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.**

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**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

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

<table>
<thead>
<tr>
<th>Self-reported Use of Medication With Possible Sedative Side Effects</th>
<th>Number of EDS Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more analgesics with sedative side effects</td>
<td>62</td>
</tr>
<tr>
<td>Tramadol</td>
<td>14</td>
</tr>
<tr>
<td>Opiates/others opiate agonists</td>
<td>39</td>
</tr>
<tr>
<td>Codeine</td>
<td>22</td>
</tr>
<tr>
<td>Anti-epileptic drugs</td>
<td>3</td>
</tr>
<tr>
<td>Baclofen</td>
<td>2</td>
</tr>
<tr>
<td>One or more anti-depressives with possible sedative side effects</td>
<td>38</td>
</tr>
<tr>
<td>One or more benzodiazepines</td>
<td>39</td>
</tr>
<tr>
<td>One or more β-blockers</td>
<td>6</td>
</tr>
</tbody>
</table>
Disorders associated with fatigue

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

- Connective tissue disorders including EDS

Double-dogged tired!!
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

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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 [Celletti et al., 2012]
EDS/JH and Fatigue
Described 12 EDS patients (6 Classic/6 HM) with CFS and orthostatic intolerance (NMH/POTS)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Percent with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue &gt;6 months</td>
<td>100%</td>
</tr>
<tr>
<td>Post-exertional malaise</td>
<td>100%</td>
</tr>
<tr>
<td>Unrefreshing sleep</td>
<td>100%</td>
</tr>
<tr>
<td>Impaired memory or concentration</td>
<td>92%</td>
</tr>
<tr>
<td>Multi-joint pain</td>
<td>83%</td>
</tr>
<tr>
<td>New headache</td>
<td>83%</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>58%</td>
</tr>
<tr>
<td>Sore throat</td>
<td>25%</td>
</tr>
<tr>
<td>Tender cervical or axillary nodes</td>
<td>25%</td>
</tr>
</tbody>
</table>

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 \( \geq 4 \) (60% versus 24%, \( P < .0001 \))
- Odds ratio for hypermobility in CFS versus healthy controls was 3.5 (\( P < .001; 95\% \text{ CI}, 1.6-7.5 \))
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)
  - Forgetfulness 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)

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


Tofts et al., 2009

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>
<thead>
<tr>
<th>Table 1: Demographics of Ehlers-Danlos Syndrome Patients, Age and Sex Distribution of EDS Patients, and Distinction Between Nonseverely and Severely Fatigued Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ehlers-Danlos Syndrome (EDS) Type</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Classic (C)</td>
</tr>
<tr>
<td>Hypermobility (H)</td>
</tr>
<tr>
<td>Vascular (V)</td>
</tr>
<tr>
<td>Kyphoscoliotic (K)</td>
</tr>
<tr>
<td>Other/Type unknown</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

*Fisher's exact test.

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

Fatigue had a greater impact on functioning

Kanjwal et al., 2010

**All explained by POTS?**

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


*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

Cluster analysis to look for hEDS subgroups
- Generated 3 clusters
- For those with other non-musculoskeletal complaints, fatigue was the most prevalent

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?
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

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”


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

2) Fatigue second greatest factor in “sickness impact”

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>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>11.55 (2.95)</td>
<td>6–16.7</td>
</tr>
<tr>
<td>BMI centile*</td>
<td>59.18 (31.17)</td>
<td>0.05–99.22</td>
</tr>
<tr>
<td>Height centile*</td>
<td>60.04 (29.13)</td>
<td>0.99–99.99</td>
</tr>
<tr>
<td>Brighton score</td>
<td>6.71 (1.53)</td>
<td>4–9</td>
</tr>
<tr>
<td>Number of painful joints</td>
<td>6.43 (3.83)</td>
<td>0–15</td>
</tr>
<tr>
<td>Pain in last week†</td>
<td>5.36 (3.49)</td>
<td>0–10</td>
</tr>
<tr>
<td>Total fatigue†</td>
<td>59.71 (21.34)</td>
<td>15.3–98.6</td>
</tr>
<tr>
<td>Total HQOOL†</td>
<td>62.74 (18.37)</td>
<td>18.5–95.7</td>
</tr>
<tr>
<td>Physical domain</td>
<td>60.71 (24.64)</td>
<td>3.13–100</td>
</tr>
<tr>
<td>Psychosocial domain†</td>
<td>64.15 (17.81)</td>
<td>26.7–96.7</td>
</tr>
</tbody>
</table>

*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 HQOOL scores range from 0 to 100 with higher scores indicating less fatigue and better quality of life.

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

### Fatigue in Marfan syndrome

#### TABLE II. Mean Scores and Distribution of Fatigue Severity Scale Item Scores [N = 72]

<table>
<thead>
<tr>
<th>Item</th>
<th>Mean</th>
<th>1-3</th>
<th>4</th>
<th>5-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>My motivation is lower when I am fatigued</td>
<td>5.8</td>
<td>8</td>
<td>6</td>
<td>88</td>
</tr>
<tr>
<td>Fatigue interferes with my physical functioning</td>
<td>5.4</td>
<td>12</td>
<td>10</td>
<td>78</td>
</tr>
<tr>
<td>Fatigue interferes with my work, family or social life</td>
<td>4.8</td>
<td>28</td>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>Fatigue is among my most debilitating symptoms</td>
<td>4.8</td>
<td>35</td>
<td>8</td>
<td>57</td>
</tr>
<tr>
<td>Fatigue interferes with carrying out certain duties and responsibilities</td>
<td>4.7</td>
<td>30</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>I am easily fatigued</td>
<td>4.7</td>
<td>25</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td>My fatigue prevents sustained physical functioning</td>
<td>4.4</td>
<td>38</td>
<td>11</td>
<td>51</td>
</tr>
<tr>
<td>Exercise brings on my fatigue</td>
<td>3.8</td>
<td>42</td>
<td>9</td>
<td>39</td>
</tr>
<tr>
<td>Fatigue causes frequent problems for me</td>
<td>3.8</td>
<td>46</td>
<td>10</td>
<td>38</td>
</tr>
</tbody>
</table>

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

Treatment of chronic fatigue

**FIGURE 2**: Therapeutic approach to managing fatigue.

**Treat underlying causes**
- Cachexia
- Anemia (transfusion/erythropoietic therapy)
- Depression/anxiety
- Infection
- Hypoxia
- Autonomic dysfunction
- Immobility (deconditioning)
- Hypogonadism
- Other

**Fatigue**

**Other hormonal Medications**

**Treat symptoms**

**Pharmacologic means**
- Corticosteroids
- Megestrol
- Methylphenidate
- Modafanil
- Emerging drugs (thalidomide, fish oil)
- Ginseng

**Nonpharmacologic means**
- Exercise
- Cognitive
- Behavioral therapy
- Physical therapy
- Occupational therapy
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]


QUESTIONS?

THANK YOU!