Clinical Autonomic Dysfunction in Ehlers-Danlos Syndrome

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Disclaimers

- “Off-label” uses of medications
- No financial conflicts of interest
Overview

- Autonomic nervous system (ANS) regulates all body processes, including sleep.
- ANS dysfunction is very common in Ehlers-Danlos syndrome (EDS), and underlies many of its symptoms.
- The most common type of sleep disorder seen in EDS appears to have an autonomic basis.
- Treatment should be aimed at correcting the underlying autonomic dysfunction as well as relieving symptoms.
Basics of the ANS

- A normally functioning ANS continuously “fine-tunes” body systems, in response to both internal and external stimuli, to maintain homeostasis.

- Sympathetic nervous system: “fight or flight,” the accelerator

- Parasympathetic nervous system: “rest and digest,” the brake
Autonomic Dysfunction in Ehlers-Danlos Syndrome

- Loss of “fine-tuning” ability causes difficulty maintaining homeostasis
- Concept of sympathetic reserve
- Central paradox: the lower the reserves, the more exaggerated the sympathetic response to even minor stresses
- The overresponse often triggers an overcorrection, then an overresponse...
Sympathetic and Parasympathetic Activity with Autonomic Maneuvers

A=Baseline, B=Deep Breathing, C=Rest, D=Valsalva, E=Rest, F=Stand
Clinical Manifestations of Autonomic Dysfunction

- **Circulatory**
  - Lightheadedness, cold hands and feet, palpitations, episodic or labile hypertension

- **Gastrointestinal**
  - Nausea, cramps, diarrhea, bloating; constipation

- **Urinary**
  - Urgency, incontinence, sluggish flow, incomplete emptying

- **Respiratory**
  - Abnormal breathing patterns, dyspnea

- **Balance**
  - Vertigo, gait problems

- **Hypoglycemia**

- **“Anxiety,” Malaise/Fatigue**

- **Insomnia/Non-restorative sleep**
ANS Testing

- QSART, sweat test, urodynamics, GI manometry, etc.
- Cardiovascular Autonomic Testing
  - Tilt table test
  - ANSAR™ testing
- Polysomnography
Vertigo Clinic
Welcome
Non-Restorative Sleep in EDS

- Frequent arousals and awakenings
- Little or no deep sleep

Normal Sleep

Non-Restorative Sleep
Heart Rate Variability Associated with Sleep Disruptions

Heart Rate

Sleep Stages

Awake
REM
N1
N2
N3
Sleep Stages

W=Awake, R=REM, N1 and N2=Shallow sleep, N3=Deep sleep

Heart Rate
Heart Rate Variability--Another Paradox

- The lower sympathetic activity is, the greater heart variability, or
- The more exhausted an EDS patient gets, the more “depleted” their energy reserves get, the more exaggerated heart rate fluctuations will be
- The more heart rate fluctuates, the more disrupted sleep (and daytime activities) get
- The more energy is wasted on autonomic fluctuations during the day, and the more disrupted sleep gets, the more exhausted one gets—a nasty vicious cycle
Non-Restorative Sleep in EDS

- Frequent arousals and awakenings
- Little or no deep sleep
“The MRI reveals that your head is riddled with conventional wisdom.”
Sympathetic and Parasympathetic Activity
Before and After Treatment

At Diagnosis

After 18 months of treatment

A=Baseline, B=Deep Breathing, C=Rest, D=Valsalva, E=Rest, F=Stand
The diagram illustrates the relationship between sleep and various factors affecting energy levels. 

- Sleep is depicted as a truck labeled "Sleep," which supplies energy.
- Energy is centralized in a tank labeled "Energy." 
- Energy is distributed to different sources including:
  - Pain
  - Fatigue
  - Dehydration
  - Cognitive Effort
  - Emotional Stress
  - Work/School
  - Other

This suggests that adequate sleep is crucial for sustaining and replenishing energy, which is then distributed to various aspects of daily life.
Restoring Homeostasis, or Refilling the Pool

• Better sleep—quantity and quality
• Adequate—really—pain control
• Don’t “push through” fatigue; take breaks
• Adequate salt and fluid
• Avoid hypoglycemia
• Minimize emotional and other stresses
Improving Sleep Quality

- Don’t overlook the basics:
  - Good sleep hygiene
  - Comfortable mattress
  - Dark and quiet, comfortable temperature
  - Relaxation, meditation, deep breathing
  - Treat sleep apnea, limb movements **only if significant**
Improving Sleep Quality: Medication

- Complex medication “regimen” is often required, using multiple medications with complementary effects:
  - Beta blockers, alpha blockers, clonidine to reduce sympathetic hyperarousal
  - Trazodone, amitryptiline, doxepin to increase deep sleep
  - Pain medication at bedtime should not be overlooked
    - Finding the right combination can be a frustrating trial and error process; pharmacogenetic testing can help guide medication choices
    - Home sleep monitoring can be helpful, if/when available
Improving Pain Control

• Chronic pain should be suppressed continuously, not treated intermittently.
  • Use of pain medication only “prn” worsens the “roller coaster” instability we are trying to improve
• Don’t Underestimate Pain!
• Patients who say
  • It’s not that bad
  • I’m used to it
  • I’ve learned to live with it
  • I don’t want to take pain medication
• Doctors who say
  • You can’t possibly have that much pain
  • Someone your age/size/etc. shouldn’t need that much pain medication

*Are part of the problem, not the solution*
Fatigue

- Can be a direct result of autonomic dysfunction, e.g. increased parasympathetic activity
- Can result from chronic pain, poor sleep, and depression
- Can be a result of metabolic deficiencies, e.g. vitamins B12 and D
- Paradoxically, many patients who are tired do not report fatigue as a symptom, because...
- Fatigue is perceived as a stress, which triggers an exaggerated sympathetic response, which masks fatigue and further depletes reserves
Treatment of Dehydration/Poor Circulation

- Maximize effective circulatory volume
  - Adequate salt and fluid—but not too much fluid!; no alcohol, caffeine, or medications that cause fluid loss; elevation of legs, support hose; non-deglycyrrhized licorice, fludrocortisone

- Medication if needed to:
  - Maintain blood pressure (e.g. midodrine, droxidopa, stimulants)
  - Reduce BP fluctuations (e.g. Beta blockers, clonidine, SSRI’s)
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“I am stunned, amazed, and grateful at the benefits of taking propanolol. The improvement in my sleep quality alone is fantastic.”

“The medicine you gave me is amazing. Two worked great but three worked even better. I forgot to take it one night and slept 12 hours and felt terrible. The next night I took it and slept 6 hours and felt great.”

The metoprolol seems to help considerably with my sleep. In fact, between metoprolol, flexeril, and good old advil, I’m able to fall asleep and stay asleep. The metoprolol really seems to be particularly important for quality of sleep.
I just wanted to let you know again how much the prazosin helps me. I am sleeping better now than I ever have in my life. If I get 7 hours of sleep, it's always uninterrupted and I awake feeling rested and ready for the day. It's changed my life!

The propranolol helps! I have slept 4 hours straight - I don't remember the last time I did that! My heart isn't racing as much. I feel better all day. I don't get "tired but wired" as much.
Summary

- Autonomic dysfunction is very common in Ehlers-Danlos syndrome, and plays a role in a surprising variety of its symptoms.

- Autonomic dysfunction can be greatly reduced with appropriate treatment, including both lifestyle measures, e.g. stress reduction and not “pushing through” fatigue, and medications, e.g. for pain and to suppress, offset, or block excessive autonomic reactivity.
Summary (continued)

- Improving sleep, reducing pain, optimizing circulation, and minimizing daytime stresses helps to replenish autonomic reserves, which in turn improves daytime autonomic stability and improves sleep, which in turn improves daytime function, which in turn improves circadian rhythms and sleep, which .....
IS HOW YOUR PATIENTS WILL GET BETTER!
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