EHLERS-DANLOS SYNDROME & DYSAUTONOMIA

Presented By
Lauren Stiles, JD
President & Co-Founder

New York Institute of Technology
December 8, 2017
Most studies are on hEDS

hEDS patients have more autonomic symptoms than other EDS types

49% of hEDS patients have POTS, 31% have OI, 20% have normal hemodynamics

In hEDS, autonomic dysfunction is classified as:

- mild (47%)
- moderate (33%)
- Severe (3.3%)
Chronic Migraine

Reflex Syncope

POTS/OI

Complex Regional Pain Syndrome

Interstitial Cystitis

IBS/CIPO/Gastroparesis

Chronic Migraine

HR increase of ≥30bpm from supine to standing within 10 minutes (≥40bpm for ages 12-18)

In the absence of orthostatic hypotension (defined as ≥20/10mmHg drop within 3 min. of standing)

Symptoms of orthostatic intolerance lasting ≥6 months

Symptoms exacerbated by standing and improved with recumbency

Absence of other overt causes of orthostatic symptoms or tachycardia
POTS SYMPTOMS

- Pronounced orthostatic tachycardia
- Palpitations
- Shortness of breath
- Lightheadedness/pre-syncope
- Syncope (20-30% with overlapping NCS)
- GI motility (33% too fast, 33% too slow)
- Nausea
- Bladder dysfunction (17%)

- Sensitivity to heat/cold
- Sensitivity to light/sounds
- Migraines
- Profound fatigue
- Weakness
- Tremulousness
- Exercise intolerance
- Dependent acrocyanosis
- Flushing
- Increased allergies
DEPENDENT ACROCYANOSIS

- Acrocyanotic legs after a few minutes of standing
- Prolonged blanching/delayed capillary refill
Common form of orthostatic intolerance
- US estimates, 500K-3M
- Newer estimates are in the higher range

For comparison...
- MS: 400K US estimate
- Parkinson’s: 1M US estimate

Mayo Clinic estimates 1 in 100 teens (~500K)
- About half of all patients have onset in adulthood
POTS IS NOT A "TEENAGE SYNDROME"

Patient Reported Age at Onset of POTS Symptoms

N=697

52% onset at 18 & under
48% onset at 19 & over

POTS “SUBTYPES” ARE NOT DISTINCT DIAGNOSES
ORTHOSTATIC PAIN

COAT HANGER PAIN

Suboccipital and paracervical pain that worsens in the upright position is common in orthostatic disorders and is believed to be caused by poor blood flow to the muscles of the upper back and neck.

www.dysautonomiainternational.org
ORTHOSTATIC PAIN

- Orthostatic Headaches
  - Blood volume dysregulation
  - Chiari
  - CSF flow issues
  - CSF leak(s)

Check out Dr. Kinsella’s 2017 Conference Lecture on our Vimeo page: www.vimeo.com/dysautonomia
## GYNECOLOGICAL ABNORMALITIES IN POTS

<table>
<thead>
<tr>
<th>Condition</th>
<th>POTS (n=65)</th>
<th>Controls (n=92)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometriosis</td>
<td>20%</td>
<td>5%</td>
<td>.009</td>
</tr>
<tr>
<td>Uterine fibroids</td>
<td>25%</td>
<td>10%</td>
<td>.015</td>
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<td>Galactorrhea</td>
<td>9%</td>
<td>0%</td>
<td>.004</td>
</tr>
<tr>
<td>Ovarian cysts</td>
<td>43%</td>
<td>13%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dysfunctional Bleeding</td>
<td>14%</td>
<td>4%</td>
<td>.042</td>
</tr>
</tbody>
</table>

BEFORE your POTS diagnosis, were you ever told by a doctor that your symptoms were due to the following diagnoses? Please check all that apply:⁴

- anxiety
- stress from work/school/family
- "all in your head"
- depression
- panic disorder
- somatoform disorder
- conversion disorder
- munchausen's syndrome
- factitious disorder
- other mental/psychological illness
- none of the above

83% of POTS patients given at least one psych label prior to diagnosis.
Other data suggests this is largely misdiagnosis...

- Mayo 1992: Psychological domains similar amongst healthy controls, CHF, COPD and POTS.
- Vanderbilt 2009: POTS patients slightly less anxious than general population, slight increase in mild depression.
- Mayo 2016: mean mental composite score normal in pediatric POTS.

When psychological comorbidity is present, it should be addressed. Patients are often afraid to ask for help.
10g salt daily (3876mg sodium)
2-3L of hydrating fluids daily (avoid sugary drinks)
Medical compression stockings
Abdominal binders
Recumbent exercises
Good sleep habits
Learning about your illness can help you manage symptoms better, and reduces fear of the unknown
Avoid heat, prolonged standing, hot showers, alcohol
Healthy diet
Cooling vests
Avoid orthostatic stress during exercise until patient builds up exercise tolerance, can take MONTHS/YEARS
Rowing, a recumbent bike, swimming, floor/core
Start SLOW and LOW
EDS - work with PT to stabilize & protect your joints
POTS: PHARMA TREATMENT

- Vasoconstrictors
  - Midodrine
  - Octreotide
  - Droxidopa (Northera)
  - Phenylephrine (Sudafed PE)

- Blood volume expansion
  - Fludrocortisone
  - Desmopressin
  - EPO
  - IV Saline

- Beta blockers (less is more!)
  - Ivabradine
  - Mestinon

- If mast cell dysfunction is present:
  - H1/H2 blockers
  - Cromolyn (Gastrocrom)
  - Omalizumab (Xolair)
  - Ketotifen
  - Quercitin
  - Vitamin C

No FDA approved treatment for POTS.
IS EDS/POTS DIFFERENT THAN NON-EDS/POTS?

- Maybe?
- Assumption...
  - stretchy blood vessels due to EDS collagen probelms leads to blood pooling, causing POTS
- Reality...
  - No research documenting collagen deficits in hypermobile EDS are causing stretchy blood vessels
  - No research showing that EDS/POTS patients have stretchier blood vessels than non-EDS/POTS
- Patients need answers backed by solid research that leads to better treatments – we deserve more than assumptions!
“STRETCHY VEINS” DON’T EXPLAIN...

- AUTOIMMUNITY
- SMALL FIBER NEUROPATHY
- HYPOVOLEMIA
- HYPERADRENERGIC STATE
- HYPERTENSION
- MAST CELL DYSFUNCTION
- PEOPLE WITH EDS/POTS WHO RECOVER OR IMPROVE
Factors suggesting autoimmunity plays a role in POTS:

- Female predominant condition (80-90% female)
- 50% have a post-viral onset
- 50% have small-fiber neuropathy
- Increased rate of estrogen dependent co-morbidities
- Mast cell abnormalities known to occur in early phases of many autoimmune diseases
Dr. Francomano reported a high rate of autoimmunity in her EDS patients in 2006, specifically:
- RA/juvenile RA, lupus, Sjogren’s

12/72 consecutive EDS patients had one of these autoimmune diseases.

7/72 had Raynaud’s, which is often seen in autoimmune disorders.

“This raises the possibility that abnormalities of the extracellular matrix might contribute to the development of autoimmunity in the presence of other genetic or environmental influences.”

THE BIG POTS SURVEY

- IRB approved structured online survey
- 3300 POTS patients, 400 variables
- Patients from more than 15 countries
- Largest POTS study to date – follow up surveys in progress, plans to link to clinical data

2 Satish R. Raj MD MScI, Lauren E. Stiles JD, Brett H Shaw MSc, Elizabeth A. Green MD, Cindy A. Dorminy MEd, Cyndya A. Shibao MD MScI, Luis E. Okamoto MD, Emily M. Garland PhD MScI, Alfredo Gamboa MD MScI, Andre Diedrich MD PhD, Italo Biaggioni MD, David Robertson MD. The Face of Postural Tachycardia Syndrome (POTS): A Cross-Sectional Community-Based Survey. Heart Rhythm 2016: 12 (5S):xx-xx (abstr) [in press].
Big POTS Survey results...

- 16% of all POTS patients report a confirmed autoimmune disease.
- 18% of POTS patients also diagnosed with EDS report a confirmed autoimmune disease.
- Most commonly Hashimoto’s, Sjogren’s, lupus, celiac.
Initial 1993 description from Mayo suggested partial immune mediated neuropathy³

2012 Mayo Clinic: auto-immunoreactive IgGs to 40 different cardiac membrane proteins found in POTS⁴

2014 Univ. of Oklahoma/Vanderbilt: 100% have adrenergic receptor antibodies (n=14),⁵ larger cohort in progress with EDS screening...

2014 Children’s Heart Institute: 15% of POTS subjects had significant expansion of double negative T cells, this correlated to the presence of serum autoantibodies (n=60)⁶
VASOMOTOR NERVES & COLLAGEN

- VIP - Sympathetic cholinergic
- CD31 - Vascular marker
- Col IV - Basement membrane

Image courtesy of Dr. Roy Freeman, Harvard Medical School.
2015 SUNY Buffalo: 20% have comorbid autoimmune disease, 33% have commonly tested autoimmune markers (n=100)\textsuperscript{7}

2015 Mayo: 45% have thyroid and/or neural antibodies (n=33) compared to healthy controls (4.4%),\textsuperscript{8} larger cohort in progress...

2015 Vanderbilt: increased IL-6, but normal CRP, in POTS\textsuperscript{9}

2016 Stiles/Gudesblatt: 41% idiopathic dysautonomia patients with dry eyes or dry mouth have novel “early” Sjögren's antibodies SP-1, PSP, CA-6 (including 6 of 10 POTS patients in the study) (n=95)\textsuperscript{10}

2016 UT Southwestern: Muscarinic receptor antibodies, 87.5% M1, 68.75% M2, 12.5% M3 (n=16), M1 & M2 statistically significant compared to 20 controls, M1 correlated to cognitive impairment,\textsuperscript{11} larger cohort in progress with EDS screening...
2016 Univ Oklahoma/Lund University: Swedish cohort of 17 POTS, 7 VVS, and 11 healthy controls. All of the POTS subjects had at least one type of adrenergic receptor antibody (12 had beta-2, 11 had beta-1, 8 had alpha-1). None of these antibodies were found in VVS or controls.\textsuperscript{12}

More research in progress...
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- HYPERTENSION
- MAST CELL DYSFUNCTION
- PEOPLE WHO RECOVER/IMPROVE
“STRETCHY VEINS” DON’T EXPLAIN...

- SMALL FIBER NEUROPATHY
  - Different types of small fiber nerves: sensory, sudomotor, vasomotor, etc.
  - Sudomotor dysfunction found in 65% of EDS patients
  - Sudomotor dysfunction found in 50% of all POTS patients
  - Vasomotor neuropathy/POTS research in progress at Harvard
  - Small fiber nerves help regulate blood vessel constriction
  - When nerves are damaged, blood vessels can’t constrict
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HYPOVOLEMIA

- Almost all POTS patients have low blood volume
- Plasma and red blood cells are equally low
- Plasma volume controlled by aldosterone
- Many other factors involved in regulating blood volume
- Partial loss of sympathetic nerves in kidney suggested as possible reason for low aldosterone (perhaps adrenergic antibodies?)
- Iron storage deficiency common in POTS
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HYPERADRENERGIC STATE

- Almost all POTS patients have elevated plasma NE
- Some more than others
- Experts don’t agree on a definition for what constitutes “hyperadrenergic” POTS
- Causes of elevated plasma NE:
  - autonomic neuropathy
  - hypovolemia
  - anxiety
  - NET: mutations, epigenetic changes & mRNA variants
  - antibodies?
  - do stretchy veins contribute?
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HYPERTENSION IN POTS

- During tilt testing:
  - 1/3 of POTS patients drop BP (not to the point of OH)
  - 1/3 of POTS patients maintain normal BP
  - 1/3 of POTS patients increase BP
- Some EDS/POTS patients increase BP on tilt
- Some EDS/POTS patients experience hypertension even sitting or laying down, or in response to stressors
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MAST CELL ACTIVATION SYNDROME

- No clear answer on % overlap between POTS/EDS/MCAS
- Vanderbilt 2005: first recognition of POTS/MCAS overlap
- Mayo 2014: many POTS patients tested positive for at least one MCAS biomarker
- NIH 2014: approx. 40 families with hereditary tryptase mutations. POTS/EDS/MCAS occur in some of these families.
  - associated with elevated baseline tryptase, which Mayo suggests is found in less than 1 in 1000 POTS patients
  - likely just a risk factor, not the “cause” of “the trifecta of EDS/POTS/MCAS”
- Univ. Toronto 2015: POTS, EDS, MCAS may frequently overlap
- Prior research in Germany: andrenergic antibodies cause mast cells to mature faster and degranulate more readily (these antibodies reported in POTS)
- More studies in progress...
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**PEOPLE WHO RECOVER/IMPROVE**

- There are some people who have POTS/EDS who see significant improvement in their POTS symptoms over time, and some who considered themselves recovered from POTS.
- Then still have EDS, so something else must have caused their POTS.
- **One example:**
  - Very hypermobile adolescent female, athletic/active
  - Acute onset POTS after a cold
  - Homebound, almost bedridden
  - Diagnosed with EDS and POTS
  - Had the adrenergic antibodies (Univ Oklahoma)
  - Received IVIG as part of a research study
  - Antibodies reduced, POTS symptoms improved, but not 100%
  - She still has EDS
OUTCOMES IN ADOLESCENT POTS

- Symptoms completely resolved: 19.2%
- Symptoms persist, severity better: 51.2%
- Remitting and relapsing: 15.7%
- Symptoms persist, severity same: 3.5%
- Symptoms persist, severity worse: 8.7%
- Not reported: 1.7%

Does Screening for Ehlers-Danlos Syndrome in Postural Tachycardia Syndrome Matter? Insights from a Cross-Sectional Community-Based Survey

Satish R. Raj MD MSc¹,³, Lauren E. Stiles JD², Brett H. Shaw MSc¹, Jessica Ng BSc¹, Elizabeth A. Green MD, Cyndya A. Shibao MD MScI³, Luis E. Okamoto MD³, Emily M. Garland PhD MScI³, Alfredo Gamboa MD MScI³, Andre Diedrich MD PhD³, Italo Biaggioni MD³ and David Robertson MD³

¹Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, AB, Canada; ²Dysautonomia International, East Moriches, NY, USA; ³Autonomic Dysfunction Center, Vanderbilt University, Nashville, TN, USA
To characterize the similarities and differences between POTS patients with and without EDS
METHODS

• Cross-sectional, web-based survey
• “Diagnosis and Impact of POTS” study
• Vanderbilt IRB Approval

• Survey links posted to Dysautonomia International website & social media channels

• Survey data collected July 2015 - October 2016

SR Raj et al., Heart Rhythm Society Scientific Sessions, Chicago IL, May 2017
RESULTS

- > 15 countries (primarily USA)
- Physician diagnosed POTS = 3389 patients

Female vs. Male

EDS vs. Non-EDS

SR Raj et al., Heart Rhythm Society Scientific Sessions, Chicago IL, May 2017
No differences in orthostatic symptom reporting between POTS patients with and without EDS.

SR Raj et al., Heart Rhythm Society Scientific Sessions, Chicago IL, May 2017
POTS patients with EDS
- were less likely to report symptom onset after a triggering event,
- had a greater tendency to report dealing with POTS-like symptoms for most of life

SR Raj et al., Heart Rhythm Society Scientific Sessions, Chicago IL, May 2017
RESULTS – GI

- GI symptoms are reported significantly more often by patients with EDS

**Graph:**
- Constipation: p=0.003
- Vomiting: p<0.001
- Stomach pain: p<0.001
- Heartburn/GERD: p<0.001
- Dysphagia: p<0.001

SR Raj et al., Heart Rhythm Society Scientific Sessions, Chicago IL, May 2017
RESULTS – SENSORY

- Sensory neuropathic symptoms reported significantly more often in patients with EDS

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No EDS</th>
<th>EDS</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Skin burning</td>
<td>40</td>
<td>80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hand tingling</td>
<td>60</td>
<td>80</td>
<td>&lt;0.001</td>
</tr>
<tr>
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<td>20</td>
<td>80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hand numbness</td>
<td>40</td>
<td>80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cold hands</td>
<td>60</td>
<td>80</td>
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<th>EDS</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Facial tingling</td>
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<td>p=0.001</td>
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<tr>
<td>Facial numbness</td>
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<tr>
<td>Foot tingling</td>
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<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Foot numbness</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cold feet</td>
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SR Raj et al., Heart Rhythm Society Scientific Sessions, Chicago IL, May 2017
There is a lot of neuropathy in EDS.

We need detailed pathology studies to know why.

- Is the collagen in/around the nerve fibers impaired?
- Are the nerves damaged by an inflammatory or immune mediated process?
- Some other reason?

Why do EDS patients have small fiber neuropathy?
~ THANK YOU ~

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