Danlos syndrome. Arthritis Care & Research 2012;64(10):1584–92.

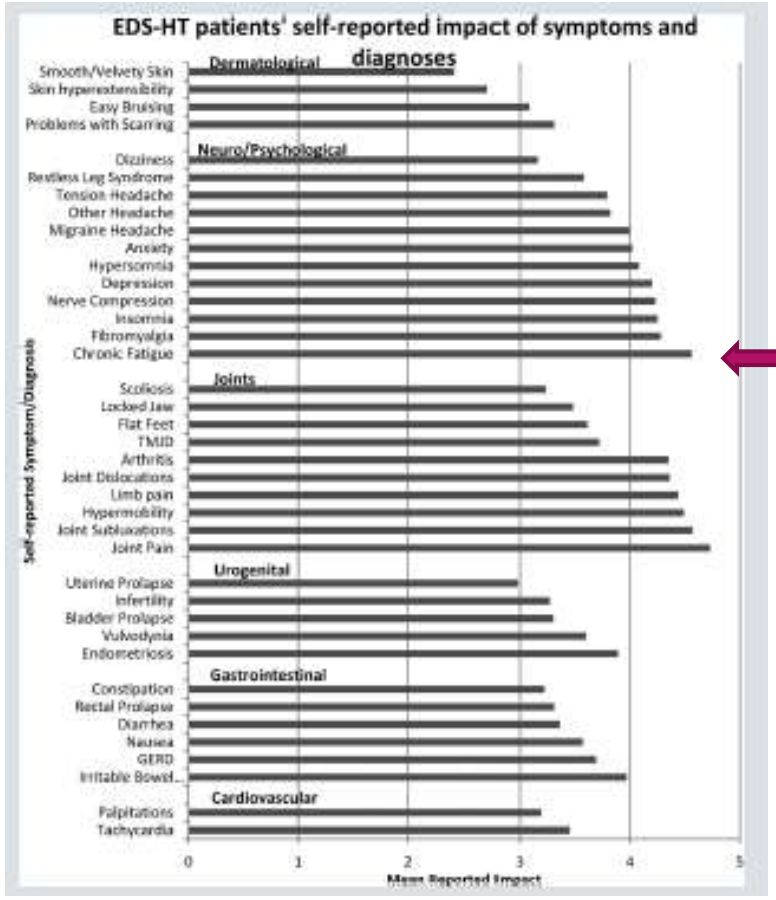
Celletti et al., 2013

- Forty-two patients with hEDS
- Chronic musculoskeletal conditions with chronic pain are often associated with fear/anxiety
- Kinesiophobia is the most extreme form of fear of movement resulting from a feeling of vulnerability to painful injury or re-injury
  - CFS [Nijs et al., 2004], fibromyalgia, and chronic low back pain [Vlaeyen et al., 1995]
- The onset of pain-avoiding strategies is related to the presence of pain but not to its intensity
- **"The clear-cut correlation between *kinesiophobia* and severity of fatigue suggests a direct link between musculoskeletal pain and fatigue"**

Nijs J, deMeirleir K, Duquet W. Kinesiophobia in chronic fatigue syndrome: assessment and associations with disability. *Archives of Physical Medicine and Rehabilitation* 2004:85(10):1586–92.
Vlaeyen JWS, Kole-Snijders AMJ, Boeren RGB, Van Eek H. Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. *Pain* 1995;62(3):363-72.

Murray et al., 2013





1) Hypermobility, joint/limb pain, dizziness, and fatigue are the most common reported symptoms

2) Fatigue second greatest factor in "sickness impact"

Murray B, Yashar BM, Uhlmann WR, Clauw DJ, Petty EM. Ehlers–Danlos syndrome, hypermobility type: A characterization of the patients' lived experience. Am J Med Genet Part A 2013;161A:2981–8.

Pacey et al., 2014

- Eighty-nine children with JHS (hEDS)
- Study in an attempt to identify subtypes
- Five subtypes identified:
  - 'joint affected' JHS
    - Multiple joint pain, recurrent joint instability and POTS
  - 'athletic'
    - More muscle endurance, balance and motor skill proficiency
  - 'systemic'
    - Skin involvement, incontinence symptoms, bowel involvement and recurrent joint instability
  - 'soft tissue affected'
    - Recurrent soft tissue injuries and reduced muscle length, and greater fatigue
  - 'high BMI' JHS
    - Increased muscle endurance and no gastrointestinal involvement, but higher levels of pain

Table 5 Characteristics of the participating children with joint hypermobility syndrome (n=89)

Characteristic	Mean (SD)	Range
Age (years)	11.55 (2.95)	6–16.7
BMI centile*	59.18 (31.17)	0.06–99.22
Height centile*	60.04 (29.13)	0.99–99.99
Beighton score	6.71 (1.53)	4–9
Number of painful joints	6.43 (3.83)	0–15
Pain in last week†	5.36 (3.49)	0–10
Total fatigue‡	59.71 (21.34)	15.3–98.6
Total HRQOL‡	62.74 (18.37)	18.5–95.7
Physical domain‡	60.71 (24.64)	3.13–100
Psychosocial domain‡	64.15 (17.81)	26.7–96.7

*Centiles for BMI and height are calculated for age from gender specific reference values.
†Pain in last week ranges from 0 to 10 with higher scores indicating worse pain.
‡Fatigue and HRQOL scores range from 0 to 100 with higher scores indicating less fatigue and better quality of life.
BMI, body mass index; HRQOL, health related quality of life.

Pacey V, Adams RD, Tofts L, Munns CF, Nicholson LL. Arch Dis Child Published Online First: May 26, 2014; doi:10.1136/archdischild-2013-304-5

Rombaut et al., 2014

Variable	EDS-HT group n=23
Age (years)	40±10.6
Duration of mss. symptoms (years)	24±12.4 (n=23)
Duration of gastro-int. symptoms (years)	14±13.5 (n=20)
Duration of fatigue (years)	15±11.0 (n=21)
Duration of pain (years)	24±12.5 (n=23)
Use of analgesics and/or antidepressants (n,%)	17 (74 %)
Use of neuropathic pain medication (n,%)	2 (9 %)

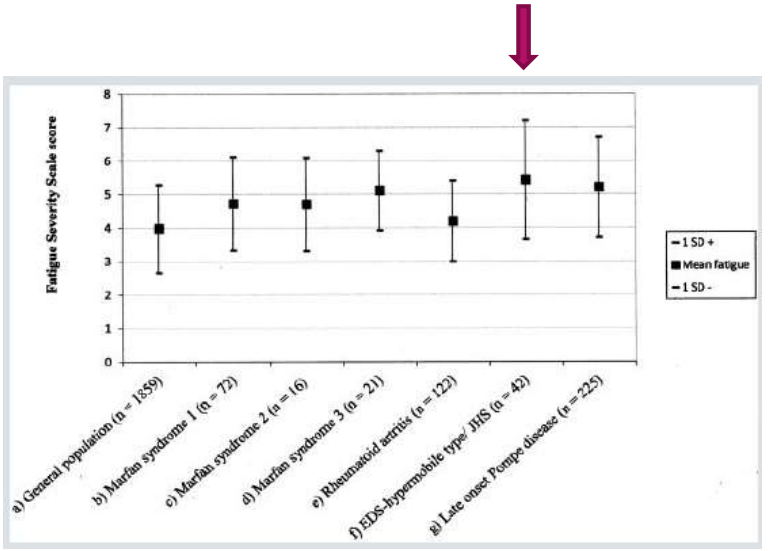
Rombaut L, Scheper M, De Wandele I, De Vries J, Meeus M, Malfait F, Engelbert R, Calders P. Chronic pain in patients with the hypermobility type of Ehlers–Danlos syndrome: evidence for generalized hyperalgesia. Clin Rheumatol, DOI 10.1007/s10067-014-2499-0

Fatigue in Marfan syndrome

TABLE II. Mean Scores and Distribution of Fatigue Severity Scale Item Scores (N = 72)

Item	Mean	Score distribution for scores 1–7 in %		
		1–3	4	5–7
My motivation is lower when I am fatigued	5.8	8	6	86
Fatigue interferes with my physical functioning	5.4	12	10	78
Fatigue interferes with my work, family or social life	4.8	28	12	60
Fatigue is among my most debilitating symptoms	4.8	35	8	57
Fatigue interferes with carrying out certain duties and responsibilities	4.7	30	10	60
I am easily fatigued	4.7	25	15	60
My fatigue prevents sustained physical functioning	4.4	38	11	51
Exercise brings on my fatigue	3.9	42	19	39
Fatigue causes frequent problems for me	3.9	46	18	36

Item scores range from 1 (strongly disagree) to 7 (strongly agree). The items are ranked by descending mean scores.



Bathen T, Velvin G, Rand-Hendriksen S, Robinson HS. Fatigue in adults with Marfan syndrome, occurrence and associations to pain and other factors. Am J Med Genet Part A 2014;9999:1–9.

Treatment of chronic fatigue

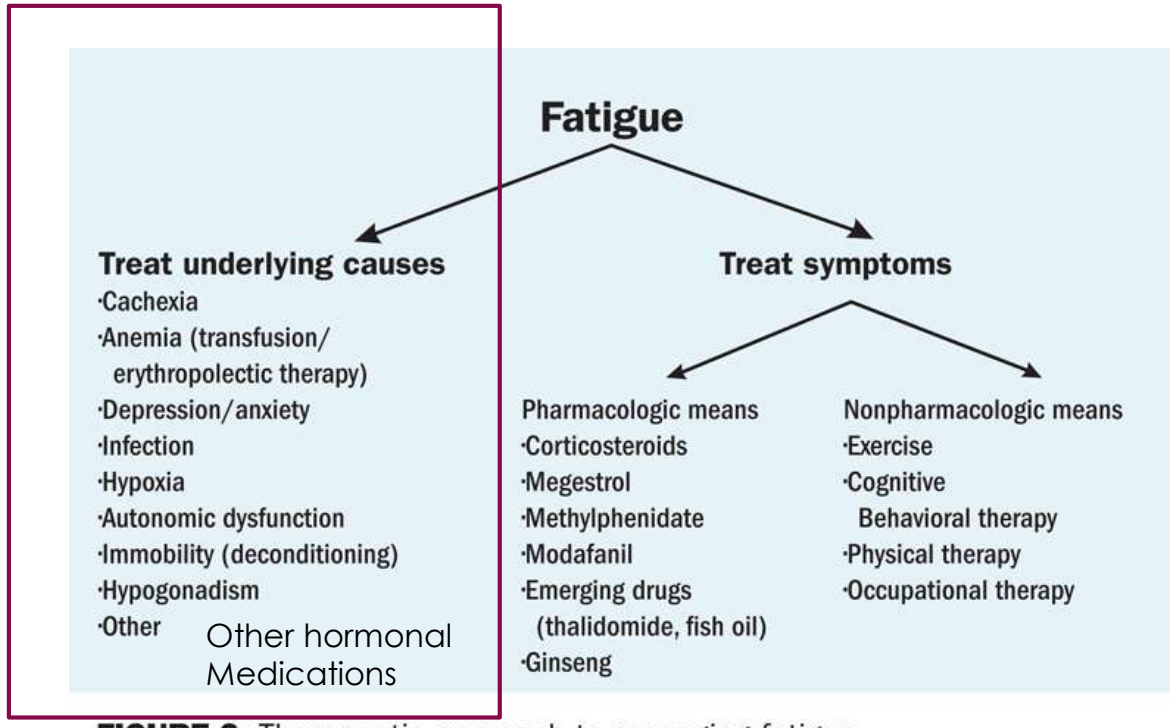
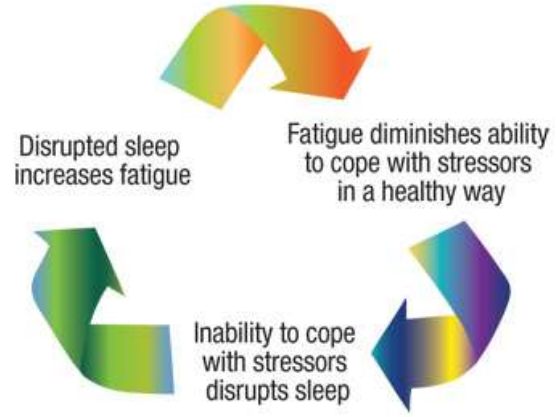


FIGURE 2: Therapeutic approach to managing fatigue.

Fatigue management- evidence-based

- Well-balanced nutrition
- Abstain from alcohol, drugs, and donating blood
- Cognitive behavioral therapy [Price et al., 2009]
- Yoga/breathing exercises
- Graded exercise program [Edmunds et al., 2004]
- Weight-reduction (if obese)
- Sleep hygiene and management including pain
  - Sleep study especially for high-arched palate? [Guilleminault et al., 2014]
- Dysautonomia treatment
- Stimulants [Kanjwal et al., 2011]
- ~~Amantadine (multiple sclerosis) [Pucci et al., 2007]~~
- Supplements
  - ~~*Ginseng (high dose?) [Adams et al., 2009]*~~
  - *L-carnitine* [Mantle et al., 2005]
  - *CoEnzyme Q10* [Mantle et al., 2005]



Fatigue management- references

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QUESTIONS?

THANK YOU!