Proving the Obvious: 
Next Steps for the Demystification of 
Ehlers Danlos Hypermobility Type 

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Why don’t doctors know about EDS?

• In my medical school (1994-1998) there was one slide (in 4 years) that mentioned EDS
• In my genetics and pediatrics residency (1998-2003), the standard was “some patients get arthritis when they are older. . .”
• Education of providers is slow
  – Educational sources have to be accessible, credible, and acceptable.
  – There are other barriers . . .
Current model of EDS-HT / JHS
How providers see the disorder . . .
What are the barriers to acceptance?

- Perception that it is a rare disorder
- Misunderstanding of diagnostic criteria
  - “You can’t make a diagnosis without a gene test/biopsy”
  - “Your skin is not stretchy”
- Lack of pathophysiology
  - How does loose collagen translate into the phenotype?
  - Why are nerves affected (dysautonomia)?
  - Where does anxiety come in?
How do we demystify the disorder?

• As providers, we see patterns among our patients
• Many of these patterns are “known” but remain un-investigated.
• Research must demonstrate that these patterns exist and place them into a meaningful context.
• No more trash cans!
EDS is *NOT* a rare disorder

- Pattern recognition: We see far more EDS than would be expected
How rare is rare?

• Current estimates vary widely
  – 1 in 10,000 to 1 in 15,000 (ednf.org 2010 MRG)
  – 0.5 - 2% of the population.
    • Based on “professional estimates” and extrapolation from estimates in fibromyalgia populations

• Study from Avon, U.K. evaluated pts. over time
  – Beighton score of ≥6, age 14. Rechecked at 17
  – Of 2901 asymptomatic, 4.7% were hypermobile
  – 9-16% developed joint problems / pain ~ 0.4 -0.7%
How common is EDS-HT?

- Bioinformatic search at Cincinnati Children’s:
  - Patients with hypermobility diagnosis between ages 5 and 18: 2,794
  - Total patients of same ages: 526,371
  - Estimate at CCHMC: ~0.5%, or 1/200

- Connective Tissue Clinic Data:
  - Over the past 2½ years, we have evaluated 2218 new patient visits (including adults), ~95% of whom are diagnosed with EDS-HT.
  - 7-10% of the entire U.S. EDS population?
The majority of our patients are local. 58% of referrals come from within 30 miles. 78% come from within 100 miles.
Most common region of referral

- Referral patterns are unevenly distributed.
- Some provider groups are “tuned in.”
- 86 pediatric referrals from population of ~38,000
- Estimate of 0.2%, or 1 in 500 suspected to have EDS-HT.
How common is EDS-HT?

• It remains unclear
• 1/10,000 to 1/15,000 is an underestimate
• Prevalence seems closer to 1/100 to 1/500.
• Regardless of population estimates, EDS-HT may be overrepresented in certain medical areas
  – Estimated 40% of pediatric pain clinic
  – 33% of adult GI clinic visits (552 evaluations)
    • Clin Gastroenterol Hepatol. 2014 Jan 16
    • doi: 10.1016/j.cgh.2014.01.014
First step to demystifying EDS

Stop saying “EDS is rare”
First step to demystifying EDS

Stop saying “EDS is rare”

In doctorspeak, “that’s rare” means:

“I don’t need to think or learn about that.”

“Go talk to a specialist.”

“This is not important enough to include in our teaching curriculum.”
Next step for demystification: *helpful* model building

- Use research to identify clinical patterns, but use them to build *testable* models with mechanism and intervention.
Research at CCHMC
EDS problems tend to be age dependent and variable
Preteen problems (< 11 y.o.)

- Hypotonia -- occasional
- “Growing pains”
- Handwriting problems
- Bleeding / bruising
- Occasional:
  - Headaches
  - Postural tachycardia
  - Joint dislocation
Teenage to adult problems

• Musculoskeletal dysfunction
  – Chronic pain and joint dislocations
  – Temporomandibular joint dysfunction
• Dysautonomia and orthostatic intolerance
• Gastrointestinal dysfunction
• Chronic headaches
  – Tension-type and migraines
• Bruising and bleeding
• Anxiety and panic disorder
Phases of the condition
Observations from the clinic:

• **Childhood**
  – mild presentation, flexible

• **Teenagers**
  – Males—often improve, flexibility decreases
  – Females—accelerate symptoms, flexibility retained and possibly increased. Seems to correlate with menarche. Symptoms can correlate with menstrual cycle

• **Adults**
  – Flexibility tends to decline
  – 9:1 ratio of affected females to males
Hypothesis: Male versus female hormones change the quality of connective tissue

• Isn’t that obvious? YES!
• Isn’t that proven? NO!

• Our approach: Start at the place where we find the biggest change in hormones--puberty.
• Our advantage: Our young population.
Over 3 months, we collected 91 young patients

112 individuals met the inclusion criteria and were consented into the study

21 individuals were excluded from analysis*

The current study sample consists of 91 individuals

19 EPP males
5 LPP males
25 EPP females
42 LPP females
Assessment Tools

- In addition to a study examination, participants were asked to complete a composite questionnaire that included:
  - Tanner puberty scale
  - Functional Disability Inventory (FDI)
  - Pediatric Quality of Life Rheumatology module (PEDSQL)
  - Orthostatic Grading Scale (OGS)
  - Migraine Disability Assessment (MIDAS or PedsMIDAS).
Comparison of Functional Disability Inventories (preliminary)

p<0.0001 (difference found)

p=0.494 (no difference)
Comparison of Orthostatic Symptoms (preliminary)

Orthostatic Grading Scale Score

Female
- Early/Pre-puberty: n=25
- p<0.0001
- Late/Post-puberty: n=42
- p=0.035

Male
- Early/Pre-puberty: n=19
- p=0.035
- Late/Post-puberty: n=5
Our data . . .

• Is incomplete for older boys, so data collection is ongoing
• Demonstrates increases in disability and dysautonomia with teenage girls.
• Average age of symptom onset = 11 +/- 1 yrs.
• Average age of menarche = 11 +/- 1 yrs.

• Supports the hypothesis that symptoms are increased by female hormones.
• Does it prove the hypothesis? No.
Tissue Quality

Lower - Higher

THRESHOLD MODEL

# of persons in population

Testosterone

Estrogen, Progesterone

Hypermobility symptoms

Asymptomatic hypermobility

Normal joint mobility

Lower ← Tissue Quality → Higher

Cincinnati Children's
Inflammation?

Nutritional factors?

Testosterone

Estrogen, Progesterone

# of persons in population

Hypermobility symptoms

Asymptomatic hypermobility

Normal joint mobility

Lower ← Tissue Quality → Higher
Baseline Connective Tissue Quality and Stability

Increase in Female Pubertal Hormones Reduces Tissue Quality

Decreased joint stability

Pain

Increase in orthostatic intolerance

Functional Disability

Dysautonomia / Norepinephrine imbalance
That’s a nice model, but where does all this stuff come from?

We need a model of pathogenesis
Implications of building a model

• A model of association
  – Helps a provider look for other problems, but should serve as a framework for . . .

• A model of pathogenesis
  – Can be tested systematically
  – Guides treatment choices
    • Hierarchies imply that some factors may lie at the root of others. Treat the root cause.
  – Can be better understood by physicians and patients
    • No longer a “collection” of problems
We have one model of pathogenesis already: Proprioception

- The sense of proprioception is impaired.
- Proprioception is spatial awareness and relative positioning of limbs.
- Without it, people tend to run into things, look clumsy as kids, have difficulty walking up and downs stairs at night . . .
Altered proprioception in EDS

• A recent metaanalysis confirmed
  – poorer lower limb joint position sense (JPS) ($p < 0.001$)
  – Increased threshold detection to movement ($p < 0.001$)
  – Difference in finger positional sense ($p < 0.001$)

• Static postural control is impaired
  – More postural sway
  – More concentration required to stabilize
Where does proprioception come from?

- Mechanoreceptors
  - Nerve fibers that sense stretch
- The sensory apparatus is a filament-like structure that stretches and contracts
- As the length of the fiber changes, so does the nerve firing rate.
- By comparing the stretch and tension of various muscle groups, the brain interprets relative body position.
Altered proprioception

• While not proven, it can be argued that altered connective tissue impairs the ability of mechanoreceptors to accurately respond to changes in stretch.

• In other words, anything that uses the “stretch” with EDS probably does not work right.

• Remember this conceptual model:
  – “Sensory mechanisms based on stretch are likely impaired”
Dysautonomia

- Autonomic nervous system controls all the unconscious functions
  - Breathing, heart rate, blood pressure, alertness

- Two halves:
  - Sympathetic
    - Activation state: “Fight or flight”
  - Parasympathetic
    - Resting and repair state: “Rest and digest”
Dysautonomia

- Commonest symptom—feeling faint or “blacking out” with standing
- Gazit, et al 2003
  - 27 JHS vs. 21 controls, >90% female,
  - Mean age 32 years.
  - 78% had some degree of orthostatic autonomic dysfunction compared to 10% in controls.

- Syncope, orthostatic intolerance and postural orthostatic tachycardia (POTS--increase of HR by 30, with less than 20/10 BP drop)
Newer dysautonomia research

• Similar results
  – “EDS” instead of “Hypermobility syndrome”
• Decreased central responsiveness to sudden shifts in blood pressure
• Increased *peripheral sympathetic activation*
Dysautonomia and the brain

• Patients with POTS have **poor sleep efficiency**
  – Anectodal evidence of sympathetic activation during sleep

• Symptoms of racing heart beat related to POTS may be interpreted as **anxiety or panic**
  – Orthostatic changes may not be the only trigger

• Poor sleep and anxiety may augment each other

Sympathetic effects

• Increased sympathetic activation would be a good explanation for
  – Racing heart beat
  – Anxiety
  – Panic
  – Sleep dysfunction

(we’ve seen this talk before . . . )
How could all these sympathetic effects come about?

• Hypothesis: Aberrant baroreceptor function causes dysregulation of norepinephrine release

• Baroreceptors are just like the muscle stretch receptors, except that they are wrapped around arteries and register blood pressure.

• With every heartbeat, norepinephrine is released to help regulate blood pressure.
Impaired baroreceptor responsiveness in POTS

- BRS directly related to arterial compliance—the “elasticity” of the vessel wall.
- With POTS, BRS decreased
- This has not been demonstrated in EDS—lots of technical problems

The old model

Weak connective tissue → Joint dislocation → Pain
The old model (revised)

- Weak connective tissue
  - Joint dislocation
  - Soft tissue herniations
- Pain
The current model

- **Coping Skills**
- **Weak connective tissue**
  - **Joint dislocation**
  - **Pain** (inflammation) (fatigue)
  - **Proprioception**
    - **Posture**
    - **Balance**

- **GI Problems**
- **POTS**
Joint dislocation

Proprioception

Blood vessel Baroreceptor

Posture Balance Dehydration Constipation

Orthostatic changes

Sympathetic Activation

Pain Headache Abdominal pain

Sleep Impairment

Anxiety & Panic

Coping Skills
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Questions?