Ehlers Danlos Syndrome. Hypermobile Type 3
The New Fibromyalgia

Allan S. Gordon MD, FRCP(C)
Neurologist and Director
Wasser Pain Management Centre
Disclosures

• The WPMC has received funding from Purdue, Allergan and Astra Zeneca
• No discussion of products or off label uses of pharmaceutical products
Objectives

- An appreciation of an Academic Pain Management Centre
- Understand Ehlers Danlos Syndrome Type 3
WPMC

- Established in 1998
- A multidisciplinary, transdisciplinary academic Pain Management Centre at MSH and U of T
- 21 staff members (Neurology, Nursing, Dentistry, Gynecology and Urology, Physiatry, Psychiatry, Sex Therapy, Behavioural Therapy, Anaesthesia, Addictionist )
- Assess and manage patients
- Use a variety of treatments including pharmacotherapy, CBT and Mindfulness, Physical Therapy and ‘Alternative Therapies’
- Strong research programs
- Well connected to HSC and UHN
Important Occurrences

- Mount Sinai Hospital has joined with Bridgepoint Hospital and Circle of Care to form the Sinai Health System
- An important opportunity to provide pain rehabilitation services
- Development of TAPMI and a Provincial Network
- Excellent connection with Medical Genetics at MSH
Programs of Care

- Pain and Addiction and the Complex Patient
- Urogenital and Pelvic Pain
- Headache and Craniofacial Pain
- Neuropathic Pain
- Musculoskeletal Pain including Fibromyalgia and Multi-joint pain
- Ehlers Danlos Syndrome
What is Fibromyalgia

- Widespread muscle pain of unexplained cause
- Pain and tender muscles in all 4 quadrants of the body
- Linked with numerous conditions
- Associated with sleep disturbance, mood changes
- May have IBS, bowel and bladder issues
- May be post traumatic or not
- Under diagnosed and over diagnosed
- Treatment with exercise, psychologic treatment, antidepressants, anti epileptics, ? Cannabinoids
- Evidence of neuropathic involvement forthcoming
Expert Panel Report on EDS

- [www.healthgov.on.ca/common/ministry/publications/reports/eds_expert_panel_en.pdf](http://www.healthgov.on.ca/common/ministry/publications/reports/eds_expert_panel_en.pdf)
- 1:5000 have the gene
- Estimate 2762 cases but an underestimation
Courtesy of Hanna Faghfoury
EDS Classification

- Six major types
  - Types 1 and 2: Classical
  - Type III: Hypermobility
  - Type IV: Vascular: severe vascular events, poor prognosis
  - Type VI: Kyphoscoliotic type: severe hypotonia at birth, scoliosis at birth, scleral fragility- globe rupture
  - Type VII: Arthrochalasia: congenital hip dislocation, severe hypermobility
  - Type VIIIC: Dermatopspraraxis type: severe skin fragility
Beighton score for hypermobility (1983)

- Passive dorsiflexion of 5th digit (1 point for each side)
- Passive apposition of thumbs to flexor aspect of forearm (1 point for each side)
The Ehlers-Danlos Syndromes

- Heterogeneous group of disorders of connective tissue
- Common features include:
  - Articular hypermobility
  - Skin hyperextensibility
  - Tissue fragility
- Nosology developed in 1988, revised in 1998. Aims:
  - Allow diagnostic uniformity
  - Describe the natural history
  - Facilitate Management and Genetic Counselling
  - Identify areas of research
Classical Type (EDS I and II)

- **Major Criteria**
  - Skin hyperextensibility
  - Widened atrophic scars (tissue fragility)
  - Joint hypermobility

- **Autosomal Dominant inheritance**

**Molecular genetics: Heterogeneous**

- Mutations in **COL5A1** and **COL5A2** (50-90%)
- Null mutations in **COL1A2**
- Homozygous mutations of **Tenascin X (TNXB)**
- Skin biopsy: Cauliflower deformity of collagen fibers on electron microscopy of skin
EDS Hypermobility Type (EDS III)

• Major Criteria
  - Generalized joint hypermobility
  - *Significant pain syndrome
  - Less skin involvement (lax but not as overtly fragile)

• Autosomal Dominant inheritance

• Molecular Basis: Mostly unknown
  - Heterozygosity for TNXB null mutations
  - Rarely COL3A1 G637S mutation
Sally

43 F with widespread pain

- Muscular and joints pains
- Painful periods
- Dizziness and faintness
- Dyspareunia
- Painful and frequent voiding
- Stretch marks before pregnancy
- Multiple symptoms after car accident
- History of hypermobility
- Poor sleep
- Migraine headache
- Recurrent right shoulder disl..

Physical exam

- Painful muscles
- Patchy area of neuropathic pain
- Numerous tenderpoints
- Beighton score 6/9
- Stretch marks
- Introital sensitivity
- Pain on rotation of both hips
- Pain on neck extension
- Orthostatic hypotension
• Daughter and mother are both hyper-mobile
• Consider an autosomal dominant condition
• No genetic test available for EDS 3
• Diagnosis is made clinically
I was minding my own business in 2013

• Began to see a trickle and then a deluge of patients with possible EDS Type III
• Invited to attend the first ILC meeting in Oakville
• Met with members of EDS Canada
• Attended the Canadian Pain Society meeting in Quebec in 2014.....
Lecture by Dr. Oaklander

“Evidence of Small-Fibre Polyneuropathy in Unexplained, Juvenile-Onset, Widespread Pain Syndromes”

Oaklander and Klein  Pediatrics 2013:131 E 1091

Seen in SFSN and Fibro and Erythromelalgia

No mention of EDS in the talk but ‘a light went off’ for several in the audience
Many conditions with widespread pain

- Possibly linked by though of a small fibre sensory neuropathy
- EDS
- Diabetes
- Fabry’s
- Idiopathic
What is Ehlers-Danlos Syndrome?

Ehlers-Danlos Syndrome (EDS) is a hereditary connective tissue disease. There are six subtypes of EDS, where EDS Hypermobility (EDS HT) is the most common. Patients with EDS HT often show joint hypermobility, skin hyperextensibility, and fragile tissue. Genetic testing to determine EDS is limited, thus most diagnoses are based on determining hypermobility through a Beighton score along with the presence of common symptoms.

Treatment

Management of EDS can include a multidisciplinary team, education about the condition, pain management, pain medication, physical therapy, psychological therapies, exercise, attention to various abdominal and pelvic symptoms, pain interventions, and appropriate investigations. In a few selected cases, surgical evaluation may be necessary.

Symptoms and Management Options

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<thead>
<tr>
<th>Symptoms</th>
<th>Management Options</th>
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<tr>
<td>Common symptoms associated with EDS HT along with treatment options and referral suggestions are provided below. Patients with EDS HT showcase different symptoms; however the ones listed below are experienced most frequently.</td>
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<tr>
<td>➢ Musculoskeletal Pain&lt;br&gt;  ❑ Physiotherapy and regular exercise&lt;br&gt;  ❑ Referral to a pain clinic</td>
<td>➢ Gastrintestinal Symptoms (Irritable Bowel Syndrome, Gastroesophageal Reflux Disease, etc.)&lt;br&gt;  ❑ Referral to a gastroenterologist</td>
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<tr>
<td>➢ Fatigue&lt;br&gt;  ❑ Physiotherapy and regular exercise&lt;br&gt;  ❑ Antidepressants</td>
<td>➢ Cardiac Symptoms (i.e., Orthostatic Hypotension)&lt;br&gt;  ❑ Remain well hydrated and stand up slowly&lt;br&gt;  ❑ Referral for tilt table testing</td>
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<tr>
<td>➢ Psychological Distress (depression, anxiety, etc.)&lt;br&gt;  ❑ Referral to a Psychiatrist</td>
<td>➢ Vulvovaginal Symptoms&lt;br&gt;  ❑ Clinical evaluation</td>
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<tr>
<td>➢ Joint Dislocations and Skin Involvement (such as frequent bruising)&lt;br&gt;  ❑ Orthopedics</td>
<td>➢ Bladder Symptoms&lt;br&gt;  ❑ Referral to a urologist&lt;br&gt;  ❑ Referral to a urogynecologist</td>
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<tr>
<td>➢ Sleep Disturbances</td>
<td>➢ Lumbar Spine MRI&lt;br&gt;  ➢ Tethered Cord&lt;br&gt;  ➢ Pelvic Prolapse&lt;br&gt;  ➢ Headaches&lt;br&gt;  ❑ Referral to a neurologist&lt;br&gt;  ➢ Referral to Genetics for EDS assessment:&lt;br&gt;  ➢ Medical history questionnaires&lt;br&gt;  ➢ Echocardiogram&lt;br&gt;  ➢ Eye assessment</td>
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Beighton Score Criteria

Hypermobility is diagnosed with a score ≥ 5/9

• One point if while standing, patient can bend forward and place palms on the ground with legs straight
• One point for each elbow that bends backwards
• One point for each knee that bends backwards
• One point for each thumb that touches the forearm when bent backwards
• One point for each little finger that bends backwards beyond 90 degrees.
Hypermobility is key

- Disturbances of collagen
- Joint issue ..hypermobile to subluxation to dislocation to osteo- and other degenerative changes
- Muscle pain, tenderness and tears in muscle
- Stretchy skin
- Chiari, scoliosis, tethered cord
- Bowel, bladder, genital pain
- Prolapse
- Sensory symptoms and pain
- Pain pain pain
Some neurological issues in EDS III

1 Widespread pain

Could a small fibre sensory neuropathy account for the pain in EDS as well as autonomic neuropathy, bowel issues?
Decided to try to test it by sending a few patients to Drs Katzberg and Breiner at TGH.

Problems: choice of patients; focused on EDS III; how to diagnose it; Issues with SFSN testing
• Resolved that need a properly vetted and funded study with clear cut diagnostic protocols

• Still it is tantalizing that just like FMS what seemed like a muscle pain problem may be due to a SFSN
2 Urogenital and pelvic pain

15-20% of patients that I see at the WPMC have pelvic or urogenital pain.

Vulvodynia, provoked vestibulodynia, interstitial cystitis, prostadynia, pudendal neuralgia, orchalgia, endometriosis, clitoral pain.

All are clinically screened for EDS including Beighton scores, physical examination, urogenital and pelvic examination.

Questions about sexual function.

Finding many linkages.
• In addition those referred for EDS are evaluated for urogenital and pelvic function
• Clinical exam. Urological evaluation
• Finding many associations
• Some may have a large fibre sensory neuropathy as well as SFSN
• Usually screen for tethered cord. Usually not found. No Standing MRI
• Concept of occult tethered cord? Surgery
• Or do these people have PNE, IC and VVD?
3 Headache

- Relationship between migraine and hypermobility
- Patients with EDS have headache
- Issue of Chiari and cranio-cervical instability
- Role of fusion. Very controversial
- Need treatment
- ?Role of orthostatic hypotension
- Individuals referred for headache are screened for EDS =/- Genetics
• Low pressure headache
• Associated with spontaneous leaks
• Seen in EDS
• Difficult to treat
• Has become a very expensive cottage industry
Another example

- 40 F referred with chronic migraine.
- Features of migraine with occasional aura
- But only on left side of head!
- Refractory to all treatments
- Occipital tenderness on left
- Had Beighton of 7 out of 9
- IBS. Bladder issues. Prolapse. Lax skin. No chiari É EDS and chronic migraine
4 Joint Issues

Spine
- Cervical spine
- Cervical instability
- Chiari malformation
- Lumbar spine
- Tethered cord
- Scoliosis

Peripheral joints
- Hips
- Knees
- Ankles
- Shoulders
- Recurrent subluxations
- Issues with fingers
5 Autonomic Instability

- POTS Postural orthostatic intolerance
- Orthostatic tachycardia
- Orthostatic intolerance
- Syncope
- Can be the source of falls and fractures
Management

Recurrent dislocations
- Premature O/A and labral thickening and tears
- Involvement of feet
- Physiotherapy specialized
- Used of finger and other splints
- Treatment of hips and knees

Pain Management
- Medication
- Psychologic therapy
- CBT and Mindfulness
- Music therapy
- Cannabinoids
- Gentle exercise
- Non aggressive therapy
- Rx of headache
Meng study (2014)

- Presented in 2014 year and at CPS in May
- Criticized because of uncertain diagnosis
- Revised with addition of Beighton
- Demonstrated large number of individuals with widespread pain and other symptoms. ?do they have EDS III or a similar variant
- This is the experience in other centres
6 Role of Cannabinoids

- Medical marijuana may provide a positive clinical role
- Many varieties: CBD vs THC
- Role in juveniles: ?Psychosis
- Very early days but many are going on it
- Is there an addiction issue?
- Many other drugs including opioids are not effective
These conditions

• Huge socio economic implications
• Huge personal implications
• Steps need to be taken to address the many issues raised
• There are too many potential mechanisms at play
• A whole generation of students and trainees at the Wasser are getting an appreciation of this set of conditions
Management

• A huge issue
• Requires knowledgeable pain practitioners with Neuro, GI, Gyn, Cardio, Rehab and Psychiatric linkages or expertise
• A team approach is necessary
• Central focus but attention to the community via linkages and communication
• Complex pharmacotherapy
Online Resources
And Peer Support Networks

Charities:

- The Ehlers Danlos Society
  http://www.ehlers-Danlos.com

- The ILC Canadian Ehlers Danlos Society Division
  http://www.theilcfoundation.org/
  http://www.caneds.org

- National Institute of Arthritis and Musculoskeletal and Skin Diseases:
  http://www.niams.nih.gov/

- The Arthritis Society- Arthritis Rehabilitation and Education Program:
  www.arthritis.ca/ontario/arep

Groups:

- Ehlers-Danlos Syndrome Canada:
  http://www.ehlers-danlossyndromecanada.org/

Finding a peer support network that works best for you is important.